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RISK OF FISH MYCOTOXICOSIS IN AQUACULTURE
(review)

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Abstract

Modern fish aquaculture is a large-scale and rapidly developing industry of global production (FAO, 2018). In order to improve the quality of the products produced, an active search is underway for effective ways to control the safety of artificial feeds (J. Bostock et al., 2010). Based on the results of monitoring projects carried out in Argentina, Brazil, the United States, China, Korea and Central European countries (C. Pietsch et al., 2013; B.T.C. Barbosa et al., 2013; M. Greco et al., 2015; L. Pinotti et al., 2016), the situation of contamination of fish feed with mycotoxins is recognized as extremely serious both in terms of prevalence and content, and in terms of combined occurrence (I. Matejova et al., 2017; C. Pietsch, 2019). For the Russian fishery, which in recent years has become a multi-destination, specialists of academic and university science, as well as industry research institutes proposed feed rations that account for age and species characteristics of fish (J.A. Zheltov, 2006; Y.V. Sklyarov, 2008), and discussed in detail the problem of microbial contamination (I.V. Burlachenko, 2008). In the Russian Federation, mandatory requirements for compliance with quality and safety indicators have been introduced for raw materials and finished feed products (GOST 10385-2014) and a modern methodological base for mycotoxicological control has been created (GOST 31653-2012, GOST 31691-2012, GOST 32587-2013, GOST 34108-2017, GOST R 51116-2017).The purpose of this review is to update information on mycotoxin contamination of domestic raw materials for the production of aquafeeds, to generalize world data on the nature of acute action of the most occurring contaminants, as well as to analyze clinical signs, pathologic-anatomical and biochemical changes accompanying chronic fish mycotoxicosis. In recent years, we have received convincing evidence that the group of the most likely contaminants of raw ingredients — wheat, barley and corn flour, bran, sunflower cake and meal — includes T-2 toxin, deoxynivalenol, fumonisins of group B and zearalenone, related to fusariotoxins, as well as alternariol, ochratoxin A, citrinin, cyclopiazonic acid, mycophenolic acid and emodin (G.P. Kononenko et al., 2018, 2019). Analysis of world data on experimental mycotoxicoses of different age groups of common carp (*Cyprinus carpio*), channel catfish (*Ictalurus punctatus*), grass carp (*Ctenopharyngodon idellus*), Nile tilapia (*Oreochromis niloticus*), rainbow trout (*Oncorhynchus mykiss*), Atlantic salmon (*Salma salar*), shows that fusariotoxins should be considered as key risk factors and efforts should continue to refine their safe thresholds. Intoxications caused by ochratoxin A remain insufficiently studied, and the situation with regard to other possible feed contaminants is unclear. Reasonable proposals for regulation in fish feed were reported only for T-2 toxin for common carp (V.T. Galash, 1988), for deoxynivalenol — for grass carp (C. Huang et al., 2018, 2019, 2020) and Atlantic salmon (A. Bernhoft et al., 2018), for fumonisin B_1 — for channel catfish (M.N. Li et al., 1994, S. Lumlertdacha et al., 1995). Data on the degree of retention of these mycotoxins in fish tissues is limited (C. Pietsch et al., 2014, 2015; A. Ananter et al., 2016), and therefore regulations on product residues have not yet been adopted. However, the search for new approaches to correctly assess the consequences of their negative effects and transmission to fish products continues, and this leaves no doubt that a solution will be found.

Keywords: aquaculture, fish mycotoxicoses, feed raw materials, combined feeds, mycotoxins

Nowadays, aquaculture is a rapidly developing global industry. The total market value of its products at initial sales prices in 2016 reached 232 billion US dollars [1]. The search for new forms, methods, techniques, technologies and novel

approaches aimed at increasing the efficiency of artificial fish farming and expanding its assortment is especially active [2]. The importance of studies of mycotoxins in fish feed became apparent for the first time in the early 1960s, when massive outbreaks of rainbow trout aflatoxicosis, accompanied by the development of hepatocellular carcinomas, were recorded in the United States with the use of cotton seed meal [3]. Surveys and experiments showed that other mycotoxins also negatively affect non-commercial fish, causing varying degrees of intoxication and specific signs [4-6].

In each country, fish feed safety is mainly related to the of mycotoxins naturally contaminating ingredients of plant origin which are the main sources of protein for fish of low trophic levels. Monitoring studies carried out in Argentina, Brazil, the United States, China, Korea and Central European countries [7-10] have assessed the real situation in the national fish farming and drown to a holistic idea of the overall scale of the threat. Feed contamination with mycotoxins is recognized as extremely high in prevalence, content, combined occurrence and leading, according to world experts, to significant economic losses [11, 12].

In recent years, due to government support [13], Russian fish farming has become a developed industry for rearing mainly carp, herbivorous fish and salmon. Russian scientists have developed balanced species-specific and age-specific recipes of compound feeds with recommendations for fish feeding procedure and feed quality control [14-17] and considered in detail the risks posed by microbial contamination [18]. However, there are few studies on the effect of mycotoxins on fish and attempts to systematize the information necessary for specialists are very schematic [19, 20].

This review aims to update information on mycotoxin contamination of raw materials used for the production of aquafeeds, to generalize world data on the acute action of the most likely contaminants, ana to analyze clinical, pathological and biochemical changes accompanying acute and chronic mycotoxicosis of fish.

Raw materials of vegetable origin in the recipes of domestic mixed feeds are mainly represented by wheat, barley and corn flour, bran, sunflower cake and meal [14, 16, 17]. For grain intended for fodder purposes, contamination with fusaryotoxins with an extensive occurrence of T-2 toxin (T-2) and deoxynivalenol (DON), sometimes together with zearalenone (ZEN), is characteristic and fumonisin B_1 (FUM B_1) is often found in corn kernels [21-25]. Focal contamination of grain with ochratoxin A (OA) was also established [26], and frequent cases of joint detection of OA and citrinin were revealed in grain of wheat, maize and in fodder products from processed sunflower seeds [27, 28]. Typical contaminants of sunflower cake and meal are OA and alternariol, as well as citrinin, cyclopiazonic acid, mycophenolic acid, and emodin [29]. Aflatoxins associated with the main threat to the aquaculture sector in most countries of the African and Asia-Pacific regions [30] are extremely rare in Russian feed raw materials, therefore, they are not considered in this work.

1. Lethal doses of mycotoxins for various fish species after a single oral (po) **and intraperitoneal** (ip) **administration**

Species	Mycotoxin	Lethal doses, mg/kg body weight	Ссылка
Cyprinus carpio	T-2 toxin	ip LD_{50} = 0.21±0.01 po LD_{50} = 0.46±0.04	[31]
Labeo rohita	Citrinin	ip LD_{100} = 12.5	[32]
Ictalurus punctatus	Cyclopiazonic acid	ip LD_{50} = 2.82	[33]
Oncorhynchus mykiss	T-2 toxin	po LD_{50} = 5.37±0.40	[31]
	Ochratoxin A	ip LD_{50} = 4.7	[34]

Mycotoxins which are relevant for fish compound feed in our country

(Table 1) became the subject of research in the 1970-1990s when their lethal doses were established and interspecific differences in fish susceptibility to these fungal metabolites were found (see Table 1).

These early works first reported the characteristic lesions from acute intoxication after injections and oral administration of mycotoxins. Under the influence of T-2 in common carp (*Cyprinus carpio*), necrosis appeared in the hepatopancreas, kidneys, anterior and middle intestine, being especially strongly manifested in the walls of blood vessels, gills, and posterior intestine. The lethal effect on fish of different age groups was the same [31]. In adult juveniles of roho labeo (*Labeo rohita*), dietary exposure to citrinin at 12.5 and 25.0 mg/kg led to a death-causing damage to the kidneys, liver, stomach and depigmentation and hyperemia of the caudal fin [32]. According to the effect on the 19 g-weighted channel catfish (*Ictalurus punctatus*), cyclopiazonic acid is a neurotoxin: 30 minutes after its injections at ≥ 2.4 mg/kg, the fish showed severe convulsions and tetanic seizure [33]. In rainbow trout (*Oncorhynchus mykiss*), OA caused necrosis of kidney and liver tubule cells [34].

The study of the impact of long-term intake of mycotoxins on fish which were fed diets added with naturally contaminated ingredients or the biomass of mycotoxin producing fungi, has disclosed disturbances occurred under close-to-real conditions. It was found at what content of mycotoxins in the feed of common carp and channel catfish there is a deterioration in morphological and fish-breeding parameters, i.e., a decrease in condition, an increase in feed costs, a decrease in vitality (Table 2).

2. Mycotoxin concentrations in feed causing a negative effect on morphological and breeding parameters in two fish species

Mycotoxin, its source (concomitant mycotoxins)	Age, initial body weight, g	Feeding period	Toxin concentration, mg/kg feed	References
Common carp *Cyprinus carpio*				
T-2 toxin, *Fusarium sporotrichioides* biomass (HT-2 toxin, neosolaniol)	Not indicated	67 days	0.14; 1.02	[31]
T-2 toxin, *F. sporotrichioides* biomass (HT-2 toxin, neosolaniol	Not indicated	122 days	0.45; 0.92	[31]
T-2 toxin, *F. sporotrichioides* biomass (HT-2 toxin, 0.45 mg/kg)	1 year of age, 23 g	4 weeks	4.11	[35]
T-2 toxin, preparation	Not indicated	4 weeks	5.3	[36]
Deoxynivalenol, contaminated feed ingredients	Young of-the-year	30 days	1.25	[37]
Deoxynivalenol, contaminated feed ingredients	2 years of age	2.5 months	1.25	[37]
Deoxynivalenol, *F. graminearum* biomass (15-acetyl deoxynivalenol, 0.33 mg/kg)	1 year of age, 23 g	4 weeks	5.96	[35]
Fumonisin B_1, prepraration	1 year of age	42 days	0.5; 5.0	[38]
Fumonisin B_1, prepraration	1 year of age	42 days	10; 100	[39]
Channel catfish (*Ictalurus punctatus*)				
T-2 toxin, preparation	Juvenile fish, 8.9 g	8 weeks	0,625; 1,25; 2,5	[40]
Deoxynivalenol, contaminated feed ingredients	Juvenile fish, 5 g	6 weeks	15; 17,5	[41]
Fumonisin B_1, *F. moniliforme* biomass	1 year of age, 1.2 g	10 weeks	20; 80; 320; 720	[42]
Fumonisin B_1, *F. moniliforme* biomass	Juvenile fish, 6.1 g	12 weeks	20; 40; 80; 240	[43]
Fumonisin B_1, *F. moniliforme* biomass	2 years of age, 31 g	14 weeks	80; 320; 720	[42, 44]
Ochratoxin A, *Aspergillus ochraceus* biomass	Juvenile fish, 6.1 g	8 weeks	1; 4; 8	[45]
Cyclopiazonic acid, preparation	Juvenile fish, 7.5 g	10 weeks	0.1	[33]

In ponds, common carp fed T-2 (0.14 and 1.02 mg/kg) for 67 days exhibited a 30 % decrease in body weight, with a 2-fold increase in feed costs per season per unit gain. The basins fish fed diets with T-2 (0.45 mg/kg and 0.92 mg/kg) for 122 days almost completely stopped growing, with a 40-50 % less average body weight by the end of the experiment compared to control [31]. In channel catfish, a decrease in gain was noted at ≤ 1 mg/kg of T-2 or OA [39, 44] and at 0.1 mg/kg

of cyclopiazonic acid [33].

The growth rate of Nile tilapia (*Oreochromis niloticus*) juveniles with a 2.7 g initial body weight decreased after 8-week when fed FUM B_1-containing feed (40, 70, and 150 mg/kg fungal biomass) [46]. In adults fed 0.5 μg/kg of OA, the fish-breeding parameters significantly ($p < 0.05$) decreased by the end of the 2-month experiment [47]. In 16-week long observation of juvenile rainbow trout with initial body weight of 1.0 g, there was a clear slowdown in growth and consumption of feed containing T-2 at ≥ 1.0 mg/kg [48]. The feed contaminated with 1.0 to 12.9 mg/kg DON slowed down both growth and feeding efficiency within 8 weeks without clinical signs of intoxication and with the preserved survival rate, whereas at 20 mg/kg DON, fish exhibited refusing to eat [49]. Later, the effect of reducing food consumption for rainbow trout with an initial body weight of 24 g was confirmed after 8-week feeding a diet with 0.3 to 2.6 mg/kg DON [50, 51]. Other researchers indicate a negative effect as early as on day 23 and day 32 of feeding this fish with 2 mg/kg DON [52, 53].

The productivity of Atlantic salmon (*Salmo salar*) decreased after 15-week consuming 3.7 mg/kg DON [54]. In an 8-week experiment on one-year-old fidh (58 g initial body weight), 5.5 mg/kg DON in the feed led to a decrease in the average body weight to 80.2 g compared to 123.2 g in the control [55]. In an 8-week experiment on smolts fed a diet added with 0.5-6.0 mg/kg of pure DON preparation, the feeding efficiency, body weight, length, and the condition factor correlated inversely with the toxin dose [56].

In all these species (common carp, channel catfish, Nile tilapia, rainbow trout, Atlantic salmon), long exposure to toxins in feeds had a negative impact on blood biochemical parameters, the activity of digestive, antioxidant and transforming enzymes, caused organ pathologies and functional disorders of body systems and decreased resistance to infectious diseases.

In common carp fed a diet supplemented with 5.3 mg/kg T-2 for 4 weeks, changes in the hemoglobin level with anemia and leukopenia were reported, the plasma glucose concentration and the alanine aminotransferase activity sharply increased while the concentration of triglycerides and ceruloplasmin activity significantly decreased [36]. T-2 at 4.11 mg/kg along with HT-2 in a smaller amount fed to one-year-old carp for 4 weeks did not cause significant differences in markers of lipid oxidation compared to control, but decreased the activity of the glutathione redox system and glutathione-S-transferase [35]. The authors hypothesized the differences in the activity of transforming and antioxidant enzymes to be explained by the long exposure to the toxin. Earlier, in a 3-day experiment on common carp exposed to T-2, a slight increase in the activity of glutathione-S-transferases in the hepatopancreas occurred [57]. In using 0.52 and 2.45 mg/kg T-2 for 7 and 28 days, the activity of both glutathione-S-transferases and glutathione peroxidases increased and the expression of *gpx4* paralogs changed but in different ways. The *gpx4a* expression significantly ($p < 0.05$) increased on day 21 and decreased on day 28, while for *gpx4b*, it remained increased both on days 21 and 28 [58].

In young of-the-year carp fish grown in aquariums and fed naturally contaminated feeds with 1.25 mg/kg DON for 30 days, the blood protein level, triacylglycerols, lipoproteins, cholesterol, the activity of aspartate aminotransferase and alkaline phosphatase decreased. The amount of β-lipoproteins decreased sharply, the glucose concentration increased, and a dysfunction of hepatopancreas occurred. When fed the same contaminated feed for 2.5 months, the two-year-old carp grown in cages exhibited an increase in activity of transferases, alkaline phosphatase, trypsin, amylase, a decrease in blood protein (due to β- and γ-globulin

fractions) [37]. Functional disorders occurred in hepatocytes, pancreatic cells and regulation of secretion, kidney tissues were damaged, vitality was reduced, and intestinal mucosa was atrophied [37]. In one-year-old carp fed DON with admixture of its natural analogue 15-acetyl-DON (a total contamination of 5.96 mg/kg) for 4 weeks, lipid oxidation and glutathione transferase activity in hepatopancreas corresponded to the control, and the concentration of the reduced form of glutathione significantly ($p < 0.05$) increased by the end of the experiment on day 28. For DON, dietary exposure over an extended period of time significantly affects the expression of *gpx4* genes which was above control on days 21 and 28 for *gpx4a* and throughout the observation period for *gpx4b* [58]. The results obtained allowed the authors to draw a general conclusion that the expression of *gpx4* paralogs depends on how long the fish were exposed to T-2 and DON though the activity of glutathione peroxidases remained unchanged [58].

In one-year-old carp regularly fed 0.5 and 5.0 mg/kg FUM B_1 for 42 days, along with a decrease in fish body weight, there were an increase in the number of erythrocytes and platelets, in the concentrations of blood creatinine and total bilirubin, and in the activity of aspartate aminotransferase and alanine aminotransferase. The changes allowed the authors to suggest that the kidneys and liver are the key organs affected by this toxin, and that the erythrocyte membrane may be disrupted or the respiratory process may be affected [38]. In carp fed 5.0 mg/kg FUM B_1, the incidence of superficial erythrodermatitis caused by *Aeromonas salmonicida* subsp. *nova* was higher [38]. In fish of the same age, receiving feed containing 10 and 100 mg/kg of added FUM B1 for 42 days, there were histological changes in blood vessels, liver, kidneys, heart and brain, as well as scattered damage to the exocrine and endocrine parts of the hepatopancreas and renal tissue, probably due to ischemia, increased endothelial permeability, or both [39]. Examination of the brain revealed deep neuronal damage [59].

After 6-week dietary exposure of young channel catfish to 1.0 and 2.0 mg/kg T-2, the mortality 21 days after infection with the virulent isolate *Edwardsiella ictaluri* was significantly higher than in the control [60]. DON-contaminated corn diets also increased susceptibility to this pathogen [61]. After 5-week experimental feeding of *Fusarium* culture material containing 35, 62, 170 and 313 mg/kg FUM B_1 to adult channel catfish, no significant lesions were seen in the brain, heart, liver, spleen, gills, head and trunk kidneys, stomach, intestines, skin, or gonads of the control or treatment groups. These findings suggest that adult channel catfish can tolerate feed contaminated with FUM B_1 up to 313 mg/kg [62]. Nevertheless, in one-year-old channel catfish, a 10-week feeding FUM B_1 at ≥ 80 mg/kg decreased the hematocrit level, the number of leukocytes and erythrocytes, and in 2-year-old fish, a 14-week exposure to 320 mg/kg FUM B_1 led to a decreased hematocrit and erythropenia with leukocytosis [42]. In the liver of 1- and 2-year-old catfish fed ≥ 20 mg/kg FUM B_1 for 10 and 14 weeks, foci of hyperplasia of subcapsular fat cells, swollen hepatocytes with vacuoles filled with lipids, infiltration of lymphocytes and scattered necrotic hepatocytes were seen [42]. In juvenile fish (initial weight 6.1 g), receiving 80 and 240 mg kg FUM B_1 for 12 weeks, the hematocrit significantly decreased, and at 40, 80, and 120 mg/kg FUM B_1, glycogen accumulation in the liver, vacuolization of nerve fibers and an increase in the perivascular lymphohistiocytic layer in the brain were seen [43]. A significant increase in the ratio of free sphingamine and free sphingosine in blood, liver, kidneys, and muscles, but not in the brain occurred in 2-year-old catfish fed a 12-week diet with *Fusarium* culture material containing ≥ 10 mg/kg FUM B_1 [63]. In 2-year-old fish, fed a 14-week diet with *Fusarium* culture material (20 and 80 mg/kg FUM B_1), resistance to *Edwardsiella ictaluri* infection was lower with

poorly formed antibodies as compared to the control group [44].

In juveniles of Nile tilapia (initial weight 2.7 g), after a 8-week feeding a diet with containing 150 mg/kg FUM B_1 of *Fusarium* culture material, the hematocrit was significantly lower, and the ratio of free sphingamine to free sphingosine in the liver increased [46].

In 8-week experimental feeding 2.6 mg/kg DON to rainbow trout (initial weight 24 g), morphological abnormalities seen in the liver were subcapsular hemorrhages, edema, changes in hepatocytes, and fatty infiltration [51]. In a one-year-old rainbow trout fed 2.0 mg/kg DON for 23 days, the mean hemoglobin concentration in the erythrocyte and biochemical parameters significantly ($p < 0.05$) decreased [64]. Histological studies revealed degeneration of epithelial cells of the convoluted tubules of the kidneys in 9 out of 10 fish [64], and in several individuals, there were hemorrhages in the liver described earlier by Hooft et al. [50]. When using a feed containing 2.0 mg/kg DON for 23 and 32 days, changes were observed in the activity of glutathione peroxidase in the kidneys, glutathione reductase in the gills and kidneys, catalase in the kidneys and liver, glutathione transferase in the gills and liver. This indicates that DON induced oxidative stress but practically did not affect lipid oxidation [65]. Later studies gave confirmed the regulatory effect of DON on the expression of key genes and the main metabolic processes in rainbow trout [52, 53].

In Atlantic salmon smolts fed a diet with 0.5 to 6.0 mg/kg DON for 8 weeks, the clinical biochemical parameters and protective immune response to *Aeromonas salmonicida* vaccine correlated inversely with the toxin dose [56].

All these findings provided important information about the effect of T-2, DON and FUM B_1 on performance and the state of internal organs based on changes in biochemical parameters, the activity of enzymes in the liver, kidneys, gills, and the susceptibility to diseases upon artificial infections. The next step was estimation of the thresholds for safe exposure to mycotoxins and elucidation mechanisms of their toxic action. To that end, a full-value, nutrient-balanced diet that does not contain plant ingredients, and, therefore, contaminants of a mycogenic nature, were added with individual preparations of mycotoxins to correctly assess the effect of the selected toxicant. For two fusariotoxins, DON and ZEN, these studies provide new insights into effects of mycotoxins at molecular level and the innate immunity responses in cyprinids, involving factors that provoke or prevent the development of inflammatory processes.

The effect of DON at the doses not affecting productivity (0.352, 0.619 and 0.953 mg/kg) was studied on young carp 12-16 cm in length in a series of 6-week experiments. At the lowest dose, the number of blood leukocytes was reduced, and the activity of antioxidant enzymes superoxide dismutase and catalase in erythrocytes was increased, which indicated the immunosuppressive effect of DON [66]. At the highest concentration, lipid oxidation in the liver, head kidney and spleen increased and fat was accumulated in the body. The changes in the activity of lactate dehydrogenase in kidneys and muscles and blood lactate accumulation indicated the effect of DON on anaerobic metabolism, while a decrease in blood albumin at medium and high doses of the toxin was characteristic of their ribotoxic effect [67]. Further, the dynamics of liver damage, changes in the activity of liver enzymes, and the immune response were studied on fish (9-12 cm long) fed 0.953 mg/kg DON for 7, 14, 26 and 56 days. During the first 2 weeks, there was an inhibition of biotransforming enzymes followed by activation of alanine aminotransferase, which indicates damage to liver tissue: after 14 and 26 days, lipid aggregation, vacuolization and hyperemia were seen in histological sections together with inhibition of enzymes involved in glutathione cycle and reduction of oxidative stress [68]. In the first 2 weeks, the intake of DON led to the activation

of enzymes and cytokines, both inhibiting and promoting the development of the inflammatory process, and after a 26-day exposure, the activation of arginases to the highest levels was detected in the leukocytes of the head kidney [69]. Despite some immunomodulatory effects at the beginning of the experiment, the authors concluded that DON has a systemic immunosuppressive effect on carp [69].

In young carp (12-16 cm in length), 0.332, 0.621, and 0.797 mg/kg ZEN fed for 4 weeks led to no decrease in growth and no estrogenic effects characteristic of other fish species, as measured by the concentration of blood vitellogenin. Nevertheless, hematological parameters underwent significant changes. The effect of medium and high doses of the mycotoxin on the number of leukocytes, granulocytes and monocytes was shown, and micronuclei seen in the erythrocytes confirmed ZEN genotoxicity [70]. In addition, the effect of ZEN on carbohydrate metabolism, lipid oxidation in organs, and oxygen metabolism was established, which indicates its ability to increase the overall metabolic load [71]. In a comparative study of nitric oxide accumulation in leukocytes from the head and trunk kidneys, a bioassay for respiratory activity, chemiluminescence test and arginase activity showed that the higher concentrations of ZEN have a distinct suppressive effect while the lower concentrations enhance immune responses [72]. In the liver, all concentrations of ZEN led to a decrease in the expression of genes regulating the immune response, antioxidant system, and sensitivity to estrogens. Also, there was a significant increase in the expression of vacuolar-type H+-adenosine triphosphatase, which was consistent with the previously established association between ZEN and lysosomal functions [73]. These studies confirmed the effect of ZEN on many key processes in carp and evidenced that the permissible concentrations of ZEN previously approved for compound feed are too high and do not prevent its damaging effect.

Chinese researchers studied the effect of DON, using another representative of the cyprinids, the grass carp (*Ctenopharyngodon idella*) [74-76]. On juveniles (initial weight approximately 12 g) fed mixed fodders with 0.318, 0.636, 0.922, 1.243 and 1.515 mg/kg DON for 60 days, it has been shown for the first time that this toxin can cause malformations in fish and lead to histopathological changes, oxidative damage, decreased antioxidant capacity, cell apoptosis and destruction of tight junctions in the intestine through signaling systems of Nuclear factor-erythroid 2-related factor 2 (Nrf2), c-Jun N-terminal kinases (JNK) and myosin light-chain kinase (MLCK). Based on the totality of the measured parameters, the DON dose of 0.318 mg/kg was called safe [74]. Further studies have shown that DON disrupts intestinal immune function by mechanisms partially associated with two signaling pathways, the nuclear factor kappa B (NF-kB) and target of rapamicin (TOR). Given the incidence of enteritis caused by *Aeromonas hydrophila*, the activity of lysozyme and acid phosphatase, and the IgM level in the proximal intestine, the recommended doses of DON were 0.252-0.310 mg/kg [75]. In the gills of these fish under the same experimental conditions, DON added to feed at > 0.318 mg/kg also led to histopathological changes, oxidative damage, decreased antioxidant capacity, cell apoptosis, and destruction of tight junctions, which was presumably due to Nrf2, JNK, and MLCK signal systems without affecting the expression of *Keap1b*, *claudin-b*, *claudin-3c*, and *claudin-15b* genes. The allowable amounts of DON calculated based on the activity of malondialdehyde and the pool of antioxidants were 0.376 and 0.413 mg/kg [76].

In grass carp, dietary ZEN (0.535, 1.041, 1.548, 2.002 and 2.507 mg/kg) caused oxidative damage, apoptosis and disruption of the intestine integrity [77]. The authors assumed these effects to be associated with signaling pathways of Nrf2, p38 mitogen activated protein kinases (p38MAPK), and myosin

light chain kinase (MLCK). There were no changes in the antioxidant genes *Keap 1b*, *GSTP1* and *GSTP2* encoding glutathione S-transferases, and *occludin*, *claudin-c*, and *claudin-3c* responsible for the intestinal integrity [77].

Aquarium fish are good models for investigating chronic effects of mycotoxins on cyprinids. In *Danio rerio*, dietary DON at 0.1-3 mg/kg generated higher levels of liver gene biomarkers and adverse effects on the reproductive system [78]. In *D. rerio* adults, based on vitellogenin (Vtg) protein levels and relative abundance of molecular biomarker *vitellogenin-1* mRNA (*vtg-1*), ZEN, in addition to its direct estrogenic effects, was established to be capable of influencing other pathways during ontogenesis [79, 80].

Significant progress has also been achieved in the study of toxicosis of fish of a high trophic level. Despite the absence of histological changes in juveniles of the rainbow trout fed a diet with T-2 (1.0 and 1.8 mg/kg) for 24 days, a distinct oxidative stress occurred, which affects the detoxifying system and may lead to an increase in the sensitivity to other stress factors [81]. At 2 mg/kg of dietary DON for 23 days, higher levels of cytokines TNF-α and IL-8 provoking inflammatory processes were detected in the head kidney of one-year-old fish [82].

In rainbow trout, ZEN has been confirmed being capable of binding estrogen receptors and inducing expression of the corresponding genes [83]. In juveniles (initial weight 55 g), no signs of liver damage occurred 24, 72, and 168 hours after a single intraperitoneal injection of ZEN at 10 mg/kg, since the activity of alanine aminotransferase and aspartate aminotransferase and the blood glucose level did not change. However, iron accumulation in the liver and ovaries significantly decreased which, according to the authors, could be both a consequence and a cause of oxidative stress [84]. In an 8-week experiment on 12-month-old Atlantic salmon (initial weight 58 g), DON (5.5 mg/kg) disrupted integrity of distal and mid-intestine, namely, the expression of barrier protein markers (*claudin 25b*, *occludin*, and *tricellulin*) decreased vs. an increase in the expression of nuclear antigen marker of proliferating cells. Importantly, in the distal intestine, the relative expression of *SOCS1* and *SOCS2* encoding two suppressors of cytokines signaling increased. However, according to the authors, though the damaging effect was mitigated by suppressors of cytokine signaling, this dysfunction of the intestinal barrier should not be underestimated [55]. In 8-week experiment, smolts of Atlantic salmon fed dietary DON (0.5 to 6 mg/kg) exhibited a relative increase in weight of organs as the dose of toxin increased, and no-observed adverse effect level (NOAEL) of the toxin was 1 mg/kg [56].

Unfortunately, so far, the problem of OA intoxication in fish has been poorly studied. In juvenile canal catfish fed a diet added with *Aspergillus ochraceus* culture material (8 mg/kg OA), the hematocrit decreased though the number of blood leukocytes did not change [45]. In the experimental fish which ate 4 mg/kg OA for 6 weeks and then was infected with the virulent isolate of *Edwardsiella ictaluri*, mortality on day 21 was significantly higher than in the control [60]. In catfish, necrosis of the renal tubules was not seen but extensive multifocal melanomacrophage centers appeared in the loose connective tissue of the kidneys at OA doses of 4 and 8 mg/kg. For OA at ≥ 1 mg/kg, the most apparent histopathological lesion was necrosis of hepatopancreatic tissues, especially exocrine cells of the pancreas surrounding the portal veins, and this pathology ultimately led to obliteration of normal pancreatic tissue [41]. In smolts of Atlantic salmon fed five diets supplemented with OA pure preparation (0.2-2.4 mg/kg), after 8 weeks, the performance indicators remained unchanged although after the first 3 weeks there was a tendency to an increase in some clinical biochemical parameters and increased expression of two immune markers in the spleen; however, it was not

possible to calculate NOAEL from the available concentration range [56].

Data on toxic effect of cyclopiazonic acid are very limited. In juvenile canal catfish (initial weight 7.5 g) fed for 10 weeks with dietary toxin (10 mg/kg), histological lesions were seen in the kidneys and stomach as protein granules in the epithelium of the renal tubules and necrosis of the gastric glands, however, liver damage and effects on hematocrit, hemoglobin concentration, leukocyte and erythrocyte counts were not revealed [33]. As to citrinin, mycophenolic acid, alternariol, and emodin, the situation remains unexplored.

As to the effect of the considered mycotoxins on silver carp (*Hypophthalmichthys molitrix*), bighead carp (*Hypophthalmichthys nobilis*), tench (*Tinca tinca*), peled (*Coregonus peled*), paddlefish (*Polyodon spathula*), goldfish (*Carassius auratus*), crucian carp (*C. carassius*), eels (*Anquila* spp.), Siberian sturgeon (*Acipenser baerii*), bester (*Huso huso* × *Acipenser ruthenus*) which form the basis of Russian fish farming no publications are available. Therefore, it is advisable to gradually involve the most commercially demanded species in research to assess their tolerance to the entire set of expected toxicants in a timely manner. In addition, the expanding range of farmed fish necessitates careful generalization and analysis of newly emerging information. It should be noted the works which showed a high sensitivity to OA in common sea bass (*Dicentrarchus labrax* L.) from the *Moronidae* family (LD_{50} 0.277 mg/kg body weight) [85], a chronic intoxication with feed-born FUM B_1 in juvenile African sharptooth catfish (*Clarias gariepinus*) [86, 87], and the effects of polycontaminated feed containing, along with DON, other fusariotoxins and alternariol, on red tilapia (*Oreochromis niloticus* × *O. mossambicus*) [88]. The effect of moniliformin, often concomitant with FUM B_1 in affected corn grain, deserves separate consideration, as it was shown that feeds supplemented with culture material of *F. moniliforme* or *F. proliferatum* which produce moniliformin can cause distinct shifts in hematological and histological parameters in channel catfish [89] and Nile tilapia [46, 90].

There is a general consensus that the identification of mycotoxins in aquatic feed and assessing their adverse effects should remain a major focus, especially due to the general trend of replacing fishmeal as a source of expensive animal proteins with cheaper vegetable proteins. In addition to the aforementioned ingredients, new recipes contain glutens (by-products of grain processing into starch and molasses) and dry grain stillage with hydrolysates [91] for which multiple mycotoxin contamination is known [92]. Expanded use of sorghum grain for compound feed is recommended [9] although its toxicological risk has not been investigated. Flaxseed, pumpkin meal [94, 95], cottonseed meal, seaweed, and grass meal should be mentioned among the minor additives which can also be sources of mycotoxins. Special examinations of the meal are still coming, but for grasses and algae intended for processing into feed meal, the possibility of multiple contamination with mycotoxins has already been established [96, 97].

Fishmeal and its substitutes which are the main source of protein in diets for salmon fish [98] can easily become infected with microscopic fungi during transportation, storage, and use. Recently, 11 potentially toxigenic species of *Penicillium* fungi have been identified in the mycobiota of fish, meat and bone meals [99], however, the contamination of commercial batches with mycotoxins was not monitored. Given prospects for transfer of aquaculture industry to the domestic feed base [100], it is necessary to coordinate regular surveys of flour lots of animal origin.

All efforts to assess the actual contamination of feed and accumulate data on the damaging effect of mycotoxins on fish aim at introducing norms for their permissible concentration. However, reasonable proposals for the regulation of

mycotoxins are still very few, i.e., for T-2 in common carp [31], for DON in grass carp [74-76] and Atlantic salmon [56], and for FUM B_1 in channel catfish [42, 43]. Another key point in the prevention of mycotoxicosis in aquaculture is to ensure the safety of fish products for consumers. In general, data on the transformation of mycotoxins in fish and their preservation in organs and muscle tissue indicate a weakly expressed or moderate accumulation and slow excretion, which is explained by the physiological peculiarities of poikilothermic organisms [54, 101-103]. This information is still limited and, probably, that is why regulations on residual amounts of mycotoxins in products have not yet been adopted. However, the search for new informative approaches to the correct assessment of the risks that mycotoxins pose to fish and, via fish products, to human health continues, and a solution, despite the complexity of the task, will most likely be found.

In Russia, the Technical Regulation of the Eurasian Economic Union (EAEU) "On the safety of fish and fish products" [104], which entered into force in September 2017, defines the maximum allowable concentrations of residues of veterinary therapeutic drugs and growth stimulants permitted for use in aquaculture. The introduction of mycotoxins as congeners in the near future is unlikely, since the block of necessary information has not yet been formed. The first step should be systematic regular monitoring surveys of compound feeds produced in all federal districts of Russia. Generalization of these data will give a reasonable methodology to study metabolism, accumulation and circulation of significant mycotoxins for species intended for fish farming, and then to determine the priority criteria for the regulation of residual contents in feed and fish products. In Russia, mandatory requirements have been introduced for the quality and safety indicators of raw materials and finished feed products (GOST 10385-2014 "Combined feeding stuffs for fishes. General specifications". Moscow, 2014) and a modern methodological base has been created for mycotoxicological control (GOST 31653-2012 "Feedstuffs. Method of immunoenzyme mycotoxin determination". Moscow, 2012; GOST 31691-2012 "Grain and products of its treatment, mixed feeds. Determination of zearalenone content using high-performance liquid chromatography". Moscow, 2012; GOST 32587-2013 "Grain and products of its processing, mixed feeds. Determination of ochratoxin A by high performance liquid chromatography". Moscow, 2013; GOST 34108-2017 "Feeds, mixed feeds and raw material. Determination of mycotoxins content by direct solid-phase competitive immunoenzymatic method". Moscow, 2017; GOST R 51116-2017 "Compound feed, grain and products of its processing. Deoxynivalenol content determination method ohm of high-performance liquid chromatography". Moscow, 2017).

Thus, to date, science has convincing evidence of the deep damaging effect of mycotoxins on non-commercial fish when fed with contaminated feed. From a practical point of view, large datasets on threshold levels at which the risk of developing alimentary toxicosis can be significantly reduced are of particular value. Data on blood biochemical parameters, the activity of digestive, antioxidant and transforming enzymes, as well as on changes in the susceptibility of fish to infections are also of significant interest. In recent years, the first studies of molecular mechanisms leading to impaired detoxifying, immune and reproductive functions in fish have been carried out, and original methodological techniques have been proposed for assessing the permissible doses of these toxicants. However, research should be consistent with the real landscape of mycotoxin contamination, in particular, combinations of two or more mycotoxins at different concentrations should be investigated. This approach and the timely systematization of the

accumulated information will ensure effective control of feed safety and sustainable veterinary welfare in the fish farming industry.

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