gredients: calicum fluoride and sodium fluoride.

a. *Description.* Although considerable information exists regarding fluoride metabolism in a variety of animal species, there are limited data on the fate of ingested fluoride in man. In certain endemic areas the fluoride content of drinking water approximates 4.0 to 5.8 ppm (Ref. 1).Ordinary drinking water, which often contains up to 1 ppm, contributes approximately 1.0 to 1.5 to the daily fluoride intake. The average daily U.S. diet also contains 0.25 to 0.30 mg fluorine (Ref. 2), although specific foods such as tea, baking powders, wines, fresh mackeral, dries salmon, or unwashed apples sprayed with fluoride-containing insecticides may contain up to 6.3 mg/liter (wines) or 2.7 mg/100 g (fresh mackeral) (Ref. 2). Fluoride is widely distributed in nature, and food contents usually reflect both soil and atmospheric concentrations of fluoride. Specific in this regard is the use of different forms of fertilizer, with fluoride contents ranging from 0.01 to 9.88 percent (Ref. 3).

The gastrointestinal tract is the major site of fluoride absorption in man, although fluorine is absorbed via the lungs following inhalation of industrial atmospheric contaminants as may occur in cryolite workers, steel and metal workers where fluorospan is used as a flux, chemical workers using hydrofluoric acids, workers in brick factories using fluorine-rich clay and those employed in the manufacture of phosphate compounds. Hydrogen fluoride is minimally absorbed by the skin although the resulting burn is of much greater consequence than the minute amount of fluoride absorbed. The degree of absorption of fluoride correlates with its solubility. Relatively soluble compounds such as sodium fluoride are well absorbed by the gastrointestinal tract, whereas relatively insoluble forms such as cryolite (Na_3AlF_6) and the fluoride found in bone meal (fluoroapatite) are poorly absorbed (Refs. 4 and 5).

Radioactive fluoride absorption studies in human subjects reveal that the isotope enters the blood extremely rapidly when given by mouth (Refs. 6 and 7). The greatest urinary fluoride concentration after the oral ingestion of a single dose of sodium fluoride occurs within 2 hours (Refs. 8 and 9). The absorption of fluoride from vitamin-containing fluoride preparations containing 0.1 mg fluoride is also quite rapid with increments of blood-fluoride concentrations from 0.15 ppm to 0.26 ppm noted 1 hour after the ingestion of a tablet containing a vitamin-fluoride combination (Ref. 10). The fluoride content of plasma of humans ingesting communal water with fluoride contents of 0.15 to 2.5 ppm is relatively constant at 0.12 to 0.15 ppm (Ref. 11). Once absorbed, renal excretion and skeletal mineral sequestration are the principal mechanisms which regulate circulating fluoride levels.

The percentage of ingested fluoride that appears in the urine amounts to 50 to 65 percent of the daily intake (Refs. 12, 13, and 14). It appears that when humans ingest small amounts of fluoride (i.e., 1 ppm) for a prolonged period, the daily urinary excretion is a greater fraction of the intake. Labile skeletal fluoride reserves are excreted more rapidly by adults than children; also, the more rapid metabolic activity of developing bone in children liberates more of the sequestered fluoride and, as such, maintains elevated blood and urine fluoride concentrations over a much longer time interval (Ref. 15).

b. *Safety.* A lethal dose of fluoride (2.5 to 5 g) produces signs of violent gastrointestinal irritation, shock, and death within 2 to 4 hours. The safety factor assuming the ingestion of a quart of water daily at 1 ppm fluoride concentration (i.e., 1 mg fluoride) is at least 2,500-fold (Ref. 16). Crippling fluorosis occurs when humans ingest or inhale 20 to 80 mg fluoride or more for 10 to 20 years, and enamel hyperplasia noted in children within the first 8 years of life with graded severity when the drinking water contains 2 to 5 ppm fluoride or more. There are reports of retinopathy and others describing optic neuritis and macular edema after daily doses of 30 mg fluoride for 6 weeks. Atopic dermatitis, urticaria, pruitis, and edema have also been reported to occur in patients using fluoride-containing vitamins and toothpastes (Ref. 16, 17, and 18).

c. *Effectiveness.* Skeletal deposition of fluoride is a continuing process in which 25 to 50 percent of the ingested fluoride is deposited daily. The concentration of fluoride in bones and teeth depends on the total daily intake and length of exposure, with skeletal levels reportedly increasing with age (Ref. 19). Studies in humans 26 to 90 years of age who have drunk water containing 0.1 to 4.0 ppm fluoride for at least 10 years reveal no significant histological changes in soft tissue and bones (Refs. 20 and 21). The concentration of fluoride in the skeleton increases in an essentially linear fashion with an increase in fluoride content of drinking water up to 4 ppm (Refs. 20 and 21). Fluoride is desposited in bone by simply ionic exchange with the hydroxyl groups of hydroxyapatite (Ref. 22). The skeletal deposition of fluoride is reversible. Skeletal mobilization is slow but predictable with a biological halftime (i.e., the period required to mobilize and remove from the body half of the skeletal fluoride) of 1 to 2 years (Ref. 12). Although ingestion of large doses of fluoride (i.e., up to 16.2 ppm) induces a variety of pathological changes in man such as mottled enamel and crippling bone disease (Ref. 23), the ingestion of water containing fluoride up to 8 ppm reportedly produces no deleterious bone changes other than dental mottling (Ref. 24) and may in fact retard the rate of bone loss which normally attends senescence (Refs. 1, 14, and 24) and dental caries (Ref. 25).

d. *Conclusion.* The Panel has reviewed the scientific literature, the submitted data, and the marketing history of vitamin and mineral ingredients. Based upon the available data, the Panel concludes that there is no justification for an OTC drug preparation containing fluoride for the prevention or treatment of deficiency.

e. *Category I conditions under which fluoride is generally recognized as safe and effective and is not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

None.

f. *Category II conditions under which fluoride is not generally recognized as safe and effective or is misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC fluoride drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

The Panel concludes that calcium fluoride and sodium fluoride for the prevention or treatment of fluoride deficiency are not justified as an OTC vitamin or mineral drug preparation since the small amounts needed for fluoride balance are easily provided in the diet.

g. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

None.

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