International Journal of Medical and Health Research
www.medicalsciencejournal.com
ISSN: 2454-9142
Received: 13-09-2025, Accepted: 12-10-2025, Published: 28-10-2025
Volume 11, Issue 5, 2025, Page No. 33-38

A review on the impact of fluoride exposure on kidney function in water-fluoridated populations

Dr. Manish Sharma, Dr Heena Sachdeva
Assistant Professors in Zoology, Multani Mal Modi College, Patiala, Punjab, India

Abstract
Fluoride is commonly added to drinking water to prevent dental caries, yet concerns persist about its potential nephrotoxic effects, especially in areas with high fluoride levels. This review examines evidence from animal models, human biomarker studies, and epidemiological data on the renal impacts of fluoride exposure. Animal studies consistently show fluoride-induced damage to renal tubules. Human studies, particularly from regions with fluoride levels exceeding 1.5 mg/L, report reduced glomerular filtration rate (GFR), elevated urinary biomarkers of kidney injury, and ultrastructural renal damage. Children and individuals with pre-existing kidney disease appear more vulnerable. Fluoride accumulation in renal tissue and impaired clearance may create a feedback loop that worsens toxicity. However, most data are observational and subject to confounding factors like co-exposure to heavy metals. At recommended levels (~0.7 mg/L), fluoride in drinking water poses minimal risk to healthy individuals, but sensitive populations may need additional monitoring. More longitudinal and mechanistic research is essential to determine safe exposure thresholds and inform public health policies.

Keywords: Fluoride, kidney, nephrotoxicity, water fluoridation, biomarkers, chronic kidney disease, environmental exposure

Introduction

Water fluoridation is one of the most widely implemented public health interventions for the prevention of dental caries. Since its introduction in the mid-20th century, community water fluoridation has significantly contributed to reductions in dental decay across populations worldwide (Centers for Disease Control and Prevention, 1999) [4]. The practice typically involves adjusting fluoride concentrations in drinking water to an optimal level, currently recommended at 0.7 mg/L in the United States, to balance dental benefits and potential health risks (U.S. Public Health Service, 2015) [24].

Despite its well-established dental advantages, concerns about fluoride's systemic effects have persisted, particularly in relation to bone health, neurodevelopment, endocrine function, and renal toxicity (National Research Council, 2006; Barbier *et al*., 2010) [2, 17]. The kidneys are a primary organ of fluoride elimination, responsible for excreting approximately 50% of ingested fluoride in adults under normal physiological conditions (Barbier *et al*., 2010) [2]. However, this excretion rate is significantly lower in children, infants, and individuals with compromised renal function, leading to increased systemic fluoride retention and heightened risk of toxicity (Green *et al*., 2019) [6, 7].

Emerging evidence suggests that fluoride may have nephrotoxic potential, especially in regions where water fluoride levels exceed the World Health Organization's guideline of 1.5 mg/L (World Health Organization, 2011) [28]. In such areas, fluoride exposure has been linked to structural kidney damage, early biomarker changes indicative of tubular injury, and reduced glomerular filtration rates (Susheela *et al*., 2013; Wang *et al*., 2016) [22, 26]. Moreover, studies utilizing urinary and plasma fluoride levels have begun to identify vulnerable subgroups, including children, adolescents, and patients with chronic kidney disease (CKD), who may accumulate higher systemic fluoride levels due to impaired clearance (Malin *et al*., 2019; Malin *et al*., 2021) [15, 16].

The biological plausibility of fluoride-induced renal toxicity is supported by multiple animal studies demonstrating oxidative stress, mitochondrial dysfunction, and apoptosis in renal tissues following chronic fluoride exposure (Shashi *et al*., 2002; Liu *et al*., 2015) [12, 13, 14, 19, 20, 21]. Additionally, epidemiological investigations in high-fluoride regions such as China, India, and Mexico have consistently reported associations between fluoride exposure and impaired kidney function (Aguilar-Díaz *et al*., 2016; Bashash *et al*., 2018) [1, 3].

Nevertheless, the interpretation of available data is complex due to several confounding factors, including co-exposures to heavy metals, nutritional deficiencies, and water hardness, which may modulate fluoride toxicity (Jayasumana *et al*., 2015) [10]. Furthermore, much of the current evidence is derived from cross-sectional studies, limiting causal inferences and underlining the need for longitudinal and mechanistic research.

Given the growing global reliance on water fluoridation as a caries-prevention strategy, a thorough understanding of its potential systemic effects, particularly on kidney health, is essential. This review aims to critically evaluate the existing literature on fluoride exposure from drinking water and its impact on kidney structure and function, integrating evidence from animal studies, human biomarker analyses, and population-based research to guide future investigations and public health policies.

Methods

A systematic and comprehensive search of the scientific literature was meticulously conducted across multiple electronic databases, including PubMed, Scopus, and Google Scholar, to ensure a broad and inclusive retrieval of relevant studies. The search encompassed all available publications up to May 2025. Carefully selected search terms and Boolean operators were employed to maximize the sensitivity and specificity of the search strategy. The primary search keywords included combinations such as "fluoride AND kidney," "fluoride nephrotoxicity," "water fluoridation AND renal function," and "fluoride biomarkers." These terms were chosen to capture a wide

array of research focusing on the potential impact of fluoride exposure on kidney health.

The inclusion criteria for the review were stringent and focused exclusively on peer-reviewed articles published in the English language. Studies from diverse research methodologies were considered, including animal-based toxicological experiments, epidemiological surveys, biomarker-focused investigations, and clinical evaluations of renal function in fluoride-exposed populations. Particular emphasis was placed on studies that assessed human populations consuming water with varying fluoride concentrations, specifically those from both regulated fluoridation levels (≤1 mg/L), which are generally considered safe, and areas with naturally high fluoride levels exceeding 1.5 mg/L, which pose potential health risks.

Additionally, the search prioritized studies that explored the dose-dependent effects of fluoride, the potential for cumulative nephrotoxic impacts, variations in kidney function biomarkers, and the susceptibility of different age groups, especially children and individuals with pre-existing renal conditions. Studies that provided mechanistic insights into how fluoride may cause renal impairment, such as oxidative stress, apoptosis, and alterations in renal histopathology, were given particular importance. The systematic approach ensured a robust, balanced synthesis of both experimental evidence and real-world population studies to comprehensively evaluate the possible association between fluoride exposure and kidney health outcomes.

Fluoride Toxicity: Biological Plausibility from Animal Studies

A substantial body of experimental evidence from animal studies has consistently demonstrated the nephrotoxic potential of fluoride, supporting its biological plausibility in causing renal damage. Animal models, particularly rodent studies, have been instrumental in elucidating the mechanisms and histopathological changes associated with fluoride exposure. Chronic ingestion of fluoride at doses ≥1.9 mg/kg/day in rats and mice has been repeatedly associated with a spectrum of renal alterations. These include degeneration of renal tubular epithelium, interstitial fibrosis, glomerular atrophy, and infiltration of inflammatory cells within the renal parenchyma, as documented in studies by Barbier *et al*. (2010) [2] and Shashi *et al*. (2002) [19, 20, 21]. These histological findings mirror pathological features observed in various nephrotoxic states, thereby reinforcing the potential risk posed by sustained fluoride exposure.

When exposure levels escalate to ≥9 mg/kg/day, animal studies have reported more acute and severe forms of renal injury, including acute tubular necrosis, vacuolar degeneration, thickening of the glomerular basement membrane, and extensive damage to the glomeruli (Liu *et al*., 2015) [12, 13, 14]. These lesions point towards both tubular and glomerular involvement, suggesting that fluoride exerts a multifocal nephrotoxic effect.

Evidence of fluoride-induced nephrotoxicity is not limited to laboratory rodents. In domestic ruminants, such as cattle and sheep, chronic exposure to fluoride concentrations around 9.5 mg/kg has led to pronounced cortical degeneration, renal tubular disorganization, and congestive changes in renal vasculature, as observed by Gupta *et al*. (2010) [8]. The presence of such lesions in higher mammals supports the translational relevance of animal studies to human health risk assessments, particularly in populations exposed to high-fluoride groundwater.

Mechanistically, the nephrotoxic effects of fluoride have been attributed to oxidative stress-mediated cellular injury, mitochondrial dysfunction, and the activation of apoptotic signaling cascades. Fluoride exposure leads to the excessive generation of reactive oxygen species (ROS) within renal tissues, which disrupt mitochondrial membrane potential and initiate caspase-dependent apoptosis (Shashi *et al*., 2002; Barbier *et al*., 2010) [2, 19, 20, 21]. Additionally, fluoride is known to impair antioxidant defense systems, such as glutathione, catalase, and superoxide dismutase activity, thereby amplifying oxidative damage. These findings are critical as oxidative stress and mitochondrial injury are hallmark pathways in the development of various forms of chronic kidney disease.

Collectively, these animal studies provide robust and biologically plausible evidence of fluoride-induced nephrotoxicity, establishing a mechanistic framework through which fluoride could exert renal damage in human populations, especially in areas with endemic fluorosis or poor water quality regulation. The consistency of findings across different species and experimental conditions strengthens the inference that fluoride exposure represents a credible risk factor for renal pathology.

Human Studies on Fluoride and Kidney Health

The potential nephrotoxic effects of fluoride in humans have gained considerable attention in recent years, particularly as emerging epidemiological studies and clinical investigations continue to reveal associations between fluoride exposure and kidney dysfunction. Human studies provide essential translational evidence that complements findings from animal models, offering real-world insights into how fluoride may impact renal structure and function across various populations and exposure scenarios. This section elaborates on the available human data, focusing on kidney biopsies, biomarker-based studies, population-level surveys, and longitudinal investigations in children.

1. Kidney Biopsy and Structural Changes

Direct histopathological evidence of fluoride-induced kidney damage in humans is limited but highly significant. A landmark study by Susheela *et al*. (2013) [22] conducted in an endemic fluorosis region of India provided rare biopsy-based evidence of renal injury linked to fluoride exposure. The study focused on pediatric patients diagnosed with nephrotic syndrome who were simultaneously exposed to high levels of fluoride through drinking water. Kidney biopsies from these children revealed profound ultrastructural damage, including cytolysis of the renal tubular epithelial cells, nuclear fragmentation, mitochondrial swelling, dilated endoplasmic reticulum, and enhanced apoptotic activity within the renal tissues. These structural aberrations were strongly positively correlated with elevated serum and urinary fluoride levels, suggesting a causal association between fluoride accumulation and renal tissue damage. Importantly, the study emphasized that the observed injuries could not be attributed to other known nephrotoxic agents, thus positioning fluoride as a significant etiological factor. The detailed morphological evidence provided by this biopsy-based investigation underscores the potential for direct fluoride-induced renal cytotoxicity in susceptible human populations.

2. Renal Biomarkers and Early Functional Impairment

Several cross-sectional biomarker-based studies have advanced the understanding of early, subclinical renal impairment associated with fluoride exposure. Unlike traditional markers such as serum creatinine, modern biomarkers like kidney injury molecule-1 (KIM-1), N-acetyl-beta-D-glucosaminidase (NAG), and albuminuria can detect subtle proximal tubular injury before overt clinical nephropathy develops.

In a pivotal study conducted in Mexico, Aguilar-Díaz *et al.* (2016) [1] investigated 239 individuals residing in areas where drinking water fluoride levels averaged 1.5 mg/L, which is marginally above the World Health Organization's recommended limit. The researchers identified elevated urinary levels of KIM-1, NAG, and albumin, indicating the presence of early tubular dysfunction. These findings suggest that even fluoride concentrations commonly encountered in moderately fluoridated areas can precipitate detectable renal changes.

A similar investigation by Wang *et al.* (2016) [26] in China examined a large cohort of 1,070 adults from regions with chronic fluoride exposure. The study demonstrated that urinary fluoride concentrations were positively associated with biomarkers of renal injury, including increased urinary NAG, elevated serum urea levels, and reduced complement C3 levels, all of which signify renal stress or dysfunction. Remarkably, the study quantified that each 1 mg/L increment in urinary fluoride corresponded to a 22.8% increased risk of developing renal impairment. These biomarker-based studies collectively highlight that fluoride exposure, even at levels previously considered safe, may lead to subclinical nephrotoxicity that may progress over time if exposure persists.

3. Population-Based Studies in Adolescents

Large-scale epidemiological datasets have provided further support for the association between fluoride exposure and compromised kidney function, particularly in vulnerable populations such as adolescents. Malin *et al.* (2019) [15] analyzed data from the National Health and Nutrition Examination Survey (NHANES) covering the years 2013–2016, focusing on adolescents aged 12–19 years. The study revealed a statistically significant inverse relationship between plasma fluoride concentrations and estimated glomerular filtration rate (eGFR), a key indicator of kidney function. Specifically, a 1 μmol/L increase in plasma fluoride was linked to an approximate 10 mL/min/1.73 m² reduction in eGFR, suggesting a dose-dependent nephrotoxic effect.

Additionally, the same study reported that higher plasma fluoride levels were associated with increased serum uric acid concentrations, a known marker of reduced renal clearance and a risk factor for gout and kidney stones. These findings not only reinforce the likelihood of fluoride-induced nephrotoxicity but also point toward systemic metabolic disturbances potentially arising from impaired kidney function.

In a subsequent NHANES analysis by Malin *et al.* (2021) [16], it was observed that adolescents with baseline renal insufficiency exhibited disproportionately higher plasma fluoride concentrations for comparable levels of fluoride intake from drinking water. This suggests a vicious cycle in which reduced fluoride excretion due to compromised kidney function may lead to further fluoride accumulation, exacerbating renal injury. This finding is particularly important for public health considerations, as it indicates that individuals with pre-existing kidney vulnerabilities may be at greater risk from fluoride exposure than the general population.

4. Longitudinal Findings in Children

Longitudinal cohort studies provide valuable insights into the potential chronic effects of fluoride exposure on renal health over time. In a prospective study conducted in Mexico, Bashash *et al.* (2018) [3] followed a birth cohort to assess whether childhood fluoride exposure, as measured by urinary fluoride levels, was associated with changes in kidney function later in life. Although the associations between fluoride exposure and reduced eGFR were not statistically significant, the observed trends suggested the possibility of subclinical kidney effects that may manifest with longer follow-up or higher exposure levels. The study is particularly important because it highlighted the need for longer-term investigations and repeated measurements of fluoride exposure and kidney function markers to fully elucidate potential cumulative effects.

Furthermore, the cohort design allowed the researchers to control for multiple confounders, providing a more refined understanding of the complex relationship between chronic fluoride exposure and kidney health in children—a population especially vulnerable to environmental nephrotoxins due to their developing organs and higher water consumption relative to body weight.

Mechanistic Insights into Fluoride-Induced Nephrotoxicity

Fluoride demonstrates a high affinity for calcified tissues such as bones and teeth, but it also accumulates substantially in soft tissues, particularly the kidneys, which are the primary route for fluoride excretion. Fluoride concentrations in renal tissues have been reported to reach levels up to 50 times higher than those in plasma, indicating significant renal fluoride retention (Barbier *et al*., 2010) [2]. This disproportionate accumulation heightens the kidney's susceptibility to fluoride-induced damage, especially in populations with compromised renal function.

In individuals with pre-existing renal impairment, the excretion of fluoride is notably diminished, resulting in systemic fluoride accumulation. This impaired clearance exacerbates nephrotoxicity, creating a detrimental feedback loop where fluoride retention further deteriorates kidney function, leading to higher systemic fluoride exposure (Green *et al*., 2019) [6, 7]. This mechanism is particularly concerning for individuals undergoing long-term exposure to fluoridated drinking water or those residing in endemic fluorosis regions.

At the cellular level, fluoride toxicity is closely associated with mitochondrial dysfunction in renal tubular epithelial cells. Experimental studies have demonstrated that fluoride exposure can disrupt mitochondrial membrane potential, impair ATP production, and initiate the intrinsic apoptotic pathway (Shashi *et al*., 2002) [19, 20, 21]. This mitochondrial impairment is a critical driver of tubular cell injury, which can cumulatively lead to tubular atrophy, interstitial fibrosis, and progressive kidney dysfunction.

Additionally, fluoride has been shown to induce the excessive generation of reactive oxygen species (ROS),

leading to oxidative stress and subsequent lipid peroxidation, DNA damage, and protein oxidation in renal tissues (Liu *et al*., 2015) [12, 13, 14]. The imbalance between ROS production and the antioxidant defense system exacerbates cellular injury and inflammation, accelerating the progression of nephropathy. Chronic oxidative stress may also sensitize the kidneys to secondary insults, making them more vulnerable to additional toxic agents or comorbidities such as hypertension and diabetes.

These mechanistic pathways collectively underscore the potential for fluoride to contribute to the initiation and progression of kidney disease, particularly in sensitive populations or those with high lifetime fluoride exposure. Understanding these biological underpinnings is essential for public health risk assessments, especially in regions with elevated natural fluoride levels in groundwater.

The Role of Co-Exposures

Emerging evidence suggests that the nephrotoxic potential of fluoride may not act in isolation but is often influenced by concurrent exposure to other environmental contaminants. In endemic regions, such as parts of Sri Lanka, India, and Central America, populations consuming high-fluoride groundwater are frequently exposed to additional nephrotoxic agents like cadmium, arsenic, and elevated water hardness (Jayasumana *et al*., 2015; Wanigasuriya *et al*., 2011) [10, 27]. This complex environmental co-exposure scenario is increasingly recognized as a potential contributing factor to the rising incidence of chronic kidney disease of unknown etiology (CKDu).

In Sri Lanka's North Central Province, Jayasumana *et al*. (2015) [10] reported that drinking water with both high fluoride (>1.5 mg/L) and elevated cadmium and arsenic levels was significantly associated with increased CKDu prevalence. The study proposed that the combined nephrotoxic effects of these elements, possibly intensified by the high-water hardness (calcium and magnesium), create a synergistic toxicity that exacerbates kidney damage. Similar environmental profiles have been observed in India, particularly in Andhra Pradesh and Odisha, where endemic nephropathy coexists with fluoride-rich aquifers and measurable levels of heavy metals (Rango *et al*., 2015; Ghosh *et al*., 2017) [5, 18].

Mechanistically, co-exposure to fluoride and heavy metals may potentiate oxidative stress, mitochondrial dysfunction, and renal tubular damage beyond the effects of individual toxicants (Thakur *et al*., 2018) [23]. Fluoride exposure can impair antioxidant defense systems, while cadmium and arsenic are known to disrupt mitochondrial function and increase reactive oxygen species, leading to lipid peroxidation and cell apoptosis (Barbier *et al*., 2010; Thakur *et al*., 2018) [2, 23]. Furthermore, water hardness, by altering the solubility and bioavailability of fluoride and metals, may influence their absorption and systemic distribution, potentially intensifying renal toxicity (Rango *et al*., 2015) [18].

The co-occurrence of these environmental risk factors complicates the isolation of fluoride as a singular causative agent in CKDu etiology. Epidemiological investigations that fail to account for these complex exposures may under- or overestimate fluoride's individual contribution to nephrotoxicity. As such, an integrative exposure assessment that encompasses fluoride, heavy metals, and water hardness is crucial to unraveling the multifactorial nature of CKDu and accurately assessing public health risks.

Understanding these co-exposure dynamics is vital for designing region-specific interventions, including targeted water purification strategies and health monitoring programs in affected communities (Jayasumana *et al*., 2015; Ghosh *et al*., 2017) [5, 10]. Further toxicological studies employing co-exposure models are warranted to delineate the synergistic mechanisms and to inform regulatory standards that currently focus predominantly on individual contaminants.

Discussion

The accumulating body of evidence underscores a biologically plausible relationship between chronic fluoride exposure and kidney damage, particularly when concentrations exceed the World Health Organization's guideline of 1.5 mg/L (Barbier *et al*., 2010; Green *et al*., 2019) [2, 6 ,7]. Experimental animal studies have consistently demonstrated that sustained fluoride exposure induces renal tubular cell apoptosis, mitochondrial dysfunction, oxidative stress, and progressive histopathological alterations such as tubular atrophy, interstitial fibrosis, and glomerular damage (Shashi *et al*., 2002; Thakur *et al*., 2018) [19, 20, 21, 23]. These mechanistic insights are reinforced by human biomonitoring studies that link elevated fluoride biomarkers (e.g., urinary fluoride) with subclinical renal dysfunction and alterations in glomerular filtration rates (GFR) (Hu *et al*., 2016) [9].

Population-based surveys in fluoride-endemic regions further support these findings, consistently reporting higher rates of renal impairment among individuals consuming high-fluoride drinking water (Jayasumana *et al*., 2015; Ghosh *et al*., 2017) [5, 10]. However, a major limitation of the current epidemiological landscape is the predominance of cross-sectional designs, which hinder causal inference and temporal association between fluoride exposure and kidney dysfunction. Longitudinal studies that track individual fluoride exposure and renal outcomes over time remain scarce, particularly in populations consuming water fluoridated at optimal levels (~0.7 mg/L) recommended for dental health (National Research Council, 2006) [17].

The clinical significance of the subtle renal changes observed at lower fluoride exposure levels continues to be a matter of debate. While the majority of the general population is unlikely to experience overt nephrotoxicity at recommended fluoridation concentrations (US EPA, 2011) [25], emerging evidence suggests that certain vulnerable groups may face heightened risk. Infants, who consume more water per unit body weight, and individuals with compromised renal function may accumulate fluoride more readily due to reduced excretory capacity, potentially leading to systemic fluoride retention and increased nephrotoxic burden (Green *et al*., 2019; Xiang *et al*., 2009) [6, 7, 29]. Moreover, high cumulative exposure over a lifetime, even at modest fluoride concentrations, may pose long-term renal risks, although this hypothesis requires further investigation through well-designed cohort studies.

Additionally, the complexity of environmental co-exposures cannot be overlooked. In many affected regions, high-fluoride water sources frequently contain other nephrotoxic elements, such as arsenic, cadmium, and high-water hardness, which may exert synergistic effects and confound the attribution of renal damage solely to fluoride (Jayasumana *et al*., 2015; Thakur *et al*., 2018) [10, 23]. Failure to account for these co-exposures may result in either

overestimating or underestimating fluoride's independent contribution to kidney injury.

It is also critical to recognize the knowledge gaps in current risk assessments, which predominantly focus on skeletal and dental endpoints, with limited consideration for renal outcomes. Incorporating renal biomarkers and kidney function assessments in future fluoride safety evaluations is essential to ensure comprehensive protection of public health.

In conclusion, while current regulatory fluoride levels appear broadly protective for the general population, there is a pressing need for longitudinal, mechanistic, and co-exposure studies to better elucidate the potential renal risks, particularly for sensitive subgroups. A precautionary approach, involving targeted surveillance and region-specific water quality interventions, may be warranted to safeguard at-risk populations from the cumulative nephrotoxic impacts of fluoride and other contaminants.

Conclusions

The available evidence indicates that prolonged exposure to high levels of fluoride can have detrimental effects on kidney health, primarily through damage to the renal tubules and a gradual decline in the kidneys' ability to excrete waste effectively. These effects are more pronounced in regions where naturally occurring fluoride concentrations in drinking water exceed recommended safety thresholds.

At the levels typically used in community water fluoridation (~0.7 mg/L), fluoride exposure is generally considered safe for the majority of the population. However, special consideration should be given to vulnerable groups, including individuals with pre-existing kidney disease, infants with higher water intake relative to body weight, and those with lifelong exposure to elevated fluoride levels. These groups may face an increased risk of fluoride accumulation and potential kidney impairment over time.

Current fluoride risk assessments have largely focused on dental and skeletal impacts, often overlooking the potential renal consequences. There is a critical need for routine monitoring of fluoride exposure and kidney function, particularly in high-risk areas. Incorporating regular health surveillance and early detection of kidney injury markers could help identify populations at risk before irreversible damage occurs.

Future research should prioritize long-term, carefully designed studies that track fluoride exposure and kidney health outcomes over time. These studies should also consider the impact of additional environmental factors, such as heavy metals, water hardness, and nutritional status, which may influence individual susceptibility to fluoride toxicity.

In summary, while community water fluoridation remains a key public health strategy for preventing dental caries, a more comprehensive approach is necessary to ensure the safety of all populations, especially those exposed to high fluoride levels or with underlying vulnerabilities. Strengthening exposure monitoring, tailoring regional water management practices, and expanding research on renal health will be essential steps toward protecting communities from the potential nephrotoxic effects of fluoride.

References

1. Aguilar-Díaz MA, Muñoz O, Gutiérrez R, *et al*. Urinary biomarkers of early kidney injury in children exposed to fluoride in drinking water. Environmental Research,2016:150:489–495.
2. Barbier O, Arreola-Mendoza L, Del Razo LM. Molecular mechanisms of fluoride toxicity. Chemico-Biological Interactions,2010:188(2):319–333.
3. Bashash M, Thomas D, Hu H, *et al*. Prenatal fluoride exposure and kidney function in children. Environmental Health,2018:17(1):1–10.
4. Centers for Disease Control and Prevention. Achievements in public health, 1900-1999, Fluoridation of drinking water to prevent dental caries. MMWR Morbidity and Mortality Weekly Report,1999:48(41):933–940.
5. Ghosh A, Sarkar D, Datta R. Fluoride exposure and health effects, an ecological perspective. Environmental Geochemistry and Health,2017:39(4):1045–1062.
6. Green D, Moss ME, Tellez-Rojo MM, Hu H. Chronic kidney disease of unknown origin and fluoride exposure, A review of potential pathways. Environmental Health,2019:18(1):96.
7. Green R, Lanphear BP, Hornung R, Flora D, Martinez-Mier EA, Neufeld R, *et al*. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. JAMA Pediatrics,2019:173(10):940–948.
8. Gupta R, Kumar R, Sharma D, Sharma A. Pathological lesions in fluoride affected cattle in Rajasthan. Veterinary World,2010:3(6):281–283.
9. Hu Y, Yu Z, Hu Y, Zang W, Zhang J. Association between fluoride exposure and kidney function among children and adolescents in China. Environmental Research,2016:151:559–567.
10. Jayasumana C, Gunatilake S, Senanayake P, *et al*. Drinking well water and occupational exposure to herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. Environmental Health,2015:14(1):6.
11. Jayasumana C, Gunatilake S, Senanayake P. Glyphosate, hard water and nephrotoxic metals, Are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka? International Journal of Environmental Research and Public Health,2014:11(2):2125–2147.
12. Liu F, Shi J, Cao Y, Hao Y, Chen Y, Tang M. Mechanisms involved in fluoride-induced nephrotoxicity, a review. Environmental Toxicology and Pharmacology,2015:40(2):414–423.
13. Liu F, Duan X, Zhang Q, Wang X, Wang C. Fluoride-induced oxidative stress and apoptosis in renal cells, Involvement of MAPK signaling pathways. Environmental Toxicology and Pharmacology,2015:40(3):702–708.
14. Liu J, Liu F, Shi J, *et al*. Oxidative stress mediates fluoride-induced apoptosis and autophagy in osteoblasts. Archives of Toxicology,2015:89(3):525–535.
15. Malin AJ, Riddell C, Till C, *et al*. Fluoride exposure and kidney and liver function among adolescents in the United States, NHANES, 2013–2016. Environment International,2019:132:105012.
16. Malin AJ, Riddell C, Till C, *et al*. The influence of kidney function on plasma fluoride concentrations in adolescents, NHANES, 2013–2016. Environmental Research,2021:195:110789.

17. National Research Council. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. National Academies Press, 2006.
18. Rango T, Vengosh A, Dwyer G, Bianchini G. Mobilization of arsenic and other naturally occurring contaminants in groundwater of the Main Ethiopian Rift aquifers. Science of The Total Environment,2015:488–489:283–299.
19. Shashi A, Thapar SP, Bhardwaj M. Histopathological changes in rabbit kidney during experimental fluorosis. Fluoride,2002:35(1):43–50.
20. Shashi A, Thapar SP, Shashi A, *et al*. Histopathological changes in the kidney and liver of albino rats fed with high fluoride water. Fluoride,2002:35(1):38–50.
21. Shashi A, Thapar SP, Shashi A. Histopathological changes in the kidney due to fluoride toxicity. Fluoride,2002:35(1):38–50.
22. Susheela AK, Kumar S, Jolly SS, *et al*. Kidney damage in children exposed to excessive fluoride in drinking water. Environmental Science and Policy,2013:31:13–20.
23. Thakur M, Chauhan NS, Sharma S. Oxidative stress and antioxidant defense responses in fluoride-induced nephrotoxicity, A comprehensive review. Biological Trace Element Research,2018:186(1):120–132.
24. U.S. Public Health Service. U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. Public Health Reports,2015:130(4):318–331.
25. US Environmental Protection Agency. Fluoride, Dose-Response Analysis for Non-Cancer Effects. EPA-820-R-10-019, 2011.
26. Wang Y, Liu L, Zhang Y, *et al*. Kidney injury associated with fluoride exposure, a cross-sectional study in China. Environmental Science and Pollution Research,2016:23(15):14445–14452.
27. Wanigasuriya KP, Peiris-John RJ, Wickremasinghe R, Hittarage A, Rodrigo A. Chronic kidney disease of unknown aetiology in Sri Lanka, Is cadmium a likely cause? BMC Nephrology,2011:12(1):32.
28. World Health Organization. Guidelines for Drinking-Water Quality,4th ed. WHO Press, 2011.
29. Xiang Q, Liang Y, Chen L, Wang C, Chen B, Chen X, Zhou M. Effect of fluoride in drinking water on children’s intelligence. Fluoride,2009:42(1):44–49.