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Review Article

Fluoride Toxicity in Animals-A Concern

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Abstract

The Fluorine, is most unstable and reactive non-metal, invariably becomes stable "fluoride" when combines with electropositive metal. Fluoride toxicity in domestic and wild animal is primarily caused by hydrogen fluoride gas, fluorosilicic acid, sodium silicofluoride, and sodium fluoride. Fluoride is more toxic than lead and slightly less toxic than arsenic. The fluoride toxicity can be acute, sub-acute and chronic form, which is based on level of intake and chemical form of fluoride. Drinking water, fluoride compounds used in domestic and agricultural applications, fodder and grasses contaminated with industrial fluoride emissions or volcanic ash are also sources of high fluoride intake for animals, and, on rare occasions, poor quality mineral mixtures and feed supplements may be source of toxicity. Fluorosis in grazing animals may also be caused by soluble fluoride-rich soil, particularly when growing vegetation is sparse. Acute fluoride poisoning in animal resulted into restlessness, stiffness, anorexia, hypersalivation, nausea, vomiting, urine and faecal incontinence, reduced milk production, convulsions, weakness, severe depression, pulmonary congestion, and respiratory and heart failure and it's all are clinical indications of acute fluoride toxicity in domestic animals. Tolerance of fluoride in animals depend upon species, age, and sex; individual resistance; fluoride uptake dose, duration, and consistency; and dietary, nutritional, and environmental factors. Public awareness must be enhanced, especially in rural areas, on the possible mitigating, ameliorative, and preventive techniques for fluorosis in livestock.

Keywords: Fluorides; Livestock; Toxicity

Abbreviations

WHO: World Health Organization; DM: Dry Matter

Introduction

In 1886, French scientist Henri Moissan synthesized a highly electronegative and reactive halogen element known as fluorine that belongs to Group 7A of periodic table. Among different fluorine isotopes, $_{22}$F has longest half-life of 109.7 minute [1]. Fluorine, as most unstable and reactive non-metal, invariably becomes stable "fluoride" when combines with electropositive metal. The term "fluoride" and "fluorine" often used interchangeably in biological science. Fluorine containing chemical compound either present naturally or produced for anthropogenic purposes (agriculture, industrial and domestic). Fluoride toxicity in domestic and wild animal is primarily caused by hydrogen fluoride gas, fluorosilicic acid, sodium silicofluoride, and sodium fluoride.

Physical and chemical properties

Fluorine is pungent and pale-yellow coloured gas at room temperature and combined with hydrogen to form irritating and highly corrosive hydrogen fluoride gas. This hydrogen fluoride gas utilize for production of fluorocarbons. Other industrial fluoride includes sodium fluoride, fluorosilicic acid and sodium fluorosilicate. Sodium fluoride is slight water soluble, odourless, white or colourless

crystal. Flurosilicic acid used in water fluoridation and production of aluminium fluoride.

Distribution of fluorides

Fluorine is 13th most abundant element in earth crust. The concentration of fluorine in groundwater varies depending on the geological, chemical, and physical properties of the water-supplying area, the consistency of the soil, the porosity of rocks, pH, temperature, other complexing activity of elements, and the depth of wells [2]. The concentration of fluoride ranges from 0.01- 0.3 mg/l and 1.2-1.5 mg/l in unpolluted freshwater and seawater, respectively [3].

Mineral	Fluorine concentration (%)
Sellaite	61
Villiaumite	55
Fluorspar	49
Cryolite	45
Bastnaesite	9
Fluorapatite	3.5

Table 1: Fluorine concentration in natural fluoride mineral.

Fluoride can be found in the atmosphere in two forms: gaseous and particle and hydrogen fluoride and sodium or calcium fluoride account for 75 percent and 25 percent of inorganic fluoride in the atmosphere, respectively [2].

Is fluoride essential for health?

Fluorine was listed in a list of 14 essential elements for life by WHO committee [4]. Similarly, American dietetic association and Federal Register of the US Food and Drug Administration considered the fluorine as essential element for health [5]. However, there is lack of sufficient experimental evidence which can support the essentiality of fluorine for health. As a result, the Food and Nutrition Board of National Research Council has now using the term "beneficial element (BE) and "apparent beneficial intake" for fluoride instead the term "essential".

Fluoride and animal health

Probably the requirement of fluoride is very low that deficiency never noticed or is difficult to create in natural or laboratory condition [6,7]. Anke., *et al.* [8] reported that feeding female goat a diet containing less than 0.3 ppm fluoride (on DM basis) for 10 generation resulted in skeletal abnormalities in female goat and reduced growth rates in offspring. However, there is lack of sufficient study to support similar findings. But some studies reported the beneficial effect of supplementation of fluoride on animal health and performance. Gutierrez., *et al.* [9] reported the improvement in growth rate of broiler chickens supplemented with 80 ug fluoride per gram of diet.

Fluoride toxicity

Any micronutrient in excess can exert toxic or adverse effect in animals. Fluoride is more toxic than lead and slightly less toxic than arsenic. The fact that the single dose of 5 mg F/ kg BW causes acute toxicity while single dose of 16 mg F/ Kg BW results in death [10]. The fluoride toxicity can be acute, sub-acute and chronic form which is based on level of intake and chemical form of fluoride.

- **Acute:** occurs when accidental ingestion of large doses of rodenticide (sodium fluoroacetate and fluoroacetamide), insecticide (sodium fluorosilicate) and acaricide (sodium fluoride). However, there is reduction in the utilization of these fluoride compounds in various household and agriculture purposes. As a result of that the incidence or occurrences of acute fluoride toxicity is rare.
- **Chronic:** occurs when the prolong ingestion of low but toxic dose of fluoride. It is also known as "fluorosis". Chronic fluoride poisoning is the most prevalent and important form of fluorosis in humans and animals, and is characterized by pathological alterations in teeth (dental fluorosis) and bones (osteofluorosis). The main route of fluorosis is the ingestion through food and water. The term "hydrofluorosis" referred to chronic fluoride toxicity occurs when drinking water is containing high fluoride level. Ingestion of water containing fluoride above 1.5 ppm resulted in osteo and dental fluorosis in almost every species of livestock [11,12]. High dosages of fluoride are toxic to almost all terrestrial and aquatic animals, though tolerance level varies depending on the species. Drinking water, soil, or plants naturally holding excess soluble fluoride compounds or polluted with fluoride compounds generated by volcanic eruptions are all key sources of excess fluoride intake for terrestrial animals. Herbivores are more vulnerable than carnivores and other animals among terrestrial vertebrates. Because domestic and wild herbivores are nonselective eaters and can ingest contaminated feed, forage, and water, they are more vulnerable to environmental contaminant. Poor quality mineral mixture and feed supplements also responsible for fluorosis in organized livestock farm. Across the world, fluorosis has been reported in wild as well as domesticated animals [13]. Probably because of larger population and economic importance, cattle and sheep have

got more attention from experts around the world but other animals like water buffaloes, horses, goats, pigs, and wild cervids are also affected by fluoride toxicity.

Sources of fluoride toxicity

Drinking water, fluoride compounds used in domestic and agricultural applications, fodder and grasses contaminated with industrial fluoride emissions or volcanic ash, and, on rare occasions, poor quality mineral mixtures and feed supplements are also sources of high fluoride intake for animals. Fluorosis in grazing animals may also be caused by soluble fluoride-rich soil, particularly when growing vegetation is sparse. Airborne fluoride toxicity is uncommon, and oral fluoride uptake remains the most common route of excess fluoride ingestion. Water fluoride levels as low as 1.5 ppm can cause chronic fluoride poisoning in numerous species, while the research suggests that most domestic animals have higher water fluoride tolerance levels. In various countries, volcanic ash-contaminated grassland has been responsible for grazing animal mortality outbreaks [14,15] (Figure 1).

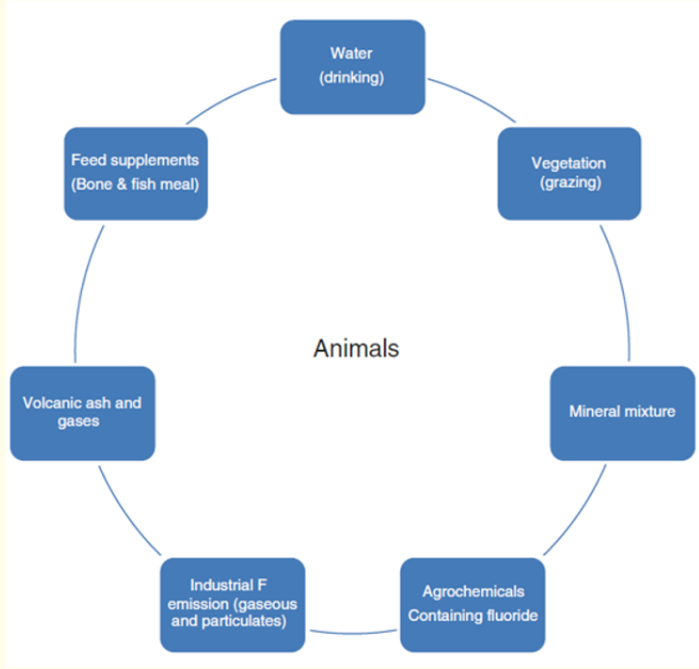

Figure 1: Sources of fluoride toxicity in animal.
Source: [13].

Fluoride kinetic and metabolism

Fluoride is absorbed through the GI tract, respiratory tract, skin, and mucous membranes and then circulated to various organs and body tissues. Unabsorbed fluoride is excreted in the faeces, while 50-70% of absorbed fluoride is excreted in the milk, saliva, urine, perspiration, and egg (in birds), with the remainder remaining in the body. Calcified tissues, primarily bone and teeth, act as a natural fluoride sink, containing nearly about 99% of the body's fluoride burden. Fluoride levels in soft tissues are extremely low, with the highest concentration seen in kidney. As evidenced by reduced transplacental fluoride passage in many animal species, the placenta appears to protect the foetus from the damaging effects of fluoride. The concentration of fluoride in normal cerebral fluid is relatively low, however it increases slightly during chronic fluoride poisoning. The exoskeletons, skeletal tissue and hair and fingernails of invertebrates, fish and vertebrates, respectively, also accumulates fluoride and may serve as bio-indicators of fluoride burden.

Toxic effect

Acute toxicity

Accidental ingestion of fluoride-containing pesticides or other compounds such as sodium fluoride, sodium fluorosilicate, and hydrofluoric or fluorosilicic acid causes acute fluoride poisoning in animals. Restlessness, stiffness, anorexia, hypersalivation, nausea, vomiting, urine and faecal incontinence, reduced milk production, convulsions, weakness, severe depression, pulmonary congestion, and respiratory and heart failure are all clinical indications of acute fluoride toxicity in domestic animals [14,16].

Following administration of sodium fluoride (200-100 mg/kg BW), buffalo calves developed profuse salivation, lacrimation, nasal discharge, dyspnoea, severe stomach discomfort, convulsions, and death within 2.5-58 hours [17]. The corrosive effect of hydrofluoric acid, which is formed in the acidic environment of the stomach, causes gastrointestinal symptoms [18]. After inhaling fluoride chemicals such as hydrogen fluoride gas, respiratory symptoms become more prominent.

Chronic toxicity

Occurs when the prolong ingestion of low but toxic dose of fluoride. It also knows as "fluorosis". Following excessive fluoride uptake, clinical symptoms of toxicity may not develop for several weeks or months [20]. Chronic form of fluoride toxicity is more common than acute form in human as well as animal. First visible sign is dental lesion followed by skeletal deformity or damage. If prolong intake of fluoride continue, dysfunction of abnormality in soft tissue, reproductive and nervous system become evident [21].

Effect on general health

Fluorosis has a variety of health impacts in animals, including stunted growth, decreased milk and wool production, altered reproductive performance, and general health problems [22]. In severe cases of fluorosis in dairy cattle, there is a considerable drop in milk production [23]. Reduced feed intake and feed conversion efficiency, as well as progressive loss of appetite and body weight in cattle, are caused by changes in volatile fatty acid concentrations and rumen microbiota [24]. Slower growth rates in new born calves and delayed postpartum estrus in cattle also reported [25].

Dental fluorosis

Dental lesions, especially in young animals, are the most sensitive indications of fluoride toxicity. Because unfavourable effects are not visible in teeth that have already erupted prior to the fluoride exposure and mottled and imperfect enamel is an indication of inorganic fluoride exposure during tooth development [26]. The developing teeth (incisor) of cow aged from 6 -30 months are more sensitive to fluoride [15]. Therefore, dental lesion will be mild in adult cattle exposed to fluoride as compared to young animal.

High fluoride intake interfere amelogenesis and dentinogenesis, resulting in abnormal or defective enamel and dentin development [15]. In chronic fluorosis, ameloblasts, dental pulp cells, and odontoblasts are the primary target cells. Fluoride has a cytotoxic effect on odontoblasts and pulp cells [27,28]. Ameloblast undergo atrophy and necrosis results in defective enamel. Fibrous and osseous metaplasia can occur in pulp cells. The atrophy of odontoblasts results in brown colouration of dentin [29].

Hypomineralized outer enamel, coronal cementum hyperplasia, disrupted subsurface pigment band, hypoplastic pits, puckered incremental lines, periodic radiolucent regions, and decreased microhardness of the outer enamel are the most common signs of dental fluorosis in animals [30]. Shupe *et al.* [31] suggested a score system (0-5) to assessed severity of dental fluorosis in animal (Table 2).

Score	Type	Description
0	Normal	Translucent, smooth, glossy white enamel, teeth are normal in shape
1	Questionable effect	Slight deviation from the usual translucency of normal enamel. Cause is not precise. May have enamel flecks; cavities, if present may be unilateral or bilateral, but no mottling is evident
2	Slight effect	Slight mottling of enamel; may have some discoloration, but no abrasion. Teeth have normal shape
3	Mild effect	Moderate mottling (large patches of chalky enamel), discoloration of enamel; teeth may have slight abrasion
4	Marked effect	Definite mottling, discoloration, hypoplasia and hypocalcification; may have pitting of enamel; enamel may be cream coloured; definite abrasion of teeth
5	Excessive effect	Definite mottling, discoloration, hypocalcification, may have pitting of enamel; enamel may be cream coloured, excessive abrasion of teeth

Table 2: Classification of dental fluorosis in Animal by Shupe., *et al.* [31]. Source: [13]

Osteoflurosis

The normal fluoride concentration in bone of animals range from 200-300 mg/kg (On DM basis) and it may exceed 1200 mg/kg in fat free bone. After high intake, initially fluoride deposit rapidly in skeletal tissue and after that deposit slowly until saturation. Capacity of bone to accumulate fluoride is lost when concentration reaches 1500-2000 mg/kg. When the fluoride concentration in bone crosses 5000 mg/kg, the radiographic lesion of abnormality usually seen. Fluoride is naturally absorbed by bone, making it a natural fluoride sink. Inorganic fluoride is predominantly absorbed by bone tissues by replacing the hydroxyl groups of calcium hydroxyapatite with inorganic fluoride and forming calcium fluorapatite. Abnormal changes in bone resulted from fluoride toxicity vary greatly, including Osteosclerosis, periosteal hyperostosis, osteoporosis, osteomalacia, or osteophytosis. Type, severity and variation in these changes may be due the cumulative response of nature, dose, and duration of fluoride exposure, age and sex, hormonal responses. Based upon fluoride concentration in bone, fluorosis classified into three stage in case of cattle [15].

Stages	Fluoride concentration in bone (mg/kg)	Comments
I	< 1500 (sometimes 2500)	No structural and functional changes
II	1500-5000	No gross changes, only alteration in microarchitecture of bone
III	>5000	Gross lesion observed

Table 3: Classification of fluorosis based on fluoride concentration in bone.

Other effects

Cytotoxic

Tokunga., *et al.* [32] suggested that the cytotoxic action of fluoride is mediated via inhibition of glucose uptake by cell rather enzyme inhibition. However, Barbier., *et al.* [33] reported the cytotoxic action fluoride is mediated through inhibition of enzyme specially involved in energy metabolism. High fluoride intake interferes collagen synthesis which results in abnormal tissue or organ [34,35].

Renal and hepatic damage

High fluoride produced structural and functional damage in kidney by inhibiting several enzymes, increasing concentration BUN and creatinine and decreasing Na, K and ATPse activity [36].

Reproductive toxicity

High fluoride induces morphological and histological changes in testes and ovary which results in abnormal reproductive performance [2]. Similarly, fluoride interfere in spermatogenesis and normal function of various hormone i.e., testosterone, oestrogen, melatonin and thyroid [37,38].

Fluoride tolerance

Tolerance of fluoride in animals depend upon species, age, and sex; individual resistance; fluoride uptake dose, duration, and consistency; and dietary, nutritional, and environmental factors. Experimental tolerance levels may be inaccurate in some cases due to a weak correlation between fluoride concentration (feed and water) and its bioavailability. Among animals, poultry are highly tolerant to fluoride followed by carnivores, simple stomach herbivores, ruminants and rodents. Tolerance level of fluoride in feed (on DM basis) and water for different animal is presented in table 4.

Animals species	Fluoride in feed (ppm)	Fluoride in water (ppm)
Beef and dairy heifers	30	2.5-4
Mature dairy cattle	30	3-6
Mature beef cattle	40	4-8
Sheep	50	12-15
Horse	60	4-8
Swine	70-100	5-8
Dog	100	-
Poultry	100	10-13

Table 4: Tolerance level of fluoride in feed (DM basis) and water for animals.

Source: NRC (1974); Shupe., *et al.* (1984); Swarup and Dwivedi (2002).

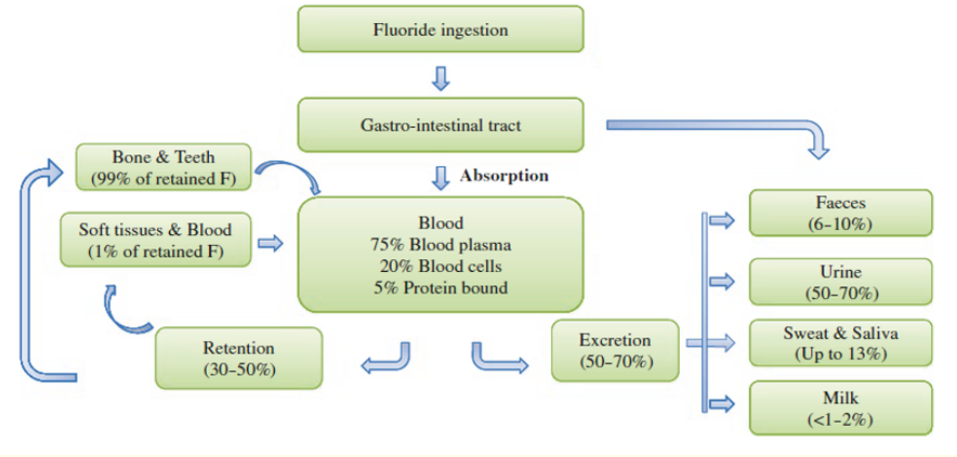

Figure 2: Fluoride metabolism in animal after oral intake.

Source: [13]

Analysis of fluoride

Estimation of fluoride concentration in environmental and biological sample is crucial for reliable and accurate diagnosis of fluoride toxicity. Fluoride analytical techniques such as titration, colorimetry, ion chromatography, potentiometric analysis, proton activation analysis, enzymatic analysis, and others have been develop [13]. A popular and globally accepted method for determining fluoride content is potentiometric analysis (an ion selective electrode).

Mitigation and prevention of fluorosis

The lack of a particular antidote and the irreversible nature of bone and dental lesions make managing fluoride toxicity difficult; thus, prevention remains the best strategy to reduce animal suffering. Surface water, rain-harvested water, or defluorinated groundwater should be supplied for drinking to animals in hydro-fluorosis-endemic areas. The Nalgonda process, the use of activated alumina, KRASS technology, reverse osmosis, distillation, and electrolysis are techniques of defluorination, but infrastructure, technical skill, and high operating costs are key impediments to their application in animal husbandry [13]. Fluorosis symptoms can be alleviated by providing supplements of various minerals, vitamins, antioxidants, and herbal products. Calcium carbonate, boron, aluminium salt and magnesium metasilicate are given intravenously to neutralize residual fluorine in the GI tract. Mineral supplements should not include more than 2% of the total grain ration. For prevention of chronic fluorosis, 30 gms of aluminium sulphate or higher doses should be given daily [39]. Using innovative technologies to reduce industrial fluoride emissions and enforcing strict legislation can help protect animal health from industrial fluorosis. In order to effectively apply the numerous ameliorative and preventive strategies available for fluorosis in livestock's, public awareness must be raised, particularly in rural areas.

Conclusion

This review provides an overview of fluoride toxicity in animals, discussing its sources, forms, clinical symptoms, and factors influencing tolerance. It also highlights the need for public awareness and prevention strategies, particularly in rural areas.

Conflict of Interest

The authors declare that there is no conflict of interest.

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