Review

Producers and Important Dietary Sources of Ochratoxin A and Citrinin

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Abstract: Ochratoxin A (OTA) is a very important mycotoxin, and its research is focused right now on the new findings of OTA, like being a complete carcinogen, information about OTA producers and new exposure sources of OTA. Citrinin (CIT) is another important mycotoxin, too, and its research turns towards nephrotoxicity. Both additive and synergistic effects have been described in combination with OTA. OTA is produced in foodstuffs by Aspergillus Section Circumdati (Aspergillus ochraceus, A. westerdijkiae, A. steynii) and Aspergillus Section Nigri (Aspergillus carbonarius, A. foetidus, A. lacticoffeatus, A. niger, A. sclerotioniger, A. tubingensis), mostly in subtropical and tropical areas. OTA is produced in foodstuffs by Penicillium verrucosum and P. nordicum, notably in temperate and colder zones. CIT is produced in foodstuffs by Monascus species (Monascus purpureus, M. ruber) and Penicillium species (Penicillium citrinum, P. expansum, P. radicicola, P. verrucosum). OTA was frequently found in foodstuffs of both plant origin (e.g., cereal products, coffee, vegetable, liquorice, raisins, wine) and animal origin (e.g., pork/poultry). CIT was also found in foodstuffs of vegetable origin (e.g., cereals, pomaceous fruits, black olive, roasted nuts, spices), food supplements based on rice fermented with red microfungi Monascus purpureus and in foodstuffs of animal origin (e.g., cheese).

Keywords: ochratoxin A; citrinin; producers; microfungi; dietary sources; foods
1. Introduction

Ochratoxin A (OTA) is a very important mycotoxin. OTA is a nephrotoxic, hepatotoxic, embryotoxic, teratogenic, neurotoxic, immunotoxic, genotoxic and carcinogenic mycotoxin [1,2].

OTA exposure may lead to the formation of DNA adducts, resulting in genotoxicity and carcinogenicity (human carcinogens of the 2B group). Now, it seems that OTA could be “a complete carcinogen” (not only an initiator, but also a promoter) and that its mutagenicity has been revised, obliging reinforcement of its monitorization in food [3–6].

Recent OTA research is focused now on the new findings of OTA, like being a complete carcinogen, information about OTA producers and new exposure sources of OTA [2]. In the Czech Republic, one of the EU Member States, a new assessment of dietary exposure and health risk characterization of OTA is currently taking place for 10 population groups of both sexes aged 4–90 years (research project No. NT 12051–3/2011, entitled “Ochratoxin A—health risk assessment for selected population groups in the Czech Republic”) [2].

Citrinin (CIT), often found in the same food as OTA [7], is a powerful nephrotoxin. In repeat dose toxicity studies, the kidney was identified as the principal target organ for CIT, and significant species differences in the susceptibility to CIT have been observed [8,9]. The renal system of humans was found to be affected, and the mitochondrial respiratory chain was identified as a possible sensitive target for CIT [10]. A few studies have also addressed its potential for immunotoxicity [11]. Nevertheless, the studies of the immunotoxicity of CIT are rather incomplete, often non-specific and do not allow a conclusive evaluation. In vitro and in vivo studies provided clear evidence for reproductive toxicity and the teratogenic and embryotoxic effects of CIT [12–22]. CIT is not mutagenic in conventional bacterial assays, either with or without metabolic activation by the S9 fraction from rat or human liver or rat kidney [23]. CIT is not carcinogenic according to recent knowledge. The International Agency for Research on Cancer (IARC) (1986) concluded that there was limited evidence for the carcinogenicity of CIT to experimental animals and that no evaluation could be made of the carcinogenicity of CIT to humans. CIT is classified in group 3 (not classifiable as to its carcinogenicity to humans) [24], but has been shown to increase OTA carcinogenicity [25,26].

Recent CIT research is oriented toward nephrotoxicity; both additive and synergistic effects have been described in combination with OTA [2,27–30]. With regard to the nephrotoxicity of CIT, the situation can be complicated by the fact that CIT interacts simultaneously with other naturally occurring mycotoxins—e.g., OTA. Besides, CIT and OTA have also been associated with alterations in renal function and/or with the development of renal pathologies. It has been demonstrated that the co-exposure to CIT and OTA simultaneously modifies DNA adduct formation with increasing formation of the C-C8dG-OTA adduct [29]. The recent CIT research has focused on the instability of CIT during food processing. The low levels of CIT in processed foods may result from the fact that CIT is heat-sensitive and decomposes during heat treatment to form other complex compounds, such as CIT H1 and CIT H2, whose cytotoxicity, compared to the original CIT, is higher and lower, respectively [31–33].
2. Ochratoxin A and Citrinin Producers

2.1. OTA Producers

OTA is produced worldwide in foodstuffs by microfungi of the genera, *Aspergillus*, mainly in subtropical and tropical areas, and *Penicillium*, especially in temperate and colder zones [34–41]. These toxigenic microfungi almost always produce several toxins at the same time, for example OTA, OTB (ochratoxin B) or OTC (ochratoxin C) [42], and this simultaneous occurrence can result in synergetic toxic effects.

Due to considerable revisions in taxonomy, particularly within the genus *Penicillium*, and difficulties in correct species assignation to isolates within that genus, this identity has changed over time [43]. Tables 1 and 2 give an overview of the current identity of microfungi *Aspergillus* and *Penicillium* species that are apparently able to produce OTA in foodstuffs [43,44].

| Genera | Section | Species | Foodstuffs (example) |
|--------|---------|---------|----------------------|
| *Aspergillus* | *Circumdati* | *A. ochraceus* G. Wilh. | Soya bean, nuts, red pepper, cereals, green coffee beans |
| | | *A. steynii* Frisvad & Samson | Coffee beans |
| | | *A. westerdijkiae* Frisvad & Samson | Coffee beans |
| | *Nigri* | *A. carbonarius* (Bainier) Thom | Grapes, red pepper, coffee beans |
| | | *A. foetidus* Thom & Raper | Grapes |
| | | *A. lacticoffeatus* Frisvad & Samson | Coffee beans |
| | | *A. niger* Tiegh | Grapes, peanuts |
| | | *A. sclerotioniger* Frisvad & Samson | Coffee beans |
| | | *A. tubingensis* Mosseray | Grapes |

| Genera | Subgenus | Series | Species | Foodstuffs (example) |
|--------|---------|-------|---------|----------------------|
| *Penicillium* | *Penicillium* | *Verrucosa* | *P. verrucosum* Dierckx | Cereals |
| | | *Verrucosa* | *P. nordicum* Dragoni & Cantoni | Dry ham, salami |

Three major OTA producing species, *Aspergillus ochraceus*, *A. carbonarius* and *Penicillium verrucosum*, have quite different ecologies and physiologies, making it relatively easy to determine which species are responsible for OTA formation in a particular food or geographical location.

In brief, *Aspergillus ochraceus* and closely related species grow at low water activities and at moderate temperatures. They are mostly associated with dried and stored foods, especially cereals. Although many papers describe *A. ochraceus* as the main producer of OTA, production by this and related species has not often been reported, and their importance appears to have been overstated [45].

The second producing *Aspergillus* species, *A. carbonarius* (and the closely related *A. niger*, which produces OTA less often), grows well at high temperatures and produces pigmented hyphae and spores, making it resistant to UV light. Consequently, *A. carbonarius* is commonly found in grapes and similar fruit that mature in sunlight and at high temperatures [45]. Black *Aspergilli* are considered as the primary...
source of OTA on grapes, produced on the berries during the growing season, mainly from maturing to ripening. In particular, *A. carbonarius* is the most important producer of OTA; however, *A. niger* and *A. tubingensis* can contribute to some extent in the vineyard. OTA contents can reach high levels in wine in some parts of the Mediterranean basin and in dried vine fruits in South America, Australia and Europe. OTA production is influenced by various factors, including climatic conditions/geographic areas, grape varieties/crop systems and berry damage caused by insects, fungal infection or excessive irrigation/rainfall. Fungicidal and insecticidal treatments can reduce infection by OTA-producing fungi and, consequently, OTA contamination [37,39,46].

The main food habitat for *Penicillium verrucosum* appears to be cereals grown in the cool temperate zones, ranging across Northern and Central Europe and Canada. It seems certain that growth of *P. verrucosum* in cereals is the major source of OTA in Northern Europe and other cool temperate zone areas. Higher amounts of OTA were produced on wheat than on other substrates, including maize, peanuts, rapeseeds and soybeans. *P. verrucosum* also produces CIT [45].

OTA can also be produced by toxigenic microfungi that grow on products made of pork meat during their ripening (*direct contamination*). *Penicillium nordicum*, a potent OTA producer, has been proven to grow on meat and meat products [47,48]. OTA is also found in meat products originating from animals that are fed with feedstuffs made from contaminated cereals as a major dietary component (*indirect contamination*) [49].

### 2.2. CIT Producers

CIT is produced worldwide in foodstuffs by microfungi of the genera, *Penicillium* [43,44,50] and *Monascus* [51]. Tables 3 and 4 give an overview of the current identity of microfungi *Penicillium* and *Monascus* species that are apparently able to produce CIT in foodstuffs [43,44,50–53].

**Table 3.** *Penicillium* species as citrinin (CIT) producers in foodstuffs.

| Genera          | Subgenus | Series | Species         | Foodstuffs (example)          |
|-----------------|----------|--------|-----------------|------------------------------|
| *Penicillium*   |          |        |                 |                              |
| Furcatum        |          |        | *P. citrinum* Thom | Cereals, nuts, fruit        |
| *Penicillium*   | Expansa  |        | *P. expansum* Link | Fruit, cereals              |
| Corymbifera     |          |        | *P. radicicola* Overy & Frisvad | Bulbs and root vegetables |
| Verrucosa       |          |        | *P. verrucosum* Dierckx | Cereals                   |

**Table 4.** *Monascus* species as CIT producers in foodstuffs.

| Genera   | Species     | Foodstuffs (example)                                      |
|----------|-------------|----------------------------------------------------------|
| *Monascus* | *M. purpureus* Went | Food supplements with fermented red rice                      |
|          | *M. ruber* Tiegh | Soya bean, sorghum, rice, oat                        |

*Penicillium citrinum* is one of the commonest microfungi on Earth, occurring in all kinds of food and feed, in almost all climates. CIT is produced over the range of 15–30 °C and optimally at 30 °C. *Penicillium expansum* is known as a postharvest pathogen of fruits (e.g., apple) and vegetables. *P. expansum* also produces patulin [45].
A recent concern, although not related to CIT as a *Penicillium* toxin, is the presence of CIT in food colorings traditionally made in Asia from rice fermented with *Monascus purpureus* ("red mold rice"), which have been used for centuries for meat preservation and food coloring [51].

3. Important Dietary Sources of Ochratoxin A (OTA) and Citrinin (CIT)

3.1. Important Dietary Sources of OTA

The consumption of foodstuffs contaminated by OTA represents a major source of exposure to OTA in humans [54], while dermal contact or inhalation exposures to OTA show minor importance for the general population [55].

As such, OTA has been detected in foodstuffs of both plant and animal origin. In foodstuffs of plant origin, OTA has been found, in particular, in cereal products, beer, coffee, cacao, chocolate, spices (e.g., dried red pepper, chili powder, black pepper, cayenne pepper, nutmeg, coriander, ginger, curcuma), vegetables, green tea, pistachios, figs, raisins, grape juice, wine [56–66], liquorice and chestnuts [67,68]. Foodstuffs of animal origin, such as raw pork meat, pork blood products, kidney or poultry liver, are indirectly contaminated by OTA when animals are fed with contaminated feedstuffs [49,54,66,69]. However, meat products, such as raw ham muscle, cured meats, salami or dry-cured ham, may also be contaminated by OTA in a direct way. In particular, OTA is produced by the ochratoxigenic microfungi, *Penicillium nordicum*, growing on products made of pork meat during their ripening [47,48,54,69,70]. Cheese is also directly contaminated by OTA. The occurrence of OTA on the surface of hard cheese wheels has been repeatedly described in the literature [71]. The occurrence of OTA in blue cheese has also been reported. The available data clearly demonstrate that the contamination did not derive from contaminated milk, but it resulted from the molded spots of the ochratoxigenic microfungi (e.g., *Penicillium nordicum* as a contaminant in protein-rich food) on blue cheese [72].

The preliminary recent results of Czech research project No. NT 12051–3/2011 concerning the occurrence of OTA in foodstuffs of plant and animal origin in the years 2011–2013 are shown in Tables 5 and 6 [66].

The occurrence of OTA in animal products is not generally considered to be of major public health concern. In line with this opinion, we do consider, preliminarily, the risk associated with the consumption of food derived from animals fed with OTA-contaminated feeds to be negligible.

The analytical results will serve as a basis for an assessment of dietary exposure and health risk characterization of OTA for ten population groups 4–90 years of age for both sexes.

The dietary exposure of humans to OTA can be assessed by analyzing levels of OTA in biological materials, too. The use of biological markers in approximately the last two decades has indicated that humans are chronically exposed to OTA [3,73–75].
Table 5. The occurrence and amount of OTA in foodstuffs of plant origin.

| Foodstuffs         | n  | n+%  | Mean * (μg/kg) | Median * (μg/kg) | Range minimum-maximum (μg/kg) |
|--------------------|----|------|----------------|------------------|-----------------------------|
| hot red pepper     | 12 | 100  | 19.00          | 12.10            | 0.2–91.8                    |
| sweet red pepper   | 12 | 100  | 16.00          | 13.50            | 0.2–38.4                    |
| chili              | 12 | 92   | 6.70           | 3.43             | 0.1–32.7                    |
| spices mix         | 12 | 83   | 1.64           | 1.06             | 0.1–9.4                     |
| coffee instant     | 12 | 92   | 1.04           | 0.79             | 0.1–4.91                    |
| cocoa powder       | 12 | 50   | 0.94           | 0.31             | 0.1–4.1                     |
| black pepper       | 12 | 92   | 0.83           | 0.66             | 0.1–2.82                    |
| non-chocolate sweets | 12 | 83   | 0.67           | 0.78             | 0.1–1.78                    |
| biscuits           | 12 | 58   | 0.57           | 0.22             | 0.1–1.69                    |
| raisins            | 12 | 42   | 0.46           | 0.10             | 0.1–2.17                    |
| rice               | 12 | 8    | 0.41           | 0.10             | 0.1–3.76                    |
| sponge biscuits    | 12 | 58   | 0.41           | 0.15             | 0.1–2.14                    |
| coffee             | 12 | 58   | 0.41           | 0.22             | 0.1–1.04                    |
| chocolate sweets   | 12 | 50   | 0.29           | 0.17             | 0.1–1.16                    |
| bitter chocolate   | 12 | 42   | 0.29           | 0.10             | 0.1–1.01                    |
| chocolate wafers   | 12 | 75   | 0.24           | 0.22             | 0.1–0.56                    |
| muesli             | 12 | 17   | 0.23           | 0.10             | 0.1–1.44                    |
| beer 10°           | 12 | 83   | 0.066          | 0.05             | 0.005–0.26                  |
| lager beer         | 12 | 100  | 0.064          | 0.05             | 0.01–0.18                   |
| red wine           | 12 | 25   | 0.069          | 0.005            | 0.005–0.7                   |
| white wine         | 12 | 42   | 0.017          | 0.005            | 0.005–0.036                 |

Abbreviations: n+ (%), percentage of positive samples; * OTA levels < 0.2 μg/kg considered ½ limit of quantification (LOQ) = 0.1 μg/kg and OTA levels < 0.01 μg/kg considered ½ LOQ = 0.005 μg/kg, respectively (for drinks).

Table 6. The occurrence and amount of OTA in foodstuffs of animal origin.

| Foodstuffs  | n  | n+%  | Mean * (μg/kg) | Median * (μg/kg) | Range minimum-maximum (μg/kg) |
|-------------|----|------|----------------|------------------|-----------------------------|
| pork kidney | 12 | 8    | 0.13           | 0.10             | 0.10–0.46                   |
| pork meat   | 12 | 8    | 0.11           | 0.10             | 0.10–0.20                   |
| chicken liver | 12 | 8    | 0.12           | 0.10             | 0.10–0.28                   |

Abbreviations: n+ (%), percentage of positive samples; * OTA levels < 0.2 μg/kg considered ½ LOQ = 0.1 μg/kg.

3.2. Important Dietary Sources of CIT

CIT was found in foodstuffs of vegetable origin, e.g., cereals and cereal products, rice, pomaceous fruits (e.g., apples), fruit juices, black olive, roasted nuts (almonds, peanuts, hazelnuts, pistachio nuts), sunflower seeds, spices (e.g., turmeric, coriander, fennel, black pepper, cardamom and cumin) and food supplements based on rice fermented with red microfungi Monascus purpureus [51,59,76–82]. Cheese is also contaminated by CIT where toxigenic strains directly grow in the cheese mass [83]. An overview of previously reported literature data on the occurrence of CIT in foodstuffs in the years 1972–2010 was prepared by European Food Safety Authority (EFSA) [84].
The results of selected recent studies (2009–2013) on the occurrence of CIT in red mold rice are shown in Table 7.

**Table 7. The occurrence and amount of CIT in red mold rice.**

| Foodstuffs         | n | n+ (%) | Mean (mg/kg) | Range minimum-maximum (mg/kg) | References |
|--------------------|---|--------|--------------|-------------------------------|------------|
| Red mold rice      | 1 | 100    | -            | 1.43                          | [85]       |
| Red mold rice      | 1 | 100    | -            | 15.21                         | [86]       |
| Red mold rice      | 12| 33     | -            | 24–189                        | [87]       |
| Red mold rice      | 50| 100    | 4.03         | 0.23–20.65                    | [88]       |

Abbreviations: \( n^+ \) (%), percentage of positive samples.

In addition to CIT, several bioactive compounds (monascin, ankaflavin, lactone and acid forms of monacolin K) were determined to be in red mold rice used as an ingredient in food supplements [89]. The maximum level of the CIT in food supplements based on red mold rice is being prepared by the European Commission (Directorate General for Health and Consumers) right now [90].

4. Conclusions

All the recent information on both the “relevant” OTA and CIT producers and the new sources of exposure to OTA and CIT is very important for health risk assessment. It is recommended to promote the correct use of agrotechnological practices with regard to raw materials (e.g., good agricultural practices (GAP)) and processed products (hazard analysis and critical control points (HACCP)) in order to reduce the concentration of OTA and CIT in foodstuffs and to avoid the harmful effects resulting from the consumption of foods contaminated by OTA and CIT.

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Conflicts of Interest

The authors have no conflict of interests.

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