REVIEW
Toxicology

An overview of the toxicology and toxicokinetics of fusarenon-X, a type B trichothecene mycotoxin

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ABSTRACT. Fusarenon-X (FX) is a type B trichothecene mycotoxin that is frequently observed along with deoxynivalenol (DON) and nivalenol (NIV) in agricultural commodities. This review aims to give an overview of the literature concerning the toxicology and toxicokinetics of FX. FX is primarily found in cereals grown in temperate regions, but it can also be found worldwide because of the global transport of products. The major toxicity of FX occurs through inhibition of protein synthesis, followed by the disruption of DNA synthesis. Moreover, FX has also been shown to induce apoptosis in in vitro and in vivo studies. The targets of FX are organs containing actively proliferating cells, such as the thymus, spleen, skin, small intestine, testes and bone marrow. FX causes immunosuppression, intestinal malabsorption, developmental toxicity and genotoxicity. In addition, sufficient evidence of carcinogenicity in experimental animals is currently lacking, and the International Agency for Research on Cancer (IARC) classifies it as a group 3 carcinogen.

KEY WORDS: fusarenon-X, toxicity, toxicokinetics, trichothecene mycotoxin

Mycotoxins are secondary metabolites produced by molds that exert adverse effects on human and animal health. Mycotoxin contamination can occur during various steps in food production, including pre-harvest, harvest and storage. The Food and Agriculture Organization of the United Nations (FAO) estimated that approximately 25% of cereals produced worldwide are contaminated by mycotoxins [30]. The primary genera of fungi that produce mycotoxins are those of the Aspergillus, Penicillium, Alternaria, Fusarium and Claviceps species. Low-level contamination by Fusarium toxins is very common, and co-contamination is frequently observed in animal feed [54]. The most relevant groups of mycotoxins that contaminate agricultural crops are aflatoxins, ochratoxins, trichothecenes, zearalenones, fumonisins and ergot alkaloids.

Trichothecenes are a group of sesquiterpoid mycotoxins that are commonly produced by Fusarium fungi. More than 180 derivatives of trichothecenes have been identified and divided into four types—A, B, C and D—depending on their functional groups. Type A is characterized by a functional group other than a ketone at the C-8 position, whereas trichothecenes that have a carbonyl function at this position are identified as type B. The third group, type C, is characterized by a second epoxide ring at C-7,8 or C-9,10, whereas type D contains a macrocyclic ring system between C-4 and C-15 with ester linkages. Among trichothecene mycotoxins, types A and B are frequently found as contaminants in food for human and animal consumption [66]. A variety of adverse effects of trichothecenes, including emesis, growth retardation, immunotoxicity, neuroendocrine changes and interference with reproductive and growth hormone signaling, have been reported in experimental animals [45].

Fusarenon-X (FX) is a member of the 8-ketotrichothecenes, or type B trichothecenes, and is produced by several Fusarium species. FX has been frequently observed, along with deoxynivalenol (DON) and nivalenol (NIV) [13, 21], as a contaminant in agricultural commodities. Compared with that of other type B mycotoxins, oral administration of FX provoked a more profound anorexia in mice. In contrast, feed refusal induced in mice after intraperitoneal (i.p.) administration of FX was not as significant as that induced by NIV [69]. This was consistent with the results in the mink model, where FX produced emetic responses similar to DON, but of stronger potency than other DON congeners, following oral (p.o.) administration [68]. These findings indicated that, of the type B trichothecenes, FX is potentially toxic in experimental animals and humans after ingestion.
**OCCURRENCE AND MODE OF ACTION**

**Chemical structure**

The molecular structure of FX (3,7,15-trihydroxy-4-acetoxy-12,13 epoxytrichothec-9-en-8-one) includes a tetracyclic 12,13-epoxy-trichothec-9-ene skeleton with an epoxide ring at C-12,13 and a double bond at C-9,10. Its chemical structure is characterized by a hydroxyl (OH) group at the C-3,7,15 position and an acetyloxy (-OCOCH₃) group at the C-4 position (Fig. 1) [21, 62].

**Occurrence of FX:** The production of trichothecene metabolites depends on many factors, including the substrate, temperature and humidity [8, 13, 21, 25, 43, 62, 65, 72]. FX was first isolated from the *Fusarium nivale* strain, Fn-2B, which primarily produced FX at a temperature between 25°C and 27°C, but was also found to produce FX at 15°C [62]. The closely related species, *F. culmorum* and *F. crookwellense*, also generated FX in both cool and warm areas [21]. Moreover, *F. sulphureum*, *F. sambucinum*, and *F. solani* have been reported as capable of either producing or accumulating FX [71]. FX was found to be generated during an early stage of fungal growth and then deacetylated during further growth [62]. Furthermore, room temperature storage (20°C) was more likely to encourage accumulation of FX and other trichothecenes (T-2, diacetoxyscirpenol (DAS) and 3-acetyldeoxynivalenol (3-ADON)) than storage at cooler temperatures [71]. FX was found together with other *Fusarium* toxins produced by the same fungal species in cereals, including wheat, barley, corn, oats, maize and multigrain. It was also observed in maize silage and extracted oil seed [8, 13, 25, 43, 65, 72]. FX has been found most commonly in the temperate regions of Europe and Asia (Table 1), because these regions provide conditions suitable for *Fusarium* growth and FX production. However, FX can be found in agricultural commodities worldwide due to global product transport. Regarding health concerns, the European commission (EC) has established maximum levels of *Fusarium* toxins allowed in cereals and cereal products for human and animal consumption [14, 15]. The maximum level of DON in cereals intended for direct human consumption is 750 µg/kg [15]. The European Food Safety Authority (EFSA) has set the tolerable daily intake (TDI) of NIV at 1.2 µg/kg body weight (BW) [16]. In 2010, the Food Safety Commission in Japan (FSCJ) set a TDI for DON and NIV of 1 and 0.4 µg/kg BW, respectively [17]. However, guidance limits and TDI recommendations are currently not available for FX [12, 14, 15].

**Mechanism of action**

Several mechanisms of action have been reported for FX. Generally, FX is known to evoke a ribotoxic stress response, which inhibits protein and DNA synthesis in eukaryotic cells [44, 64]. FX bound to ribosomes and inhibited the second peptide bond formation, but not the polypeptide chain initiation [10, 11, 38]. Furthermore, FX dose-dependently encouraged DNA strand breakage of both dividing and differentiated Caco-2 cells. This action was stronger than that produced by its metabolite, NIV [7]. These proposed mechanisms of action suggest that FX is genotoxic to intestinal cells, although, in a previous study, FX exhibited a weak clastogenic effect on Chinese hamster V79-E cells [61]. The mechanisms of action of FX are yet to be fully understood. To elucidate this issue, further studies are needed.

**TOXICOKINETICS**

**Absorption and distribution**

FX is a highly lipid-soluble compound that is rapidly absorbed from the gastrointestinal tract of mice [48], broilers, ducks [47] and piglets [51]. The maximum plasma concentration of FX occurred after approximately 5 min in piglets [51], 12 min in ducks [47] and 30 min in mice [48]. Its oral bioavailability was higher in piglets (74%) [51], than in ducks (19.5%) and broilers (9.8%) [47]. Furthermore, the oral bioavailability of FX was reported to be higher than that of NIV in mice [9, 48].

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**Fig. 1.** Chemical structure of FX.
The maximum concentration of FX was detected in the liver, kidney and spleen of piglets 3 hr after oral exposure [51]. Its metabolite, NIV, was found in plasma as soon as 10 min after p.o. administration of FX in broilers and ducks [47]. These results concur with an in vitro study of microsomal nonspecific carboxyesterase in rats and rabbits that demonstrated that the C-4 acetyl residues of FX were hydrolyzed by microsomal carboxyesterase to yield NIV [41]. Altogether, these findings suggested that FX was rapidly metabolized to NIV (Fig. 2) after being absorbed from the gastrointestinal tract. In addition, in vitro studies concerning FX metabolism indicated that FX to NIV conversion occurred in the liver and kidney [41, 47, 48, 51]. Indeed, in vivo studies in mice, piglets, broilers and ducks [47, 48, 51], the liver and kidney were observed to be the primary organs for FX to NIV conversion. The highest conversion percentage was observed in the liver rather than the kidney in mice (93.99% vs. 27.91%). The conversion percentage was similar in the liver and kidney of ducks (98.95% vs. 94.32%) and piglets (90.91% vs. 89.72%), whereas the pattern was reversed in broilers (94.39% in the kidney vs. 70.12% in the liver) [47, 48, 51]. It is noteworthy that NIV was found in fetal and suckling mice via the placenta and the mother’s milk, respectively, after being metabolized to NIV in the maternal body [49]. In addition, NIV was reported to be metabolized to a de-epoxidated form by microorganisms [67]. The intestinal microflora is important for the biotransformation of trichothecenes. The presence or absence of particular intestinal microflora species can influence the extent to which an animal is sensitive to NIV, because the de-epoxidated products were shown to be less toxic than the parental molecules [26].

Elimination

After intravenous (i.v.) and p.o. administration of FX in piglets, both FX and NIV were observed in the urine and feces for up to 24 and 48 hr, respectively. Large amounts of NIV were detected in the urine after FX exposure [51]. FX and NIV were also detected in excreta of broilers and ducks after i.v. and p.o. administration of FX [47]. An early study [48] that administered 3H-FX to mice reported high and low radioactivity of NIV and FX in urine, respectively. Similarly, the feces of mice administered 3H-FX revealed a similar radioactivity pattern (high for NIV and low for FX). These findings suggested that FX was rapidly excreted.

### Table 1. Natural occurrence of FX

| Country          | Sample                  | Year  | Positive samples/Total numbers | Mean content (µg/kg) | References |
|------------------|-------------------------|-------|--------------------------------|----------------------|------------|
| Belgium          | Barley                  | 2014  | 1/65                           | NQ                   | [65]       |
| Belgium          | Wheat                   | 2014  | 1/93                           | 508                  | [65]       |
| Belgium          | Bread                   | 2014  | 2/25                           | 505                  | [65]       |
| Belgium          | Breakfast cereals       | 2014  | 3/20                           | 796                  | [65]       |
| Czech & U.K.     | Extracted oil seed      | 2008–2012 | 1/14               | 114                  | [72]       |
| Czech & U.K.     | Maize silage            | 2008–2012 | 1/77             | 77                   | [72]       |
| Czech & U.K.     | Complex feed for daily cows | 2008–2012 | 1/80                      | 80                   | [72]       |
| Italy            | Maize                   | 2005  | 5/31                           | 137                  | [8]        |
| Italy            | Oat                     | 2013  | 3/7                            | 21 ± 30 (26–75)      | [25]       |
| Italy            | Splet                   | 2013  | 2/3                            | 91.8 ± 54 (53.7–130) | [25]       |
| Italy            | Wheat                   | 2013  | 14/57                          | 18.44 ± 27 (12.5–102)| [25]       |
| Italy            | Barley                  | 2013  | 4/9                            | 18.43 ± 20 (27.5–47.3)| [25]       |
| Italy            | Rye                     | 2013  | 5/11                           | 28.52 ± 31 (42.4–70.2)| [25]       |
| Italy            | Whole cereals           | 2013  | 5/6                            | 40 ± 38.4 (23.4–102) | [25]       |
| Korea            | Conventional cereals    | 2009  | 9/99                           | 10.7 (6.8–18.7)      | [42]       |
| Korea            | Organic cereals         | 2009  | 16/88                          | 7.3 (0.9–18.7)       | [42]       |
| Korea            | Rice                    | 2009  | 10/65                          | 9.1                  | [43]       |
| Korea            | Glutinous rice          | 2009  | 2/11                           | 5.4                  | [43]       |
| Korea            | Brown rice              | 2009  | 1/48                           | 18.7                 | [43]       |
| Korea            | Barley                  | 2009  | 6/39                           | 6.8                  | [43]       |
| Korea            | Mixed grains            | 2009  | 13/40                          | 11.0                 | [43]       |
| Korea            | Corn                    | 2009  | 6/25                           | 8.7                  | [43]       |
| Korea            | Wheat                   | 2009  | 4/54                           | 7.9                  | [43]       |
| Korea            | Wheat flour             | 2009  | 2/38                           | 9.0                  | [43]       |
| Korea            | Breakfast cereals       | 2009  | 7/18                           | 7.1                  | [43]       |
| Japan            | Rice                    | 2005  |                                | 1900                 | [59]       |
| Poland           | Corn                    | 2014  |                                | 7.9–36.47            | [3]        |
| Saudi Arabia     | Commercial animal feed  | 1997–2000 |                          | 3.13–600             | [1]        |
| Spain            | Barley                  | 2007  | 2/100                          | 17.45                | [22]       |
| Spain            | Barley                  | 2008  | 1.5/100                        | 3.6                  | [23]       |
| Spain            | Multigrain              | 2009  | 2/46                           | 27.2 (15.2–42.4)     | [39]       |
| Spain            | Wheat-based cereals     | 2012  | 1/119                          | 10.8                 | [50]       |

NQ: not quantifiable.
(before 24 hr) or almost totally transformed into NIV [26, 67] and excreted in urine. FX tissue concentrations were found to be similar among the tissues tested in mice (heart, lung, liver, stomach, kidney, spleen, thymus, mesenteric lymph nodes, bone marrow, small and large intestine, cecum, muscle, brain and skin) [48]. This led researchers to speculate that the toxicity of FX on thymus, spleen, bone marrow and mesenteric lymph nodes was not strictly related to FX accumulation, but also to that of its metabolites.

**TOXICITY**

Table 2 summarizes the 50% lethal doses of FX to animals. In mice, signs of acute toxicity were similar following administration of a single dose of FX via a variety of routes [62]. Oral exposure of FX exerted equipotent toxicity in newborn mice and rats [62]. FX primarily affected organs containing rapidly proliferating cells, including the thymus, spleen, small intestine, testes, skin and hematopoietic tissues [21]. It led to a variety of adverse effects reported below.

**Cytotoxicity**

FX alone showed greater toxicity than NIV and other type B trichothecenes in various cell lines, including U-937 macrophages [55], HL-60 cells [36], RAW 264.7 murine macrophages [40], SF-9 insect cells [18] and Caco-2 cells [2, 7]. Binary combinations of DON-FX and NIV-FX administered at low concentrations exhibited synergistic toxicity on Caco-2 cells, but a tertiary combination (DON-NIV-FX) exhibited antagonistic effects [2].

**Table 2. Comparative LD<sub>50</sub> values (mg/kg) of FX by various routes of administration in different animal species [62]**

| Animal species | FX LD<sub>50</sub> (mg/kg) |
|---------------|---------------------|
|               | IV      | IP    | SC  | PO    | IM    |
| Mouse         | 3.4     | 3.4   | 4.2 |       |       |
| Newborn mouse | 0.2     | 4.5   |     |       |       |
| Rat           | 0.5     | 4.4   |     |       |       |
| Guinea pig    | 0.5     | 0.1   |     |       |       |
| Cat           | <5.0    |       |     |       |       |
| Duckling      | 2.0     |       |     |       |       |
| Chick         | 33.79   |       |     |       |       |
Oryzias latipes (medaka) demonstrated no evidence of carcinogenetic effects, whereas other toxins (aflatoxin B1 and G1) of tumorigenicity [52]. These facts might indicate that FX lacks mutagenic and tumorigenic abilities. Furthermore, treatment with test assay [63]. In male Donryu rats, daily ingestion of FX (7 or 3.5 mg/kg FX in the diet) for 1 or 2 years showed slight incidences [21]. Carcinogenicity has been classified as a group 3 carcinogen by the International Agency for Research on Cancer (IARC), which indicates it is not carcinogenic to humans [6]. Mixed mycotoxins (aflatoxin B1 and G1, sterigmatocystin, ortho-aminoazotoluene, methylazoxymethanol acetate and \(-\text{nitrosodiethylamine}) induced hepatic carcinomas in rats [57].

FX caused cell cycle delay, chromosomal aberrations and sister chromatid exchanges in Chinese hamster V79-E cell lines through the inhibition of protein synthesis [61]. In addition, FX produced DNA strand breaks in dividing and differentiating human intestinal (Caco-2) cells in a dose-dependent manner [7].

Carcinogenicity

Many studies have evaluated the carcinogenicity of FX, as its carcinogenic properties have long been suspected. Among the tested toxins (aflatoxin B1 and G1, sterigmatocystin and O-acetylsterigmatocystin), FX failed to induce mutagenesis by the Ames test assay [63]. In male Donryu rats, daily ingestion of FX (7 or 3.5 mg/kg FX in the diet) for 1 or 2 years showed slight incidences of tumorigenicity [52]. These facts might indicate that FX lacks mutagenic and tumorigenic abilities. Furthermore, treatment with FX in medakas (Oryzias latipes) demonstrated no evidence of carcinogenetic effects, whereas other toxins (aflatoxin B1 and G1, sterigmatocystin, ortho-aminoazotoluene, methylazoxymethanol acetate and \(-\text{nitrosodiethylamine}) induced hepatic carcinomas [20]. Despite these findings, there is insufficient evidence to show that FX is carcinogenic in experimental animals. In addition, FX has been classified as a group 3 carcinogen by the International Agency for Research on Cancer (IARC), which indicates it is not carcinogenic to humans [21].

Developmental toxicity

FX can transfer its toxicity to fetuses via the placenta after being metabolized to NIV in the maternal body [49]. A single subcutaneous injection of FX (0.63–2.6 mg/kg BW) caused abortion in pregnant mice in a dose dependence manner, whereas FX ingestion (5, 10 and 20 mg/kg BW) inhibited embryonic implantation during the early phase and throughout the pregnancy period [24]. Oral administration of FX (3.5 mg/kg BW) to pregnant mice induced apoptosis in fetal brains, especially in the telencephalon [57].

Other toxicities

Other toxicities of FX have been also reported. Application of FX (5 µg/site) alone on the shaved skin of guinea pigs induced erythema and hardening due to degenerating fibrocytes and infiltrating cells in the corium [6]. Furthermore, when mycotoxin mixtures were tested, a synergism appeared after DAS-FX treatment, whereas T-2 toxin-FX mixtures provoked an antagonistic effect [6]. The antiviral activity of FX was demonstrated against herpes simplex virus type 1 (HSV-1) (50 ng/ml) and HSV type-2 (HSV-2) (26 ng/ml). This occurred at the viral replication stage after virus adsorption in the host cells [60].

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CONCLUSION

FX is a type B trichothecene and is produced by several Fusarium species. This toxin is predominantly found in temperate regions, but is likely present worldwide because of the global movement of products. FX is usually found as a co-contaminant with DON and NIV in agricultural commodities. Although FX is detected at low levels as a contaminant, its toxicity in experimental animals has been found to be stronger than that reported for other members of the same trichothecenes type B family. However, no regulations or guidelines currently exist for FX. This toxin primarily impacts organs containing actively dividing cells. Common adverse effects include immunosuppression and intestinal malabsorption. The major mechanism of action of FX is inhibition of protein synthesis, but FX can induce apoptosis and alter genetic material causing cell cycle delays, chromosomal aberrations and sister chromatid exchanges. Moreover, FX exhibits a developmental toxicity by inducing abortion and inhibiting embryonic implantation. Carcinogenicity in experimental animals and humans is yet to be completely clarified. For this reason, additional research in this field is warranted.

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