National Kidney Foundation
Fluoride Intake in Chronic Kidney Disease
April 15, 2008

Background:

The National Kidney Foundation (NKF) 1981 position paper on fluoridation[1] has recently been challenged by a lawyer, an individual with public health training, and an academic dentist, who all oppose water fluoridation. The statement from that position paper regarding insufficient evidence to recommend fluoride-free drinking water for the susceptible kidney disease population has drawn the most criticism. The availability of new information published after 1981, particularly the National Research Council's (NRC) report[2] on fluoridation of March 2006 is an additional critique. A recently published review by Kidney Health Australia[3] also suggested the NKF position statement is outdated. Lastly, the American Dental Association's listing of the National Kidney Foundation as an organization that recognizes the public health benefits of water fluoridation to prevent tooth decay has been questioned.

All four conclusions of the NKF position paper follow, italics added for emphasis and explanation in brackets inserted.

1. For patients undergoing long term dialysis, water used for preparation of dialysate be treated and appropriately monitored according to the AAMI proposed standards for hemodialysis systems. [Association for the Advancement of Medical Instrumentation (AAMI) sets the hemodialysis water quality standard for fluoride at less than 0.2 mg/L, a level that has remained constant since it was established in 1981.][4]

2. Water treatment officials should develop and maintain emergency plans so that susceptible individuals and health officials are promptly notified of the occurrence of any situations involving water used for dialysis which may pose a major health risk.

3. Fluoride concentration monitoring at treatment plants should be capable of detecting the actual fluoride levels directly.

4. It would also seem prudent to monitor the fluoride intake of patients with chronic renal impairment, particularly those living in areas of high naturally occurring fluoride, children, those with excessive fluoride intake, and those with prolonged disease. *There is insufficient evidence at this time to recommend the use of fluoride-free drinking water for all patients with renal disease.*

Issues Involved:

Fluoride Regulatory Activities, 1981 to 2006: Drinking water in the U.S. is regulated by the Environmental Protection Agency (EPA), according to the Safe Drinking Water Act. The EPA does not regulate or promote the fluoridation of water. In 1986, EPA established the maximum contaminant level goal (MCLG) for fluoride and maximum

contaminant level (MCL) at a concentration of 4 mg/L or parts per million (ppm).[5] The MCL is an enforceable standard. Aside from federal enforcement of the MCL, the level of fluoridation is determined at the local level, generally this practice uses fluoride at approximately 1 ppm. In 1991, the Public Health Service reaffirmed optimal fluoridation of water concentration of 0.7 -1.2 mg/L.[6] The NRC, a branch of the National Academy of Sciences, reviewed the health effects of fluoride and found the EPA's MCL of 4 mg/L to be an appropriate interim standard, but further research regarding exposure and toxicity were recommended in 1993.[7]

2006 NRC Report: Fluoride in Drinking Water: The major conclusion of the 507-page NRC Scientific Review of EPA's Standards is relevant to the entire population (page 2 paragraph 4), "After reviewing the collective evidence, including studies conducted since the early 1990s, the committee concluded unanimously that the present MCLG of 4 mg/L for fluoride should be lowered." The potential health risks are skeletal fluorosis, bone fractures and severe enamel fluorosis, which may increase the risk of dental decay. Another conclusion is important for individuals with chronic kidney disease (CKD), page 9, paragraph 1, "However, a potentially susceptible subpopulation comprises individuals with renal impairments who retain more fluoride than healthy people do." The EPA is evaluating how to best implement the findings of this report. Note that reduction of the MCLG of 4 ppm would not affect the practice of fluoridation of water at approximately 1 ppm.

Fluoride Health Benefits: The major benefit of water and dental products containing fluoride is the prevention of dental caries in people of all ages. This has been recognized by the US Public Health Service since at least 1950. The Centers for Disease Control and Prevention, the World Health Organization and other respected health organizations also promote water fluoridation. Increasing the proportion of the U.S. populations served by community water systems with optimally fluoridated water is a goal of Healthy People 2010.[8] Mechanisms through which fluoride provides this benefit include a systemic effect due to the replacement of hydroxyl ions in hydroxapatite by fluoride ions during tooth development in children during enamel formation, a topical effect to remineralize teeth after bacterial demineralization, and a topical effect to inhibit bacterial acid release.[9,10]

Fluoride Exposure: The major sources of fluoride are water, dental products, and diet. Rarely, drugs and inhalation are significant sources. Approximately 67 % of public US water systems deliver optimally fluoridated water (0.7 – 1.2 ppm).[11] Soduim fluoride, sodium fluorosilicate, and fluorosilic acid are added to the water systems. Public water systems in the US serving about 1.6 million people have naturally occurring levels that significantly exceed this optimal concentration recommendation. The majority of bottled water, which unlike drinking water is regulated by FDA, contains low levels of fluoride, although there may be significant variation depending on the source. Toothpaste sources contain approximately 1,000 fold more fluoride or 1,000 to 1,500 ppm, which may be a significant source of exposure for individuals with inability to control the swallowing reflex such as children under age 6 years. Of course the level of fluoride in water used to prepare food and beverages will be reflected in the product. Exposure from food and beverages is difficult to monitor, since FDA food labels do not quantify fluoride content.

Rich dietary sources of fluoride include teas and marine fish. Many medications contain fluoride such as quinolone antibiotics and statins, but the exposure is probably minimal as long as their metabolism does not release free fluoride. One inhalational drug exposure example is the hepatic biotransformation of the anesthetic methoxyflurane to release free fluoride, resulting in nephrotoxicity.[12,13] However, other anesthetics that resulted in commensurately increased systemic fluoride levels were not associated with nephrotoxicity. One recent paper concluded that the nephrotoxicity of methoxyflurane is related at least in part to the dichloroacetic acid metabolite.[13]

Fluoride Health Risks: Dental or enamel fluorosis is a hypomineralization of the enamel surfact of the tooth that develops in children 8 years old and younger exposed to excess fluoride levels from any source during critical periods of tooth development. This affects the appearance of the teeth. Milder forms are primarily cosmetic, but may have effects on self-esteem. Severe forms include pitting of the enamel.

Skeletal fluorosis is a rare condition associated with high levels of fluoride exposure over many years. There are six cases reported in the US, two of which had CKD.[2] Symptoms may include bone pain and arthralgias.[14,15] Characteristics include increased bone mass and increased radiographic bone density or osteosclerosis. Renal osteodystrophy may be difficult to distinguish from skeletal fluorosis on imaging studies. The mechanism of renal osteodystrophy development is complex including calcium, phosphorus, parathyroid hormone and vitamin D interactions. A bone biopsy series to assess the effects of trace metals in 153 CKD patients treated with hemodialysis or peritoneal dialysis revealed that increased fluoride was associated with poor mineralization and increased osteoid content.[15] There were no cases of skeletal fluorosis in this series.[15] Fluoride may interact with aluminum to worsen osteomalacia. The interaction of fluoride with magnesium is poorly understood.

The NRC committee noted that under certain conditions fluoride can weaken bone and increase the risk of fractures. 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 to exposure of 1 mg/L, particularly in subgroups that are prone to accumulate fluoride into their bones (e.g., people with CKD).[2] However, there is insufficient evidence to validate the concerns regarding persons with CKD, even at fluoride concentrations of 4 mg/L.

Fluoride Risks in CKD:

CKD Stages 1-3: Patients with an estimated GFR of 30 ml/min/1.73 m^2 or more probably have a similar risk to individuals without CKD, although there is little specific data to support this conclusion.

CKD Stages 4, 5 and 5 D: Patients with an estimated GFR less than approximately 25 ml/min/1.73m^2 retain more fluoride than healthy individuals based on older studies that used creatinine clearance to assess kidney function.[2,16,17] Fluoride blood levels are approximately 4-fold higher or about 4 umol/L in patients with CKD stages 4 and 5. The significance of this finding is

not clear. Additional clinical studies are required to reliably determine the safe level of serum fluoride for people with advanced CKD. There is no consistent evidence that the retention of fluoride in people with these stages of CKD who consume optimally fluoridated drinking water results in any negative health consequences.[3]

Acute Fluoride Intoxication in CKD 5 D treated with hemodialysis:

- Annapolis, Maryland, 1979: Hemodialysis is a unique essentially intravenous exposure to water. Approximately 1,000 gallons of 22 % hydrofluorosilic were accidentally added to the Annapolis, Maryland public water system, resulting in fluoride tap water levels of 30 to 50 ppm.[18,19] A dialysis unit served by this system treated water only with a softener to prepare dialysate in the absence of deionizer or reverse osmosis. Two days after the accident, 8 hemodialysis patients became ill with hypotension, nausea, substernal pain, diarrhea, vomiting and itching. One patient died at home. Another patient was resuscitated after a cardiopulmonary arrest that may have been the result of fluoride-induced hyperkalemia.[18]

- Chicago, Illinois, 1993: A Chicago dialysis unit utilized a water treatment system with completely exhausted ion exchange resin in the deionization tanks. This allowed fluoride to be released into the dialysate. At the unit, 12 of 46 patients became ill with pruritis and vomiting. Three patients with pre-existing cardiac disease died after cardiac arrests (ventricular fibrillation documented in all three).[20] Both the Annapolis and Chicago incidents involved dialysis units that did not follow AAMI standards. These standards were only in draft form at the time of the first incident.

<u>Analysis and Recommendations:</u>

1. Dietary advice for patients with CKD should primarily focus on established recommendations for sodium, potassium, calcium, phosphorus, energy/calorie, protein, fat, and carbohydrate intake.[21-25] Fluoride intake is a secondary concern.

2. Specific recommendations regarding fluoride intake in CKD patients are not possible based on available limited data. The current evidence regarding fluoride exposure and risks is comprised of case reports, case series, and extrapolations that assume exposure is directly proportional to water fluoride levels. There are no randomized trials of fluoride exposure for individuals with CKD. Additional research on the risks and extent of fluoride exposure for the potentially susceptible population of CKD patients with impaired kidney function is recommended.

3. Although several position statements recommend monitoring intake in the potentially susceptible CKD population,[1,3] the absence of fluoride concentrations on food and beverage labels and lack of data about fluoride intake from dental products and other sources makes this difficult to implement.

4. Failure to adhere to AAMI hemodialysis water treatment standards has resulted in several deaths in the US in 1979 and 1993. AAMI standards should continue to be followed by all dialysis programs.[4]

5. Individuals with CKD should be notified of the potential risk of fluoride exposure by providing information on the NKF website including a link to the report in brief of the NRC[2] and the Kidney Health Australia position paper.[3] The risk is likely greatest in areas with naturally high water flouride levels.

6. **The NKF has no position on the optimal fluoridation of water**. The oral health of people with CKD is of certainly of interest to the NKF, but balancing the overall benefits and risks of fluoride exposure is the primary concern.

7. **The 1981 NKF position paper on fluoridation is outdated. The paper is withdrawn and will no longer be circulated, effective from the 10/06/07 NKF Board of Director's meeting.**

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