Review

# The intestine as a possible target for fumonisin toxicity

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Fumonisins constitute a family of toxic and carcinogenic mycotoxins produced by *Fusarium verticillioides* (formerly *F. moniliforme*), a common fungal contaminant of corn. Contamination with fumonisin $B_1$ ($FB_1$) is of concern as this mycotoxin causes various animal diseases. The gastrointestinal tract represents the first barrier against ingested chemicals, food contaminants, and natural toxins. Following ingestion of fumonisin-contaminated food or feed, intestinal epithelial cells could be exposed to a high concentration of toxin. In this review, we have summarized the data dealing with the impact of $FB_1$ on the intestine. Although $FB_1$ is poorly absorbed and metabolized in the intestine, it induces intestinal disturbances (abdominal pain or diarrhea) and causes extra-intestinal organ pathologies (pulmonary edema, leukoencephalomalacia, or neural tube defects). The main toxicological effect of $FB_1$ reported *in vivo* and *in vitro* is the accumulation of sphingoid bases associated with the depletion of complex sphingolipids. This disturbance of the sphingolipid biosynthesis pathway could explain the other observed toxicological effects such as an alteration in intestinal epithelial cell viability and proliferation, a modification of cytokine production, and a modulation of intestinal physical barrier function.

**Keywords:** Barrier integrity / Fumonisin $B_1$ / Intestine / Pathology / Sphingoid bases

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## 1 Introduction

Mycotoxins are secondary metabolites produced by fungi. They are not essential to mold growth but they sporadically contaminate crops, causing major economic losses every year. Most of the mycotoxins of concern are produced by *Aspergillus*, *Penicillium*, *Fusarium*, *Claviceps*, and *Stachybotrys*. The consumption of food or feed contaminated by mycotoxins is a potential health hazard for both humans and animals [1, 2].

Fumonisins are ubiquitous contaminants of corn and other grain products produced by *Fusarium verticillioides* (formerly *F. moniliforme*) and several other *Fusarium* species. Contamination with fumonisin $B_1$ ($FB_1$) is of concern as this mycotoxin causes various animal diseases: leukoencephalomalacia in horses, pulmonary edema in pigs, nephrotoxicity in rats, rabbits and lambs, and hepatotoxicity in all species examined [3]. This toxin has also been reported to be a carcinogenic agent in rodents and a contributing factor in human esophageal cancers [4]. It has been postulated that fumonisin exerts its toxicological effects *via* inhibition of the enzyme ceramide synthase, leading to the increase in the concentration of sphingoid bases (sphinganine (Sa) and sphingosine (So) and their phosphorylated derivatives) as well as the depletion of ceramide and complex sphingolipids [5–7]. The gastrointestinal tract has two conflicting roles: first, it plays a major function in the absorption of nutrients; secondly at the same time, it maintains a barrier between the internal and external environments [8]. The continuous monolayer of epithelial cells that lines the small and large intestine restricts the passage of potentially harmful molecules from the intestinal tract into the surrounding tissues. Intestinal epithelial cells are also able to secrete defense molecules such as mucus, antimicrobial peptides, Igs, and cytokines [9].

The gastrointestinal tract represents the first barrier against ingested chemicals, food contaminants, and toxins. Following ingestion of mycotoxin contaminated food or feed, intestinal epithelial cells could be exposed to a high concentration of $FB_1$ [10]. This paper will review the effects of this mycotoxin on the intestinal tract and on the exposed intestinal epithelial cells (Fig. 1).

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**Abbreviations: $FB_1$,** fumonisin $B_1$; **Sa,** sphinganine; **So,** sphingosine

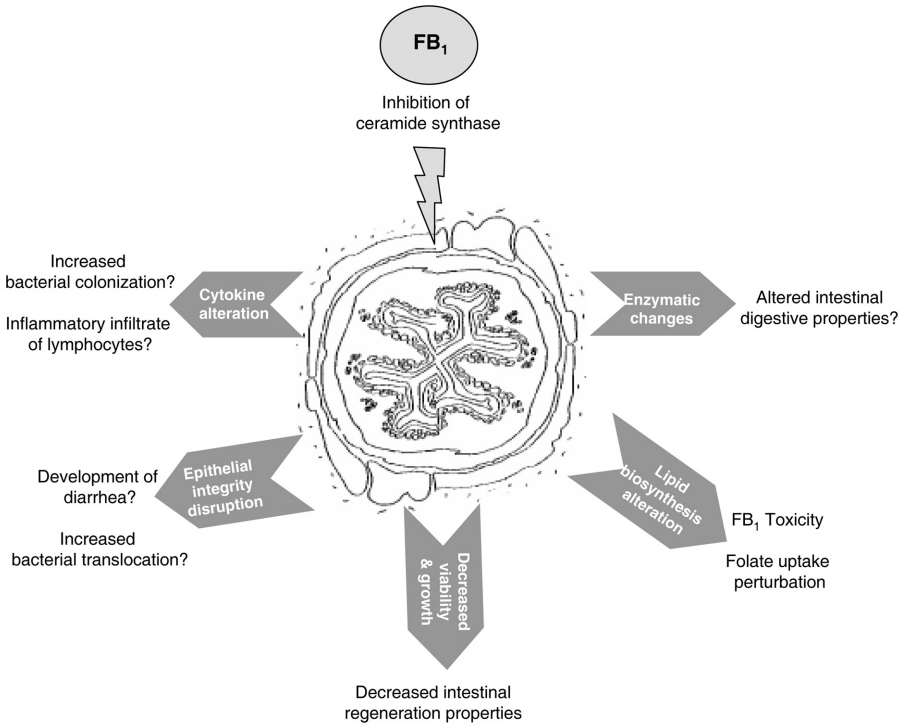


**Figure 1.** Summarized impacts of $FB_1$ on the intestine and intestinal cells. The hypothetical consequences of $FB_1$ in terms of pathologies and intestinal disturbances are presented with a question mark.

## 2 $FB_1$ toxico-kinetics

### 2.1 Absorption, distribution, and elimination of $FB_1$

In rats and most other animals, the absorption kinetic of $FB_1$ indicates a rapid distribution and elimination that is adequately described by a two- or three-compartment model [11]. Only a low level of $FB_1$ is detected in plasma and tissues after oral administration, indicating that the absorption is negligible. Indeed, in cows and laying hens, systemic absorption of orally given $FB_1$ is less than 1% [12, 13]. In pigs, the bioavailability of $FB_1$ following intragastric administration is estimated to be 3–6% [12]. In rats, after intragastric administration of the toxin, up to 80% of the radiolabel is recovered in feces and up to 3% in urine [14]. After a prolonged animal exposure, small traces of $FB_1$ are found in the liver and kidneys, while no detectable quantity is reported in other organs [15]. The poor absorption of this mycotoxin has been qualified by Shier [15] as the "fumonisin paradox" (how can a toxin cause agriculturally significant diseases and possibly human cancers if it is not effectively absorbed after oral administration?). Whether this poor absorption and consequent low bioavailability is due to poor transport across the epithelium of the intestine or due to the strong association of fumonisin with the intestinal content remains uncertain.

The absorption of $FB_1$ by enterocytes has also been studied *in vitro*. Using Caco-2 cells that, despite their colonic origin, are representative of human small intestine enterocytes, Caloni *et al.* [16] showed no absorption of $FB_1$ and partially hydrolyzed metabolites by undifferentiated or differentiated cells. By contrast, absorption of totally hydrolyzed $FB_1$ (aminopentol, also named AP1 or HFB1) was evident in differentiated Caco-2 cells, which expressed enzymatic and metabolic characteristics of mature enterocytes [17]. Involvement of the P-glycoprotein in the influx/efflux mechanisms of aminopentol in the intestinal cells has been suggested in the same study [17]. A preferential accumulation of FB1 in nonintestinal organ such as kidney has also been demonstrated [7].

Intestinal cells are exposed to a substantial portion of the fumonisin that is ingested. Indeed, 24 h after administration of radiolabeled $FB_1$, intestinal epithelial cells of nonhuman primates contained 25% of the dose [18]. The major route of elimination of $FB_1$ is *via* bile and the excreted toxin is still biologically active [19]. Therefore, enterohepatic circulation probably increases the exposure of the intestine to the mycotoxin, at least for rats and pigs [10, 14, 20]. Recent data have indicated an interaction between $FB_1$ and cholesterol and/or bile salts, which may lead to the incorporation of dietary $FB_1$ into mixed micelles. This would facilitate the $FB_1$ intestinal absorption and its biliary excretion [21].

 

### 2.2 Biotransformation of $FB_1$

Although the liver plays a major role in drug metabolism (*e.g.* by oxidative cytochrome P450 (CYP)-dependent phase I and conjugation or phase II reactions), drug metabolizing enzymes are also present at other sites. For example, the intestinal mucosa contains at least three CYP families [22] and is able to metabolize drugs *via* phase I and II reactions [23]. There is little or no evidence that fumonisin is metabolized *in vitro* or *in vivo*. Indeed, Cawood *et al.* [24] failed to indicate any metabolism of fumonisins by microsomal esterases or by cytochrome P-450 monooxygenases. More recently, Spotti *et al.* [25] reported no metabolism of $FB_1$ by bovine liver microsomes.

Fumonisins are excreted primarily in the feces, either unchanged or depleted of one ester-linked tricarballylic acid (at the C14-position). Only trace amounts of aminopentol, the fully hydrolyzed $FB_1$, were found in feces [26]. As no hydrolyzed product has been found in the urine or bile, it is assumed that the hydrolysis occurs in the gut, probably performed by microorganisms [18, 26, 27].

Aminopentol is a substrate for the ceramide synthase. The product of this reaction, *N*-palmytoyl-hydrolyzed $FB_1$ also called PAP1, is at least ten times more toxic than $FB_1$ or aminopentol as demonstrated by *in vitro* studies on the human colonic intestinal cell line HT-29 [28]. However, it is not known if this compound is formed *in vivo*.

## 3 Pathologic manifestations in the gastrointestinal tract following $FB_1$ ingestion

### 3.1 Data obtained from human studies or from laboratory and domestic animal studies

In various regions of the world, an association has been established between the occurrence of *F. verticillioides* on maize and the incidence of the development of esophageal cancer in humans [29]. An epidemiological survey in India also indicated that consumption of moldy sorghum and maize containing $FB_1$ (in the range of 0.14–7.8 and 0.25–64.7 mg/kg, respectively) resulted in human gastrointestinal disease characterized by abdominal pain, borborygmi, and diarrhea [30]. As in humans, $FB_1$ concentrations up to 8.5 mg/kg were associated with diarrhea in laying hens and 1-day-old cockerels [30].

Epidemiological studies are now being conducted to establish the correlation between $FB_1$ concentrations in food and the development of other pathologies such as liver cancers and neural tube defects [31].

### 3.2 Histological alterations of the intestine

Despite the fact that, after oral contamination, the small intestine is exposed to the highest concentration of $FB_1$, this is not the organ most affected by the toxin. In the rat, subchronic experimental mycotoxicosis (100 ppm $FB_1$, 90 days) induces lymphocytic infiltrate in the small intestine and also increases the number of mitotic figures in the intestinal crypts [32]. Similarly, an inflammatory infiltrate and a necrosis were observed in 50% of mice fed for 60 days with a diet contaminated with 10 ppm $FB_1$ [33].

In domestic animals, hyperplasia of intestinal goblet-cells was observed in broiler chicks receiving the toxin (300 mg $FB_1$/kg body weight (b.w.) for 2 wk; [34]). In pigs, we recently showed that ingestion of pure $FB_1$ (1.5 mg/kg b.w., for 7 days) induces a marked proliferation of lymphatic nodules in the terminal part of the ileum and in the cecum as well as a diffuse infiltration of lymphocytes in these parts of the intestine [35]. These observations have been confirmed by Piva *et al.* [36] which recently showed a severe infiltration of lymphocytes and monocytes as well as a moderate infiltration of eosinophils in all parts of the small intestines of weaning piglets exposed to a diet containing 30 mg of $FB_1$/kg of feed.

### 3.3 Functional impairments in the intestine

Consumption of pure $FB_1$ or $FB_1$-contaminated feed can induce a reduction of body weight in piglets. Indeed, average daily gain for castrated growing pigs decreased by 8 and 11% for animals exposed for 8 wk to feed contaminated with 1 and 10 ppm of pure $FB_1$ respectively [37]. Nevertheless, a shorter exposure to the toxin (10 ppm for 1 or 4 wk) does not affect the weight gain of weaned piglets [38, 39]. The former data suggest that $FB_1$ could impair the intestinal absorption of nutrients. This could be explained, at least in part, by the villous fusion and atrophy observed in the intestine of pigs treated with 30 mg of $FB_1$/kg of feed [34] and in the intestine of chicks fed with 61–546 ppm of $FB_1$ [40]. In this later study, fibrinoid necrosis of the tunica media of arteries and veins in the muscularis layers of the small intestines has also been observed [40].

*In vitro* treatment of Caco-2 cells with $FB_1$ also inhibits folate uptake by this human intestinal cell line [41]. This effect is due to the inhibition of sphingolipid biosynthesis and the subsequent inhibition of the GPI-anchored folate receptor. Because folate deficiency causes neural tube defects, fumonisins are considered as potential risk factors for embryonic development [42].

### 3.4 Susceptibility to intestinal infections

$FB_1$ can be considered as a predisposing factor to intestinal infectious diseases. Indeed, in our laboratory, we have examined the effect of dietary exposure of $FB_1$ on the intestinal colonization by opportunistic pathogenic *Escherichia coli*. For six days weaned pigs received daily a low concentration of $FB_1$ as a crude extract or as a purified $FB_1$ (0.5 mg/kg b.w./day) and, on the last day of the mycotoxin

 

treatment, pigs were orally inoculated with *E. coli*. We observed that colonization of the ileum, cecum, and colon by the pathogenic *E. coli* strain was significantly increased (10–100-fold) in animals that received the mycotoxin [39]. Using a similar approach, a recent study dealing with the impact of consumption of *F. verticillioides* culture material containing $FB_1$ on progress of *Salmonella gallinarum* infection in Japanese quail revealed that clinical signs of diarrhea with bloody discharges were more pronounced in the *Salmonella*-infected birds on the $FB_1$ diet [43].

## 4 Intestinal toxicity of $FB_1$

Two major modes of action have been proposed to explain $FB_1$-induced animal diseases. Both involve the disruption of lipid metabolism as the initial molecular event. They lead ultimately to lipid-mediated alterations in signaling and metabolic pathways which are crucial to cell biological processes such as cell cycle regulation, differentiation, and apoptosis. One mechanism involves changes in the PUFA and phospholipid pools in the liver caused by the disruption by $FB_1$ of *Delta6* desaturase and cyclooxygenase metabolic pathways [3, 44]. The other mechanism is based on an inhibition of ceramide synthase, a key enzyme in the *de novo* biosynthesis of sphingolipids [3, 5]. This latter mechanism has been proposed to explain most of the effects of $FB_1$ on the intestine.

### 4.1 Disruption of the sphingolipid biosynthesis pathway in the intestine

$FB_1$ inhibits ceramide synthase which causes a rapid increase in the intracellular concentrations of Sa, and to a lesser extent in So. As this disruption in the sphingolipid pathway occurs before other indicators of cell injury, the Sa/So ratio has been proposed as a biomarker of fumonisin exposure [45].

Mice treated subcutaneously or orally with $FB_1$ (25 mg/kg b.w., single dose) presented a transient increase of Sa and So in the small intestine [19]. The rapid rate of cell turnover in the intestine could contribute to the transient nature of the elevation in free Sa in this organ. Data obtained *in vitro* indicate a direct fumonisin inhibition of ceramide synthase in intestinal epithelial cells. Indeed, studies performed on the human colonic epithelial intestinal cell line, HT-29, demonstrated an increase in free sphingoid bases by $FB_1$, in time- and dose-dependent manner [46].

$FB_1$ metabolites also alter the sphingolipid pathway in intestinal epithelial cells. The hydrolyzed form of $FB_1$, AP1, causes an elevation in Sa and toxicity in HT-29, although the potency of this compound is reduced by at least five-fold [47]. By contrast, PAP1, which also inhibits ceramide synthase in Caco-2 cells, another human colonic cell line, seems more toxic than $FB_1$ or AP1 [28].

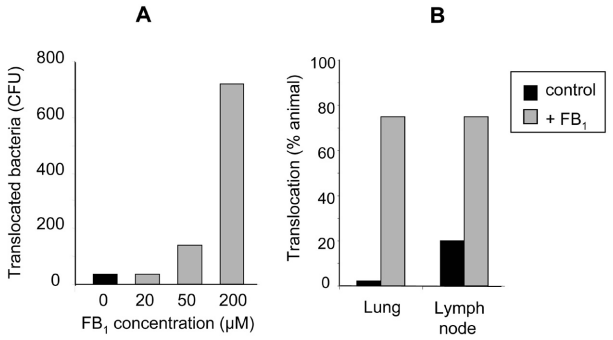


**Figure 2.** $FB_1$ increases bacterial translocation across the intestinal epithelium. Panel A: *In vitro* translocation of bacteria through a monolayer of porcine intestinal epithelial cells. IPEC-1 cells were differentiated in Transwell filters with 3 μm pores and treated with 0–200 μM $FB_1$. $2 \times 10^6$ CFU of *E. coli* strain 28C strain were then added in the apical compartment of the Transwell filters. Bacterial translocation was evaluated 4 h later by counting the number of bacteria present in the basal compartment following plating on tryptic soy agar plates. Panel B: *In vivo* translocation of bacteria in the lungs and lymph nodes of piglets orally treated with $FB_1$. Pigs were dosed for 7 days with 0.5 mg/kg b.w. of a crude extract of $FB_1$ or with PBS. On the last day of $FB_1$ administration, the animals were orally inoculated with $1 \times 10^9$ *E. coli* strain 28CNal$^r$ and were euthanized 1 day later. Lungs and mesenteric lymph nodes were sampled, homogenized, and plated on tryptic soy agar plates supplemented with nalidixic acid. For each organ, data represent the percent of animals for which bacteria were counted in the examined organs. Data from [39].

### 4.2 Impact of $FB_1$ on the viability and proliferation of intestinal epithelial cells

The increase in free Sa observed in the HT-29 cell line, following $FB_1$ treatment, induces a significant reduction in cell number *via* growth inhibition and apoptosis induction [46]. The well-characterized human colonic cell line, Caco-2, is also very sensitive to $FB_1$: mitochondrial metabolism is affected with an $IC_{50}$ of 21 μM as revealed by the MTT test [47]. By contrast, $FB_1$ has no impact on other viability parameters as membrane permeability detected by neutral red test [47] and as cellular macromolecule synthesis [16]. Using the epithelial IPEC-1 cell line, derived from the small intestine of a newborn piglet, we reported an inhibition of cell proliferation by $FB_1$, due to a blockade of cells in the G0/G1 phase of the cell cycle [48].

At higher doses, a cytotoxic effect of $FB_1$ on intestinal epithelial cells has been reported [46, 48]. Both studies indicate that proliferating cells are more sensitive than confluent cells to the toxic effect of $FB_1$.

### 4.3 Impact of $FB_1$ on the physical barrier function of intestinal epithelial cells

Intestinal epithelial cells form a physical barrier which can be reproduced *in vitro* by the culture of intestinal epithelial

 

cells on a porous filter. In this model, the barrier function and the monolayer integrity can be assessed by the determination of the transepithelial electrical resistance (TEER). Using the porcine intestinal cell line, IPEC-1, we demonstrated that a prolonged exposure of the intestinal monolayer to $FB_1$ prevents the establishment of the TEER and alters the resistance of an already established monolayer [48]. Consequently, we showed that *E. coli* bacteria added on the apical side of an $FB_1$-treated intestinal cell monolayer translocated to the baso-lateral compartment (unpublished data, Fig. 2, panel B). Such results may explain the *in vivo* translocation of experimentally inoculated pathogenic *E. coli* from the intestinal tract to the extra intestinal organs (mesenteric lymph nodes, lungs, and kidneys) observed in piglets fed with $FB_1$ ([39], Fig. 2, panel B).

### 4.4 Effects of $FB_1$ on intestinal epithelial cell cytokine production

Intestinal epithelial cells are major sources of cytokines and chemokines, molecules involved in the regulation of the immune system [6, 49]. Among them, IL-8 is of particular interest because it is involved in the recruitment of polymorphonuclear neutrophils at the site of infection, mediating the nonspecific acute inflammatory response.

Even though $FB_1$ has been shown to alter cytokine production in several organs and cell types [49–54] only limited data are available concerning the impact of $FB_1$ on cytokine production in the intestine. We investigated the effect of $FB_1$ on inflammatory cytokine production in the intestine. We showed that ingestion of $FB_1$ (0.5 mg/kg b.w., 7 days) by piglets decreases the expression of IL-8 mRNA in the ileum [55]. Such results were confirmed by *in vitro* experiments: $FB_1$ decreases the expression of IL-8 from porcine epithelial intestinal cells, both at the mRNA and protein level [55]. This decrease in IL-8 caused by $FB_1$ may lead to a reduced recruitment of inflammatory cells in the intestine during infection and may participate in the observed increased susceptibility of $FB_1$-treated piglets to intestinal infections [39].

## 5 Conclusion

In conclusion, ingestion of purified $FB_1$ and/or contaminated cereals induces species specific pathologies in humans and animals. Even if this mycotoxin has not been associated with a specific intestinal disease, the data available indicate that it disturbs the intestinal lipid biosynthesis pathway and induces cytotoxicity on intestinal epithelial cells. $FB_1$ also inhibits intestinal epithelial cell proliferation and disrupts their barrier function. In addition, recent data from our laboratory indicate that $FB_1$ affects cytokine production at the intestinal level (Fig. 1). All these effects may affect human and animal health and contribute to the specific pathologies observed in humans and animals as well as the increased susceptibility to intestinal infections.

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