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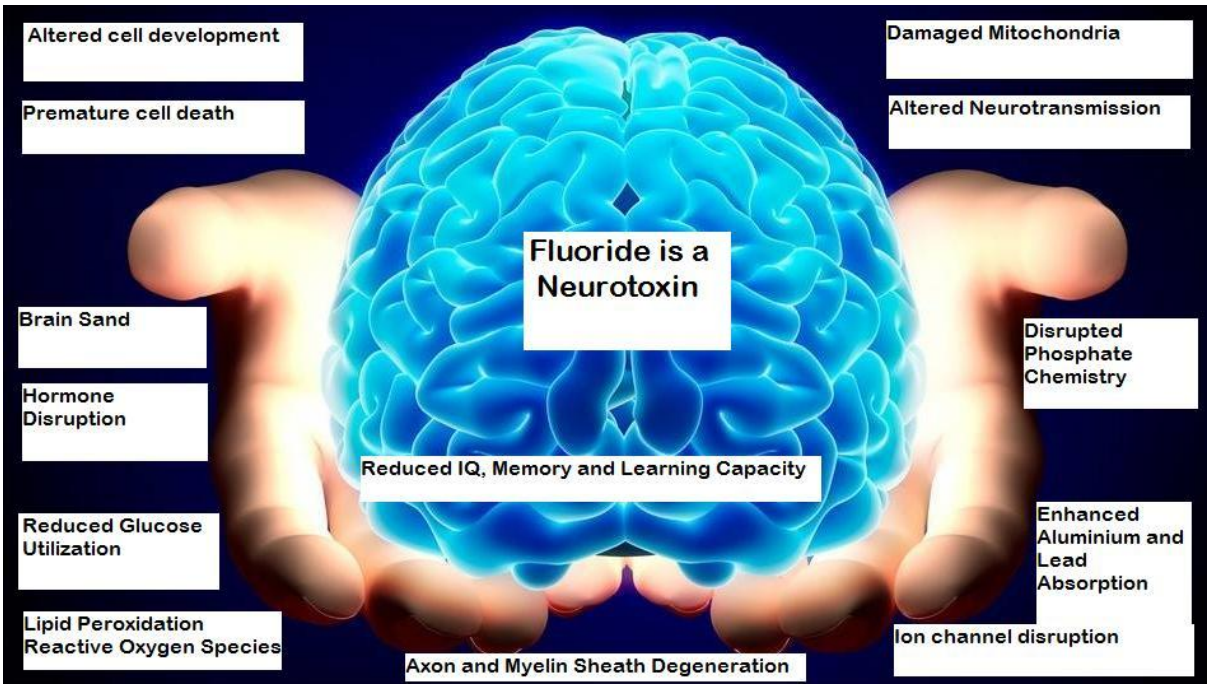


Abstract

Fluoride is a developmental neurotoxin that has been linked to human brain damage since the 1920s when Fluoride induced cretinism was investigated and confirmed with animal studies. With advances in imaging, chemical analytical techniques including proteomics, detailed molecular mechanisms of Fluoride damage to the brain, spinal cord and nerve networks have been investigated with ever increasing levels of detail. The current peer-reviewed scientific publication rate regarding Fluoride neurotoxicity is about one paper per week. This literature guide provides a snapshot of the science as easily obtained in early 2017, to help inform those interested in the depth of knowledge and where the ongoing studies are directed.

Keywords: Aggression, Aluminium, Amyotrophic Lateral Sclerosis, Anxiety, Autism, Bipolar Disorder, Brain, Cognitive Dissonance, Cretinism, Crime, Depression, Foetus, Fluoridation, Fluoride, Friedreich’s ataxia, Headache, Hormone, Huntington's disease, Hydroxyapatite, Intelligence, Learning, Memory, Mitochondria, Neurotoxin, Parkinson's disease, Placenta, Plumbosolvency, Psychosis, Review, Schizophrenia, Tremor, Violence

Introduction

In 2016, the United States National Toxicology Program released its systematic literature review on the effects of fluoride on learning and memory in animal studies and announced that it would embark on new animal sacrifice studies on fluoride neurotoxicity [NTP 2016].

In November 2016, a group of US organizations lodged a formal petition [Connett 2016] with the USEPA requesting that the agency use its existing powers [EPA 1979; 1985; 1998; 2011; 2016] to order an immediate end to water fluoridation in the United States. This action was the result of years of preparation and study of the published science that demonstrates, on the weight of evidence, that the risks of harm from addition to public drinking water of toxic industrial fluoride waste from the phosphate fertilizer and other industries far outweigh any perceived benefit.

The focus of the petition was evidence of neurological damage as well as the obvious dental fluorosis as a marker for the level of exposure, as outlined in over 300 exhibits.

The only reason that a few remaining countries persist with fluoridation is the belief that ingestion of fluoride will reduce the incidence of dental caries.

Recently most proponents of fluoridation have claimed that the effect is topical, in the hope that a tiny concentration of fluoride in saliva, travelling through the bloodstream from the gut, will reduce the dissolution of the tooth enamel by forming a slightly less soluble surface coating doped with fluoride, replacing hydroxyl ions in the mineral Hydroxyapatite.

However recently it was shown that the penetration depth of topical fluoride is only of the order of a few lattice constants in Hydroxyapatite, at most [Müller 2010]. This is to be expected because substitution requires a driving diffusion concentration gradient and thermodynamic energy release which can't happen when the negatively charged fluoride ion approaches a negatively charged hydroxyl group at body temperature.

Indeed, substantial incorporation of fluoride can only occur in tooth enamel when the HF molecule reacts with the hydroxyl group. For this reason fluoride gels applied to teeth are strongly acid and they simultaneously etch the tooth surface and expand tooth pores.

Significantly, leading toothpaste manufacturer Colgate Oral Care has stated in testimony that brushing teeth twice per day with high concentration fluoride toothpaste will not guarantee 24-hour protection against tooth decay [Advertising Standards Authority 2016] and has begun marketing fluoride-free toothpaste, especially targeted at young children.

The Colgate funded Cochrane Collaboration found no evidence that water fluoridation confers any benefit to adults [Iheozor-Ejiofor 2015].

Clearly if toothpaste at 1000 ppm fluoride is ineffective, fluoridation at 0.7 ppm is farcical as well as dangerous.

The present review is provided to give some further pointers to the details of the mechanisms of neurological harm caused by fluoride and a very brief overview of issues including total dietary and inhalation intake of fluoride, an introduction to the historical timeline and further convenient access to a larger list of references. Not all references are discussed here and interested readers, perhaps including ethical science writers, might find references of particular interest by browsing the titles or tracking particular authors. This review is deficient because it does not attempt to do justice to the extensive science published in languages other than English, unless abstracts or translations are available. References marked as # were deliberately excluded from the Australian National Health and Medical Research Council reviews of water fluoridation [NHMRC 2007; 2016].

Fluoride is a systemic poison

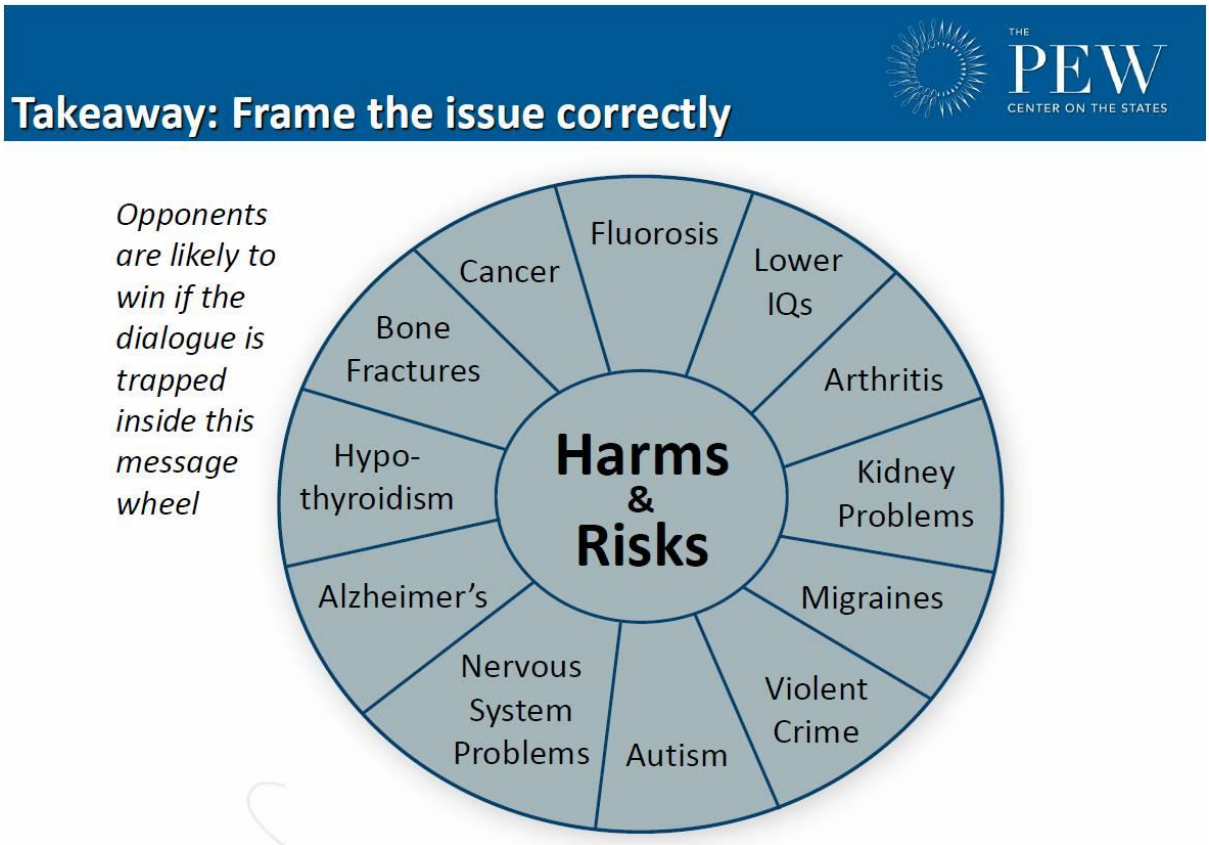
Fluoride is a bio-accumulative poison that works its way through the food chain and contaminates numerous body sites [Kalisinska 2012, 2014]. Concentrations of 10,000 ppm Fluoride have been recorded in bone in contaminated animals [Flueck 2016]. The World Health Organization ranks Fluoride toxicity between that of Lead and Arsenic [WHO 2014].

Humans lack the means to cope with high fluoride exposure in contrast to certain strains of bacteria [Banerjee 2016]. Many plants concentrate fluoride and some species convert it to fluoroacetate and fluorocitrate, devastating neurotoxins beyond the scope of this review.

Fluoride is absorbed directly into the bloodstream through the oral tissues although there has been more concern over the quantity of fluoride that is swallowed while using toothpaste, gels or rinses [Ekstrand 1983; Bentley 1999; Marinho 2003; Erdal 2005; Zohoori 2012; Falcao 2013]. Fluoride entering the stomach is converted to the soluble gas and weak acid Hydrogen Fluoride (HF) which readily passes into the bloodstream.

Because all mammalian cells are damaged by fluoride, much of the fundamental understanding of its toxicology has been the result of sophisticated molecular biology techniques applied to cells extracted or cultured from various organs [Barbier 2010; Ge 2011; Agalakova 2012; Zhang 2012; Niu 2014; Niu 2015; Pan 2015; Zhang 2015].

The fluoridation waste disposal and fracking industries are acutely aware of the rising public awareness of the dangers of systemic fluoride poisoning and advise avoidance of discussion of harms and risks that those industries recognize, as shown in this figure [PEW].



Six of the 12 harms illustrated relate to fluoride neurotoxicity. Note the mention of autism.

Fluoride is a Low-Dose Endocrine Disruptor

Fluoride is classified as a Low-Dose Endocrine Disruptor linked to obesity and diabetes [Bergman 2012; Vandenberg 2012; Pain 2015b; Zhou 2016]. Fluoride inhibits the production of thyroid hormones and this leads to damage to the brain of the foetus [Goldemberg 1930; Galetti 1958; Guan 1988; Shoback 1998; Klein 2001; Wang 2001; Huang 2008; Zachariassen 2009; Basha 2011; Banji 2013; Murphy 2015; Peckham 2015; Sarkar 2015; Korevaar 2016; Zhou 2016]. To maintain normal thyroxin levels the body increases the capacity for thyroxin production, often leading to Goitre which is a compensatory mechanism. Endemic Goitre is widespread in many high-fluoride areas, even where dietary access to iodine is adequate. When people from such areas arrive in a low-fluoride area, their elevated capacity to produce thyroid hormones may lead to hyperthyroidism and subsequently to psychosis [Zachariassen 2009]. The knock-on effects of hormone disruption are well understood for the thyroid, but other hormone systems are still being studied in the context of consequential diseases.

There is recent evidence that Fluoride might modify the secretion and activity of hypothalamus-pituitary- ovarian [HPO] axis hormones. Epigenetic response to Fluoride by Follicle Stimulating Hormone Receptor [FSHR] gene polymorphism may be involved [Zhao 2015]. Fluoride reduces melatonin production affecting, among other things, pubertal development [Luke 1997]. Fluoride doped hydroxyapatite precipitates build up in the pineal gland and other parts of the brain with age and have been linked to reduced melatonin secretion [Bharti 2009, NRC 2006, p. 256] and schizophrenia [Savel'ev 2004].

Neurological disorders associated with fluoride

Fluoride is a recognized neurotoxin [Mullenix 1995; Varner 1998; Ortega Garcia 2006; Connett 2008; Connett 2010; Madhusudhan 2010; Valdez-Jiménez 2011; Agalakova 2012; Hamid 2012, Zhang 2012 #; Grandjean & Landrigan 2014; Grandjean 2015; Mundy 2015; Connett 2016; Dec 2016]. The reader is encouraged to download the petition to the EPA [Connett 2016] in order to fully appreciate the extent of the science reviewed there with the aid of figures and tables of data. The petition [Connett 2016] gives an extensive coverage of the epidemiology, not attempted in this brief review. Fluoride ingestion has been linked to the following manifestations of neurological damage and the list continues to grow:

- Cretinism
- Low Intelligence (IQ)
- Headache
- Attention Deficit Hyperactivity Disorder
- Delirium
- Insomnia
- Increased pain sensation
- Tremors
- Seizures
- Paralysis
- Decreased learning ability
- Decreased long-term memory
- Anxiety and depression

Cretinism, low intelligence, decreased learning ability and memory loss

It was demonstrated in the 1920s with the aid of animal experiments, that cretinism was associated with high fluoride levels and the hypothyroidism that it causes [Goldemberg 1930]. Endemic skeletal fluorosis and neurological manifestation was also reported in Prakasam district in Andhra Pradesh in the year 1937 [Raja 2009 #].

It was recognized by the US Defense Department during the Manhattan Project that the fluoride in Uranium Hexafluoride posed a neurological hazard to people handling the substance [Manhattan Project 1944].

Cretinism associated with high-fluoride, low-iodine intake has also been reported in China [Lin 1991] and similar large scale problems in India, Mexico and elsewhere led to international support for detailed study and defluoridation programs using foreign aid coordinated by UNICEF [Lin Fa-Fu 1991, Susheela 1999, UNICEF 2001].

Some studies have not found a clear relationship between IQ and dental fluorosis status, thus suggesting that a person's susceptibility to fluoride-induced neurotoxicity may be distinct from their susceptibility to dental fluorosis [Ding 2011; Asawa 2014; Li 2010].

Central nervous system problems indicating brain dysfunction, including headache, insomnia, increased pain sensation, tremors, seizures, and paralysis have been associated with Fluoride poisoning for more than eighty years [Shashi 2003, Ranjan 2012]. Fluoride exposure has been shown to affect the peripheral pain sensitivity in mice [Ma 2015].

Double blind placebo testing was used to prove that a percentage of people suffer headaches when given small doses of fluoride [Waldblott 1958, Feltman 1961].

Decreased learning ability and long-term memory has been demonstrated in animals and humans and correlated with brain damage by Fluoride [Zhang 2001; Wang 2004; Wang 2006; Wu 2006; Andreatini 2007; Zhang 2008; Gao 2009; Gui 2010; Liu 2010; Pereira 2011; Yazdi 2011; Wang 2013; Han 2014; Jiang 2014; Dong 2015; Li 2015; Shalini 2015; Zhang 2015; Jetti 2016]. Zhang's data "indicated that the changes of synaptosome membrane fluidity and PSD-95 expression level in hippocampus might be the one synaptic mechanism of learning-memory injury induced by chronic fluorosis in brain." [Zhang 2008; Zhang 2015].

Effects on the spontaneous behaviour and learning and memory of baby rats whose mothers drank different concentrations of fluoride have been demonstrated and the superoxide dismutase (SOD) and malondialdehyde (MDA) contents in the brains of the baby rats might be associated with the neurotoxic damage [Zhang 2009].

Territorial aggression, sexual behaviour and fertility are all adversely affected by Fluoride administered to male rats [El-lethey 2011].

Fluoridation has been associated with increase crime levels in the USA [Seavy 2005].

Tissue fluoride levels of hippocampus, neocortex, cerebellum, spinal cord and sciatic nerve all increased significantly in fluoride treated rats and correlated with neurodegenerative changes observed by electron microscopy. Axon deterioration, myelin sheath degeneration and dark cells with scanty cytoplasm, vacuolated swollen mitochondria in the neocortex, hippocampus and cerebellum have been reported [Reddy 2011].

Rats exposed to 100 ppm fluoride showed significant neurodegenerative changes in the motor cortex, including decrease in size and number of neurons, chromatolysis and gliosis [Hamid 2012].

Exposure to neurotoxic chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function [Grandjean 2006]. The transfer of Fluoride to the human placenta, foetus and the baby has been studied [Feltman 1961; Gedalia 1961; He 2008; Yu 2008; Needham 2011].

Evidence has shown that the loss of IQ is permanent. By changing the water of children with heavy dental fluorosis, not significant improvement in IQ was observed in a 200 child sample of 8 to 12 year olds [He 2010]. Similarly, changing to non-fluoridated water did not affect permanent Fluoride injury to the spinal cord in rats [Shen 2014].

Daily Fluoride Intake

Fluoride is not a nutrient [Pain 2015a]. Administration of Fluoride “supplements” is known (as expected) to directly cause Fluorosis in children from 0-3 years [Morgan 1998 #].

In 1975 the United States Food and Drug Administration wrote to manufacturers requiring them to withdraw fluoride “supplements” from the market. They are banned in numerous countries.

A small sample study in Japan showed that an increase to approximately 0.5 ppm Fluoride in drinking water doubled total daily intake of the element with dental fluorosis found even at this low level [Nohno 2006 #].

Estimates of total Fluoride intake have been made [Mahaffey 1976; Levy 1993; Guha-Chowdhury 1996; Levy 1999; Cardoso 2006; Oliveira 207; Li 2008b; Chankanka 2011b; Wang 2012; Zohoori 2012, 2013; Waugh 2016]. In one study [Erdal 2005], exposure pathways considered included fluoridated drinking water, beverages, cow's milk, foods, and fluoride supplements, and consumption of infant formula for infants as well as inadvertent swallowing of toothpaste while brushing and incidental ingestion of soil for children. Reasonable maximum exposure [RME] estimates were above the upper tolerable intake limit [UTIL] with fluorosis as the endpoint.

Diets rich in fluoride from fish and tea have been found to increase the rate of severe dental fluorosis and behavioural problems. Extended breastfeeding to more than 18 months has been recommended to minimize infant fluoride exposure [Wondwossen 2006 #].

Inhalation exposure

Blood plasma concentration of Fluoride in humans can be greatly increased by metabolism of anaesthetics such as sevoflurane and isoflurane during and after surgery, with levels up to 39 microM reported [Artru 1997 #] and this can result in death through hyperthermia, increased cerebrospinal fluid volume, intracranial elastance and long term memory loss. Sevoflurane has acute side effects, including seizures during induction and maintenance, and increased incidence of emergence delirium [Moos 2005 #].

Sevoflurane caused long-term deficits in hippocampal function and decreased hippocampal PSD-95 expression without neuronal loss in P7 rats exposed for 4 h to 2.5% sevoflurane.

The rats had significant spatial learning and memory impairment 7 weeks after anesthesia. In addition, PSD-95 expression in the hippocampus decreased at P56 without neuronal loss [Wang 2013].

Inhalation of Fluoride from coal burning and other industrial emissions has been shown to reduce IQ and this correlated with reduced hair zinc levels. The authors considered decrease of 5-hydroxyindoleacetic acid and the increase of norepinephrine in animal brains correlates with decreased brain function [Li 2008].

Urine and Serum Fluoride Levels

It is known that fluoride is a bio-accumulative bone-seeking poison and it is generally reported that healthy individuals excrete about one half of their intake, mostly through urine.

It is known that the placenta and growing foetus absorb the majority of fluoride intake. Therefore measurements of mothers' urine or serum fluoride will always present a substantial underestimate of the mother's intake. Despite this limitation, researchers have used urine analysis as a convenient means for comparative toxicology [Rocha Amador 2016; Thomas 2014].

A linear relationship between fluoride in drinking water and urine and serum levels has been demonstrated [Singh 2014].

Mechanisms of Harm caused by Fluoride

A number of reviews have considered the multiple established mechanisms of fluoride toxicity and there is greatly increased understanding of the molecular mechanisms of fluoride's neurotoxicity [Connett 2008; Connett 2010; Barbier 2010; Dec 2016].

Fluoride disturbs gene expression

Fluoride creates damage from the moment of conception. Fluoride disturbs the gene expression patterns of human embryonic stem cells [Fu 2016].

Altered gene expression results in numerous devastating effects on the brain structure and function [Horgan 1984; Schwarze 1996; Zhang 2007, 2008; Niu 2008a, b; Luo 2011; Zhang 2011; Zhu 2011; Zhu 2012; Chen 2013; Li 2013; Wang 2013; Dong 2014; Jiang 2014; Lou 2014; Zhou 2014; Dong 2015; Mukhopadhyay 2015; Niu 2015a; Ke 2016; Yan 2016].

Lasne suggested morphological transformation with both genetic and non-genotoxic mechanisms [Lasne 1988]. Autopsies reveal damage by Fluoride clearly visible with optical or electron microscopy [Fazal-ur-Rehman 2014]. Fluoride exposure has been shown to reduce or remove Nissl substance and result in deformation and chromatolysis in Purkinje cells in the brains of rabbits [Shashi 2003].

Interleukin 1 beta[IL-1β] protein levels increase in the brain of carp exposed to Fluoride, accompanied by reduction of total anti-oxidant capacity [Chen 2013].

The raised level of apoptosis in cortical neurons resulting from chronic fluorosis may be regulated by Bax and Bcl-2 [Lou 2014].

Fluoride may damage the hippocampus by significantly decreasing the expression of TGF-B1 gene and protein, possibly by an unknown post-transcriptional mechanism [Zhou 2014].

Fluoride acts as a stress response inducer, increasing heat-shock protein70 levels [Cheng 1998 #].

Fluoride DNA damage, inhibition of DNA synthesis and repair has also been reported [Aardema 1989; Chen 2002; Tiwari 2010].

Fluoride damages Mitochondria

It is observed that Fluoride damages the cell organelles. Mitochondrial damage by fluoride and its consequences have received much attention [Anuradha 2001; Chlubek 2003; Reddy 2008; Lee 2008; Reddy 2011; Rao 2012; Basha 2013; Lou 2013; Samanta 2016].

Damage to brain cell mitochondria has been linked to neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis (ALS), and Friedreich’s ataxia [Reddy 2008].

Fluoride inhibits enzymes

Fluoride is known to inhibit numerous enzymes involved in critical biochemical transformations and might be bound as the Fluoride ion or as HF [Edwards 1984].

Fluoride can act on enzymes alone or in combination with elements such as Aluminium through formation of coordination complexes that can mimic phosphate [Mittal 1996].

Measurement of blood erythrocyte antioxidant enzyme activities shows that Fluoride from drinking water increases levels of superoxide dismutase [SOD], glutathione peroxidase [GPx], and catalase [CAT] [Akdogan 2004].

Disturbances in mitochondrial enzyme complexes [I-IV] and decrements in TCA enzymes (ICDH, SDH, and aconitase) were noted in discrete brain regions of Swiss mice given 270 ppm fluoride (600 ppm NaF) in their drinking water for 30 days [Basha 2013].

Decreased succinate dehydrogenase [SDH] activity indicates an alteration in mitochondrial structure and function caused by Fluoride [Rao 2012].

Fluoride decreases brain glucose utization [Jiang 2014]. “NaF treatment impaired learning and memory in these rats. Furthermore, NaF caused neuronal degeneration, decreased brain glucose utilization, decreased the protein expression of glucose transporter 1 and glial fibrillary acidic protein, and increased levels of brain-derived neurotrophic factor in the rat brains. The developmental neurotoxicity of fluoride may be closely associated with low glucose utilization and neurodegenerative changes.”

Fluoride inhibition of pancreatic superoxide dismutases CuZn-SOD and mitochondrial [Mn-SOD] has been demonstrated associated with Fluoride induced hyperglycemia [Chlubek 2003].

Further details of fluoride inhibition of enzymes relevant to brain function have been reported [Gao 2009; Flora 2009; Reddy 2009; Basha 2013; Mahaboob Basha 2013; Sandeep 2013].

Fluoride enhances Oxidative Stress and Lipid Peroxidation

Oxidative stress is a primary cause of brain damage [Butterfield 2006; Bond 2007].

Oxidative stress caused by fluoride has been extensively studied [Anuradha 2001; Chlubek 2003; Akdogan 2004; Wang 2004; Zhang 2007; Gao 2008, 2009; Flora 2009; Akinrinade 2015b; Inkielewicz-Stepniak 2010; Basha 2011a; Xi 2012; Cao 2013; Yan 2013; Banala 2015; Zhang 2015].

Several authors have reported the influence of fluoride on lipid peroxidation [Guan 1998; Song 2002; Akdogan 2004; Wang 2004; Chauhan 2008; Reddy 2014; Basha 2014; Basha 2011a; Banala 2015; Bharti 2009; 2013; Adebayo 2013; Chauhan 2013; Dong 2014; Ke 2016].

Use of anti-oxidants to ameliorate neurotoxicity of Fluoride

A range of natural product anti-oxidants and other strategies have been tested in an effort to reduce the neurotoxicity to the foetus and adult mammal [Guan 1998; Bharti 2009; Hassan 2010, 2015; Madhusudhan 2010; Basha 2011, 2013, 2014; Chauhan 2011; Nabavi 2011, 2012a, 2012b, 2012c; Rao 2012; Inkielewicz-Stepniak 2012; Banji 2013; Atmaca 2014; Pal 2014; Sarkar 2014; Banala 2015; Hamza 2015; Wu 2015; Mesram 2016; Samanta 2016].

Fluoride initiates apoptosis

Apoptosis is different from necrosis, being genetically programmed cell death, with characteristic features of cell shrinkage, chromatin condensation, and DNA fragmentation [Ruppova 1999 #]. Fluoride is known to induce apoptosis in a wide range of body tissues including the lung [Refsnes 2002 #, Schwarze 1996 #] and increases the percentage of CD3-positive cells [T-lymphocytes] after exposure.

It has been demonstrated that Fluoride initiates a sequence of events leading to cell death, including alteration of calcium homeostasis, elevated levels of Ca2+/CaM dependent protein kinase II gamma [CaMKIIg], oxidative stress through enhanced superoxide formation, lipid peroxidation, loss of mitochondrial membrane potential, increase in extracellular signal-regulated kinases [ERK], decreased expression of the anti-apoptotic protein Bcl-2 and increased caspase-3 activation [Anuradha 2001 #, Song 2002 #, Refsnes 2003 #,Song 2005 #, Bogatcheva 2006, Haojun 2012, Singh 2016].

Fluoride can induce cell cycle arrest from S to G2/M and inhibit activities of 5'-NT,SDH and ACP in astrocytes [Li 2010].

Antioxidants N-acetyl cysteine [NAC], glutathione [GSH] protect cells from fluoride induced loss of mitochondrial membrane potential [Anuradha 2001 #]. Protein kinases C [PKC] and p38 have been shown to be involved in Fluoride induced apoptosis [Refsnes 2012 #].

In the pancreas treatment of human and rat islet cells with the G-protein activator fluoride causes a marked increase in apoptosis [Otsuki 2005 #]. In the liver, using human embryo hepatocyte L-02 cells, Fluoride causes an increase of lipid peroxide [LPO] level, reduced glutathione [GSH] content, DNA damage and apoptosis [Wang 2004 #, He 2006].

Oral mucosal cells exhibit similar damage by Fluoride [He 2006].

Fluoride reduces the cell viability of human gingival fibroblasts [HGF] in a dose- and time-dependent manner. Fluoride increased the level of cytochrome c released from the mitochondria into the cytosol, enhanced the caspase-9, -8 and -3 activities, the cleavage of poly [ADP-ribose] polymerase [PARP], and up-regulated the voltage-dependent anion channel [VDAC] 1 and the Fas-ligand [Fas-L], a ligand of death receptor [Lee 2008].

Studies of NaF-induced apoptosis and glycolysis in human promyelocytic leukemia HL-60 cells found utilization of glucose was nearly halted by NaF. NaF enhanced the expression of Bad protein and reduced HIF-1alpha mRNA expression [Otsuki 2005 #].

Fluoride interferes with neurotransmission

Neurotransmitter and receptor changes were measured directly and correlated with fluoride content in the brains of aborted human foetuses from areas of endemic fluorosis [Yu 2008].

Fluoride directly inhibits Acetylcholinesterase and thus stops termination of impulse transmissions at cholinergic synapses within the nervous system [Westendorf 1975; Gardiner 1990; Long 2002; Zhao 2002; Gao 2009; Bharti 2012; Singh 2013; Singh 2014; Thadani 2014; Akinrinade 2015].

Nicotinic acid receptors play a role in learning and memory and are altered by exposure to fluoride [Long 2002].

Dong's results "suggest that the mechanism for the deficits in learning and memory of rats with chronic fluorosis may be associated with the decreased expressions of M1 and M3 in mAChRs, in which the changes in the receptors might be the result of the high level of oxidative stress occurring in the disease." [Dong 2014].

Increased fluoride content leads to increased levels of certain neurotransmitters such as epinephrine, histamine, serotonin and glutamate and decreased levels of norepinephrine, acetylcholine and dopamine in a dose-dependent manner. NaF exposure led to the decrease in the levels of CD4, NK cells and IgG1 coupled with marked increase in lipid peroxidation and impairment of the antioxidative defense system [Reddy 2014]

Norepinephrine [NE], dopamine [DA], DA metabolites dihydroxyphenylacetic acid [DOPAC] and homovallic acid, indoleamine serotonin [5-hydroxytryptamine] and its metabolite 5-hydroxyindoleacetic acid [5-HIAA] were all found to be affected by Fluoride in adult male rats [Tsunoda 2012].

Water labyrinth performance has been correlated with monoamine neurotransmitter levels in the brains of rats [Zhu 2012].

Synaptosomal-associated protein is an important factor for extracellular secretion and transmitter release, and it is involved in learning consolidation in the hippocampus [Li 2013].

Fluoride disrupts phosphate pathways

Critical biochemical pathways depend on phosphate chemistry. Fluoride adverse impacts on phosphate metabolism have received much attention [Bencherif 1991; Guan 1998; Shoback 1998; Liu 2011; Gutowska 2012; Basha 2013]. Brain phospholipids including phosphatidylethanolamine, phosphatidylcholine, and phosphatidylserine, are decreased in a time and dose dependent manner by Fluoride [Guan 1998].

Fluoride interferes with normal metabolism of inositol phosphates [Bencherif 1991]. In dispersed bovine parathyroid cells Fluoride stimulates the accumulation of inositol phosphates, increases intracellular free calcium, and inhibits parathyroid hormone release [Shoback 1998]. Fluoride increases inositol phosphates in rat PC 12 cells by up to a factor of ten. Accumulation of inositol phosphates is a feature of manic depression or bipolar disorder.

Fluoride delivers more Lead to the Brain

Those looking for possible confounders to epidemiology studies of Fluoride neurotoxic damage sometimes refer to neurotoxins Lead or Arsenic as contributing factors.

It is well known that Lead levels in drinking water are increased by the presence of fluoride, a process known as plumbosolvency [Mahaffey 1976; Masters 2000; Bernard 2003; Burgstahler 2003; Macek 2006; Coplan 2007; Maas 2007; Niu 2008a,b; Niu 2009; Leite 2011; Luo 2011; CDC 2013a; Niu 2014, 2015b; Pain 2015c].

Given the facts, continued fluoridation cannot be justified due to the plumbosolvency risk alone.

The relative contributions of Fluoride and Arsenic to brain damage have been well studied [Zhang 1998; Wu 2006; Rocha-Amador 2007; Wang 2007; Flora 2009; Kang 2011; Bharti 2012; Flora 2012; Xiang 2013; Bai 2014; Jiang 2014; Sarkozi 2015; Ma 2016]

Fluoride delivers more Aluminium to the Brain

Aluminium, a proven neurotoxin, forms complex ions with fluoride over a wide pH range and this facilitates absorption from the gut and transport to the brain with resultant damage [Kraus 1992; Mittal 1996; Varner 1998; Kaur 2009; Yazdi 2011; Akinrinade 2013, 2015b; Hassan 2015; Li 2015; Mirza 2017]. Fluoride coordinated to Aluminium can mimic phosphate.

Given that the neurotoxin Aluminium is commonly added to drinking water as part of its treatment to reduce turbidity, it is reckless to deliberately add industrial waste fluoride as well.

Conclusion

According to experts, a maximum contaminant level goal (MCLG) for F in drinking water should be 0.1 mg F/L and evidence suggests that the only assuredly safe level of F in drinking water is zero [Spittle 2014]. This is consistent with the World Health Organization of ranking of Fluoride between Lead and Arsenic, both of which have target levels in drinking water of zero.

Some abbreviations encountered in the literature cited

5-HIAA	5-HydroxyIndoleAcetic Acid
ADHD	Attention Deficit Hyperactivity Disorder
ADP	Adenosine Diphosphate
Bcl-2	B-cell lymphoma 2
BGC	Bergmann glia cells
BMD	Benchmark Dose
BMR	BenchMark Response
Ca2+/CaM	Calcium Calmodulin
CaMKIIg	Ca2+/CaM dependent protein kinase II gamma
CAT	Catalase
CD3	Cluster of Differentiation 3
CDC	Centers for Disease Control and Prevention (USA)
COMT	Catechol-O-MethylTransferase
DA	Dopamine
DMFS	Decayed Missing or Filled Surfaces
DMFT	Decayed Missing or Filled Teeth
DNA	DeoxyriboNucleic Acid
DOPAC	3,4-Dihydroxyphenylacetic acid
DWEL	Drinking Water Equivalent Level
eEF2	Eukaryotic Translation Elongation Factor 2
EPA	Environmental Protection Agency (USA)
EPA OW	Environmental Protection Agency Office of Water
ERK	Extracellular signal-Regulated Kinase
F	Fluoride
Fas	First apoptosis signal
FSHR	Follicle Stimulating Hormone Receptor

GPx	Glutathione Peroxidase
GSH	Glutathione
HF	Hydrogen Fluoride
HFSA	HexaFluoroSilicic Acid
HGF	Human Gingival Fibroblast
HPO	Hypothalamus-Pituitary- Ovarian
ICDH	IsoCitrate Dehydrogenase
IL-1β	Interleukin 1 beta
IQ	Intelligence Quotient
LOAEL	Lowest Observable Adverse Effect Level
LPO	Lipid Peroxide
MCLG	Maximum Contaminant Level Goal
MDA	Malondialdehyde
mg/L	Milligram per litre
Mn-SOD	Manganese SuperOxide Dismutase
NAC	N-Acetyl Cysteine
nAChR	Nicotinic acetylcholine receptor
NE	Norepinephrine
NHANES	National Health and Nutrition Examination Survey (USA)
NHMRC	National Health and Medical Research Council (Australia)
NIDR	National Institute of Dental Research
NOAEL	No Observable Adverse Effect Level
NRC	National Research Council (USA)
NTP	National Toxicology Program (USA)
PARP	Poly (ADP-Ribose) Polymerase
PC 12	Pheochromocytoma cell line from rat adrenal medulla
PKC	Protein kinase C

ppm	Parts Per Million
RfC	Reference Concentration
RfD	Reference Dose
RME	Reasonable Maximum Exposure
S to G2/M	Synthesis to Gap 2 Mitosis
SDH	Succinate Dehydrogenase
SDWA	Safe Drinking Water Act (USA)
SES	SocioEconomic Status
SH-SY5Y	Human derived cell line clone
SOD	SuperOxide Dismutase
TCA	Tricarboxylic Acid
TSCA	Toxic Substances Control Act
UF	Uncertainty Factor
UNICEF	United Nations International Children's Emergency Fund
UTIL	Upper Tolerable Intake Limit
Val/met	Valine/ Methionine
VDAC	Voltage-Dependent Anion Channel
WHO	World Health Organization

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