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Food Safety Risk: Ochratoxin A in Türkiye

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ABSTRACT

Ochratoxin A (OTA) is a mycotoxin produced by fungi of the genus *Aspergillus* and *Penicillium*. OTA causes damage to the kidneys and liver in experimental animals and is even classified as a possible human carcinogen. As an occasional phenomenon, many foods in a particular region may be contaminated with OTA. Regardless of whether it is a developed or developing country, OTA contamination poses both public health and economic risks. We have compiled studies on OTA in food and humans (milk and blood) in Turkey over the last 25 years and discussed what needs to be done to reduce the public health risk.

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1. Ochratoxin A (OTA)

Ochratoxin A is a mycotoxin produced mainly by fungi of the *Aspergillus* and *Penicillium* genera and contaminates foods in which these fungi grow in it (Malir et al., 2016; Wang et al., 2016). The effects of OTA exposure (up to 2 years) on experimental animals have been studied, and it causes damage to many tissues, especially the kidney and liver, in experimental animals (IARC, 1983; NTP, 1989). While kidney tumors were observed especially in male rats, an increase in kidney and liver tumors was observed in mice. Based on the data obtained from these animal experiments, OTA has been classified as a possible human carcinogen.

It is frequently observed that exposure to OTA causes fibrosis, oxidative stress and apoptosis in cells/tissues (Atroshi et al., 2000; Palabiyik et al., 2012; Chae et al., 2022). The harmful effects of OTA have been reported to occur through many pathways such as inhibition of macromolecule synthesis, oxidative stress, lipid peroxidation, genotoxicity, mitochondrial dysfunction, alteration of Ca^{2+} homeostasis, disruption of glucose homeostasis, cellular differentiation, and apoptosis. These mechanisms of action have been discussed in various

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reviews (Kőszegi & Poór, 2016; Khoi et al., 2021). There is disagreement on whether OTA creates DNA adducts (Delatour et al., 2008; Mantle et al., 2010). It is thought that the disagreements on whether OTA can be classified as a genotoxic toxin that forms a DNA adduct or not will not remain an inconclusive disagreement in the long term, as it will be important in determining the legal limit of OTA that can be found in foods. It is reported that a non-genotoxic carcinogen is 10 times less risky for human health compared to a carcinogen that has the ability to form defined DNA adducts (Mantle et al., 2010). Therefore, if it is definitively proven that OTA is genotoxic, the permissible limits in foods will need to be further reduced. However, if OTA does not have a genotoxic effect, the measures to be taken to keep the OTA level in foods much lower will be costly for society and will cause serious economic losses by causing many harmless foods to be classified as unsafe for consumption.

OTA can be found in many agricultural foods (coffee, tea, grapes, apricots, figs, wheat, etc.) regardless of developed or developing countries (within the legally permitted limits) and in some cases, it can exceed the legal limits. Apart from agricultural foods, OTA can reach the consumer through the meat, milk and eggs of animals that eat OTA-contaminated feed. Moreover, OTA can directly reach babies through the milk of mothers exposed to it. OTA can be found in human blood for a long time (plasma half-life ~36 days) after exposure (Studer-Rohr et al., 2000), and it has also been observed that OTA can cross the placenta in OTA exposure in pregnant animals, which increases OTA exposure (Hallén et al., 1998; Minervini et al., 2013). This makes OTA exposure more concerning. To evaluate the risk posed by this alarming toxin for Türkiye, it was aimed to compile studies showing OTA contamination in foods frequently consumed by Turkish people over the last 25 years.

2. OTA in Turkish Teas

Türkiye is one of the world's largest tea producers (FAO, 2015). Türkiye first tried to grow tea with seeds purchased from Japan in 1838, but no successful results were obtained under the conditions of those days (Honda, 2012). However, positive results were obtained from the studies carried out in 1924-1937 and tea cultivation started in Türkiye. The first tea factory in Türkiye was established in 1947 (Çaykur, 2023). As tea production increases in Türkiye, tea has become the most preferred beverage. Türkiye is the country with the highest per capita tea consumption in 2019 in the world (Yildirim & Karaca, 2022). Between 2017 and 2022, Türkiye consumed 14-15 kg of tea per person (Erkal, 2023). Therefore, the presence of OTA in tea has become a more important issue for Türkiye.

Gazioglu and Kolak (2018) found that the OTA concentration in Turkish tea could reach 139.5 µg/kg, but this was only a measurement obtained from a single tea sample. This amount is at least approximately 14 times higher than the permitted limit for dried herbs in the Turkish Food Codex (TOB, 2023). In another study (Toman et al., 2018), OTA levels were investigated in 46 tea samples taken from Türkiye and the Czech Republic, also OTA transfer to the drinking part of the tea was examined. OTA concentration in 36 tea samples from the Czech Republic was observed to vary between 0.35 ng/g and 56.7 ng/g, but OTA was not detected in any of 14 different (9 teapots and 5 filtered teabags type) Turkish teas. There may be many reasons for the difference in OTA levels in Turkish tea in the studies of Gazioglu and Kolak (2018) and Toman et al. (2018). The storage conditions in the markets, the duration and conditions of tea storage starting from harvesting to packaging, can directly affect OTA formation and accumulation. Taking tea samples from homes as well as products purchased from markets is important in observing the OTA exposure of the population through tea. Because it is highly possible for various fungi to grow and produce fungal toxins in tea that is not consumed for a long period after it is opened at home. Taking samples to determine OTA concentration from tea stored at home in Türkiye can be a tool to investigate the public's exposure to OTA.

It was observed that 41.5±7% of the toxin in the tea passed into the drinking part during the tea brewing/preparation (150 ml of boiling water was added to 5 grams of tea and left to brew for 15 minutes) process (Toman et al., 2018). The tolerable weekly OTA intake has been reported as 112 ng/kg (WHO, 1991; Micco et al., 1995), and based on this information, the tolerable weekly OTA amount for a 70 kg person is 7.84 µg. If OTA risk is ignored, the 'tea-loving' population in Türkiye may consume more than 25% of this limit directly from tea. As seen in the study of Toman et al. (2018) when 5 g of tea with an OTA concentration of 55 µg/kg is taken and 150 ml of tea is brewed, 0.275 µg passes into the liquid part of the tea. An individual who consumes this much tea every day consumes 1.925 µg of OTA in 7 days. This means approximately 25% of the tolerable limit for a 70 kg person. OTA concentration in consumed tea and 'tea addiction' of person increase, a significant portion of the tolerable limit is wasted only through tea.

Since there is a serious transfer of OTA from the tea leaves to the drinking part of the tea through Turkish brewing and the society has a high tea consumption habit, OTA contamination of teas poses a serious public health risk for Turkish society. It is important for Turkish public health that keep lower the permitted OTA level in tea than the legal OTA limits allowed in Europe and other countries.

3. OTA in Grapes and Products Originated from Grapes

In Türkiye, grapes are produced at a significant level in the Aegean, Mediterranean, Southern and Western Anatolia and Marmara Regions, and it has been reported that 3 650 thousand tons of grapes are produced in 461 thousand hectares of land throughout the country (Bashimov, 2017). In Türkiye, the grape itself and its leaves are used in various ways. While grapes can often be eaten directly, grapes can be dried and made into pekmez (grape molasses) or wine. Depending on the region, period and facility, OTA can be found in different concentrations in grapes and grape-derived products.

Grapes can be eaten or used as raw material for other products. The OTA concentration in the starter grapes may increase or decrease at the end of the production process. OTA amounts in these products vary according to the process. No detectable levels of OTA were found in the raisin samples (17 samples) taken from the market in Burdur province in 2015 (Yurdakul et al., 2019). However, OTA was detected in 50 raisins, 10 grape juice and 25 pekmez samples collected from İstanbul between 2008 and 2009 for OTA analysis (Akdeniz et al., 2013). It was reported by Akdeniz et al. (2013) that OTA concentration exceeded the limit of quantification in 8% of 50 raisin samples, 2% of 10 grape juice samples and 92% of 25 pekmez samples (limit of quantification 0.15 µg/kg for raisins and 0.3 µg/kg for grape juice and pekmez samples). OTA concentration ranged between 0.19-2.59 µg/kg (Average 1.15 µg/kg) in raisins, 0.90-1.90 µg/kg (mean 1.4 µg/kg) in grape juice and 0.44-5.32 µg/kg (mean 2.04 µg/kg) in pekmez samples.

Pekmez is a sweet traditional food made by boiling and condensing grapes. This boiling process does not reduce the OTA level in grapes; in fact, it is observed that the OTA concentration increases as condensation occurs (Arici et al., 2004). Therefore, the OTA concentration in grapes used in pekmez production must be below legal limits. Other studies also show that pekmez contains more OTA than other grape products. Tosun et al. (2014) analyzed 82 grape pekmez samples (55 homemade, 7 organic and 20 commercial) from Niğde, Manisa, Çanakkale, Denizli, Sivas, Yozgat, Mardin, İzmir and Kayseri. There were 37 OTA positive pekmez samples (73% of homemade pekmez, 71% of organic pekmez and 35% of commercial pekmez). The average OTA amounts were 9.2 µg/L in organic pekmez, 3.5 µg/kg in homemade pekmez and 1.4 µg/kg in commercial pekmez. The maximum OTA level was found to be 31.2 µg/L in organic pekmez, 15 µg/L in homemade pekmez and 12 µg/L in commercial pekmez. However, OTA was detected in only one of the 16 grape pekmez samples taken from markets in Burdur province in 2015, and the detected OTA concentration was 20.48 µg/kg (Yurdakul et al., 2019). Although OTA cannot be detected in some pekmez samples or the average OTA concentration is below the legal limits, it is observed that the OTA concentration can reach high levels in some samples.

Wine is an alcoholic beverage produced by the fermentation of grapes and is widely preferred around the world. OTA levels of 95 wine samples (2005-2006) originating from various provinces of Türkiye were investigated (Var & Kabak, 2007). The average OTA concentration in these wines was determined to be 158 ng/L in wines of Thracian origin (44 samples), 60 ng/L in wines of Aegean origin (28 samples) and 27 ng/L in wines of Eastern Anatolia origin (8 samples). In total, OTA at the level of 500-815 ng/L was found in only 3 samples. The samples in this study are below the limit specified in the Turkish Food Codex (2.0 µg/kg). In addition, when evaluated together with wine samples from other countries, it is seen that Turkish wines with low OTA concentration are better positions among EU originated wines (Czerwiecki et al., 2005).

4. OTA in Bread

White bread has 8.7 grams of protein, 58.3 grams of carbohydrates and 1.5 grams of fat per 100 grams (Karaağaoğlu et al., 2008) and is consumed as a common food in Türkiye. Bread is produced daily or even hourly, and is consumed by the consumer immediately or within two days after purchase. Since it is a popular food, investigating the OTA level in bread is important for Türkiye. Various types of bread produced from different flours are consumed in Türkiye, the most common of which is white bread. The OTA concentration in flour affects the OTA concentration of the final product. A total of 132 flour and bread samples (34 white flour, 14 whole wheat flour, 10 corn flour, 36 white bread, 28 whole wheat bread and 10 corn bread) taken from different points of Bursa in 2005-2006 were analyzed (Cengiz et al., 2007). OTA was detected in 83% of the samples. The average OTA concentrations seen in this study were determined: 6.89±0.46 µg/kg in white flour, 9.30±1.33 µg/kg in whole wheat flour, 6.39±1.10 µg/kg in corn flour, 7.84±0.39 µg/kg in wholemeal bread, 4.94±0.46 µg/kg in corn bread and 6.38±0.48 µg/kg in white bread purchased from civilian markets and bakeries.

Although bread fermentation and baking processes reduce the amount of OTA in bread, the OTA level in bread is related to the amount of OTA in flour. It was studied how the bread making process affects the OTA level. By contaminating OTA-free white flour with OTA at 5 and 10 µg/kg, the effect of the bread preparation process on this contamination level was investigated (Var et al., 2018). This flour was mixed with α-amylase, cellulase, glucose oxidase mixture, salt, water and fresh yeast and kneaded for about 20 minutes to prepare the dough. An average OTA concentration of 2.76 µg/kg was found in dough made with flour containing 5 µg/kg OTA and 7.36 µg/kg in dough made with flour containing 10 µg/kg OTA. This decrease in concentration is related to the added water. The divided dough was shaped into bread and incubated at 30 °C for 75 minutes for fermentation. After fermentation, 1.35 µg/kg OTA was detected in the dough made from flour containing 5 µg/kg OTA and 4.69 µg/kg OTA was detected in the dough made from flour containing 10 µg/kg OTA. They suggest that the decrease in OTA concentration observed after fermentation is a result of *S. cerevisae* activity. After fermentation, bread was produced by baking the dough at 240 °C for 30 minutes. OTA concentrations of 0.63 µg/kg and 2.37 µg/kg were detected in bread made with flour containing 5 µg/kg and 10 µg/kg OTA, respectively. Unlike the pekmez production process, where OTA concentration increases, this study does not provide information about other OTA derivatives, but it has been reported that cooking at 240 °C for 30 minutes reduces the OTA level by approximately 50%. If the amount of OTA in the raw material flour is not excessive, the risk of OTA exposure will decrease as the bread-making process reduces the amount of OTA.

5. OTA in Seafoods

Fish feed consisting of fishmeal, wheat, soybean and corn can be used to feed the fish in aquaculture (Pietsch, 2020). With the increase in vegetable ingredients in fish feed, the exposure of fish to OTA has increased (El-Sayed et al., 2009). It has been shown that a significant amount of OTA can form in fish feed during a one-month storage period (Pietsch et al., 2020). Eating OTA-contaminated feed causes loss of growth and/or survival rate in fish and tissue damage in fish embryos (Manning et al., 2003; Srour, 2004; Wu et al., 2016). However, exposure of fish to OTA does not only create economic risks. Through the food chain, OTA in the body of fish can reach human consumption. Various studies have reported that OTA is found in seafood in markets. OTA of 0.36-1.51 µg/kg was found in 33% of 40 dried seafood products (including fish, shrimp and mussel) purchased from the Zhanjiang seafood market (Deng et al., 2020). In another study, 27 seafood samples (muscles, entrails of fresh fish and dried seafood) were taken from a local supermarket in Shanghai, and OTA was detected in 4 of these samples at a concentration of 0.5-1.9 µg/kg (Sun et al., 2015).

No study has been found that determined OTA level in fish or fish feed sold in the market in Türkiye. However, the presence of other mycotoxins has been investigated. Between 1998 and 2000, 85 fish food samples (only 20 of which were outside Türkiye) were taken, and aflatoxin was detected in the range of 21.2-42.4 ppb in 20 of these samples (Altug & Beklevik, 2003). The presence of mycotoxin in a feed indicates that this environment is suitable for fungal growth, and this indicates the possibility of OTA presence in the feed. OTA and aflatoxin can co-occur in the same samples (Kara et al., 2015). Therefore, determining the amount of OTA in fish feed and the amount of OTA in the edible parts of fish bought from farms will contribute to elucidating the risk of OTA in fish in Türkiye.

6. OTA in Milk and Dairy Products

Milk and dairy products (such as yoghurt, ayran and cheese types) have an important place in the diet of children and adults. While cheese is preferred for breakfast, yoghurt and ayran (a drink made from yoghurt) is a traditional food and beverage consumed with many foods. The amount of OTA in this traditional beverage food is dependent on the amount of OTA in milk. The presence of OTA in the range of 2-270 ng/L was detected in 37 of the samples from 40 milk collection tanks in Burdur (Keyvan et al., 2018). In another study, an average of 119±9 ng/L OTA was found in 105 cow milk samples (Turkoglu & Keyvan, 2019). It did not make a significant difference whether the milk was raw, pasteurized or UHT. The presence of low levels of OTA in cow's milk may be due to microbial activity in their digestive tract and/or exposure to low doses of OTA. Undoubtedly, this is a desired situation for later products.

Additionally, yoghurt making production reduces the OTA concentration. Škrinjar et al. (1996) prepared skimmed milk powder culture medium and contaminated with OTA (at concentrations of 50-1500 µg/L) in order to investigate the effect of fermentation with yoghurt culture and various bacteria on OTA concentration. Fermentation significantly reduces OTA in OTA-contaminated culture media (No OTA residues were detected between 50-1000 µg/L OTA contaminated culture). This indicates that yoghurt produced under appropriate fermentation conditions and ayran produced from this yoghurt will be reliable in terms of OTA.

Surf cheese is a traditional dairy product produced especially in Hatay province. Various spices and herbs are added to the cottage cheese, kneaded and shaped, then dried in the air for 3-4 days and surf cheese is produced. A total of 30 surf cheese samples were taken from random sellers in Hatay province. OTA was detected in 28 of the cheese samples taken (between 0.058 and 5.04 µg/kg) and its mean concentration was 0.615 ± 0.228 µg/kg (Sakin et al., 2018). However, the mean OTA concentration seems to be compatible with the acceptable limits in other products. The amount of OTA found in this cheese may be due to the OTA concentration in milk, added spices and herbs, or the drying process.

7. OTA in Baby Supplementary Foods

Baby supplementary foods have an important role in baby nutrition. Since they may contain wheat and various fruits, they are likely to contain OTA. In 2011, 62 baby formula products (6 infant formula, 36 follow-on formula and 20 toddler formula) from 8 different brands from Çorum was investigated for the presence of mycotoxins (Kabak, 2012). Although OTA was detected in 12 of 62 samples, OTA concentrations are 0.017-0.184 µg/kg (average 0.103 µg/kg) and do not exceed the limit (0.5 µg/kg) according to the European Commission and the Turkish Food Codex. Although high amounts of OTA contamination were not found in the supplemented infant formulas investigated in this study, we cannot say that babies can be completely protected from OTA exposure. Because OTA is found even in breast milk.

8. OTA in Breast Milk

OTA is found in the meat, eggs and milk of animals that consume foods contaminated with OTA. Humans are not to be exceptions. OTA is found in the milk of mothers who consume foods containing OTA, and in this way, OTA is passed to newborn babies. It has been reported that experimental animals exposed to OTA in utero and throughout development exhibit more renal lesions compared to adults (Bondy et al., 2021). Therefore, since breast milk is the primary nutritional source for human infants, OTA concentration in breast milk is of critical importance.

OTA may be found in breast milk taken from mothers. Milk samples were taken from 75 mothers in Ankara and OTA was detected in 100% of the samples (Gürbay et al., 2010). It was observed that the OTA level was approximately between 0.62–13.11 µg/L. In this study, it was reported that the OTA concentration was between 0.6-1.5 µg/L in 28 samples, the OTA concentration was between 1.5-3 µg/L in 34 samples, and the OTA concentration was higher than 3 µg/L in 13 samples (3 µg/L is the upper limit allowed for many beverages). In another study, OTA was found at concentrations between 0.40 µg/L and 2.72 µg/L (OTA concentration above 0.5 µg/L in 97.5% of the milk) in 122 breast milk samples taken from mothers living in Ankara in 2017-2018 (Memiş & Yalçın, 2021). In addition to breast milk samples collected from Ankara, OTA has also been detected in breast milk samples in various countries; 20% of samples from Italy have OTA concentration of 0.1-12 µg/L (Micco et al., 1995), 36% of samples from Egypt have OTA concentration of 5-45 µg/L (El-Sayed et al., 2002), 35% of samples from the Republic of Sierra Leone 0.2-337.0 µg/L OTA concentration was observed (Jonsyn et al., 1995).

A study conducted in Egypt evaluated OTA levels in breast milk and infant kidney functions. In this study, OTA concentration in the serum and milk of 50 mothers and OTA levels in the serum of the babies of these mothers (who were breastfed for 4 months and did not receive any additional nutrition) were measured and the kidney functions of the babies were evaluated (Hassan et al., 2006). The mean OTA concentrations were found to be 4.28 µg/L in mothers' serum samples and 1.87 µg/L in the milk samples (Hassan et al., 2006). Considering the mean values, it is seen that there is 2.2 times as much OTA in serum as the OTA value in milk. Therefore, it can be assumed that mothers are also exposed to OTA. It was observed that the serum of the babies in the Egyptian study had 1.26±1.1 µg/L OTA. In this study, they stated that microalbuminuria and β2 microglobulinuria were found to a greater extent in babies exposed to OTA, compared to those not exposed. This indicates that kidney functions may be affected by OTA exposure. The study did not include any short or long-term observations of these babies. Therefore, we cannot comment further. However, such observation studies need to be carried out for longer periods. These studies will be useful in showing the impact of OTA exposure on society.

9. Conclusion

Contamination of agricultural products with OTA can occur in many different steps. OTA production may be the cause of fungal activity in many plant-based products, in the field, in production, factory, storage and distribution processes, on market shelves and even while keeping the product at home (Figure 1). The mean OTA contamination level of some products is given in Table 1, and there are some samples in some products where the OTA level exceeds the permissible limits. That indicates that OTA is produced independently in many steps.

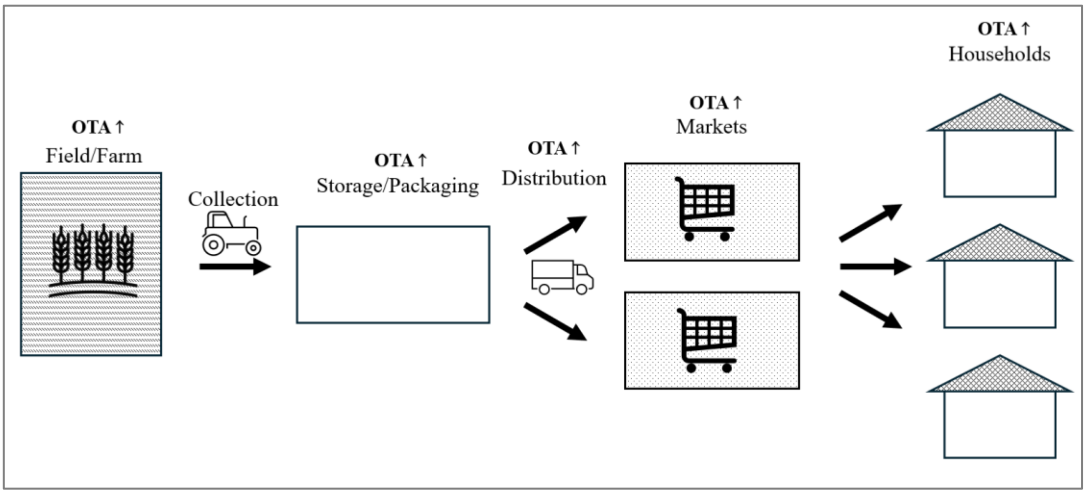

Figure 1. Possible steps that increase the OTA level in food from production to consumption.

Table 1. Mean OTA concentration in some frequently consumed foods and beverages in Türkiye.

Product	Sample	OTA Concentration	Reference
Tea (İstanbul)	1	139.5 µg/kg	Gazioglu and Kolak (2018)
Tea	14	-	Toman et al. (2018)
Raisins (Burdur)	17	-	Yurdakul et al. (2019)
Raisins (İstanbul)	50	1.15 µg/kg	Akdeniz et al. (2013)
Grape juice (İstanbul)	10	1.4 µg/kg	Akdeniz et al. (2013)
Commercial pekmez (İstanbul)	25	2.04 µg/kg	Akdeniz et al. (2013)
Commercial pekmez (Multiple Cities)	20	1.4 µg/kg	Tosun et al. (2014)
Organic pekmez (Multiple Cities)	7	9.2 µg/L	Tosun et al. (2014)
Homemade pekmez (Multiple Cities)	55	3.5 µg/kg	Tosun et al. (2014)
Wine (Thrace)	44	158 ng/L	Var and Kabak (2007)
Wine (Aegean)	28	60 ng/L	Var and Kabak (2007)
Wine (Eastern Anatolia)	8	27 ng/L	Var and Kabak (2007)
White flour (Bursa)	12	6.89±0.46 µg/kg	Cengiz et al. (2007)
Whole wheat flour (Bursa)	14	9.30±1.33 µg/kg	Cengiz et al. (2007)
Corn flour (Bursa)	10	6.39±1.10 µg/kg	Cengiz et al. (2007)
Whole wheat bread (Bursa)	28	7.84±0.39 µg/kg	Cengiz et al. (2007)
Cornbread (Bursa)	10	4.94±0.46µg/kg	Cengiz et al. (2007)
White bread (Bursa)	11	6.38±0.48 µg/kg	Cengiz et al. (2007)
Milk from collection tank (Burdur)	40	2-270 ng/L	Keyvan et al. (2018)
Raw, pasteurized or UHT milk (Burdur)	105	119±9 ng/L	Turkoglu and Keyvan (2019)
Surf cheese (Hatay)	30	0.615 ± 0.228 µg/kg	Sakin et al. (2018)
Baby supplementary food (Çorum)	62	0.103 µg/kg	Kabak (2012)

Therefore, by tracking the products leaving the factory by government officials or company officials or researchers, identifying and publishing the hot spots where OTA formation is maximum, it will be possible to take special measures on the basis of these points. By reducing fungal activity in these hot spots, the amount of OTA in more products can be kept at acceptable levels. In addition, informing not only the state administration but also the public about fungal toxins will contribute to reducing the risk of OTA in foods at home or will ensure that risky foods are not consumed. Thus, by reducing the OTA level in foods, people can keep their OTA exposure below the tolerable weekly OTA intake level.

Conflict of Interest

The authors declare no conflict of interest.

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