Review

Journal of Food Safety and Hygiene

Journal homepage: http://jfsh.tums.ac.ir

The potentially nephrotoxic substances in food: a review

Parisa Sadighara[1], Sara Mohammadi[2]*, Namra Irshad[3], Melina Sadighara[4], Reyhaneh Ramezankhani[5]

[1]Division of Food Safety & Hygiene, Department of Environmental Health, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
[2]Department of Food Hygiene, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran.
[3]Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[4]Department of Pharmacology, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
[5]Department of Medicinal Chemistry, Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

ARTICLE INFO

Article history:
Received 05 Dec. 2022
Received in revised form
23 Aug. 2023
Accepted 29 Aug. 2023

Keywords:
Nephrotoxin;
Food;
Contamination;
Detection;
Mycotoxin

ABSTRACT

Food is the most unavoidable substance for contamination. It can be contaminated naturally and unintentionally by toxins. Some of these food contaminants contain nephrotoxins. For this purpose, a narrative review study was performed to identify the types of nephrotoxin found in food. This study was performed with the keywords; nephrotoxin, contamination, pollution, and food. The nephrotoxic toxins consist mainly of three categories of toxins; mycotoxins, heavy metals, and Aristolochic acids. About 70% of the selected studies investigated ochratoxin A (OTA). Evaluation of OTA contamination in baby food and infant formula should be considered. We can mention nickel, lead, and cadmium from the category of nephrotoxic heavy metals in food. Also, from compounds with radionucleotide activity, contamination with uranium was observed. Onions and carrots can be good biomarkers for contaminating an area with Aristolochic acids. Some of the nephrotoxins occurred more than permissible levels. Given that the kidneys are a vital organ of the body, human biomonitoring of nephrotoxins is recommended in countries where food is over the permissible level.

Citation: Sadighara P, Mohammadi S, Irshad N, Sadighara M, Ramezankhani R. **The potentially nephrotoxic substances in food: a review**. J Food Safe & Hyg 2023; 9 (3): 134-141.DOI: 10.18502/jfsh.v9i3.13905

1. Introduction

Exposure to food is permanent. Various chemical compounds are found in food. If foods contain nephrotoxic toxins, consumers may have chronic kidney disease (1).

Plastic packaging is used to increase the shelf life of food. However, these packages contain a variety of

---

*Corresponding author. Tel.: +98 3832324401
E-mail address: saramohamadi12@yahoo.com

chemicals that may migrate to the food. Some radioactive compounds, including Ra-226, K-40, and Th-232 can lead to chronic kidney disease (2).

Ra-226 and K-40 are indicators of natural radionuclides (3). Ochratoxin A (OTA) is produced by Penicillium and Aspergillus species, which have been confirmed to be nephrotoxin (4,5). The probable cause of Balkan endemic nephropathy was OTA. This toxin is one of the primary causes of urinary tract tumors (6). Contamination of this toxin is frequently reported in several foods, including cereals, baby food, dried fruits, and coffee (4, 5, 7). Citrinin is another mycotoxin that is nephrotoxic (8). Citrinin contamination is sometimes seen with OTA contamination because some fungal species, such as *Penicillium verrucosum*, can produce both (8). Chronic exposure to low doses of lead and cadmium can cause kidney damage (1). In addition, these two heavy metals have synergistic properties on the kidneys and lead to increased kidney damage (1). Aristolochic acid is another nephrotoxic compound found in plants. This compound causes chronic kidney damage and kidney cancer. Medicinal plants containing this compound are prohibited (9). It is also identified in some crops and vegetables, which also have a cumulative property (10). Furthermore, antibiotics are widely used in the treatment and prevention of diseases in livestock breeding. Therefore, it is possible that the residues of these compounds can be found in food of animal origin (11). Aminoglycoside antibiotics are nephrotoxic compounds (12). There is also scattered evidence of sodium benzoate nephrotoxicity (13). Uranium is one of the compounds of radionuclides that lead to serious damage to the kidneys. In some cases, water contamination with this dangerous compound is reported (14). The kidneys are the body's excretory organs and have several physiological roles in the body. Protecting this vital organ from toxins and chemicals is essential. This review aimed to describe the different types of nephrotoxic toxins that were isolated from food.

2. Materials and Methods

2.1. Strategy of search

The manuscripts in the English language were searched in July 2021. There was no limitation for time. The selected databases were Web of Science, PubMed, Scopus Science Direct, and Google Scholar. The keywords for searching were set: nephrotoxin AND contamination OR pollution AND food.

2.2. Inclusion and exclusion criteria

In this narrative review, the chosen papers were extracted. Inclusion criteria for this study included toxins which their renal toxicity was documented and measured in food by valid methods and their amount was announced. Studies that did not specify the nature of the food were excluded from this study. A significant percentage of nephrotoxic agents, ochratoxin A, were reported. Studies identifying ochratoxin-producing species were excluded.

3. The nephrotoxic agents, measurement and detection methods

The extracted data included the name of the first author, year of publication, type of food, type and amount of toxin, unit of measurement, and method of measurement (Table 1). According to the extracted data, the most reported nephrotoxic agent in food is OTA. Its measurement and detection methods were mainly HPLC and ELISA. Moreover, heavy metals were one of the next agents that were investigated in the studies (Table 1).

Table 1. The extracted data

Author/year	Country	Type of nephrotoxin	Sample size	Type of food and amount	Unit	Detection method	Ref
Jayalal et al., 2020	Sri Lanka	Lead Cadmium Mercury	196	Rice Mean lead = 84 Mean cadmium = 112 Mercury = 0	µg/kg	ICP-MS	(1)
Assaf et al., 2004	Lebanon	Ochratoxin A	102	Wheat = 0.15 ± 0.03 Burghul = 0.21 ± 0.04 Other sample = 0	µg/kg	HPLC	(5)
Au et al., 2020	Hong Kong	Aristolochic acids	230	Cucumber = 0.23 ± 0.35 Paprika = 3.46 ± 6.77 Tomato = 0.44 ± 0.56 Carrot = 73.3 ± 102.6 Potato = 0.07 ± 0.05	ng/g	LC-MS/MS	(9)
Benites et al., 2017	Portugal	Ochratoxin A	6	Roasted coffee = 1.84 ± 0.03 Ground roasted coffee = 1.45 ± 0.02	µg/kg	HPLC-FD	(15)
Beretta et al., 2002	Italy	Ochratoxin A	338	Baby foods-based semolina formulas = 0.14-0.65 Baby food-based rice formulas = 0.24-0.74 Baby food-based maize and tapioca formulas = ND	µg/kg	HPLC-FD	(16)
Elaridi et al., 2019	Lebanon	Ochratoxin A	84	infant formulae = 0.37 ± 0.10	µg/kg	ELISA	(17)
Fazekas et al., 2002	Hungary	Ochratoxin A	Baking wheat = 36 Wheat flour = 16 Maize coarse meal = 6 Commercial coffee = 50	Baking wheat = 0.29 Wheat flour = 0.13 Maize coarse meal = 0.4 Commercial coffee = 0.57	ng/g	IAC-HPLC	(18)
Gopinandhan et al., 2008	India	Ochratoxin A	50	Green coffee = 2.17 ± 2.45	ng/g	HPLC-FD	(19)
Habib et al., 2017	Iran	Ochratoxin A	220	Domestic rice = 3.15 Foreign rice = 3.87	µg/kg	ELISA	(20)
Hampikyan et al., 2015	Turkey	Ochratoxin A	50	Infant formulae 42 of sample = ND 6 of sample = 0.025–0.05	µg/kg	ELISA	(21)
Li et al., 2016	China	Aristolochic acids	Three for each plant	Lettuce = The results are shown as a graph Tomato = 28.95 ± 4.22 Onion = 135.3 ± 3.76	ng/g	HPLC-FLD	(10)

Manda et al., 2016	France	Ochratoxin A	90 (30 for each spice)	Ginger = 0.12 ± 0.15 Chili = 57.48 ± 174 Pepper = ND	µg/kg	HPLC-FLD	(22)
Munoz et al., 2014	Chile	Ochratoxin A	21	Breast milk =44 ± 18	ng/L	HPLC-FLD	(23)
Rubio-Armendáriz et al., 2021	Spain	Pb Cd	126	Cereals = The results are displayed in graphs	mg/kg	ICP-OES	(24)
Solfrizzo/2015	Italy	Ochratoxin A	13	Food coloring based on grape powder = <1.16–20.23	µg/kg	HPLC-FLD	(25)
Turkogl et al., 2019	Turkey	Ochratoxin A	105	Raw milk = 137 ± 57 Pasteurized milk = 135 ± 8 UHTmilk = 85 ± 4	ng/L	Elisa	(26)
Zaied et al., 2012	Tunisia	Citrinin	200	Wheat grains average = 28	µg/kg	HPLC-FLD	(27)
Famurewa/2023	Nigeria	Nickel	-	Coconut oil 0.01 ± 0.00	mg/kg	ICP-OES	(28)
Al –Hamzawi/2022	Iraq	Uranium	12	Crop 0.01927 ± 0.0054	PPM	CR -39 detector	(14)

4. Nephrotoxicity of each compounds

In this study, nephrotoxic compounds that enter the human body from food were investigated. These compounds include mycotoxins, heavy metals, radionucleotide compounds, natural compounds found in plants, and food additives.

4.1. Nephrotoxicity of mycotoxin

About 500 mycotoxins have been identified, of which a smaller number are toxic. The target of some mycotoxins is the renal glomerular and urinary tubules (29). According to the extracted data, the most reported nephrotoxic agent in food is OTA. This mycotoxin accumulates inside kidney cells (29). It prevents the synthesis of proteins (30). Its measurement and detection methods were mainly HPLC and ELISA. Ochratoxin A has cumulative properties in food (31). OTA has been studied in various foods. Codex Alimentarius does not have a standard for Ochratoxin A for many food products (32).

Two studies have worked on Ochratoxin A in green coffee and roasted coffee. According to previous studies, the major mycotoxin in coffee is Ochratoxin A (19). In both studies, the amount of OTA was within the permissible range. The amount of green coffee was more than roasted coffee. Studies show that roasting reduces Ochratoxin A (15). In three studies, the levels of OTA in baby food and infant formula were measured (16,17,21). The OTA concentration reported in the Beretta and Elaridi studies was higher than in the Hampikyan study. The first study was on baby food based on cereal (Table 1). Most likely contamination was due to their cereal. However, in the Elaridi study, high amounts were found in food that was not based on cereal. In this study, 33% of the samples were higher than the EU limit. However, the measurement method of these three studies was different, one with HPLC and the other with ELISA. Based on previous studies, both methods were valid. These methods showed high recovery and low LOD (33). Evaluations of baby food indicate that some of these products are contaminated with the nephrotoxic compound; Ochratoxin A. This should be taken into account as infants and children receive more nutrients than their body weight. Therefore, children will receive more toxins than adults. A study was performed on the amount of OTA in Foreign and domestic rice in Iran. The amount of OTA in foreign rice was higher than in domestic rice (20). A study was also conducted on spices in France. A considerable amount was found in Chili (22). According to EU regulations, the permissible level of Ochratoxin A in spices is 15 μg/kg (22). Therefore, the safety of this type of product needs more monitoring and investigation. In the Munoz study, the amount of OTA in breast milk was evaluated (22). The average amount of OTA in breast milk in a six-month-old baby was 44 ng/L detected (Table 1). Normally, this amount enters the baby's body, so the safety of the food received by the mother should be considered. One of the interesting things about this systematic review was the presence of Ochratoxin A in food colors of plant origin (25). The pomaces of some fruits, such as grape pomaces, are used to produce food coloring. If the raw material is contaminated, the resulting dye will also be contaminated. The permissible limit of Ochratoxin A in milk is 5 μg/kg according to the European Union (26). Aflatoxin M1 is more important in milk, but the results of the Turkoglu study showed that Ochratoxin A should also be evaluated. It is also possible to detect this toxin from milk. The amount of this toxin was high in raw and pasteurized milk (Table 1). Another nephrotoxic toxin is citrinin. This mycotoxin is produced from the genera Penicillium and Aspergillus (34). It disturbs the function of mitochondria (29). It also leads to a decrease in blood flow in the renal glomerular (34). In some cases, it leads to irreversible damage to the kidneys (35). Geographical and climatic conditions are involved in the proliferation of the fungus that produces this toxin (27). In a study of wheat in Tunisia, 50% of the samples were positive.

4.2. Nephrotoxicity of heavy metals

After OTA, heavy metals are nephrotoxic agents in food. There is strong evidence of heavy metals and serious kidney damage (36). Even low amounts of heavy metals lead to changes in kidney function (37). In 2020, Jayalal measured nephrotoxic heavy metals in rice. Mercury was not detected in any of the samples and nine percent of the samples contained cadmium and lead more than permissible level (1). Mercury increases the secretion of pro-inflammatory cytokines and leads to the progression of inflammation. Lead is reabsorbed in the urinary tubules and causes serious damage to the mitochondria. Cadmium leads to a decrease in filtration in the kidneys (36). Another study was conducted to measure cadmium and lead in 126 Cereals samples (24). The amount of lead in the cereal husk is higher, so grinding the product leads to a decrease in lead. One of the prominent food contaminants that has nephrotoxic ability is nickel (28). In a study that was conducted on coconut oils exported to Nigeria, amounts of nickel were observed. But it was less than the limit (28). Among the reported nephrotoxins, two studies are related to aristolochic acids (9,10). In these studies, the amounts of this compound were measured in some vegetables. It is observed that the highest amounts were measured in carrots and onions. Evidence shows the accumulation of this compound in these two plants. Normally, the plant absorbs this compound from the soil, which is more absorbed in onions and carrots than other plants. Of course, the amount of this compound in plants is also affected by the age of the plants (10).

4.3. Nephrotoxicity of radionuclides

The degree of food contamination with radionuclides is directly related to the concentration of these compounds in the soil. Another food pollutant that is nephrotoxic is uranium. Uranium is a nephrotoxic compound based on human and animal evidence (38). Uranium can accumulate in the kidneys (39). It leads to a decrease in the filtration rate in the kidneys (40). In a study in Iraq, the amount of uranium in some agricultural products was evaluated. Significant amounts were found in turnips (14).

5. Conclusion

Kidneys are the vital excretory organ in our body. Three main toxins that produce nephrotoxicities are ochratoxin, heavy metals, and Aristocholic acids. The most-reported nephrotoxic agent is ochratoxin A which is mainly measured and detected by HPLC. OTA is produced by Aspergillus and Penicillium species, which cause urinary tract tumors. The amount of OTA in green coffee is more than roasted coffee as roasting reduces the OTA. Evaluation of baby food indicates the presence of OTA and subsequent nephrotoxicity. The safety of the food consumed by the breastfeeding mother is also important as OTA can be present in breast milk. The amount of OTA in foreign rice in comparison to local rice is higher. According to the European Union, the acceptable amount of OTA is 5 ug/kg. The amount of lead is higher in cereal husk. Therefore, grinding the product results in less Pb. Aristocholic acid is accumulated in onions and carrots and its amount in plants is affected by the age of the plants. Geographical and climatic conditions play an important role in the proliferation of the fungus that produces citrinin. A considerable number of studies were on the biomonitoring of Ochratoxin A in humans, therefore this subject is suggested for future studies.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgment

This study was supported by Shahrekord University.

References

1. Jayalal A. Mapping of the Cadmium, Lead and Mercury in rice of paddy fields within a CKDu hotspot in Sri Lanka. 2020; 15: 328-35.
2. Chandrajith R, Seneviratna S, Wickramaarachchi K, et al. Natural radionuclides and trace elements in rice field soils about fertilizer application: a study of a chronic kidney disease area in Sri Lanka. Environ Earth Sci 2010: 60: 193-201.
3. Sadighara P, Mohajer A, Shamloo E, et al. The radionuclides contamination in eggs as an environmental marker: a systematic review. Rev Environ Health 2023; 38: 187-92.
4. Dhungana B, Ali S, Krishnan P, et al. Effect of oat cultivar on ochratoxin A accumulation following grain inoculation with *Penicillium verrucosum*. Cereal Chem 96: 2019: 324-31.
5. Assaf H, Betbeder AM, Creppy EE, et al. Ochratoxin A levels in human plasma and foods in Lebanon. Human Experimen Toxicol 2004; 23: 495-501.
6. Arrúa AA, Mendes JM, Arrúa P, et al. Occurrence of deoxynivalenol and ochratoxin A in beers and wines commercialized in Paraguay. Toxin 2019; 11: 308.
7. Pardo E, Sanchis V, Ramos A, et al. Non-specificity of nutritional substrate for ochratoxin A production by

isolates of *Aspergillus ochraceus*. Food Microbiol 2006 ;23: 351-58.

8. Ali N. Co-occurrence of citrinin and ochratoxin A in rice in Asia and its implications for human health. J Sci Food Agri 2018; 98: 2055-59.
9. Au CK, Zhang J, Chan CK, et al. Determination of aristolochic acids in vegetables: Nephrotoxic and carcinogenic environmental pollutants contaminating a broad swath of the food supply and driving incidence of Balkan endemic nephropathy. Chem Res Toxicol 2020; 33: 2446-54.
10. Li W, Hu Q, Chan W. Uptake and accumulation of nephrotoxic and carcinogenic aristolochic acids in food crops grown in Aristolochia clematitis-contaminated soil and water. J Agri Food Chem 2016; 64: 107-12.
11. Butovskaya E, Gambi L, Giovanetti A, et al. Screening of antibiotic residues in raw bovine milk in Lombardy, Italy: Microbial growth inhibition assay and LC-HRMS technique integration for an accurate monitoring. Heliyon 2023; 9: e15395.
12. Li Z, Liu Y, Chen X, et al. Affinity-based analysis methods for the detection of aminoglycoside antibiotic residues in animal-derived foods: a review. Food 2023; 12: 1587.
13. Morozov V, Luzin V. Histomorphometric parameters of parathyroid glands after 60 days of sodium benzoate administration. Bioscientifica 2023; 90 EP137.
14. Padhi M, Mukherjee M, Baksi S, et al. Study of extent of global uranium contamination in groundwater. J Survey Fish Sci 2023; 10: 6470-79.
15. Benites AJ, Fernandes M, Boleto AR, et al. Occurrence of ochratoxin A in roasted coffee samples commercialized in Portugal. Food Control 2017; 73: 1223-28.
16. Beretta B, Domenico RD, Gaiaschi A, et al. Ochratoxin A in cereal-based baby foods: occurrence and safety evaluation. Food Add Contamin 2002; 19: 70-75.
17. Elaridi J, Dimassi H, Hassan H. Aflatoxin M1, and ochratoxin A in baby formulae marketed in Lebanon: occurrence and safety evaluation. Food Control 2019; 106: 106680.
18. Fazekas B, Tar A, Zomborszky-Kovács M. Ochratoxin A contamination of cereal grains and coffee in Hungary in the year 2001. Acta Veterinaria Hungarica 2002; 50: 177-88.
19. Gopinandhan T, Kannan G, Panneerselvam P, et al. Survey on ochratoxin A in Indian green coffee destined for export. Food Add Contamin 2008; 1: 51-57.
20. Habib V, Mohammad G, Zeinal–Abedin B, et al. Ochratoxin A detection in rice samples in Mazandaran province. Pharmacophore 2017; 8: 10-21.
21. Hampikyan H, Bingol E, Colak H, et al. Determination of ochratoxin A in baby foods by ELISA and HPLC. Acta Alimentaria 2015; 44: 578-84.
22. Manda P, Adanou KM, Ardjouma D, et al. Occurrence of ochratoxin A in spices commercialized in Abidjan (Côte d'Ivoire). Mycotoxin Res 2016; 32: 137-436.
23. Muñoz K, Blaszkewicz M, Campos V, et al. Exposure of infants to ochratoxin A with breast milk. Arch Toxicol 2014; 88: 837-46.
24. Rubio-Armendáriz C, Paz S, Gutiérrez ÁJ, et al. Toxic metals in cereals in Cape Verde: risk assessment evaluation. Int J Environ Res Public Health 2021; 18: 3833.
25. Solfrizzo M, Piemontese L, Gambacorta L, et al. Food coloring agents and plant food supplements derived from Vitis vinifera: a new source of human exposure to ochratoxin A. J Agri Food Chem 2015; 63: 3609-14.
26. Turkoglu C, Keyvan E. Determination of aflatoxin M1 and ochratoxin A in raw, pasteurized, and UHT milk in Turkey. Acta Sci Veterin 2019; 47.
27. Zaied C, Zouaoui N, Bacha H, et al. Natural occurrence of citrinin in Tunisian wheat grains. Food Control 2012; 28: 106-09.

28. Famurewa AC, Ekeleme-Egedigwe CA, Onyeabo C, et al. Comparative assessment of different coconut oils: Chromatographic and spectrometric analyses of pesticide residues, toxic heavy metals, and associated contents. Measure: Food 2023; 10: 100082.
29. Ráduly Z, Price RG, Dockrell ME, et al. Urinary biomarkers of mycotoxin induced nephrotoxicity—Current status and expected future trends. Toxin 2012; 13: 848.
30. Ringot D, Chango A, Schneider YJ, et al. Toxicokinetics and toxicodynamics of ochratoxin A, an update. Chem-Biologic Interact 2006; 159: 18-46.
31. Merla C, Andreoli G, Garino C, et al. Monitoring of ochratoxin A and ochratoxin-producing fungi in traditional salami manufactured in Northern Italy. Mycotoxin Res 2018; 34: 107-16.
32. Ingenbleek L, Verger P, Gimou MM, et al. Human dietary exposure to chemicals in sub-Saharan Africa: safety assessment through a total diet study. Lancet Planet Health 2020; 4: e292-e300.
33. Varga J, Kozakiewicz Z. Ochratoxin A in grapes and grape-derived products. Trend Food Sci Technol; 2006; 17: 72-81.
34. Wu TS, Yang JJ, Yu FY, et al. Evaluation of nephrotoxic effects of mycotoxins, citrinin, and patulin, on zebrafish (Danio rerio) embryos. Food Chem Toxicol 2012; 50: 4398-04.
35. Phillips RD, Wallace Hayes A, Berndt WO, et al. Effects of citrinin on renal function and structure. Toxicol 1980; 16: 123-37.
36. Kaur G, Kaur M, Sharma S. Potential mechanisms of heavy metals induced nephrotoxicity. World J Pharm Res 2014; 3: 4689-4702.
37. Al-Saleh I, Al-Rouqi R, Elkhatib R, et al. Risk assessment of environmental exposure to heavy metals in mothers and their respective infants. Int J Hyg Environ Health 2017; 220: 1252-78.
38. Dorne JL, Kass G, Bordajandi LR, et al. Human risk assessment of heavy metals: principles and applications. Met Ions Life Sci 2011; 8: 27-60.
39. Chiegwu H, Odoh F, Ogwuanyi D, et al. Natural radionuclides in commonly consumed food items in Enugu State, Nigeria. Trop J Health Sci 2020; 27: 40-6.
40. Vicente-Vicente L, Quiros Y, Pérez-Barriocanal F, et al. Nephrotoxicity of uranium: pathophysiological, diagnostic and therapeutic perspectives. Toxicol Sci 2010; 118: 324-47.