bone fluoride content, but a given concentration of bone fluoride does not necessarily correspond to a certain stage of skeletal fluorosis in all cases. Other factors (e.g., calcium intake) appear to influence fluorosis severity at different concentrations of bone fluoride.

Overall, the committee finds that the predicted bone fluoride concentrations that can be achieved from lifetime exposure to fluoride at 4 mg/L (10,000 to 12,000 mg/kg bone ash) fall within or exceed the ranges of concentrations that have been associated with stage II and stage III skeletal fluorosis. Based on the existing epidemiologic literature, stage III skeletal fluorosis appears to be a rare condition in the United States. As discussed above, the committee judges that stage II skeletal fluorosis is also an adverse health effect. However, the data are insufficient to provide a quantitative estimate of the risk of this stage of the affliction. The committee could not determine from the existing epidemiologic literature whether stage II skeletal fluorosis is occurring in U.S. residents who drink water with fluoride at 4 mg/L. The condition does not appear to have been systematically investigated in recent years in U.S. populations that have had long-term exposures to high concentrations of fluoride in drinking water. Thus, research is needed on clinical stage II and stage III skeletal fluorosis to clarify the relationship of fluoride ingestion, fluoride concentration in bone, and clinical symptoms.

EFFECT OF FLUORIDE ON CHONDROCYTE METABOLISM AND ARTHRITIS

The two key chondrocyte cell types that are susceptible to pathological changes are articular chondrocytes in the joint and growth plate chondrocytes in the developing physis. The medical literature on fluoride effects in these cells is sparse and in some cases conflicting.

From physical chemical considerations, it might be expected that mineral precipitates containing fluoride would occur in a joint if concentrations of fluoride and other cations (such as Ca^{2+}) achieved a high enough concentration. A single case report by Bang et al. (1985) noted that a 74-year-old female who was on fluoride therapy for osteoporosis for 30 months had a layer of calcified cartilage containing 0.39% fluoride (or 3,900 mg/kg) by ash weight in her femoral head. The calcification was also visible on x-ray. Unfortunately, the limitation of this observation in a single patient is the lack of information on the preexistence of any calcified osteophytes. Nevertheless, it does indicate that at high therapeutic doses fluoride can be found in mineralizing nodules in articular cartilage.

Studies evaluating patient groups with a greater number of subjects found that the use of fluoride at therapeutic doses in rheumatoid patients showed a conflicting result. In one report (Duell and Chesnut 1991), fluoride exacerbated symptoms of rheumatoid arthritis, but, in another case

(Adachi et al. 1997), it was "well tolerated" with no evidence of worsening of the arthritis. No indications from either study implied that fluoride had a causal relationship with the rheumatoid arthritis. Perhaps the only study in the literature that attempts to link fluoride exposure to the induction of arthritis (osteoarthritis) is from Savas et al. (2001), who indicated that Turkish patients with demonstrated endemic fluorosis had a greater severity of osteoarthritic symptoms and osteophyte formation than age- and sex-matched controls.

The veterinary literature also contains a report indicating that, in 21 dairy herds consuming fluoride-containing feed and water, of the 100 cows examined and determined to have arthritic changes, the bone fluoride concentrations ranged from 2,000 to 8,000 mg/kg (Griffith-Jones 1977).

There are no data from which a dose-response relationship can be drawn regarding fluoride intake and arthritis in humans. However, in a rat study, Harbrow et al. (1992) showed articular changes with fluoride at 100 mg/L in drinking water but no effect at 10 mg/L. The changes with fluoride at 100 mg/L were a thickening of the articular surface (rather than a thinning as would be expected in arthritis) and there were no effects on patterns of collagen and proteoglycan staining. There are no comprehensive reports on the mechanism of fluoride effects in articular chondrocytes in vitro.

The effect of fluoride on growth plate chondrocytes is even less well studied than the effect on articular chondrocytes. It has been demonstrated that chronic renal insufficiency in a rat model can increase the fluoride content in the growth plate and other regions of bone (Mathias et al. 2000); however, this has not been known to occur in humans. Fluoride has also been shown to negatively influence the formation of mineral in matrix vesicles at high concentrations. Matrix vesicles are the ultrastructural particles responsible for initiating mineralization in the developing physis (Sauer et al. 1997). This effect could possibly account, in part, for the observation that fluoride may reduce the thickness of the developing growth plate (Mohr 1990).

In summary, the small number of studies and the conflicting results regarding the effects of fluoride on cartilage cells of the articular surface and growth plate indicate that there is likely to be only a small effect of fluoride at therapeutic doses and no effect at environmental doses.

FINDINGS

Fluoride is a biologically active ion with demonstrable effects on bone cells, both osteoblasts and osteoclasts. Its most profound effect is on osteoblast precursor cells where it stimulates proliferation both in vitro and in vivo. In some cases, this is manifested by increases in bone mass in vivo.