

affected, but it is characterized by chronic joint pain, arthritic symptoms, slight calcification of ligaments, and osteosclerosis of the cancellous bones. Whether EPA's MCLG of 4 mg/L protects against these precursors to more serious mobility problems is unclear.

Few clinical cases of skeletal fluorosis in healthy U.S. populations have been reported in recent decades, and the committee did not find any recent studies to evaluate the prevalence of the condition in populations exposed to fluoride at the MCLG. Thus, to answer the question of whether EPA's MCLG protects the general public from stage II and stage III skeletal fluorosis, the committee compared pharmacokinetic model predictions of bone fluoride concentrations and historical data on iliac-crest bone fluoride concentrations associated with the different stages of skeletal fluorosis. The models estimated that bone fluoride concentrations resulting from lifetime exposure to fluoride in drinking water at 2 mg/L (4,000 to 5,000 mg/kg ash) or 4 mg/L (10,000 to 12,000 mg/kg ash) fall within or exceed the ranges historically associated with stage II and stage III skeletal fluorosis (4,300 to 9,200 mg/kg ash and 4,200 to 12,700 mg/kg ash, respectively). However, this comparison alone is insufficient for determining whether stage II or III skeletal fluorosis is a risk for populations exposed to fluoride at 4 mg/L, because bone fluoride concentrations and the levels at which skeletal fluorosis occurs vary widely. On the basis of the existing epidemiologic literature, stage III skeletal fluorosis appears to be a rare condition in the United States; furthermore, the committee could not determine whether stage II skeletal fluorosis is occurring in U.S. residents who drink water with fluoride at 4 mg/L. Thus, more research is needed to clarify the relationship between fluoride ingestion, fluoride concentrations in bone, and stage of skeletal fluorosis before any conclusions can be drawn.

Bone Fractures

Several epidemiologic studies of fluoride and bone fractures have been published since the 1993 NRC review. The committee focused its review on observational studies of populations exposed to drinking water containing fluoride at 2 to 4 mg/L or greater and on clinical trials of fluoride (20-34 mg/day) as a treatment for osteoporosis. Several strong observational studies indicated an increased risk of bone fracture in populations exposed to fluoride at 4 mg/L, and the results of other studies were qualitatively consistent with that finding. The one study using serum fluoride concentrations found no appreciable relationship to fractures. Because serum fluoride concentrations may not be a good measure of bone fluoride concentrations or long-term exposure, the ability to show an association might have been diminished in that study. A meta-analysis of randomized clinical trials reported an elevated risk of new nonvertebral fractures and a slightly decreased risk of vertebral

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fractures after 4 years of fluoride treatment. An increased risk of bone fracture was found among a subset of the trials that the committee found most informative for assessing long-term exposure. Although the duration and concentrations of exposure to fluoride differed between the observational studies and the clinical trials, bone fluoride content was similar (6,200 to more than 11,000 mg/kg ash in observational studies and 5,400 to 12,000 mg/kg ash in clinical trials).

Fracture risk and bone strength have been studied in animal models. The weight of evidence indicates that, although fluoride might increase bone volume, there is less strength per unit volume. Studies of rats indicate that bone strength begins to decline when fluoride in bone ash reaches 6,000 to 7,000 mg/kg. However, more research is needed to address uncertainties associated with extrapolating data on bone strength and fractures from animals to humans. Important species differences in fluoride uptake, bone remodeling, and growth must be considered. Biochemical and physiological data indicate a biologically plausible mechanism by which fluoride could weaken bone. In this case, the physiological effect of fluoride on bone quality and risk of fracture observed in animal studies is consistent with the human evidence.

Overall, there was consensus among the committee that there is scientific evidence that under certain conditions fluoride can weaken bone and increase the risk of fractures. The majority of the committee concluded that lifetime exposure to fluoride at drinking-water concentrations of 4 mg/L or higher is likely to increase fracture rates in the population, compared with exposure to 1 mg/L, particularly in some demographic subgroups that are prone to accumulate fluoride into their bones (e.g., people with renal disease). However, 3 of the 12 members judged that the evidence only supports a conclusion that the MCLG *might not* be protective against bone fracture. Those members judged that more evidence is needed to conclude that bone fractures occur at an appreciable frequency in human populations exposed to fluoride at 4 mg/L and that the MCLG is not *likely* to be protective.

There were few studies to assess fracture risk in populations exposed to fluoride at 2 mg/L in drinking water. The best available study, from Finland, suggested an increased rate of hip fracture in populations exposed to fluoride at concentrations above 1.5 mg/L. However, this study alone is not sufficient to judge fracture risk for people exposed to fluoride at 2 mg/L. Thus, no conclusions could be drawn about fracture risk or safety at 2 mg/L.

Reproductive and Developmental Effects

A large number of reproductive and developmental studies in animals have been conducted and published since the 1993 NRC report, and the