# EXECUTIVE SUMMARY

This report is a comprehensive review and evaluation of the public health benefits and risks of fluoride from drinking water and other sources. Fluoride was first added to public drinking water in the 1940's to prevent tooth decay. While controversy has sometimes surrounded community water fluoridation, over half of the U.S. population is served by drinking water that is fluoridated naturally or adjusted. Additionally, since the 1950's, fluorides have been incorporated into toothpaste, other dental products, and dietary supplements.

The Assistant Secretary for Health, Dr. James O. Mason, requested an analysis of the benefits and risks of fluorides upon the receipt of the preliminary results of a study in which animals were given sodium fluoride in the drinking water. The study, conducted by the National Toxicology Program (NTP), a research and testing program within the U.S. Public Health Service (PHS), found a small number of malignant bone tumors (osteosarcomas) in male rats. The NTP study concluded that there was "equivocal" evidence of carcinogenic activity in male rats (HHS, 1990).

"Equivocal" evidence is one of five standard categories that are employed in NTP studies to describe the strength of the evidence of individual experiments. According to NTP's standard definition, "equivocal evidence of carcinogenicity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related." The independent peer review panel which evaluated the NTP study requested the addition of a statement that further defined the term "equivocal evidence" of carcinogenicity as a category "for **uncertain findings** (emphasis added) demonstrated by studies that are interpreted as showing a marginal increase in neoplasms that may be chemically related" (HHS, 1990). The NTP study found no evidence of carcinogenic activity of sodium fluoride in female rats, or in mice of either sex.

Animal studies conducted at a range of dose levels, often at doses that are the maximum which can be tolerated without shortening the lifespan of the animal, are used to identify potential hazards to human health. The identification of a potential hazard from animal studies, which is one of the first steps in assessing a health risk to humans, does not necessarily mean that there is a risk to humans. Further steps are taken to determine potential human risks. Human epidemiological studies can help to determine if a hazard to humans exists. The results of epidemiological studies are then analyzed in combination with information from animal studies, dose-response relationships, and patterns of human exposure in order to characterize the magnitude of the risk to humans. This process of characterizing human risk—the likely harm to human health—is called risk assessment.

This report qualitatively assesses fluoride's health benefits as well as fluoride's health risks. It was prepared by the Ad Hoc Subcommittee on Fluoride of the PHS Committee to Coordinate Environmental Health and Related Programs (CCEHRP) and approved by CCEHRP. The data analyzed in the report include: the NTP study of sodium fluoride; human and animal studies published in the biomedical literature on both the benefits and the risks of fluoride; the U.S. Food and Drug Administration's (FDA) review of a chronic bioassay animal study sponsored by the Procter and Gamble Company; and new epidemiological studies performed by the National Cancer Institute (NCI). To ensure public input, an announcement was published in the **Federal Register** on March 1, 1990, soliciting peer-reviewed published articles on fluorides. **A total of 24 individuals submitted over 100** articles which were considered by the Subcommittee.

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# MAJOR FINDINGS[1]

*ASSESSMENT OF THE HEALTH BENEFITS OF FLUORIDE*

Fluoride has substantial benefits in the prevention of tooth decay. Numerous studies, taken together, clearly establish a causal relationship between water fluoridation[2] and the prevention of dental caries. While dental decay is reduced by fluoridated toothpaste and mouth rinses, professional fluoride treatments and fluoride dietary supplements, fluoridation of water is the most cost-effective method. It provides the greatest benefit to those who can least afford preventive and restorative dentistry and reduces dental disease, loss of teeth, time away from work or school, and anesthesia-related risks associated with dental treatment.

In the 1940's, children in communities with fluoridated drinking water had reductions in caries scores of about 60 percent as compared to those living in non-fluoridated communities. Recent studies still reveal that caries scores are lower in naturally or adjusted fluoridated areas; however, the differences in caries scores between fluoridated and non-fluoridated areas are not as great as those observed in the 1940's. This apparent change is likely explained by the presence, in non-fluoridated areas, of fluoride in beverages, food, dental products, and dietary supplements.

Fluoride has been used for nearly 30 years as an experimental therapy to treat osteoporosis, but has only recently been evaluated in controlled clinical trials. Two new U.S. clinical trials showed no significant reduction in the rates of bone fractures related to the administration of fluoride. An FDA advisory panel has concluded that fluoride therapy has not been shown to be effective in reducing the frequency of vertebral fractures.

*ASSESSMENT OF THE HEALTH RISKS OF FLUORIDE*

Among the more significant health conditions evaluated in relation to fluoride intake are cancer, dental fluorosis, and bone fractures. Other conditions are evaluated in the full report.

**Cancer.** Two major scientific approaches have been used to determine whether an association exists between the use of fluoride and cancer: carcinogenicity studies in rodents, and human epidemiological analyses which compare cancer incidence and mortality between communities with fluoridated water and those with negligible amounts of fluoride in drinking water.

Five carcinogenicity studies in animals have been reported in the biomedical literature. Three studies, conducted before 1970 and interpreted as negative, had significant methodological limitations, as judged by current standards of experimental design. Two subsequent studies were conducted using current standards to evaluate the carcinogenicity of sodium fluoride in experimental animals.

One of the two carcinogenicity studies was conducted by the National Toxicology Program (NTP). This peer-reviewed study provided sodium fluoride in drinking water to rats and mice and determined the occurrence of tumor formation many different organ systems. The peer review panel concluded that, "Under the conditions of these 2-year dosed water studies, there was equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals. There was no evidence of carcinogenic activity in female F344/N rats receiving sodium fluoride at concentrations of 25, 100, or 175 ppm (0, 11, 45, 79 ppm fluoride) in drinking water for 2 years. There was no evidence of carcinogenic activity of sodium fluoride in male or female mice receiving sodium fluoride at concentrations of 25, 100, or 175 ppm in drinking water for 2 years." The Ad Hoc Subcommittee on Fluoride concurs with this conclusion.

The other carcinogenicity study was sponsored by the Procter and Gamble Company using Cr:CD (Sprague-Dawley) rats and Crl:CD-1 (ICR) mice both treated with 0, 4, 10, or 25 milligrams/kilogram/day sodium fluoride added to a low fluoride-basal diet. A second control group received powdered rodent chow. There was no evidence of malignant tumors associated with sodium fluoride in mice and rats of either sex in the Procter and Gamble study. While there were two osteosarcomas in the low dose female rats, one osteosarcoma in a high dose male rat, and one fibroblastic sarcoma in a mid-dose male rat, these findings in treated animals were not statistically different from controls. Male and female mice in the study did have a statistically significant increase in benign bone tumors (osteomas). The significance of a Type C retrovirus, detected in the osteomas, remains to be determined. Osteomas and osteosarcomas are different in anatomical site and clinical course. The FDA also noted difficulty in assessing the dose-related aspects of the osteomas in mice (see page 75-6). Furthermore, osteomas and osteosarcomas are so rare normally in rodents that the relationship between these tumors cannot be accurately stated.

When the NTP and the Procter and Gamble studies are combined, a total of eight individual sex/species groups are available for analysis. 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.

There have been over 50 human epidemiology studies of the relationship between water fluoridation and cancer. Epidemiological studies of fluoride usually attempt to identify statistical associations between cancer rates and county- or city-wide patterns of water fluoridation. Expert panels which reviewed this international body of literature agree that there is no credible evidence of an association between either natural fluoride or adjusted fluoride in drinking water and human cancer (LARC, 1982; Knox, 1985). Interpretation of these studies is limited by the inability to measure individual fluoride exposures or to measure other individual predictors of cancer risk, such as smoking or occupational exposures.

In March of 1990, the National Cancer Institute (NCI) updated and expanded an earlier analysis of cancer deaths, by county in the United States, to determine whether there is or is not an association between cancer and fluoride in drinking water. The new studies evaluated an additional 16 years of cancer mortality data, and also examined patterns of cancer incidence between 1973 and 1987 in the Surveillance, Epidemiology and End Results (SEER) Program cancer registries. SEER, an NCI sponsored network of population-based cancer incidence registries, started in 1973 and represents about 10 percent of the U.S. population. The SEER registries were used to obtain incidence data on all cancers, with special emphasis placed on trends in osteosarcoma. Because mortality data do not contain information on tumor-specific pathology, analysis of osteosarcomas is limited to the incidence data.

The NCI study identified no trends in cancer risk which could be attributed to the introduction of fluoride into drinking water. The study examined nationwide moronity data and incidence data from counties in Iowa and the Seattle, Washington, metropolitan area. There were no consistent differences in the trends in cancer mortality rates among males and females living in counties having initiated relative mortality rates from cancer, including cancer of the bones and joints, were similar after 20-35 years of fluoridation as they were in the years preceding fluoridation. In addition, there was no relationship between the introduction and duration of fluoridation and the patterns of cancer incidence rates, including those of the bone and joint, and the subset of osteosarcomas (Appendix E). For example, there were 91 observed cases of osteosarcoma in the fluoridated areas, when 93 cases were expected based on rates in non-fluoridated areas.

The NCI also conducted a more detailed evaluation of osteosarcomas using nationwide age-adjusted incidence data from the entire SEER database for the years 1973-1987 (Appendix F). Osteosarcoma is a rare form of bone cancer, the cause of which is under study. Approximately 750 newly diagnosed cases occur each year in the United States, representing about 0.1 percent of all reported cancers. Between two time periods, 1973-1980 and 1981-1987, there was an unexplained increase in the annual incidence rates of osteosarcoma in young males under age 20 from 3.6 cases per 1,000,000 people (88 registry cases) to 5.5 cases per 1,000,000 people (100 registry cases). This compares to a decrease in young females of the same age group from 3.8 cases per 1,000,000 people (87 registry cases) to 3.7 cases per 1,000,000 people (63 registry cases). The amount of increase observed in young males was greater in fluoridated than in non-fluoridated areas. Although the reason for the increase in young males remains to be clarified, an extensive analysis reveals that it is unrelated to the introduction and duration of fluoridation.

In studying rare cancers, such as osteosarcoma, small increases in risk, on the order of 5 to 10 percent, would not likely be detected. While descriptive epidemiological studies are useful in determining whether or not there is a credible association, the qualitative nature of any association, if one exists, can best be determined through more refined methods, such as case-control studies.

**Dental Fluorosis.** Dental fluorosis has been recognized since the turn of the century in people with high exposure to naturally occurring fluoride in drinking water. It has always been more prevalent in fluoridated than non-fluoridated areas. Dental fluorosis only occurs during tooth formation and becomes apparent upon eruption of the teeth. It ranges from very mild symmetrical whitish areas on teeth (very mild dental fluorosis) to pitting of the enamel, frequently associated with brownish discoloration (severe dental fluorosis). The very mild form barely is detectable even by experienced dental personnel. Moderate and severe forms of dental fluorosis, considered by some investigators as presenting a cosmetic problem, do not appear to produce adverse dental health effects, such as the loss of tooth function, and represents less than 6 percent of the cases of fluorosis nationally.

In the 1940's, about 10 percent of the population displayed very mild and mild dental fluorosis when the concentration of fluoride found naturally in the drinking water was about 1 part per million (ppm). Over the last 40 years, in areas where fluoride is added to the drinking water to bring the total level of fluoride to about 1 ppm (optimally fluoridated areas), there may have been an increase in the total prevalence of dental fluorosis. In non-fluoridated areas, there is clear evidence that the total prevalence of dental fluorosis has increased over the last 40 years.

The greater the fluoride exposure during tooth development, the greater the likelihood of dental fluorosis. In the 1940's and 1950's, the major sources of fluoride were from drinking water and food. Since then, numerous sources of fluoride have become available, including dental products containing fluoride (e.g., toothpastes and mouth rinses) and fluoride dietary supplements. The inappropriate use of these products can contribute significantly to total fluoride intake.

Increases in the prevalence of dental fluorosis in a population should be taken as evidence that fluoride exposure is increasing. Because dental fluorosis does not compromise oral health or tooth function, an increase in dental fluorosis, by itself, is not as much of a dental public health concern as it is an indication that total fluoride exposure may be more than necessary to prevent tooth decay. Prudent public health practice generally dictates using no more of a substance than the amount necessary to achieve a desired effect.

**Bone Fractures.** 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.

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1For other findings, see Other Effects section page 87 of the report.

2Fluoridated area means that drinking water supplied to that area contains fluoride at least at the optimal level (0.7-1.2 ppm depending on temperature) either naturally or by the water's having been adjusted to that level. Non-fluoridated area means that the drinking water does not contain fluoride at the optimal level. The level of fluoride naturally present in the non-fluoridated areas varies from study to study, but generally ranges from negligible levels to less than 0.3 ppm.

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# CONCLUSIONS

- Extensive studies over the past 50 years have established that individuals whose drinking water is fluoridated show a reduction in dental caries. Although the comparative degree of measurable benefit has been reduced recently as other fluoride sources have become available in non-fluoridated areas, the benefits of water fluoridation are still clearly evident. Fewer caries are associated with fewer abscesses and extractions of teeth and with improved health. The health and economic benefits of water fluoridation accrue to individuals of all ages and socioeconomic groups, especially to poor children.
- Since the addition of fluoride to drinking water in the 1940's, other sources of fluoride have become available, including toothpastes, mouth rinses, and fluoride dietary supplements. These sources of fluoride also have proven to be effective in preventing dental caries.
- Estimates developed for this report show that fluoride exposure is generally greater in fluoridated areas; however, there is fluoride exposure in both fluoridated and non-fluoridated areas because of the variety of fluoride sources besides drinking water. Beverages and foods are sources of fluoride, especially if they have been prepared with fluoridated drinking water.
- Optimal fluoridation of drinking water does not pose a detectable cancer risk to humans as evidenced by extensive human epidemiological data available to date, including the new studies prepared for this report. While the presence of fluoride in sources other than drinking water reduces the ability to discriminate between exposure in fluoridated as compared to non-fluoridated communizes, no trends in cancer risk, including the risk of osteosarcoma, were attributed to the introduction of fluoride into drinking water in these new studies. During two time periods, 1973-1980 and 1981-1987, there was an unexplained increase of osteosarcoma in males under age 20. The reason for this increase remains to be clarified, but an extensive analysis reveals that it is unrelated to the introduction and duration of fluoridation.
- There are two methodologically acceptable studies of the carcinogenicity of fluoride in experimental animals. The Procter and Gamble study did not find any significant evidence of carcinogenicity in rats and mice of either sex. In the NTP study there was no evidence of carcinogenicity in mice and in female rats. Male rats showed "equivocal" evidence of carcinogenicity based on the finding of a small number of osteosarcomas. "Equivocal" evidence is defined by NTP as "...interpreted as showing a marginal increase in neoplasms that may be chemically related" (HHS, 1990). Taken together, the data available at this time from these two animal studies fail to establish an association between fluoride and cancer.
- By comparison with the 1940's, the total prevalence of dental fluorosis has increased in non-fluoridated areas and may have increased in optimally fluoridated areas. Such increases in dental fluorosis in a population signify that total fluoride exposures have increased and may be more than are necessary to prevent dental caries. For this reason, prudent public health practice dictates the reduction of unnecessary and inappropriate fluoride exposure.
- In the 1940s, drinking water and food were the major sources of fluoride exposure. Since then, additional sources of fluoride have become available through the introduction of fluoride containing dental products. Although the use of these products is likely responsible for some of the declines in caries scores, the inappropriate use of these products has also likely contributed to the observed increases in the prevalence of very mild and mild forms of dental fluorosis.
- Further epidemiological studies are required to determine whether or not an association exists between various levels of fluoride in drinking water and bone fractures.
- Crippling skeletal fluorosis is not a public health problem in the United States, as evidenced by the reports of only five cases in 30 years. Crippling skeletal fluorosis, a chronic bone and joint disease associated with extended exposure to high levels of fluoride, has been more prevalent in some regions outside the United States.
- Well-controlled studies have not demonstrated a beneficial effect of the use of high doses of fluoride in reducing osteoporosis and related bone fractures.
- 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 different 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.
- Chronic low level fluoride exposure is nor associated with birth defects. Studies also fail to establish an association between fluoride and Down Syndrome.
- There is no indication that chronic low level fluoride exposure of normal individuals presents a problem in other organ systems, such as the gastrointestinal, the genitourinary, and the respiratory systems. The effects of fluoride on the reproductive system merit further investigation in animal and human studies.

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# POLICY RECOMMENDATIONS

- The U.S. Public Health Service should continue to recommend the use of fluoride to prevent dental caries.
- The U.S. Public Health Service should continue to support optimal fluoridation of drinking water. Currently, the optimal level for water fluoridation is between 0.7 - 1.2 parts per minion, depending on mean daily air temperature for a geographic area.
- The U.S. Public Health Service should sponsor a scientific conference(s) to recommend both the optimal level of total fluoride exposure from all sources combined (including drinking water) and the appropriate usage of fluoride containing dental products in order to achieve the benefits of reduced dental caries and to minimize the occurrence of dental fluorosis.
- The U.S. Environmental Protection Agency should review its regulations concerning naturally occurring fluoride in drinking water based on the outcome of the scientific conference(s) recommended above and based on this report.
- In accordance with prudent health practice of using no more than the amount necessary to achieve a desired effect, health professionals and the public should avoid excessive and inappropriate fluoride exposure. For example, health professionals should prescribe fluoride dietary supplements only when the fluoride level of the home water supply is known to be deficient. Parents should educate young children to minimize swallowing of fluoridated toothpaste and to use only small amounts of toothpaste on the brush.
- The U.S. Food and Drug should review the labeling required for toothpaste and other fluoride containing products to ensure that the public has adequate knowledge to make informed decisions about their use, especially for young children (those under 6 years of age).
- Manufacturers of toothpaste should be encouraged to make the fluoride levels in their products easily known. Manufacturers should determine whether toothpaste can be dispensed in a dose limited container for use by children. Manufacturers of dental products should explore whether the levels of fluoride can be reduced while preserving clinical effectiveness.
- State health and drinking water programs should keep physicians, dentists, pharmacists, physician extenders, and communities informed about the fluoridation status of drinking water. This information will enable residents and health professionals to determine the need for water fluoridation or for supplemental forms of fluoride.
- Communities with high natural fluoride levels in the public drinking water supply should comply with EPA regulations as mandated by the Safe Drinking Water Act. The current primary and secondary maximum contaminant levels are 4 and 2 parts per million, respectively.
- An action plan to implement research and policy recommendations should be developed.

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# RESEARCH RECOMMENDATIONS

*RESEARCH ON THE BENEFITS OF FLUORIDE*

- Conduct surveys to evaluate the prevalence of dental caries over time and accurately assess exposure to fluoride.
- Undertake studies to elucidate further the role of fluoride in preventing coronal and root decay in adults. Undertake studies to identify effective means of providing fluoride to individuals at high risk of dental caries.
- Continue longitudinal studies of caries scores in cities after defluoridation or the discontinuation of fluoridation to supplement past information which covers only 2-5 years of follow-up period.
- Document the marginal risks, costs, and benefits of providing multiple fluoride regimens in the prevention of dental caries.
- Determine the relationship among socioeconomic status, water fluoridation status, and the use of fluoride products.
- In scoring dental caries, researchers should count individual surfaces rather than just the number of teeth because such scoring provides more information and greater sensitivity.
- Researchers should express reductions in caries scores as the number of tooth surfaces saved from caries, in addition to the percentage.

*RESEARCH ON THE RISKS OF FLUORIDE*

- Continue studies to elucidate the mechanisms of fluoride action on bone and teeth at the molecular and physical chemical levels.
- Develop a method of quantitatively identifying dental fluorosis that is sensitive, specific, reliable and acceptable to the public.
- Continue to study dental fluorosis to determine the ecology and trends in the prevalence of dental fluorosis.
- Conduct analytical epidemiological studies of osteosarcoma to determine the risk factors associated with its development. Fluoride exposure and bone levels of fluoride should be included in the study design.
- Evaluate the scientific merit of conducting further animal carcinogenicity studies which use a wide range of chronic fluoride doses. Industries sponsoring studies of fluoride should be encouraged to make their data publicly available to aid in this evaluation.
- Conduct analytical epidemiological studies to determine the relationship, if any, among fluoride intake, fluoride bone levels, diet, body levels of nutrients such as calcium, and bone fractures.
- Conduct studies on the reproductive toxicity of fluoride using various dose levels including the minimally toxic maternal dose.
- Conduct further studies to investigate whether or not fluoride is genotoxic.

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