COMBINED TOXICITY OF FLUORIDE AND CADMIUM

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ABSTRACT: Fluoride (F-) and cadmium (Cd) are toxicants found ubiquitously in the human environment. The aim of this review was to identify and characterize studies that attempted to determine the combined toxicity of F- and Cd. The effects of F- and Cd on liver and kidney (with a special focus on chronic kidney disease of unknown etiology), bone, tooth enamel, dental caries, and brain were taken into consideration. Based on the results of the studies described in this review, various types of combined toxicity of F- and Cd might occur: additive, synergistic, or antagonistic, with the latter two being true interactions. However, the type of combined action occurring seems to depend on many factors, such as which toxic effect is considered, the dose levels of F- and Cd and their dose ratio, exposure duration, presence of other elements, etc. Moreover, when analyzing the combined toxic effects of F- and Cd, the possible interactions of these toxicants with other elements (e.g., fluoride with aluminum and arsenic; cadmium with lead, arsenic, zinc, selenium, and calcium) should also be taken into consideration. We also may not exclude the independent action of F- and Cd on some selected functions/health outcomes. Due to the huge gaps in knowledge, additional studies are required to address this important public health issue, i.e., the combined effects of exposure to these common environmental toxicants, especially among people with high exposure to these elements.

Keywords: Cadmium; Fluoride; Toxicity.

INTRODUCTION

Fluoride (F-) and cadmium (Cd) are toxicants found ubiquitously in human environment. The main sources of exposure to Cd include ingestion of food, inhalation of ambient air, ingestion of drinking water, and tobacco smoking, while for F- they are ingestion of drinking water and non-dairy beverages, consumption of some foodstuffs, the use of F-containing dental products (including toothpastes), and inhalation of indoor air.

Cd and F- coexist in the environment. For example, F- and Cd co-occur in drinking water. Mullenix demonstrated that Cd is found as a contaminant of some F- additives used for drinking water fluoridation, such as hydrofluorosilicic acid. However, the Cd concentration was below the established method detection limit (MDL) in 23–25% of raw samples of the additives and it remained insignificant. Similarly, according to the NSF Fact Sheet on Fluoridation Products (2013) none of 216 samples from 2007–2011 had detectable levels of Cd as compared to 1% of samples from 2000–2006 with detectable Cd levels. The majority of fluoridation products do not contribute measurable amounts of Cd to the drinking water.

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Fluoride and cadmium have some features in common, i.e., a broad distribution in the environment, similar sources of exposure, a long half-life in the human organism, a high level of toxicity to humans, similar target organs for their toxicities (e.g., liver, kidney, and brain), and similar clinical symptoms in the teeth and bones of people intoxicated.\textsuperscript{1,2,7-10}

Various types of combined toxic action of metal compounds can be identified: independent action, additivity, synergism, potentiation, and antagonism.\textsuperscript{11} A number of reviews have been published that dealt with the toxicity of Cd\textsuperscript{7,12-17} and/or the toxicity of F\textsuperscript{−}\textsuperscript{8,9,12,13,17,18} However, to our knowledge, there is no review dedicated solely to the effects of the combined action of these elements. Therefore, the aim of this review was to identify and characterize studies that attempted to determine the combined toxicity of F\textsuperscript{−} and Cd, including interactions between them. The following aspects will be reviewed: the effects of F\textsuperscript{−} and Cd on liver and kidney (with a special focus on chronic kidney disease of unknown etiology), bone, tooth enamel, dental caries, and the brain and cognitive functions.

**HEPATIC AND RENAL EFFECTS**

Zhang et al. examined the chronic effects of Cd and F\textsuperscript{−} on liver and kidney function in male rats.\textsuperscript{19} Animals were exposed to Cd in a dose of 50 mg/L or F\textsuperscript{−} in a dose of 100 mg/L or to a combination of both elements in drinking water for 12 weeks. The following parameters were assessed: serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities (a measure of liver function), \(\beta_2\)-microglobulin and albumin in urine (a measure of kidney injury), and superoxide dismutase (SOD) activity and malondialdehyde (MDA) level in kidney and liver (a measure of oxidative stress). Significantly higher serum ALT activity was found in the group of rats treated with either F\textsuperscript{−} or Cd as compared to the control. The effect of co-exposure to F\textsuperscript{−} and Cd on ALT activity appeared to be synergistic.\textsuperscript{19} Urinary \(\beta_2\)-microglobulin levels were significantly higher in the F\textsuperscript{−} group and in the Cd group compared to the control group. The combined action of Cd and F\textsuperscript{−} resulted in a significantly higher \(\beta_2\)-microglobulin content in the combination group as compared to the either F\textsuperscript{−} or the Cd groups.\textsuperscript{19} Exposure to either F\textsuperscript{−} or Cd caused significantly decreased SOD activities and significantly increased MDA levels in both the kidney and liver of the rats as compared to the control group. Combined exposure to Cd and F\textsuperscript{−} resulted in significantly lower SOD activities and significantly higher MDA content in the kidney and liver as compared to the control, F\textsuperscript{−}, and Cd groups.\textsuperscript{19} Based on these results and histological analyses, the authors came to the conclusion that combined exposure to Cd and F\textsuperscript{−} caused more severe liver and kidney damage as compared to Cd or F\textsuperscript{−} exposure alone.\textsuperscript{19}

In another study, Adachi et al. examined the acute toxicity of cadmium fluoride (CdF\textsubscript{2}) after intravenous administration in rats.\textsuperscript{20} In the mentioned study, the following parameters were assessed: serum hepatic enzyme activities, serum glucose concentration, blood urea nitrogen (BUN) and creatinine concentration, serum electrolyte levels such as potassium, calcium and phosphates, and urine volume.\textsuperscript{20} The authors demonstrated that CdF\textsubscript{2} in a dose of 2.67 mg/kg body...
weight (bw) and 4.01 mg/kg bw caused severe hepatic damage as confirmed by significantly increased activities of AST and ALT and decreased serum glucose concentration compared to the saline group.\textsuperscript{20} CdF\textsubscript{2} administration resulted also in renal injury as confirmed by increased BUN and decreased urine volume compared to the saline group. However, the acute renal failure due to CdF\textsubscript{2} exposure was unlikely to result from the effects of F\textsuperscript{-}, because the BUN and urine volume in the NaF group and in the saline group did not differ significantly. CdF\textsubscript{2} exposure caused also abnormal changes in the serum electrolytes, which was probably the effect of ionized F.\textsuperscript{20} In the conclusion of their study, Adachi et al. are of the opinion that CdF\textsubscript{2} has the strongest lethal and hepatic toxicity among all Cd-containing compounds.\textsuperscript{20}

Another issue worth discussing is the potential role of Cd and F\textsuperscript{-} exposure in drinking water in causation of chronic kidney disease of unknown etiology (CKDu).\textsuperscript{5,21-24} Wasana et al. demonstrated a strong positive correlation between the presence of F\textsuperscript{-}, Cd, and water hardness in drinking water and the prevalence of CKDu in Sri Lanka, indicating the synergistic effect of these factors for the etiology of the disease.\textsuperscript{5} The other studies gave divergent results. Jayatilake et al. conducted a cross-sectional study to determine the prevalence of CKDu and the risk factors for that disease.\textsuperscript{22} Based on the obtained results, i.e., significantly higher urinary excretion of Cd in CKDu patients and the dose-effect relationship between Cd level in urine and CKDu stages, the authors suggested that exposure to Cd was a risk factor for the pathogenesis of CKDu.\textsuperscript{22} However, Chandrajith et al. exclude Cd as a contributing factor to CKDu and show that no single geochemical parameter could be clearly and directly related to CKDu in Sri Lanka. The authors suggest that a unique hydrogeochemistry of drinking water might be closely associated with the incidence of disease.\textsuperscript{21} Rango et al. suggest the presence of non-water sources of toxic chemicals such as Cd, As, Pb, and U in the region from food and other sources (for example tobacco consumption).\textsuperscript{23} Wanigasuriga, in a review article, concludes that the etiology of CKDu in Sri Lanka is multifactorial, with one or more environmental agents being involved in addition to genetic predisposition.\textsuperscript{24}

**BONE AND DENTAL EFFECTS**

As regards the effects of F\textsuperscript{-} and Cd in combination on bone, only one study can be identified in literature so far,\textsuperscript{25} although the influence of either Cd or F\textsuperscript{-} alone on bone was discussed in other studies.\textsuperscript{10,12,13,17,26-29} Tang et al. conducted a pilot study in a fluorotic rural area of China and demonstrated that naturally occurring Cd in areas with endemic fluorosis associated with coal combustion acts as a critical but hidden health hazard that may underlie the risk of F\textsuperscript{-}.\textsuperscript{10} Since the symptoms of either F\textsuperscript{-} or Cd intoxication are similar in bone and teeth, the occurrence of dental and skeletal health problems in the population from the study area has been explained entirely by fluorosis, without taking into consideration the contribution of Cd.\textsuperscript{10} For example, half of the urine samples of local residents from the study area had F\textsuperscript{-} levels within the
normal range for a non-exposed population, whereas all the urine samples had Cd levels higher than in the control and non-exposed population.\textsuperscript{10}

Chen et al. examined the effects of subchronic (12 weeks) exposure to F\textsuperscript{−} in a dose of 20 mg/L, Cd in a dose of 50 mg/L, or their combination via drinking water on bone in male rats.\textsuperscript{25} The authors suggested that F\textsuperscript{−} might influence the Cd absorption in the gut, since the blood Cd level of rats treated with F\textsuperscript{−} and Cd in combination was higher than in rats treated with Cd only. The vertebral bone mineral density (BMD) of rats exposed to Cd decreased significantly (by about 9\%) compared to the control. The BMD in rats exposed to F\textsuperscript{−} increased insignificantly (3\%) relative to control. However, the BMD of rats co-exposed to both F\textsuperscript{−} and Cd was significantly higher as compared to rats exposed to Cd only.\textsuperscript{25} Based on the results presented above, one can suggest that there is an antagonistic interaction between Cd and F\textsuperscript{−} in their effects on BMD. The authors conclude that F\textsuperscript{−} could reverse the decrease of vertebral BMD caused by Cd.\textsuperscript{25}

Chen et al. also assessed the mechanical property of the femur, i.e., bending strength, bending load, and elastic modulus. Exposure to F\textsuperscript{−} and Cd, either alone or in combination, resulted in a worsening of all the analyzed parameters relative to the control. The combined exposure to F\textsuperscript{−} and Cd slightly decreased the bending strength and elastic modulus of femur compared to rats exposed to Cd alone.\textsuperscript{25} The serum levels of tartrate-resistant acid phosphatase 5b (Tracp-5b), measured by the enzyme immunoassay method, in rats exposed to Cd and F\textsuperscript{−} or their combination, were significantly higher than in the control group. The Tracp-5b level in the Cd+F\textsuperscript{−} group was higher than in the F\textsuperscript{−} or Cd groups, indicating excessive osteoclast formation and bone resorption.\textsuperscript{25} One can speculate on the occurrence of an additive effect of Cd and F\textsuperscript{−} on serum Tracp-5b levels.

Exposure to F\textsuperscript{−} and Cd is one of the environmental risk factors for osteoporosis and osteomalacia.\textsuperscript{9,12,28,29} Kakei et al. examined the effect of Cd ions on crystal formation in developing rat tooth enamel.\textsuperscript{28} Three-week-old male rats were exposed to Cd in a dose of 100 mg/L via drinking water for 5 weeks. Since the basic mechanism of crystal formation is the same in enamel, dentin, and bone, the results can be extrapolated to bone.\textsuperscript{28} The authors demonstrated Cd-induced perforations in the developing tooth enamel and concluded that Cd inhibited the crystal nucleation process.\textsuperscript{28} Moreover, the authors found that the catalytic activity of carbonic anhydrase, a critical enzyme in the initiation of the crystal nucleation process, in the Cd-exposed rats declined significantly to 30\% of that in the control rats.\textsuperscript{28} Kakei et al. concluded that impaired mineralization may be one of the causal factors of osteoporosis.\textsuperscript{28}

In another study, Kakei et al. investigated the effects of F ions on crystal formation in rat hard tissues.\textsuperscript{26} Similarly to Cd, F ions were found to interrupt the crystal nucleation process.\textsuperscript{26} Fluoride, even at low concentrations, interfered with the synthesis of carbonic anhydrase, thus indirectly affecting crystal formation.\textsuperscript{26} Kakei et al. suggested that F\textsuperscript{−} intake has harmful effects on both tooth and bone formation,\textsuperscript{26} and questioned the use of F\textsuperscript{−} in the treatment of osteoporosis, since exposure to F\textsuperscript{−} might accelerate osteoporotic changes in postmenopausal women.\textsuperscript{29}
Kakei et al. also compared the harmfulness of F⁻ and Cd on the crystal nucleation process of developing rat tooth enamel.²⁷ Rats received water containing either F⁻ (2 mg/L) or Cd (20, 40, and 100 mg/L). The authors demonstrated similar harmfulness of 2 mg/L F⁻ and 40 mg/L Cd on the crystal nucleation process, suggesting that F⁻ harmfulness to hard tissue formation was 20 times greater than that of Cd.²⁷ However, it is worth noting the other studies indicating that F⁻, apart from some toxic effects at high doses, might be beneficial for bone (or hard tissues) at low doses.¹²,¹³ Taking into consideration the results of the studies discussed in this review, we speculate that the combined toxic action of F⁻ and Cd, in terms of bone and tooth formation, might be additive, especially at higher doses of these agents.

**EFFECTS ON DENTAL CARIES**

Another aspect of a possible interaction between F⁻ and Cd could be their effect on dental caries. In 1980, Shearer et al. investigated the effect of Cd on caries and the cariostatic properties of F⁻ in rats.³⁰ In the first experiment, the following doses of Cd (as cadmium chloride) were administered to rats at their tooth developmental period: 0.25, 0.50, and 0.75 mg Cd/kg bw.³⁰ The experiment demonstrated the caries-promoting effect of Cd in female rats: the number of carious lesions was proportional to the Cd dose.³⁰ In the second experiment, the effects of developmental Cd on the cariostatic properties of post-developmental F⁻ (15 mg F⁻/L added to drinking water of pups after weaning) were examined.³⁰ For the first time, the interaction between Cd and F⁻ on the caries scores was shown: Cd exposure during tooth development caused partial negation of caries prevention by F⁻ in both male and female rats, i.e., enamel caries scores in the F⁻+0.50 mg Cd/kg bw group and buccal and enamel caries scores in the F⁻+0.75 mg Cd/kg bw group were significantly higher as compared to the F⁻ groups.³⁰ Based on the results obtained, one can suggest that the effect of Cd and F⁻ on caries scores involves the occurrence of an antagonistic interaction between Cd and F⁻.

In another study, Shearer et al. investigated the effects of post-developmental exposure to Cd on caries and the cariostatic properties of F⁻ in rats.³¹ In one of the experiments, the authors demonstrated the lack of a significant influence of post-developmental Cd (30 and 50 mg/L in drinking water) on the number of carious lesions in male rats.³¹ The addition of 30 or 50 mg Cd/L to fluoridated (10 mg F⁻/L) drinking water did not alter significantly the cariostatic properties of F⁻.³¹ Based on the results of two studies by Shearer et al.,³⁰,³¹ the authors suggested that exposure to Cd during the period of tooth development is critical for caries promotion by Cd.³¹

In turn, in a cross-sectional study carried out among US children aged 6–12 yr, Arora et al. examined the association of environmental Cd exposure with dental caries.³² The authors found that such an exposure was significantly associated with caries scores in the deciduous teeth of children with low environmental tobacco smoke (ETS) exposure.³² An interquartile range (IQR) increase in creatinine-corrected Cd concentrations (0.21 µg/g creatinine) corresponded to a 30% increase in the odds of having experienced caries (prevalence odds ratio (OR))
Combined toxicity of fluoride and cadmium

Olszowski, Sikora, Chlubek

= 1.30; 95% CI, 1.01–1.67). The authors of that study were concerned that the consumption of fluoridated water might be the confounding factor for the observed association. However, based on sensitivity analyses, it appeared unlikely that the differences in water fluoridation could explain the observed association between Cd exposure and dental caries experience.

**NEUROTOXIC EFFECTS**

Another problem of F⁻ and Cd toxicity of particular concern, might be their potential combined neurotoxic effects. Cd and F⁻ were found to be neurotoxic. Since these two toxicants might reach the fetus/infant/child via different routes (mother’s milk, maternal blood or drinking water, and food and air later in life), and no barrier (such as the placenta, mammary gland, or blood-brain barrier) offers complete protection from their exposure, they may accumulate in brain resulting in neurotoxic effects. Unfortunately, to our knowledge, none of studies examined the combined neurotoxic effects of Cd and F⁻. We were able to identify only studies that concentrated on either the neurotoxic effects of cadmium or the neurotoxic effects of fluoride.

A very important issue is the suspected developmental neurotoxicity of Cd and F⁻. Choi et al. conducted a systematic review and meta-analysis of published studies to assess the effect of exposure to F⁻ on children’s neurodevelopment. The authors included 27 eligible epidemiological studies in their meta-analysis. They found the standardized weighted mean difference in IQ scores between the exposed and the reference populations of children, across studies that gave the average difference in standard deviations (SDs), was −0.45 SDs (95% CI: −0.56, −0.35) using a random-effects model, which means that children living in areas with a high F⁻ exposure had significantly lower IQ scores as compared to children living in low-F⁻ areas. For commonly used IQ scores with a mean of 100 and a SD of 15, 0.45 SDs is equivalent to 6.75 points (rounded to 7 points). The results therefore showed an average IQ decrement of about 7 points in children with increased F⁻ exposure and point to the possibility of adverse effects of F⁻ exposure on children’s neurodevelopment. Such result also raises questions about the legitimacy and safety of drinking water fluoridation in some areas of the world.

Rodriguez-Barranco et al. conducted a systematic review and meta-analysis to evaluate the association of exposure to Cd with neurodevelopment and behavioral disorders in children. Of the six studies that met the authors’ inclusion criteria, only two found such association. However, these studies were of high methodological quality. Tian et al. in a prospective cohort study demonstrated a lower full-score IQ and performance IQ at 4 years of age in children who had higher concentrations of Cd in the cord blood at birth. Bao et al. in a cross-sectional study found that higher Cd levels in the hair of children, aged 7–16 years, were associated with a higher frequency of withdrawal, social problems, and attention problems.

Some authors link exposure to multiple environmental factors, including Cd and/or F⁻, with learning-memory ability depression, autism, cognitive
impairment, and neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease.

Ciesielski et al. assessed the association between urinary Cd concentrations among US children, aged 6–15 years, and reported learning disability. The authors found a significantly higher odds ratio for learning disability for children in the highest quartile of urinary Cd compared with those in the lowest quartile (OR=3.21, 95% CI: 1.43, 7.17), suggesting that children with higher urinary Cd levels may have an increased risk of learning disability. Kaoud and Kalifa examined the effects of exposure to F (100 mg NaF/L), Cd (100 mg CdCl₂/L), and arsenic (50 mg As₂O₃/L) in drinking water on the learning-memory ability in rats. The authors demonstrated that the learning-memory ability of rats treated with either fluoride, cadmium, or arsenic was depressed as compared to the control group.

Blaylock focuses in his review article on the role of excitotoxic food additives and suggests that they have synergistic effects with other environmental toxins (such as fluoride, lead, cadmium, and aluminum) on the pathological and biochemical changes characteristic of autism spectrum disorders (ASD). Roberts et al. examined the hypothesis that perinatal exposure to air pollutants is associated with ASD in the children of the participants of the Nurses’ Health Study II. They found that perinatal exposure to the highest versus the lowest quintile of Cd was significantly associated with ASD (OR=1.5). The authors of the cited study concluded that perinatal exposure to such air pollutants as diesel, lead, manganese, and cadmium may increase the risk of ASD.

Sanders et al. performed a literature search for epidemiological studies (published between 2009 and 2015) examining the association of prenatal and childhood metal exposures (mainly cadmium or manganese) and metal mixtures with children’s cognitive outcomes. The authors suggest that prenatal/childhood Cd exposure may be associated with poorer cognition but also emphasize the need for further studies. Emsley et al. evaluated the association of concentrations of several elements (cadmium, fluoride, calcium, iron, lead, selenium, and zinc) in drinking water with cognitive function among elderly residents (n=1016) in rural China. Fluoride showed a significant positive linear relation with cognitive function (p=0.02). However, the effect of F⁻ appeared to be insignificant after the adjustment for the other analyzed elements. Cd appeared not to exert a significant effect on cognitive function in univariate analysis, but the results from the mixed effects models demonstrated that the interaction between Cd and zinc on cognitive function was significant, even after the adjustment for the elements that were correlated with zinc.

CONCLUSION

To sum up, based on the results of the studies described in this review, various types of combined toxicity of Cd and F⁻ might occur: additive, synergistic, or antagonistic, with the latter two being true interactions. Such effects relate to the liver, kidney function (including CKDu), bones, teeth (including dental caries), and the brain. However, the type of combined action occurring seems to depend on
many factors, such as which toxic effect is considered, the dose levels of Cd and F– and their dose ratio, exposure duration, and the presence of other elements, etc. 43 Moreover, when analyzing the combined toxic effects of F– and Cd, the possible interactions of these toxicants with other elements (e.g., F– with aluminum and arsenic, Cd with lead, arsenic, zinc, selenium, and calcium) should also be taken into consideration.3,43-49 In addition, we may not exclude the independent action of F– and Cd on some selected functions/health outcomes. Due to the huge gaps in our knowledge, additional studies are required to address this important public health issue, i.e., the combined effects of exposure to these common environmental toxicants, especially among people with a high exposure to them.

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