Introduction
**Water and Fluoride**

Water is life, so central to human life, yet over one billion people across the world have no access to safe drinking water. Of late, there has been increasing global attention focused on resolving water quality problems especially in developing countries, as the lack of access to clean water denies the most essential of all rights, the right to life (WHO, 1994). The latest estimates suggest that around 200 million people, from among 25 nations the world over, are under the dreadful fate of fluorosis. India and China, the two most populous countries of the world, are the worst affected. India is plagued with numerous water quality problems due to prolific contaminants mainly of geogenic origin and fluoride stands first among them (Manik Chandra and Biswapati, 2009; Ozsvath, 2009). The weathering of primary rocks and leaching of fluoride-containing minerals in soils yield fluoride rich groundwater in India which is generally associated with low calcium content and high bicarbonate ions. The unfettered ground water tapping exacerbates the failure of drinking water sources and accelerates the entry of fluoride into groundwater. Most of the scientific literature substantiates the benefits of low fluoride concentrations in preventing dental decay. However, as a surprising paradox, incidence of dental, skeletal and crippling skeletal fluorosis was reported in India with average fluoride concentrations as low as 0.5, 0.7 and 2.8 ppm respectively (WHO,
Fluorosis turns out to be the most widespread geochemical disease in India, affecting more than 66 million people including 6 million children less than 14 years age (Horowitz, 1989). Though fluoride has spread its tentacles in 36,988 habitations and the number of people falling prey to fluoride poisoning have been steadily increasing, an exact exposure-health relationship is yet to be properly elucidated. There is an essential relation between poverty and fluorosis as malnutrition is found to play an aggressive role in its severity (Ozsvath, 2009).

Fluorine, the 13th most abundant element of the earth, represents about 0.3g / kg of earth’s crust. It occurs mainly in the form of chemical compounds such as sodium fluoride or hydrogen fluoride, which are present in minerals fluorospar, fluorapatite, topaz and cryolite. In India, fluorite and topaz are widespread and contain a high percentage of fluoride (WHO, 1984). Fluoride pollution in the environment occurs through two channels, namely natural and anthropogenic sources (Cengeloglu et al., 2002). Fluoride is frequently encountered in minerals and in geochemical deposits and is generally released into subsoil water sources by slow natural degradation of fluorine contained in rocks. Fluorine is an important element for human beings, as it helps in growth and prevents the enamel of the teeth from dissolving under acidic conditions. Various dietary components influence the absorption
of fluorides from gastrointestinal tract and the absorbed fluorides are distributed throughout the body. Drinking water and seafood are good sources of fluoride (Ray et al., 1981).

Fluoride is beneficial to health if the concentration (CF) of the fluoride ion (F-) in drinking water is less than 1.5 mg/L (WHO 1994). A higher concentration causes serious health hazards. The disease caused manifests itself in three forms, namely, dental, skeletal, and non-skeletal fluorosis. Dental fluorosis produces widespread brown stains on teeth and may cause pitting (Bulusu and Nawlakhe, 1998). Skeletal fluorosis causes crippling and severe pain and stiffness of the backbone and joints (Bulusu and Nawlakhe, 1998; Manik Chandra and Biswapati, 2009).

Renal fluoride toxicity in human beings is difficult to assess in the literature. Although experimental studies and research on methoxyflurane toxicity have shown frank renal damage, observations of renal insufficiency related to chronic fluoride exposure are scarce. A case of fluoride intoxication related to potomania of Vichy water has been reported with a high mineralized water containing 8.5 mg/L of fluoride. Features of fluoride osteosclerosis were prominent and end-stage renal failure was present. The young age of the patients, the long duration of high fluoride intake, and the absence of other cause of renal insufficiency such as hypertension and diabetes suggest a causal
relationship between fluoride intoxication and renal failure (Lantz et al., 1987).

**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 (Leone et al., 1970). 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. Halfway through the twentieth century, fluoride piqued the interest of toxicologists due to its deleterious effects at high concentrations in human populations suffering from fluorosis and in *in vivo* experimental models. Until the 1990s, the toxicity of fluoride was largely ignored due to its “good reputation” for preventing caries via topical application and in dental toothpastes. However, in the last decade, interest in its undesirable effects has resurfaced due to the
awareness that this element interacts with cellular systems even at low doses. In recent years, several investigations demonstrated that fluoride can induce oxidative stress and modulate intracellular redox homeostasis, lipid peroxidation and protein carbonyl content, as well as alter gene expression and cause apoptosis. Genes modulated by fluoride include those related to the stress response, metabolic enzymes, the cell cycle, cell–cell communications and signal transduction (Barbeier et al., 2010).

**Exposure to Fluoride**

Water and water-based beverages are the largest contributors to an individual’s total exposure to fluoride, although there are other sources of exposure (Krishnamachari, 1996). For the average person, depending on age, drinking water accounts for 57% to 90% of total fluoride exposure at concentrations of 2 mg/L and accounts for 72% to 94% of total fluoride exposure at concentrations of 4 mg/L. Non-beverage food sources containing various concentrations of fluoride are the second largest contributor to fluoride exposure (Karram and Ibrahim, 1992). The greatest source of nondietary fluoride in dental products, primarily toothpastes. The public is also exposed to fluoride from background air concentrations and from some pesticide residues. Other sources include some pharmaceuticals and consumer products (Karram and Ibrahim, 1992).
Sources of Fluoride

Fluoride, a naturally occurring element, exists in combination with other elements as a fluoride compound and is found as a constituent of minerals in rocks and soil. When water passes through and over the soil and rock formations containing fluoride it dissolves these compounds, resulting in the small amounts of soluble fluoride present in virtually all water sources (Leone et al., 1970).

Fluoride in Drinking Water

Fluorine (fluoride) is beneficial to human health in low concentration but is toxic in excess. One of the main exposure routes is via drinking water (Fordyce, 2011). Different age groups have different fluoride intake capabilities (Gopalan Viswanathan et al., 2010; Shulaman, 2010). In some communities, fluoride is added to public water supplies, a process known as fluoridation. Water fluoridation involves adjusting the natural level of fluoride to the levels recommended to prevent tooth decay. There is no difference in potential health effects between naturally occurring fluoride and that added through fluoridation (Kumar and Harper, 1963).
Fluoridation of drinking water can be controversial. Opponents argue fluoridation violates individual rights and goes against religious beliefs that ban medication (Horowitz, 1989). The courts have established fluoridation is not an unconstitutional invasion of religious freedom or other individual rights guaranteed by the First, Fifth or Fourteenth Amendments to the U.S. Constitution. It has been the position of courts that a significant government interest in health and welfare of the public generally overrides individual objections to public health regulation (WHO, 1984).

Opponents also argue that drinking fluoridated water promotes a variety of physical and mental ailments including sickle-cell anemia, cancer and cardiovascular disease, AIDS, Down syndrome and Alzheimer's disease. Since the 1930's, many scientific studies have shown that water fluoridation, at the concentrations recommended for good oral health, has no harmful effects. A 1992 policy statement on water fluoridation by the Surgeon General of the U.S. Public Health Service and the Assistant Secretary of Health recommended fluoridation of community water supplies is continued in areas where naturally occurring fluoride levels are deficient (Dhar and Bhatnagar, 2009).
Fluoridation is endorsed by both the American Dental Association and the American Medical Association, as well as numerous national and international organizations including the American Academy of Pediatrics, American Academy of Pediatric Dentistry, American Pharmaceutical Association, American Society of Dentistry for Children, Mayo Clinic, National Academy of Sciences, National Cancer Institute, National Health Council and U.S. Public Health Service Centers for Disease Control and Prevention, Food and Drug Administration and National Institute of Health (WHO, 1994).

**Indications of Fluoride**

Fluoride in drinking water cannot be detected by taste, sight or smell. Testing is the only way to determine the fluoride concentration (Krishnamachari, 1996).

**Potential Health Effects**

The dental benefits from consuming water containing optimum levels of fluoride are well-documented. The American Dental Association has stated that fluoride benefits people of all ages. When children are young and their teeth are still forming, fluoride makes tooth enamel harder and more resistant to decay-causing acid. Studies indicate that people who drink optimally
fluoridated water from birth will experience up to 40 percent less
decay over their lifetimes (Fejerskov et al., 1990). For adults,
fluoride helps repair the early stages of tooth decay even before
it becomes visible, a process known as remineralization. For
older adults, fluoride has been effective in decreasing problems
with root caries (Decay along the gumline).

Although low levels of fluoride are beneficial, excessive
amounts can be harmful. Excessive fluoride in drinking water
may produce fluorosis (Mottling of teeth), which increases as the
optimum level of fluoride is exceeded (Fejerskov et al., 1990).
Dental fluorosis appears during tooth formation and is caused by
excessive fluoride ingestion, which leads to enamel protein
retention, hypomineralization of the dental enamel and dentin
and disruption of crystal formation. The effects range from barely
perceptible white striations or specks on teeth to severe pitting
and/or permanent brown to brownish gray stains on teeth.
Continued consumption of water containing more than 2 mg/l
fluoride will likely produce mild to moderate dental fluorosis (Aoba
and Fejerskov, 2002). Continued consumption of water containing
increasingly higher concentrations of fluoride will generally
produce more severe dental fluorosis. However, according to the
American Academy of Pediatrics, the effect of fluorosis is only
cosmetic. Teeth affected by fluorosis seem to be resistant to dental caries (Hussain et al., 2010; Ozsvath, 2009). Fluoride has its effect on various organs, including the reproductive system, although there are controversial reports over it (Naresh Kumar et al., 2010). Sometimes fluoride can also cause apoptosis of certain cells like osteoblasts (Xiaoyan Yan et al., 2011).

Like other trace elements, excessive quantities of fluoride can result in acute or chronic toxicity. Consumption of an excessive amount of fluoride (300 to 750 milligrams depending on body weight) in a single dose can cause acute toxicity resulting in nausea or vomiting (Rao, 2009). This level of fluoride intake would only occur as a result of some type of accidental event, such as small children consuming an overdose of fluoride supplements (Kumar and Harper, 1963). At the optimum fluoridation level of 1 mg/l, it would take ingesting 80 to 200 gallons of water to reach the acute toxicity level, an amount impossible to drink at any one time.

The National Academy of Sciences has studied the possibility of adverse health effects from continuous consumption of fluoride over long periods of time (Krishnamachari, 1996). The Academy reported daily intake required to produce chronic
toxicity after years of consumption, is 20 to 80 milligrams or more per day depending upon body weight. This level of fluoride intake has been associated with water supplies containing at least 10 mg/l of natural fluoride, as in parts of India and where water consumption was high because of extreme climatic conditions.

Fluoride in India

In India, the states of Andhra Pradesh, Bihar, Chattisgarh, Haryana, Karnataka, Madhya Pradesh, Maharashtra, Orissa, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh and West Bengal are affected by fluoride contamination in water. This involves about 9000 villages affecting 30 million people (Nawalakhe and Paramasivam, 1993). It must be noted that the problem of excess fluoride in drinking water is of recent origin in most parts. Digging up of shallow aquifers for irrigation has resulted in declining levels of ground water. As a result, deeper aquifers are used, and the water in these aquifers contains a higher level of fluoride (Gupta and Sharma, 1995; Manik Chandra and Biswapati, 2009; Hussain et al., 2010; Tamer, 2011).

In 2005, a Central Pollution Control Board countrywide survey found 66 per cent of samples had unacceptable organic values, while 44 per cent had coliform, occurring generally from feces (Verma et al., 1990). Chemical contamination through over-exploitation of
groundwater, resulting in excessive iron, nitrates, arsenic and fluoride is equally widespread. Reports say that there are high fluoride-levels in drinking-water in villages with a prevalence of deformed children from Madhya Pradesh, Jharkhand, Assam and Uttar Pradesh. The problems of chemical contamination are thus prevalent in India with 1, 95,813 habitations in the country are affected by poor water quality (Ayoob and Gupta, 2006). It is surprising to note that states like Bihar and Haryana do not show any problem related to chemical contamination.

The health burden of poor water quality is enormous. It is estimated that around 37.7 million Indians are affected by waterborne diseases annually (Viral hepatitis, cholera, jaundice, typhoid are examples), 1.5 million children are estimated to die of diarrhoea alone and 73 million working days are lost due to waterborne disease each year. The resulting economic burden is estimated at $600 million a year (Kirti Avishek et al., 2010). Ten million people are vulnerable to cancers from excessive arsenic and another 66 million are facing risk of fluorosis, now endemic in 17 States (Petraborg, 1974). Fluorosis is affecting future generations too through pregnant mothers whose anemia is caused by fluorosis. Anemia produces low birth-weight babies who in turn manifest their mothers’ nutritional deficiencies through physical and mental deformities. Besides, there prevail health impacts
of drinking-water with other environmental pollutants such as industrial wastes.

**National Prevalence**

- Fluorosis is an endemic disease prevalent in 20 states out of the 35 states and Union Territories of the Indian Republic.
- 70-100% districts are affected in Andhra Pradesh, Gujarat and Rajasthan.

40-70% districts are affected in Bihar, National Capital Territory of Delhi, Haryana, Jharkhand, Karnataka, Maharashtra, Madhya Pradesh, Orissa, Tamil Nadu and Uttar Pradesh 10-40% districts are affected in Assam, Jammu & Kashmir, Kerala, Chattisgarh and West Bengal. While the endemicity for the rest of the states are not known. The Table-1 and Fig. 2, explain the fluoride levels in India as well as the prevalence.

**Metabolism of fluoride**

Biological effects of fluoride intoxication are related to the total amount of fluoride ingested whatever the source be it food, water or air.
Fig. 1. Percentage of affected habitations chemical contamination wise (as per ARWSP Norms) Source: http://www.ddws.nic.in/

Table 1. Fluoride levels in the different states of India

<table>
<thead>
<tr>
<th>State</th>
<th>Fluoride level</th>
<th>State</th>
<th>Fluoride level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andhra Pradesh</td>
<td>0.4 - 29.0 mg/L</td>
<td>Kerala</td>
<td>0.2 - 5.40 mg/L</td>
</tr>
<tr>
<td>Assam</td>
<td>1.6 - 23.4 mg/L</td>
<td>Madhya Pradesh</td>
<td>1.5 - 4.20 mg/L</td>
</tr>
<tr>
<td>Bihar</td>
<td>0.2 - 8.32 mg/L</td>
<td>Maharashtra</td>
<td>0.01 - 10.00 mg/L</td>
</tr>
<tr>
<td>Chhattisgarh</td>
<td>Information awaited</td>
<td>Orissa</td>
<td>0.6 - 9.2 mg/L</td>
</tr>
<tr>
<td>Delhi</td>
<td>0.2 - 32.0 mg/L</td>
<td>Punjab</td>
<td>0.4 - 42.0 mg/L</td>
</tr>
<tr>
<td>Gujarat</td>
<td>1.5 - 18.0 mg/L</td>
<td>Rajasthan</td>
<td>0.10 - 10.0 mg/L</td>
</tr>
<tr>
<td>Haryana</td>
<td>0.2 - 48.32 mg/L</td>
<td>Tamil Nadu</td>
<td>0.1 - 7.0 mg/L</td>
</tr>
<tr>
<td>Jammu &amp; Kashmir</td>
<td>0.5 - 4.21 mg/L</td>
<td>Uttarakhand</td>
<td>Information awaited</td>
</tr>
<tr>
<td>Jharkhand</td>
<td>0.5 - 14.32 mg/L</td>
<td>Uttar Pradesh</td>
<td>0.2 - 25.0 mg/L</td>
</tr>
<tr>
<td>Karnataka</td>
<td>0.2 - 7.79 mg/L</td>
<td>West Bengal</td>
<td>1.1 - 14.47 mg/L</td>
</tr>
</tbody>
</table>
Fig. 2. Fluoride prevalent states in India
(UNICEF State of Art report, 1999; FR & RDF data bank)
Table 2. Physicochemical properties of common forms of fluoride

<table>
<thead>
<tr>
<th>Property</th>
<th>Sodium fluoride (NaF)</th>
<th>Hydrogen fluoride (HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>white, crystalline powder</td>
<td>Colourless liquid or gas with biting smell</td>
</tr>
<tr>
<td>Density (g/cm³)</td>
<td>2.56</td>
<td>--</td>
</tr>
<tr>
<td>Water solubility</td>
<td>42 g/L at 10 °C</td>
<td>readily soluble below 20 °C</td>
</tr>
<tr>
<td>Acidity</td>
<td>--</td>
<td>strong acid in liquid form; weak acid when dissolved in water</td>
</tr>
</tbody>
</table>
Fig. 3. Geographical region of Nellore district in Andhra Pradesh
(FLouride affected area, where work done, samples collected)
Review of literature

Sources of fluoride

1. Foods

Nearly all foods contain small quantities of fluoride and the total daily intake through any average human diet is small except in endemic regions. In certain endemic regions of India the fluoride content of vegetables and food may be very high (Chari and Naidu, 1998; Hussain et al., 2010). The contribution of food to the total daily intake of fluoride varies from region to region. Staple diets rich in Sorghum, Ragi or Bajra containing high silicon besides fluoride seem to aggravate fluoride toxicity in some endemic areas of India (Anasuya et al., 1996).

2. Water and Beverages

In case of natural waters, the variation in the fluoride content from region to region is dependent upon such factors as the source of water, type of geological formation and the amount of rainfall. Surface waters generally have low fluoride while ground waters may have high concentrations of fluoride as has been found in many parts of the world. The highest fluoride concentration of 28.9 ppm was reported from India (Chari and Naidu, 1998). The fluoride content of seawater varies from 0.8 to 1.4 ppm, which explains why the fluoride content of diet rises when sea foods are consumed (Teotia et al., 1998). Among beverages tea has an exceptionally high fluoride content which varies in different
brands from 122-260 ppm or more. Each cup of tea may supply 0.3-0.5 mg of fluoride.

The fluoride intake dependent upon consumption of drinking water and beverages is determined by factors such as body size, physical activity, food habits and variations in atmospheric temperature and humidity. That is why in tropical countries like India, the daily fluoride intake is very high. Farm laborers drink lot of water from wells and naturally have high fluoride intake and are at risk of developing fluorosis (Anasuya et al., 1996).

3. Air

The atmosphere has very low fluoride content and in 97% of non-urban areas fluoride is hardly detectable. The fluoride content of atmosphere is seen to have risen wherever there is volcanic action or industrial activity (Jacyszyn and Marut, 1986). Volcanic fumarole vapors have high concentration of fluoride and industrial emissions from those engaged in mining or manufacture of fluoride containing minerals may be hazardous. Low-grade coal has high levels of fluoride and smoke may be a source of fluoride pollution (Chandrajith et al., 2011).
**Total daily fluoride intake**

The fluoride contents from all the sources determine the human intake of fluoride. In majority of endemic areas around the world, the main contribution is from water and only in few areas of India and China significant amounts come from foods and rarely the polluted air is the culprit (Jolly et al., 1969). The estimated range of safe and adequate intake of fluorides for adults is 1.5 to 4.0 mg per day and it is less for children. The daily intake of fluoride in endemic regions varies from 10 to 35 mg and can be even higher in summer months (Saralakumari and Ramakrishna Rao, 1993).

**Absorption of fluorides**

Soluble inorganic fluorides ingested through water and foods are almost completely absorbed and also those inhaled from the respiratory tract. But absorption of less soluble inorganic and organic fluorides varies from 60-80% (Cremer and Buttner, 1970). Fluorides are absorbed from the gastro-intestinal tract by a process of simple diffusion without any mechanism of active transport being involved. Various dietary components apparently influence the absorption of fluoride from the gut. It has been noticed that salts of calcium, magnesium and aluminum when added to diet reduce the quantum of fluoride absorption on account of the formation of their less soluble compounds. This is the reason why waters with high calcium and magnesium content check the
incidence of fluorosis, as indicated by epidemiological studies (Jolly et al., 1969). Therefore, it is to be expected that all other factors being equal, the incidence of skeletal fluorosis would be less where the calcium and magnesium content of drinking water is high. It is noteworthy that administration of magnesium salts (serpentine and magnesium hydroxide) to patients suffering from fluorosis and experimental animals has increased the fecal and urinary excretion of fluorides. Similarly, increased absorption of fluoride from gastrointestinal tract ensues from the addition of substances like phosphates, sulphates and molybdenum to the diet and these can increase fluoride toxicity (Ericsson and Ribeliu, 1971).

Distribution of fluorides

About 96-99% of the fluoride retained in the body combines with mineralized bones, since fluoride is the most exclusive bone seeking element on account of its affinity for calcium phosphate (Armstrong et al., 1973). But it has been noticed that there is no significant retention of it in the body if very small quantities of fluorides are ingested (McClure et al., 1945). In fact, there was no discernible retention of fluoride when upto 4-5 mg was ingested daily. But when more than 5 mg were ingested about half of it appeared to have been retained by the skeleton and rest excreted through urine. Observations show that after absorption from the gut fluoride enters the circulation, the plasma
fluoride accounting for the three-fourths of the total amount of fluoride found in the whole blood and cells for the rest (Chandrajith et al., 2011). Fluoride in plasma exists in free ionic and bound forms, the latter bound to the serum albumin forming about 85% of the total amount fluoride in plasma (Taves et al, 1968). Plasma fluoride in normal individuals in non-fluoridated areas ranges from 0.14-0.19 ppm and is higher in fluorotic patients (Singer and Armstrong, 1977). Newer methods, which only measure ionic component of plasma fluoride levels are lower and range between 0.004-0.008 ppm when drinking water contained traces of fluoride and varied from 0.1-0.02 ppm. Plasma fluoride concentrations tend to increase slowly over the years. It is seen that plasma levels of fluoride do not fluctuate widely despite a wide variation of fluoride levels in drinking water presumably because of the action of some regulatory mechanisms, which have not yet been clearly identified (Singer and Ophaug, 1982). The sequestration of fluoride into the skeleton, urinary excretion and loss sustained through sweat help in regulation of plasma fluoride. The levels of fluoride in most soft tissues of the body are lower than 1 ppm but are higher than those of plasma. The fluoride content of brain is 0.4-0.68 ppm and the concentration in CSF is 0.1 ppm, which is lower than that of plasma (Hodge and Smith, 1977).
The uptake of fluoride by the skeleton is very rapid and depends upon the vascularity and the rate of its growth. The fluoride uptake of young bones is faster than that of mature bones. The fluoride is incorporated more readily in the active, growing areas than in the compact regions. It has been observed that skeletal fluoride concentration increases almost proportionately to the amount of fluoride ingested and the duration of its ingestion (Spencer et al., 1981). The amount of fluoride present in various bones of same skeleton differs from bone to bone with pelvis, vertebrae registering higher fluoride content than limb bones. Even in the limb bones amount of fluoride deposited in them depends upon the activity of muscles attached to them. In caged monkeys fluoride content of upper limb bones is more than the lower limb bones. It is this increase in the fluoride content of skeleton that provides the most reliable clue to excessive fluoride intake (Singh and Jolly, 1970). The other indicators such as urine and soft tissue levels, which manifest wide fluctuations, cannot be relied upon. Once incorporated into the hard tissues, the fluoride is retrievable, though with difficulty and entails an extremely slow process of orthoclastic resorption spread over many years (Chuttani et al., 1962).
Excretion of fluorides

Feces

Fluoride present in feces results from two sources: the ingested fluoride that is not absorbed and the absorbed fluoride that is excreted into the gastrointestinal tract. About 10-25% of daily intake of fluoride is excreted in the feces (Kono et al., 1995; Dhar and Bhatnagar, 2009).

Urinary

The elimination of absorbed fluoride occurs almost exclusively via the kidneys. Urinary fluoride in normal individuals fluctuates widely between 0 and 1.2 ppm with an average of about 0.4 ppm when fluoride content of drinking water is 0.3ppm (Singer et al., 1969). Urinary levels of fluoride are higher in individuals exposed to higher intake of fluoride. The renal clearance of fluoride is directly related to urinary pH, and under some conditions, to urinary flow rate. In alkaline urine the fluoride is present in ionic form and hence its renal clearance is rapid. In the acidic urine on the other hand, fluoride is present in nonionic form (HF) and hence it is rapidly reabsorbed in renal tubules (Singer and Ophaug, 1982). The excretion of fluoride is much less if person concerned is suffering from chronic kidney disease resulting in renal failure, which inevitably leads to high concentrations of fluoride in serum as well as in bone (Chouhan and Flora, 2010). In experiments on rats with renal insufficiency increased intake of fluoride caused decreased glomerular...
filtration rate and increased blood urea nitrogen along with increase in serum and bone concentrations of fluoride. Since disturbed renal function predisposes to excessive retention of fluoride, individuals suffering from chronic renal failure may, therefore, develop skeletal fluorosis even at a considerably low level of 1PPM of fluoride in drinking water.

**Sweat**

Some fluoride is also lost from the body through sweat and so appreciable amounts may be lost in situations marked by excessive sweating. Sweat fluoride concentrations are similar to plasma (Carlson et al., 1960; Dhar and Bhatnagar, 2009).

**Other routes**

The amount of fluoride in breast milk is low and same is true of saliva.

**Clinical features**

Fluoride intoxication presents an extraordinary degree of uniformity in its clinical manifestations. It occurs in humans as dental and skeletal fluorosis. They are separated by a prolonged, relatively symptom free interval, during which the skeleton does not stop accumulating fluoride. In its advanced stages, skeletal fluorosis causes
crippling deformities and neurological complications (Sharma et al., 2009; Hanen Bouaziz et al., 2010).

**Dental fluorosis**

Dental fluorosis mainly involves enamel but severe intoxications may affect dentine as well as pulp. Enamel fluorosis occurs when fluoride concentrations in or in the vicinity of the forming enamel are excessive during its pre-eruptive development. Mottling of teeth is one of the earliest and most easily recognizable features noticed in the first decade of life (Jolly et al., 1968).

Both sexes are equally affected. It is the permanent teeth that are affected and they lose their normal creamy white translucent color and become rough, opaque and chalky white. Pitting and chipping are other marks of fluorosis (Whitford and Pashley, 1982). Brown or black pigment gets deposited on the defective enamel and once established tends to remain there permanently. Incidence of dental fluorosis in endemic areas exhibits a linear relationship to the fluoride content of water but it may also vary with other factors (Jolly et al., 1968). Dental fluorosis does not obviously occur, when there has been no exposure to fluoride in the first decade of life.
**Pre skeletal stage**

The duration of this stage may vary with the amount of fluoride daily ingested. Reportedly, it ranges from 10 to 30 years or even longer in endemic areas and from 10 to 15 years or longer in cases of industrial fluorosis (Franke et al., 1970; Singh and Jolly, 1970). It is usually free of any signs or symptoms in its early stages in endemic regions. The persons concerned may occasionally complain of pains in the small joints of the limbs and back, which are often mistaken for rheumatoid arthritis or ankylosing spondylitis. However, various reports from Europe and America suggest that there would be symptoms corresponding to gastrointestinal, musculoskeletal, respiratory and visceral systems during this stage (Petraborg, 1974).

**Skeletal fluorosis**

Early in the development of fluorotic changes in the skeleton, the patients often complain of a vague discomfort and paresthesiae in the limbs and the trunk. Pain and stiffness in the back appear next, especially in the lumbar region, followed by dorsal and cervical spines. Restriction of the spine movements is the earliest clinical sign of fluorosis (Chuttani et al., 1962).

The stiffness increases steadily until the entire spine becomes one continuous column of bone manifesting a condition referred to as
'poker back'. In man the spine is most likely to be affected first and severely because of its being required to sustain the erect posture (Hrishikesh Kumar et al., 2009). When the condition becomes severe and chronic, various ligaments of the spine become calcified and ossified. The stiffness that first appears in the spine soon spreads to various joints in the limbs owing to the involvement of the joint capsules, the related ligaments, tendons attachments to the bones and interosseous membranes.

**Neurological manifestations of skeletal fluorosis**

The prolonged ingestion of F may cause significant damage to health and particularly to the nervous system. Therefore, it is important to be aware of this serious problem and avoid the use of toothpaste and items that contain F, particularly in children as they are more susceptible to the toxic effects of F (Valdez-Jiménez et al., 2010).

The neurological sequelae in skeletal fluorosis manifesting usually as radiculo- myelopathy arise principally because of the mechanical compression of the spinal cord and nerve roots brought about by osteophytosis and sclerosis of the vertebral column (Nayak et al., 2009). However, it is only in later stages owing to pressure on the radicular vessels in the intervertebral foraminae that vascular
complications may supervene. But the neural toxicity attributable to fluorides is yet to be established.

Neurological complications arise at a late stage of the disease in about a tenth of the total number of skeletal fluorosis cases (Sharma et al., 2009). Shortt and his colleagues reported them from India in 1937 based on ten chronic cases with a history of 30 to 40 years intake of water containing 2-10 ppm of fluoride.

**Myelopathy**

Patients suffering from fluorosis usually experience difficulty in walking because of the progressive weakness in the lower limbs. With the spreading of this weakness to the upper limbs, neurological disabilities occur that make the patient bedridden (Dhar and Bhatnagar, 2009). These disabilities are due to motor and sensory deficits, which are followed by sphincter disturbances. In such a condition motor disabilities predominate over the others and sensory defects affecting touch, vibration, position and joint sense tend to be bizarre and widespread.

**Radiculopathy**

Nerve root compression leads to atrophy of various muscle groups in both upper and lower limbs. With the onset of fasciculation
motor neuron disease may be mimicked. The upper limbs appear to be affected more than lower limbs which may be traced to the commoner involvement of the cervical region or even the anatomical features of the cervical spine (Rao and Siddiqui, 1962). Sensory changes may not be as striking as disabilities of motor function and root pains do not usually occur. In advanced cases, marked cachexia develops on account of disuse atrophy of limb and trunk muscles (Catalano et al., 1993).

Cranial nerve lesions

The skull is not much affected in fluorosis and basal cranial nerve foraminae are not usually encroached upon except at advanced stages of the disease (Singh and Jolly, 1970; Bhagavan and Raghu, 2005). Of the cranial nerves, the most frequently affected, in a quarter of the cases investigated, has been the eighth nerve. In all such cases calvarial changes caused by fluorosis are discernible. A progressive high frequency perceptive deafness is observed. Moreover, the bone conduction is affected more than air conduction. Nevertheless, total deafness rarely occurs. It is perhaps, the compression of the nerve in the sclerosed and narrowed auditory canal that accounts for the deafness in fluorosis (Rao and Siddiqui, 1962; Kundu and Mandal, 2009).
Peripheral neuropathies

Exostoses, which mainly develop around the knee, elbow and ankle may press upon the median and ulnar nerves. Pain, paresthesiae followed by weakness in the limbs may be caused by such bony growths. Even neuralgia paresthetica has been reported to occur in fluorosis (Chuttani et al., 1962; Chandrajith et al., 2011). Fluorotic patients may also manifest entrapment syndromes involving other peripheral nerves.

Cerebrovascular accidents

Involvement of vertebrobasilar circulation caused by the compression of cervical osteophytes may occasionally occur (Singh and Jolly, 1970). Increased calcifications of major vessels and disturbance of lipid metabolism that has been reported in fluorosis may bring about cerebrovascular accidents.

Renal failures

Generally chronic renal failure associated with heavy metal contamination of drinking water (Bawaskar, 2010). But, Liver and kidney are the target organs markedly attacked by excessive amount of fluoride. High doses of fluoride intake lead to changes of structure, function and metabolism in liver and kidney (Yang and Liyang, 2011).
Kidneys are among the most sensitive body organs in their histopathological and functional responses to excessive amounts of fluoride (Rao and Rao, 2009; Rohan Chandrajith et al., 2010). They are the primary organs concerned with excretion and retention of fluoride and thus are generally involved in chronic fluoride intoxication. In humans, only a few reports pertaining to kidney involvement in endemic fluorosis are available (Reddy et al., 1969). Kono et al. (1995) reported impaired renal functions in fluoride-exposed workers. In contrast to cases of acute intoxication, the records of only a few autopsy reports of patients dying of chronic fluoride intoxication are traceable in the literature (Reddy et al., 1969; and Singh and Jolly, 1970; Rao, 2009). No renal abnormality ascribed to fluoride was found at the autopsy examination of an elderly woman who for 30 years had consumed water containing 8 ppm fluoride (Leone et al., 1960). In three autopsy cases Reddy et al. (1969) found multiple pyaemic abscesses in the fluorotic kidneys which grossly appeared like pyelonephritic kidneys with dilated ureters (Kono et al., 1995).

Considerable discussion has ranged on the issue of whether the addition of fluoride to water supplies used in cooking, drinking, and dialysis would add an appreciable burden of fluoride to the body and whether this burden could account for some of the toxic features of chronic renal failure (Kaye et al., 1960; Siddiqui et al., 1971). Raised
concentrations of fluoride have been found in the plasma and bone of patients with renal failure (Taves et al., 1968; Kim et al., 1970; Fournier et al., 1971; Nayak et al., 2009). As normal people absorb fluoride easily it seemed important to determine at what level of renal function, fluoride excretion failed to match absorption. The fluoride ion has been shown to cross the dialysis membrane freely (Taves, 1968). So in patients on regular dialysis treatment fluoride from dialysis fluid might collect in the blood to be excreted. After transplantation homoeostatic mechanisms for the excretion of fluoride should come into play and reduce the plasma level, then fluoride excretion might reflect the degree of tissue loading, particularly of bone, whose turnover might be increased during the recovery of normal renal function.

Role of fluoride in urolithiasis is a subject of controversy. One group of scientists confirmed its role in stone formation (Anasuya, 1982; Verma et al., 1990), while other denied its any role in urolithiasis (Teotia et al., 1998). A report from New York described that fluoride content vary from nil to 1800 ppm and was not in correlation with stone former’s age. Li et al. (1992) from China suggested the inhibitory effect of fluoride on renal stone formation in rats (Li et al., 1992). A report from Hyderabad (Anasuya, 1982) suggested the role of fluoride in the formation of urinary calculi by observing the urinary stone formation in rats by feeding them with high fluoride diet. Verma et al. (1990) from
Rajasthan showed higher concentration of fluoride in serum and urine of stone formers (SF) as compared to non-stone formers (N). A high intake of fluoride provoked nephrolithiasis in tribal higher in endemic area than non-endemic area (Singh et al., 2001).

**Reasons for kidney (Renal) failures**

There are several conditions and diseases that can lead to chronic kidney disease (CKD). Hypertension and diabetes are just two of the most common causes. When we talk about hypertension, we are talking about blood pressure. Blood pressure is determined by the force of blood being pumped from the heart, and force of blood against the walls of the arteries. When uncontrolled, blood pressure can be life threatening. Blood pressure that is high can make the heart work too hard, harden the walls of arteries, and can lead to a stroke or brain hemorrhage. It can also cause the kidneys to function poorly or not at all. A blood pressure reading of 140/90 mmHg or higher is considered high. Normal blood pressure is less than 120/80 mmHg.

More than 65 million American adults have high blood pressure according to the National Institute of Health (NIH). The disease is more common among African Americans, and can lead to worse complications (WHO, 1994). Therefore, African Americans are at greater risk, not only to develop the disease, but also to suffer its consequences. African Americans are more likely to develop the type of
hypertension that can be controlled by salt restriction. It is especially important for African Americans to undergo screening tests for hypertension and seek treatment early (Gesang et al., 2002).

Over time, uncontrolled high blood pressure can damage the blood vessels and nephrons (functional units of the kidneys) in the kidneys. This causes the nephrons to stop doing their job of filtering out wastes, sodium and excess fluids from the blood. With no place to go, the extra fluids and sodium linger in the bloodstream, putting extra pressure on the walls of the blood vessels, and raising the blood pressure (Kono et al., 1995). This extra pressure damages the kidneys even further. Reports from US suggest that most of the kidney disorders were developed due to the above said problems (Fig. 4). But in addition to that some of the people are getting these failures due to the consumption of pollutant water (USRDS, 2007).
Fig. 4: Annual data of US showing the causes of kidney failures
Significance of the study

Fluoride toxicity is the more abundant threat to the common people who are living in the content areas in the globe. Fluoride toxicity will affect all the parts of the human system leads to the altered life span. In India it is the foremost problem in different parts of the country (Saralakumari and Ramakrishna Rao, 1993). Andhra Pradesh has also become popular with the curse particularly districts like Nalgonda. Almost all the relevant problems with fluoride poisoning was established by the researchers, but the people in and around the Nellore district were more repeatedly targeted by the renal failures without any other disorders like hypertensions or diabetes. To identify the relations between the increased fluoride content in the drinking water and the renal failures the study has been established (Singh et al., 2001; Brindha et al., 2010).

Studies related to exact evidence of fluoride involvement in the renal failures are no more. Most of the experiments were conducted in the renal failure patients under the supplementation of fluoride water. To know the specific mechanism of fluoride toxicity in the renal failures, we have designed the work in the patients who are not having hypertension as well as diabetes. Since the diabetes patients are going to develop the renal problems due to hyperglycemic activity. From this background the study was started in the Nellore district region of
Andhra Pradesh, which is geographically southern part of the India near to the Bay of Bengal. Questionnaires have been prepared to identify the samples in and around the selected areas. The villagers were identified with the present problem and further analysis was conducted with the following aims and objectives.

**Aims and objectives of the present study**

1. Identification of high fluoride containing areas in Udayagiri mandal of Nellore district by drinking water analysis (pH, Salinity, Alkalinity, Hardness and Fluoride).

2. Renal risk assessment by gathering the information from the people of villages and from local health department sectors.

3. Measurement of serum and urinary fluoride concentrations in selected population (Should be without hypertension and diabetes) from the selected villages.

4. Evaluation of hematological parameters viz. neutrophil, basophil, acidophil, leukocyte, total WBC, Hb level etc. in the selected subjects and control subjects.

5. Evaluation of biochemical parameters viz. Total protein, Glucose, Lipid profiles, SOD, SGOT, SGPT etc.

7. Studies on association of insertion and deletion (I/D) polymorphism in ACE gene 1 in renal failures evaluated patients.