Note from Fluoride Action Network Pesticide Project.
The following excerpts from the 2006 fluoride report by the National Research Council present an excellent and clear overview of many of the studies on fluoride's adverse effects on brain. We submitted several brain studies to the committee for their consideration. Unfortunately, none of the studies we submitted that were published in a foreign language (mainly Chinese) were translated by the NRC. See our April 2004 submission for a list of those studies at *http://www.fluoridealert.org/pesticides/nrc.brain.april.2004.htm*

Excerpts from
Chapter 7: Neurotoxicity and Neurobehavioral Effects
Fluoride in Drinking Water: A Scientific Review of EPA's Standards
March 22, 2006
National Research Council of the National Academies
Committee on Fluoride in Drinking Water
Available at: http://www.nap.edu/catalog/11571.html

HUMAN STUDIES

Cognitive Effects
(pages 173–176)

Several studies from China have reported the effects of fluoride in drinking water on cognitive capacities (X. Li et al. 1995; Zhao et al. 1996; Lu et al. 2000; Xiang et al. 2003a,b). Among the studies, the one by Xiang et al. (2003a) had the strongest design. This study compared the intelligence of 512 children (ages 8-13) living in two villages with different fluoride concentrations in the water. The IQ test was administered in a double-blind manner. The high-fluoride area (Wamiao) had a mean water concentration of 2.47 ± 0.79 mg/L (range 0.57-4.50 mg/L), and the low-fluoride area (Xinhuai) had a mean water concentration of 0.36 ± 0.15 mg/L (range 0.18-0.76 mg/L). The populations studied had comparable iodine and creatinine concentrations, family incomes, family educational levels, and other factors. The populations were not exposed to other significant sources of fluoride, such as smoke from coal fires, industrial pollution, or consumption of brick tea. Thus, the difference in fluoride exposure was attributed to the amount in the drinking water. Mean urinary fluoride 1 concentrations were found to be 3.47 ± 1.95 mg/L in Wamiao and 1.11 ± 0.39 mg/L in Xinhuai. Using the combined Raven's Test for Rural China, the average intelligence quotient (IQ) of the children in Wamiao was found to be significantly lower (92.2 ± 13.00; range, 54-126) than that in Xinhuai (100.41 ± 13.21; range, 60-128).

The IQ scores in both males and females declined with increasing fluoride exposure. The distribution of IQ scores from the females in the two villages is shown in Figure 7-1. A comparable illustration of the IQ scores of males is shown in Figure 7-2. The number of children in Wamiao with scores in the higher IQ ranges was less than that in Xinhuai. There were corresponding increases in the number of children in the lower IQ range. Modal scores of the IQ distributions in the two villages were approximately the same. A follow-up study to determine whether the lower IQ scores of the children in Wamiao might be related to differences in lead exposure disclosed no significant difference in blood lead concentrations in the two groups of children (Xiang et al. 2003b).

A study conducted by Lu et al. (2000) in a different area of China also compared the IQs of 118 children (ages 10-12) living in two areas with different fluoride concentrations in the water (3.15 ± 0.61 mg/L in one area and 0.37 ± 0.04 mg/L in the other). The children were lifelong residents of the villages and had similar social and educational levels. Urinary fluoride concentrations were measured at 4.99 ± 2.57 mg/L in the high-fluoride area and 1.43 ± 0.64 mg/L in the low-fluoride area. IQ measurements using the Chinese Combined Raven's Test, Copyright 2 (see Wang and

Qian 1989), showed significantly lower mean IQ scores among children in the high-fluoride area (92.27 ± 20.45) than in children in the low-fluoride area (103.05 ± 13.86). Of special importance, 21.6% of the children in the high-fluoride village scored 70 or below on the IQ scale. For the children in the low-fluoride village, only 3.4% had such low scores. Urinary fluoride concentrations were inversely correlated with mental performance in the IQ test. Qin and Cui (1990) observed similar negative correlation between IQ and fluoride intake through drinking water.

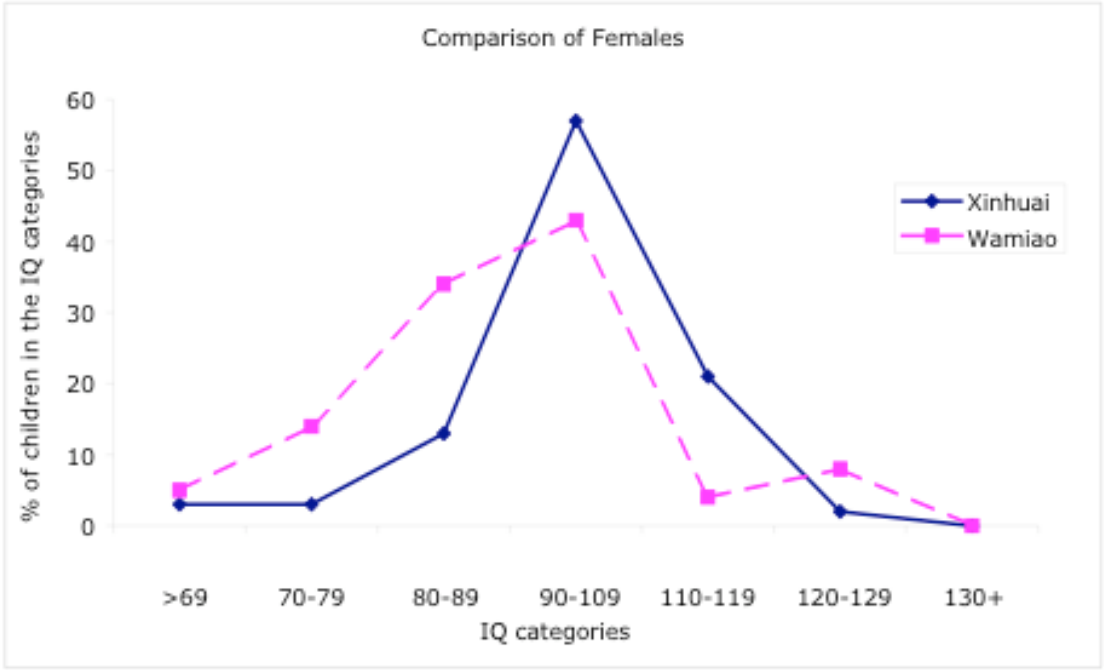

FIGURE 7-1 Distribution of IQ scores from females in Wamiao and Xinuai (data from Xiang et al. 2003a).

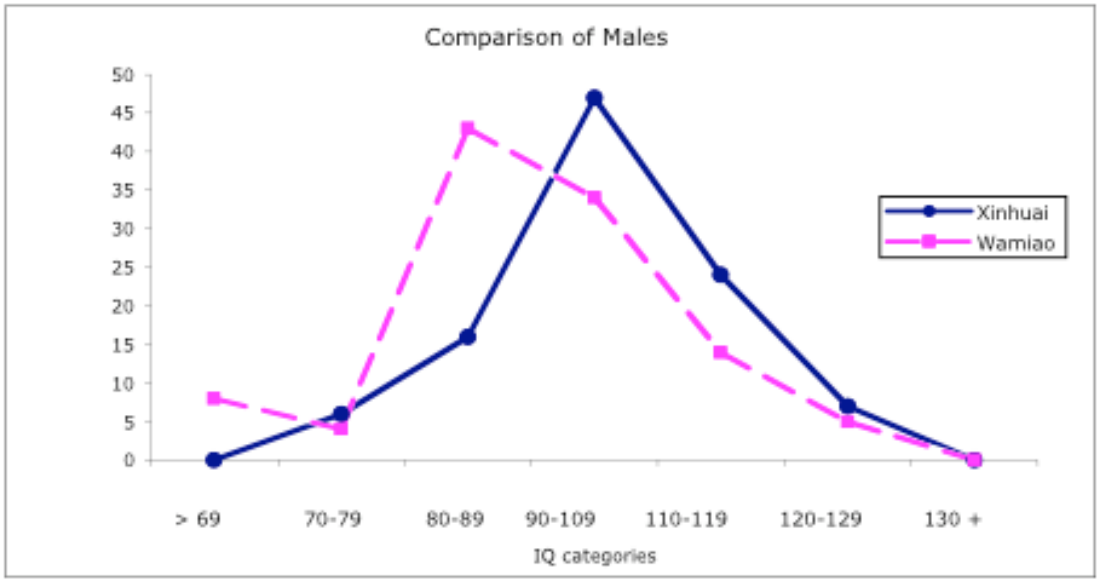

FIGURE 7-2 Distribution of IQ scores from males in Wiamiao and Xinuai (data from Xiang et al. 2003a).

Zhao et al. (1996) also compared the IQs of 160 children (ages 7-14) living in a high fluoride area (average concentration of 4.12 mg/L) with those of children living in a low-fluoride area (average concentration 0.91 mg/L). Using the Rui Wen Test, the investigators found that the average IQ of children in the high-fluoride area (97.69) was significantly lower than that of children in the low-fluoride area (105.21). No sex differences were found, but, not surprisingly, IQ scores were found to be related to parents' education. The investigators also reported that enamel fluorosis was present in 86% of the children in the high-exposure group and in 14% of the children in the low-exposure group and that skeletal fluorosis was found only in the high exposure group at 9%.

Another Chinese study evaluated fluoride exposure due to inhalation of soot and smoke from domestic coal fires used for cooking, heating, and drying grain (Li et al. 1995). Many of the children exhibited moderate to severe enamel fluorosis. The average IQ of 900 children (ages 8-13) from an area with severe enamel fluorosis was 9-15 points lower than the average IQ of children from an area with low or no dental fluorosis. Urinary fluoride concentrations were found to be inversely correlated with IQ, as measured by the China Rui Wen Scale for Rural Areas, and were monotonically related to the degree of dental fluorosis. Studies based on fluoride exposure from the inhalation of smoke from coal fires are difficult to interpret because of exposure to many other contaminants in smoke.

The significance of these Chinese studies is uncertain. Most of the papers were brief reports and omitted important procedural details. For example, some studies used a modification of the Raven Progressive Matrix test but did not specify what the modifications were or describe how the test was administered. Most of the studies did not indicate whether the IQ tests were administered in a blinded manner. Some of the effects noted in the studies could have been due to stress induced by the testing conditions. Without detailed information about the testing conditions and the tests themselves, the committee was unable to assess the strength of the studies. Despite this, the consistency of the collective results warrants additional research on the effects of fluoride on intelligence in populations that share similar languages, backgrounds, socioeconomic levels, and other commonalities. It should be noted that many factors outside of native intelligence influence performance on IQ tests. One factor that might be of relevance to fluoride is impairment of thyroid gland function (see Chapter 8). For example, hypothyroidism produces tiredness, depression, difficulties in concentration, memory impairments, and impaired hearing. In addition, there is some evidence that impaired thyroid function in pregnant women can lead to children with lower IQ scores (Klein et al. 2001).

Dementia

(pages 177–178)

For more than 30 years it has been known that Alzheimer's disease is associated with a substantial decline in cerebral metabolism (Sokoloff 1966). This original observation has been replicated many times since then. The decrease is reflected in the brain's metabolic rate for glucose, cerebral rate for oxygen, and cerebral blood flow. In terms of reduced cerebral blood flow, the reduction found in Alzheimer's patients is about three times greater than in patients with multi-infarct dementia. As early as 1983, Foster et al. (1983) demonstrated a general decline in the rate of utilization of glucose with the marker F-2-fluorodeoxyglucose with a positronemission tomography scan. Recently, over and above the general decline in aerobic metabolism, several patterns of enhanced decreases in energy utilization have been demonstrated. The temporal, parietal, and frontal regions are areas with some of the greatest reductions (Weiner et al. 1993; Starkstein et al. 1995). It is possible that the decline in glucose utilization is an early sign of the onset of dementia (Johnson et al. 1988; Silverman and Small 2002). In addition there is evidence from a number of sources that alterations induced by Alzheimer's disease can be observed in many body regions and in blood. This indicates that the disease has system-wide effects in the body. One system particularly sensitive to carbohydrate utilization is the collection of areas involved with the synthesis of ACh. The release of this transmitter is also negatively affected by the interruption of aerobic metabolism and the effect can be noticed in the projection fields of the

cholinergic systems. Fluoride produces additional effects on the ACh systems of the brain by its interference with acetylcholinesterase.

Most of the drugs used today to treat Alzheimer's disease are agents that enhance the effects of the remaining ACh system. Nevertheless, it must be remembered that one certain characteristic of Alzheimer's disease is a general reduction of aerobic metabolism in the brain. This results in a reduction in energy available for neuronal and muscular activity.

Because of the great affinity between fluorine and aluminum, it is possible that the greatest impairments of structure and function come about through the actions of charged and uncharged AlF complexes (AlFx). In the late 1970s and through the early 1990s there was considerable interest in the possibility that elemental aluminum was a major contributing factor to the development of dementia of the Alzheimer's variety as well as to other neurological disorders. In a study of more than 3,500 French men and women above the age of 65 (Jacqmin et al. 1994), a significant decrease in cognitive abilities was found when their drinking water contained calcium, aluminum, and fluorine. Only aluminum showed any relation to cognitive impairment and that depended on the pH of the drinking water being below 7.3. Curiously, at higher pH values, a favorable effect on cognitive actions was found. In recent work with animals, aluminum-induced behavioral changes similar to those found in human dementia, as well as correlated histological changes in animals' brains, were found (Miu et al. 2003). Active research continues at the cellular level on the neural mechanisms disturbed by aluminum (Becaria et al. 2003; Millan-Plano et al. 2003). On the epidemiological side there are inconsistencies in the results of different studies. For example, a recent review concludes that "the toxic effects of aluminum cannot be ruled out either, and thus exposure to aluminum should be monitored and limited as far as possible" (Suay and Ballester 2002). In addition to a depletion of acetylcholinesterase, fluoride produces alterations in phospholipid metabolism and/or reductions in the biological energy available for normal brain functions (see section later in this chapter on neurochemical effects). In addition, the possibility exists that chronic exposure to AlFx can produce aluminum inclusions with blood vessels as well as in their intima and adventitia. The aluminum deposits inside the vessels and those attached to the intima could cause turbulence in the blood flow and reduced transfer of glucose and O2 to the intercellular fluids. Finally histopathological changes similar to those traditionally associated with Alzheimer's disease in people have been seen in rats chronically exposed to AlF (Varner et al. 1998).

Anatomy

(pages 182–183)

The complete analyses of the changes found in the brains of rats given one of the three doses of AlF3 used by Varner et al. (1994) were reported in a separate paper (Varner et al. 1993). All groups of the AlF3-exposed rats had significant losses of cells in the CA1 and CA3 areas of the hippocampus, but the losses were not dose dependent. Two types of cellular anomalies were found in the treated animals: (1) argentophilic cells throughout the hippocampus and dentate gyrus with considerable sparing of cells in the CA2 region; and (2) increased aluminum fluorescence in most of the brain, especially in the inner and outer linings of a large number of blood vessels, both large and small. Intravascular inclusions of aluminum particles were sometimes noted within blood vessels. Cells containing aluminum inclusions were not uncommon. This enhancement of aluminum deposits is not surprising because the amount of aluminum found in the brain was almost double that found in control animals.

Varner et al (1998) undertook a second study to determine the relative contribution of fluoride to the high mortality found in the 0.5-mg/L group of the earlier study, to extend the histological procedures used to evaluate the brains, and to determine whether the high death rates after this low dose would be found on replication. Three groups of nine adult rats were administered AlF3 at 0.5 mg/L, NaF at 2.1 mg/L (containing the same amount of fluoride as the AlF3 group), or double-distilled deionized water for 1 year. During that time six of nine animals drinking the AlF3

water died, three of the nine animals drinking the NaF died, and one animal from the control group died. Aluminum content in brain, kidney, and liver was measured by a direct current plasma technique modified for use with tissues containing substantial fat. Brains from both the NaF and the AlF3 groups had more than twice as much aluminum as the brains of the control animals. This supports the work of Strunecka et al. (2002) indicating that fluoride enhances the uptake of aluminum. But, the uptake was organ specific. There was no increase of aluminum found in the kidneys or liver. Sections from the brains of all animals were processed in a manner that allowed their staining with hematoxylin and eosin, the Morin stain for aluminum (and counterstained with cresyl violet), and a modified Bielschowsky silver stain as well as with antisera specific for IgM, β-amyloid, or amyloid A.

There was a progressive decline in the appearance of the AlF3 treated rats compared with the NaF or control animals before their demise. Their hair was sparse and their skin had a copper color. Toenails and teeth indicated a condition reflecting a hypermelanosis. Body weights, however, did not vary among the groups. Hemispheric differences in the brain were found in the distribution of aluminum using the Morin staining ultraviolet microscopic procedure. A greater amount of aluminum fluorescence was seen in layers 5 and 6 of the parietal neocortex and hippocampus of the left relative to the right hemisphere in the AlF3-treated rats. Areas CA3 and CA4 were the most affected regions of the hippocampus.

The occurrence of abnormal cells was also determined for all brains. Signs of neuronal anomalies included chromatin clumping, enhanced protein staining, pyknosis, vacuolation, ghost-like swollen appearances of cells, and enhanced silver staining in cell bodies and their processes. Both NaF and AlF3 treatments produced cellular distortions in cortical layers 2 and 3 of both hemispheres, but enhanced cellular abnormalities in layers 5 and 6 were found only in the left hemisphere. Both treatments also produced a diminished number of cells in the left CA3 region of the hippocampus but only the AlF3 treatment reduced cell numbers in this region of the left hemisphere. These observations are similar to previous findings reported in the brains of cats after intracerebroventricular administration of aluminum chloride (Crapper and Dalton 1973).

Both the AlF3 and the NaF treatments increased staining of neurons for IgM in the right hemisphere. No differences were found among the groups in the presence of IgM on the left side of the brain. Minor amounts of IgM were found in the hippocampus and dentate gyrus but without any group differences. The control group had few instances of β-amyloid but the brains of the AlF3-treated animals demonstrated a bimodal distribution of deposits in the vasculature of the dorsal thalamus. Staining was either very high or nonexistent. The NaF-treated group showed a similar bimodality of accumulation of β-amyloid in the right lateral posterior thalamic region.

The pattern of neuronal degeneration found by Varner et al. (1998) was also found in two other studies (Bhatnager et al. 2002; Shivarajashankara et al. 2002). In the study by Bhatnagar et al. (2002) described earlier in this chapter, the investigators observed a significant number of degenerated nerve cell bodies in hippocampal subregions CA3 and CA4 and in the dentate gyrus. Shivarajashankara et al. (2002) exposed Wistar rats to NaF in utero during the last week of gestation and for 10 weeks after birth. Animals received either 30 or 100 mg/L in their drinking water. At the end of the 10 weeks the animals were sacrificed and their brains were sectioned and stained with cresyl violet. Little change was seen in the 30-mg/L treated animals but the brains of the 100-mg/L treated animals showed large amounts of neurodegeneration. There were only a few normal appearing pyramidal cells in regions CA1 and CA3 of the hippocampus. Almost all the cells in these areas were pyknotic and showed intensely stained protein in their shrunken cytoplasm. Neuronal degeneration, but to a lesser degree, was found in the upper layers of neocortex, the amygdala, and the cerebellum. These areas were not extensively studied by Varner et al. (1998).

The interactions between fluoride and aluminum have been studied in laboratories and in the environment. There is evidence that fluoride enhances the uptake of aluminum and that aluminum reduces the uptake of fluoride (Spencer et al. 1980, Ahn et al. 1995). This complicates

predicting the effect of exposure to aluminum- or fluorine-containing complexes in natural situations.

NEUROCHEMICAL EFFECTS AND MECHANISMS

(pages 184–185)

A number of studies have examined biochemical changes in the brain associated with fluoride. For example, Guan et al. (1998) reported alterations in the phospholipid content of the brain of rats exposed to NaF at 30 or 100 mg/L for 3-7 months. The most prominent changes were found in phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine. After 7 months of treatment, ubiquinone was clearly elevated, likely due as a compensatory reaction to the increase in free radicals in the brain. Fluoride has been shown to decrease the activities of superoxide dismutase (Guan et al. 1989) and glutathione peroxidase (Rice-Evans and Hoschstein 1981), the consequences being increased free radicals.

NaF injected subcutaneously into rabbits altered brain lipid metabolism (Shashi 1992b) and concentrations of protein, free amino acid, and RNA in the brain (Shashi et al. 1994).

Using slices of rat neocortex, Jope (1988) found that NaF stimulated the hydrolysis of phosphoinositide by activation of a G protein, Gp. This protein acts as a transducer between receptors and phospholipase C. He also found that a metal chelator added to the preparation eliminated this effect. This information and other observations led to the conclusion that the effective agent in the hydrolysis was an AlFx complex. Under his experimental conditions, the AlF4 was most likely formed from trace amounts of aluminum derived from the glass or from a fluorine-containing contaminant in a reagent. The addition of increasing amounts of aluminum did not increase the hydrolysis effect. In fact, adding substantial amounts of aluminum inhibited it. As in several types of experiment, it is the low aluminum fluoride concentrations that produce the greatest biochemical or physiological effects. In this regard, it is important to note that, even if aluminum bioavailability is low in rats and in other laboratory species, only a small amount is needed to produce untoward effects (Yokel et al. 2001).

Many of the untoward effects of fluoride are due to the formation of AlFx complexes. AlFx and BeFx complexes are small inorganic molecules that mimic the chemical structure of a phosphate. As such they influence the activity of phosphohydrolases and phospholipase D. Only micromolar concentrations of aluminum are needed to form AlFx (Sternweis and Gilman 1982). The G protein effects produced by AlFx are not limited to enzymes that bind phosphates or nucleoside-polyphosphate (Chabre 1990). AlFx also impairs the polymerizationdepolarization cycle of tubulin. This could account for some of the intensely stained neurofilaments in cells in the brains of animals exposed to chronic NaF (Varner et al. 1993, 1998). AlFx appears to bind to enzyme-bound GDP or ADP, thus imitating GTP or ATP and, in a sense, generating “false messages” within the brain. This binding ability is probably due to the molecular similarities between AlF3(OH) and a phosphate group in the molecular structure, in particular, a tetrahedral arrangement (Strunecka and Patocka 2002).

G protein-coupled receptors mediate the release of many neural transmitters including the catecholamines, serotonin, ACh, and the excitatory amino acids. They also are involved in regulating glucagons, vasopressin, neuropeptides, endogenous opioids, prostaglandins, and other important systemic influences on brain and behavior. AlFx is also involved in regulating the pineal melatonin system as well as the thyroid-stimulating hormone-growth hormone connection. It has been said in this regard “every molecule of AlFx is the messenger of false information” (Strunecka and Patocka 2002, p. 275). This may be an accurate synopsis of the AlFx effect at a single synapse, but the brain is a highly redundant and dispersed communication system containing millions of synapses. Because of this, observable alterations in mental or motor actions might require the formation of a multitude of false messages in a number of brain circuits acting over a prolonged period of time. Thus, the number of false messages required to disrupt an “action pattern” in the brain probably will vary according to the nature of the ongoing activities.

An especially important neurochemical transmitter that reaches almost all areas of the brain is ACh. As discussed above, some studies show that NaF and SiF inhibit cholinesterases, including acetylcholinesterase. The progressive accumulation of ACh at synaptic locations produced by the diminished esterase activity leads to a number of complex effects that can be summarized as an initial increase in stimulation of the target cells but ultimately leads to diminished stimulation—even a blockade of all activity. This earlier dialogue properly emphasized the behavioral importance of cholinergic activity in the brain and body more generally.

Long et al. (2002) reported changes in the number of acetylcholine receptors (nAChRs) in the rat brain due to fluoride. Rats were administered NaF in drinking water at 30 or 100-mg/L for 7 months. Decreased numbers of nAChRα7 subunits were found in the brains of rats from both treatment groups, but only the brains of the 100-mg/L group had diminished nAChRα4 subunits of this receptor. These results are of interest because changes in the nicotinic receptors have been related to the development of Alzheimer's disease (Lindstrom 1997; Newhouse et al. 1997) and, in frontal brain areas, to schizophrenia (Guan et al. 1999).

FINDINGS

Human Cognitive Abilities

(page 185)

In assessing the potential health effects of fluoride between 2-4 mg/L, the committee found three studies of human populations exposed at those concentrations in drinking water that were useful for informing its assessment of potential neurologic effects. These studies were conducted in different areas of China, where fluoride concentrations ranged from 2.5-4 mg/L. Comparisons were made between the IQs of children from those populations with children exposed to lower concentration of fluoride ranging from 0.4-1 mg/L. The studies reported that while modal IQ scores were unchanged, the average IQ scores were lower in the more highly exposed children. This was due to fewer children in the high IQ range. While the studies lacked sufficient detail for the committee to fully assess their quality and their relevance to U.S. populations, the consistency of the collective results warrant additional research on the effects of fluoride on intelligence. Investigation of other mental and physiological alterations reported in the case study literature, including mental confusion and lethargy, should also be investigated.

Neurochemical and Biochemical Changes

(page 186)

Lipids and phospholipids, phosphohydrolases and phospholipase D, and protein content have been shown to be reduced in the brains of laboratory animals subsequent to fluoride exposure. The greatest changes were found in phosphatidylethanolamine, phosphotidylcholine, and phosphotidylserine. Fluorides also inhibit the activity of cholinesterases, including acetylcholinesterase. Recently, the number of receptors for acetylcholine has been found to be reduced in regions of the brain thought to be most important for mental stability and for adequate retrieval of memories.

It appears that many of fluoride's effects, and those of the aluminofluoride complexes are mediated by activation of Gp, a protein of the G family. G proteins mediate the release of many of the best known transmitters of the central nervous system. Not only do fluorides affect transmitter concentrations and functions but also are involved in the regulation of glucagons, prostaglandins, and a number of central nervous system peptides, including vasopressin,

endogenous opioids, and other hypothalamic peptides. The AlFx binds to GDP and ADP altering their ability to form the triphosphate molecule essential for providing energies to cells in the brain. Thus, AlFx not only provides false messages throughout the nervous system but, at the same time, diminishes the energy essential to brain function.

Fluorides also increase the production of free radicals in the brain through several different biological pathways. These changes have a bearing on the possibility that fluorides act to increase the risk of developing Alzheimer's disease. Today, the disruption of aerobic metabolism in the brain, a reduction of effectiveness of acetylcholine as a transmitter, and an increase in free radicals are thought to be causative factors for this disease. More research is needed to clarify fluoride's biochemical effects on the brain.

Anatomical Changes in the Brain

(page 186)

Studies of rats exposed to NaF or AlF3 have reported distortion in cells in the outer and inner layers of the neocortex. Neuronal deformations were also found in the hippocampus and to a smaller extent in the amygdala and the cerebellum. Aluminum was detected in neurons and glia, as well as in the lining and in the lumen of blood vessels in the brain and kidney. The substantial enhancement of reactive microglia, the presence of stained intracellular neurofilaments, and the presence of IgM observed in rodents are related to signs of dementia in humans. The magnitude of the changes was large and consistent among the studies. Given this, the committee concludes further research is warranted in this area, similar to that discussed at a February 2-3,1999, EPA workshop on aluminum complexes and neurotoxicity and that recommended for study by NTP (2002).

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