Kim *et al. Applied Biological Chemistry* (2024) 67:38
https://doi.org/10.1186/s13765-024-00879-6

KSABC
The Korean Society for Applied Biological Chemistry

ARTICLE

Open Access

Investigation of safety and efficacy of febantel and fenbendazole in fish and exposure assessment

Min Ji Kim[1], Ji Young Kim[1*], Dong Woo Shin[1] and Hyun-Kyung Kim[1]

Abstract

Fish are susceptible to blood-sucking parasite infections, which cause severe anemia, dyspnea, and ultimately death. However, veterinary drugs available for fish to treat such infectious diseases are lacking; thus, livestock drugs have been repurposed as aquatic animal drugs. Febantel (FBT) and fenbendazole (FBZ) are representative antiparasitic agents for livestock such as cattle, swine, and poultry, and are considered suitable as aquatic animal drugs. Therefore, we investigated the safety and efficacy of FBT and FBZ in fish and performed a risk assessment to determine the maximum residue limit in fish. Most studies indicate that FBT is rapidly converted to FBZ, which is metabolized to oxfendazole and oxfendazole sulfone. FBZ was frequently detectable in the plasma and tissues (e.g., muscle, skin, and the liver) in significant quantities than other metabolites. We regarded the liver as the target organ because reversible hepatocytic changes were observed in fish after administration of 100 mg/kg FBT for 9 days. No toxicological effects, such as increased mortality or decreased appetite, were observed when the fish were administered 50 mg/kg FBT for 3 days. The efficacy of the drugs was verified in various parasites, including *H. heterocerca, H. okamotoi or Z. japonica*, and *M. seriolae*, as causative agents of beko disease through laboratory and field trials. Although toxicity studies on FBZ in fish are limited, its safety has been demonstrated from toxicity studies in a wide range of animal models. The risk from using FBT and FBZ was negligible for human health because the ratio of the estimates of dietary exposure and acceptable daily intake was 78.4%.

Keywords Maximum residue limit, Safety, Febantel, Fenbendazole, Fish

Introduction

Aquaculture has increasingly become the most important food-producing sector in terms of global food security and nutrients [1]. Korean annual seafood consumption reached an average of 58.4 kg per capita during 2013–2015, indicating that Koreans were the top consumers of seafood among the countries investigated by the Food and Agriculture Organization [2].

*Correspondence:
Ji Young Kim
jykim98@korea.kr
[1] Pesticide and Veterinary Drug Residues Division, National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety, 187 Osongsaengmyeong 2-Ro, Osong, Cheongju, Chungcheongbuk-Do 28159, Republic of Korea

To meet the growing consumption of aquatic foods, aquaculture is growing at high densities; however, intensive circumstances represent a risk of disease outbreaks [3]. Hence, the use of effective aquatic animal drugs is inevitable in aquafarms to prevent and treat infectious diseases (i.e., parasitic diseases with high prevalence and intensity) [4].

Commonly, gill flukes, including *Dactylogyrus sp.*, *Heterobothrium okamotoi*, and *Zeuxapta japonica* are among the most critical parasites in food-producing fish, such as rohu (*Labeo rohita*), Japanese amberjack (*Seriola quinqueradiata*), and Great amberjack (*Seriola dumerilli*). These gill flukes cause anemia and dyspnea, leading to decreased swimming ability and eventually death [3, 5].

Some studies indicate that fish farm workers use prohibited chemicals (e.g., formalin and malachite green) to control the prevalence of infectious diseases in fish [5, 6]. In line with American veterinary medical association, there are only a limited number of approved drugs for aquatic animals, so the demand for the development of new effective drugs against various parasites is high. To fulfill these demands, trials for repurposing livestock drugs as aquatic animal drugs have been reported. Oxytetracycline (OTC) is a useful example. OTC is a widely used antibacterial agent in various food-producing animals (e.g., mammals, birds, and fish) because of its pharmacological properties [7–9]. It is actively used for farmed fish (e.g., salmonids, olive founders, and sea breams) worldwide [9].

Febantel (FBT) and fenbendazole (FBZ) are approved for use in multispecies animals, such as ruminants (cattle, sheep, and goats), nonruminants (swine and equine), and birds (growing turkeys), for controlling internal parasites, such as gastrointestinal roundworms or lungworms [10–12]. FBT is a pro-benzimidazole anthelmintic with broad-spectrum activity against various nematode parasites in canine and feline species [13]. FBT is metabolized to FBZ in vertebrates [14]. FBZ is metabolized to oxfendazole (OXF) and further sulfoxidized to oxfendazole sulfone ($OXFSO_2$) [15]. FBZ is interconvertible to OXF, which is considered the most toxic compound compared with FBT and FBZ [14]. FBZ, the active metabolite of FBT, binds to microtubules in parasites and irreversibly blocks glucose uptake, leading to the depletion of energy stores and, ultimately, death [10].

Although the safety and efficacy of FBT and FBZ have been established in laboratory animals and livestock [11, 12], research on FBT and FBZ in aquatic animals is lacking. Therefore, we investigated the efficacy and safety of FBT and FBZ in fish and performed exposure assessment to establish their maximum residue limits in fish.

The remainder of the study has been organized as follows. The *materials and methods* section provide details regarding searching materials and exposure assessment. The *results* section presents the analysis of toxicity studies, metabolism studies, residue depletion studies, pharmacological studies, and exposure assessment. Finally, the *conclusion* section summarizes the study and discusses future research directions.

Materials and methods

Searching materials

Metabolism, safety pharmacology, and other related data of FBT and FBZ for fish were gathered from publications, such as the evaluation reports released by the Food and Drug Administration (FDA), Food Safety Commission of Japan (FSCJ), and European Medicinal Agency (EMA).

In addition, we investigated relevant studies by searching PubMed and Google databases. The searched keywords were the following: "febantel and fish," "fenbendazole and fish(es)," "fenbendazole and aquatic animals," "benzimidazoles and fish(es)," "febantel and efficacy" or "fenbendazole and efficacy."

Exposure assessment

To estimate the amount of FBT and FBZ exposure, the tentative maximum residue level was used, which is proposed by Ministry of Food and Drug Safety and Ministry of oceans and fisheries. An exposure model was applied to the global estimate of chronic dietary exposure, with a slight modification [16]. This model was recommended by the Joint WHO/FAO Expert Committee on Food Additives (JECFA). The final calculation method is as follows,

$$\frac{\begin{array}{l}high\ dietary\ exposure\ for\ one\ food\left(90,\ 95\ or\ 97.5\ percentile\ consumption\ by\ consumers\ \times\ tMRL\right)\\ +\ mean\ dietary\ exposure\ for\ all\ other\ foods(average\ consumption\ by\ generalpopulation\ \times\ tMRL)\end{array}}{body\ weight\,(kg)}$$

The minimum number of subjects for which percentiles could be used in dietary exposure assessment was obtained from the European Food Safety Agency guidance document [17]. The acceptable daily intake (ADI) values by international bodies were investigated (see Additional file 1: Tables S1 and S2 for summarized version). In this study, the ADI was 0.007 mg/kg bw/day, as recommended by the JECFA and FSCJ (Additional file 1: Table S3).

Results

Toxicity studies

Toxicity studies on FBT and FBZ were conducted in early life or at specific developmental stages in several species, including Japanese amberjack (*Seriola quinqueradiata*), great amberjack (*Seriola dumerili*), Japanese pufferfish (*Takihugu rubripes*), rainbow trout (*Oncorhynchus mykiss*), zebrafish (*Danio rereio*), silver perch (*Bidyanus*

Table 1 Metabolism, toxicology, and residue depletion studies of febantel and fenbendazole

	Compound	Study design (species, dosage, and admin. regime)	Results	References
Toxicity	FBT	Japanese Amberjack (*S. quinqueradiata* & *S. dumerili*); 0–10 mg/kg bw/day for 5 day; feed	Concentration of FBT was dependent on cumulative mortality at the end of experiment	Kawakami et al. [18]
Toxicity	FBT	Juvenile Japanese Amberjack (*S. Quinqeradiata);* 0–1000 mg/kg bw/day (6 experiments) for 3–28 day; feed	Increased mortality over 50 mg/kg bw/day; decreased growth rate in all treated groups; histopathological change in liver (absence of vacuoles) and brain (rarely Nissl bodies distribution in medulla oblongata); effective dose and duration were demonstrated: max 15 mg/kg bw/day for 10 days	Shirakashi et al. [19]
Toxicity	FBT	Japanese Amberjack (*S. quinqueradiata, S. dumerili*); 0, 10 mg/kg bw/da for 5 day; feed (different four locations, total four trials)	No apparent avoidance to medicated feed and no signs of toxicity in treated group	Shirakashi et al. [20]
Toxicity	FBZ	Silver perch (*Bidyanus bidyanus*); bath at 10 mg/L for 48 h or feed at 75 mg kg bw/day for 6 day	Neither behavioral abnormalities nor adverse physical signs of toxicity were observed by bath or oral application of FBZ; no impact on survival rate by both application	Forwood et al. [36]
Toxicity	FBT	Zebrafish embryo (*Danio rerio*); 0.02–2.0 mg/L for 144 hpf; WB (flow-through system)	NOEC for 0.20 mg/L at 144 hpf; EC_{50} [95% CI] 0.34 mg/L [0.26–0.044 mg/L] at 144 hpf	Carlsson et al. [21]
Toxicity	FBZ	Zebrafish embryo (*Danio rerio*); 0.002–0.2 mg/L for 144 hpf; WB (flow-through system)	NOEC for 0.02 mg/L at 144 hpf; EC_{50} [95% CI] 0.024 mg/L [0.021–0.030 mg/L] at 144 hpf	Carlsson et al. [21]
Toxicity	OXF	Zebrafish embryo (*Danio rerio*); 0.1–10 mg/L for 144 hpf; WB (flow-through system)	NOEC for 4.6 mg/L at 144 hpf; EC_{50} [95% CI] 6.8 mg/L [5.6–8.3 mg/L] at 144 hpf	Carlsson et al. [21]
Toxicity	FBT	Tiger puffer (*T. rubripes*); 0, 12.5, or 25 mg/kg bw/day for 5 day; feed (total six trials)	No adverse effects observed [i.e., good appetite, all feed eaten with 5–10 min.; high survival, low daily mortality (< 0.1%)]	Kimura et al. [35]
Toxicity	FBZ	Young and adult three-spined sticklebacks *(G. aculeatus);* 0–50 µg/mL for 2 or 6 day; bath *tolerance test, 1–100 µg/mL for 100 h; bath	Misshapen sporogonial plasmodia under treatment with FBZ at 5 µg/mL for 2 h, and malformation of the prespores under 1 µg/mL for 1 h; In tolerance test, no visible adverse effects or other negative effects on the vital functions or on behavior	Günter Schmahl and Jochen Benini, [32]
Toxicity	FBT	*Gyrodactylus* sp. obtained from infected rainbow trout (*O. mykiss*); 2.5 or 10 mg/L for 3 h; WB (noncirculating system)	Observation of signs of toxicity at the highest concentration	Santamarina et al. [28]
Toxicity	FBZ	Rainbow trout (*O. mykiss*); 25 mg/L for 3 or 12 h; 0.77, 1.5, 6.2, or 12.5 mg/L for 12 h; WB (non-circulating system)	Presence of signs of toxicity at a concentration of 25 mg/L	Tojo et al. [29]
Metabolism	FBT	Juvenile Japanese Amberjack (*S. Quinqeradiata);* 0–20 mg/kg bw/day for 5 day; feed or intubation	FBT was not detected in muscle, liver, and kidney after 1d from last treatment; FBZ and its metabolites were detected in the liver and kidney until 7d after last treatment; 20 mg/kg bw/day, higher total BL, lower TG, and lower plasma CRE observed but not change of histopathology	Shirakashi et al. [22]

Table 1 (continued)

	Compound	Study design (species, dosage, and admin. regime)	Results	References
Metabolism	FBT	Tiger puffer (*T. rubripes*); 12.5 and 25 mg/kg/day for 5 day; 50 mg/kg/day for 3 day; feed	FBT peaked at 4 h after admin. and decreased to 30% of the peak at 8 h and gradually reduced thereafter in plasma; $OXFSO_2$ peaked at 12 h in plasma and was detected until 72 h after admin	Kimura et al. [5]
Metabolism	FBZ	Channel catfish (*Ictalurus punctatus*); intravenously 1 mg/kg bw or orally 5 mg/kg bw	FBZ was detected in muscle at all sampling time; but it appeared in urine at a low concentration; $OXFSO_2$ was main metabolite in urine and intestinal contents	Kiztman et al. [25]
Comparative Metabolism	FBZ	Liver tissue from catfish (young nonbreeding) at 25 or 37	OXF was the majority; $OXFSO_2$ with small quantities; absence of $FBZNH_2$; no metabolic difference of temperature	Short et al. [26]
Residue depletion	FBZ	Rainbow trout (*O. mykiss*); 6 mg/kg bw/day (single) or 1.5 mg/L (12 h); intubation or bath	FBZ was detected in muscle until 4d after last treatment per oral; Tmax (24 h) and sharply reduced thereafter in both routes; the concentration of skin was more than that of muscle; FBZ was detected until 1d after last treatment via bath exposure; OXF was observed in muscle up to 1d after cessation; OXF was detected in skin until 4d after cessation	Iosifidou et al. [23]
Residue depletion	FBZ	Rainbow trout (*O. mykiss*); 50 mg/kg bw/day (single); intubation	FBZ was detected in liver and muscle at 24 h after treatment, and concentration of both organs sharply declined thereafter; appropriate withdrawal period as 497.6-degree days was confirmed	Soukupova-markova et al. [24]
Residue depletion	FBT	Japanese amberjack (*S. quinqueradiata*); 10 mg/kg bw/day for 5 day; feed	Residues were detectable until 14 days in liver and kidney, but not in muscle; highest concentration of residues were reported in liver followed by kidney and muscle	FSCJ [27]
Residue depletion	FBT	Greater amberjack (*S. dumerili*); 10 mg/kg bw/day for 5 day; feed	In muscle, $OXFSO_2$ was detectable no longer than 5 day after cessation	FSCJ [27]
Residue depletion	FBT	Greater amberjack (*S. dumerili*); 10 mg/kg bw/day for 5 day; feed	Residues were not detectable in muscle over 5d after last treatment; highest concentration: liver > kidney > muscle at 3 day after cessation; residues were detected until 14 day in liver and kidney	FSCJ [27]
Residue depletion	FBT	Japanese pufferfish (*T. rubripes*); 50 mg/kg bw/day for 5 day; feed	Absence of FBT in muscle and skin after 24 h after cessation, and $OXFSO_2$ was detectable in both tissues ranging from 0.51 to 2.64 μg/*g* (skin > muscle)	FSCJ [27]
Residue depletion	FBT	Japanese pufferfish (*T. rubripes*); 50 mg/kg bw/day for 5 day; feed	Absence of FBT in muscle and skin; $OXFSO_2$ was detected in one muscle sample among five samples at a concentration of 0.08 μg/*g* at 7 day after cessation; none of residues were observed at 14 day after cessation	FSCJ [27]

FBT febantel, *FBZ* fenbendazole, *BL* Bilirubin, *TG* triglyceride, *CRE* creatine, *hpf* hours post-fertilization, *SOD* superoxide dismutase, *GST* glutathione-S-transferase, *CAT* catalase activity, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *OXF* oxfendazole, *OXF* SO_2 oxfendazole sulfone, *Vd* volume of distribution, *WHP* withdrawal period, *WB* waterborne

bidyanus), and sticklebacks (*G. aculeatus*). Table 1 presents additional toxicity data in detail.

Mortality rates in amberjacks (*S. quinqueradiata* and *S. dumerili*) were dependent on the exposure concentration and duration. For example, the mortality rate reached above 90% when fish were exposed to more than 50 mg/kg bw/day for 28 consecutive days, and the growth rate decreased by approximately 6.8% compared to that of the control. The mortality rate among fish was zero in exposure group with same dose for 14 consecutive days [18–20]. According to Kimura et al. [35], no detrimental effects are observed when tiger puffers are administered up to 25 mg/kg bw/day FBT for five consecutive days. Fish consumed all feed within 5–10 min, and low daily mortality rates are observed at all concentrations.

An analysis using zebrafish embryos demonstrated the metabolism by embryos of FBT into FBZ and FBZ into OXF. Various malformations, such as underdeveloped eyes, head, and curved tail, were reported in embryos exposed to FBT at 0.043 or 2 mg/L levels. No observed effect concentration of FBZ and FBT were 0.02 and 0.2 mg/L at 144 h-post-fertilization, and 50 percent of effect concentration of FBZ and FBT corresponded to 0.024 and 0.34 mg/L, respectively. These findings suggest that FBZ may have harmful effects on the early life stages of fish exposed to FBT [21].

Metabolism studies

Metabolism studies of FBT and FBZ intended for various fish species, including Japanese amberjack (*S. quinqueradiata*), Japanese pufferfish (*T. rubripes*), channel catfish (*Ictalurus punctatus*), and rainbow trout (*O. mykiss*), were performed (see Table 1 for the detailed information).

In a persistence assessment using Japanese amberjack (*S. quinqueradiata*), FBT was not detected in any edible tissue (e.g., the liver, muscle, or kidney) at 1 day-post-administration (dpa); in contrast, FBZ was observed in the liver and kidney at 7 dpa. No compounds, including FBT, FBZ, OXF and $OXFSO_2$ were detected in any of the organs at 14 dpa. This study highlighted that the total degradation of FBT in *S. quinqueradiata* took more than a week; therefore, the appropriate withdrawal period from the last treatment was 21 dpa, which was comparable to that of *T. rubripes* [5, 22].

In *O. mykiss*, depletion time differed between the two species. In a previous study, FBZ was detected up to 4 dpa in muscle exposed to FBZ after oral treatment, whereas the compound was detected in muscle until 1 dpa after bath treatment [23]. Furthermore, another study revealed that FBZ remained until 20 dpa at a mean level of 0.13 mg/kg [24].

Research conducted on channel catfish (*I. punctatus*) showed that FBZ was detected in muscle at all time points when the fish were exposed to FBZ via intravenous injection at a concentration of 1 mg/kg bw or orally at 5 mg/kg bw. However, FBZ was observed in urine at insignificant levels, and $OXFSO_2$ was mainly detected in urine and bowel [25].

In an in vitro test, hepatocytes obtained from channel catfish were treated with FBZ, revealing that FBZ was primarily transformed into OXF, followed by p-hydroxyfenbendazole. Only small quantities of $OXFSO_2$ were detected, and fenbendazole amine was not present [26].

Residue depletion studies

Tissue depletion of FBZ was studied in a generally used laboratory model (rainbow trout) and in important fish species consumed in Japan (Japanese amberjacks and tiger puffers). Table 1 presents the study design and additional information.

A study conducted on rainbow trout via the gastrointestinal tract by a stomach tube at a single dose of 50 mg/kg bw/day indicated that FBZ was observed in the liver and muscle 24 h after administration, and the levels in both tissues sharply decreased thereafter [24]. Another study of rainbow trout by intubation or bathing revealed that the peak concentrations of both routes reached 24 h and then rapidly decreased. FBZ was detected in muscle at 4 days with a maximum concentration, whereas OXF was present in the skin until 4 days after administration [23]

In a residue depletion trial using Japanese amberjack (*S. quinqueradiata*) administered via feed to a final dose of 10 mg/kg bw/day FBT for 5 consecutive days, compounds that could be transformed to $OXFSO_2$ were below the limit of quantification (LOQ) at all time points over 3 days after the last administration [27]. However, the FBT, FBZ, and OXF levels were not reported in this study. The highest concentration of residues that could be metabolized into $OXFSO_2$ was found in the liver, followed by the kidneys and muscle. In particular, muscle was below the LOQ at all time points 3 days after the last treatment. After 14 days post the last treatment, levels above the LOQ were observed in both the liver and kidneys. The residues ranged from 0.0730 to 0.0842 μg/*g* in the liver and from 0.0578 to 0.0837 μg/*g* in the kidneys [27].

In a residual study in which greater amberjack (*S. dumerili*) was exposed to a dose of 10 mg/kg bw FBT via feed for 5 days, the levels of $OXFSO_2$ in muscle ranged from 0.0192 to 0.0582 μg/*g* 3 days after the last treatment. However, $OXFSO_2$ levels in muscle samples were below the LOQ at all time points after 5 days. Similar to

the results for greater amberjack (Kanpachi), the highest concentration of $OXFSO_2$ was observed in the liver, followed by the kidneys. At day 3 from cessation, levels of $OXFSO_2$ ranged from 0.0192 to 0.0582, 2.14 to 3.42, and 0.775 to 1.50 μg/*g* in muscle, the liver, and kidneys, respectively. After 5 days from the last treatment, residues were not observed in muscle at all sampling points. On day 14 after suspension, the levels of $OXFSO_2$ in the liver and kidneys were detected at a range of 0.0924–0.135 and 0.134–0.142 μg/*g*, respectively [27].

Another residue depletion trial using Japanese pufferfish (*T. rubripes*) administered 25% formulation of FBT via feed at a dose of 50 mg/kg bw for 5 consecutive days showed that no compounds were detected in muscle without skin 7 days after the last feeding. In muscle without skin, FBT was absent in all fish 24 h after cessation, whereas $OXFSO_2$ was detectable at 0.51–1.39 μg/g. At 24 h after cessation of treatment, the concentrations of $OXFSO_2$ in skin tissues of fish ranged from 1.00 to 2.64 μg/*g* [27].

In addition to the aforementioned residual trials, a similar study was conducted using pufferfish. The study indicated that at 1 day post-termination, residue concentration of FBT 0.27–0.41 μg/*g*, FBZ, OXF and, $OXFSO_2$ as an equivalent to $OXFSO_2$ of 1.40–5.00 μg/*g* in skin sample; however, in muscle sample, residue concentration of FBT 0.11–0.15 μg/*g*, FBZ and its metabolites as an equivalent to $OXFSO_2$ of 0.80–2.80 μg/*g*. None of the compounds were observed in both tissue samples (i.e., muscle and skin) after 14 days from the last dietary administration.

In the two residue trials conducted with pufferfish, the elimination of FBT and its metabolites in muscle tissue appeared to be faster than in the skin. This was observed because the concentration of FBT and its degradation products in muscle samples without skin was approximately twofold lower than in the skin samples. Additionally, OXFSO2 persisted longer than the parent compound in both tissues.

Pharmacological studies

Detailed pharmacological studies of FBT and FBZ in different fish species, including rainbow trout, pufferfish, and amberjacks, are outlined in Table 2.

In vivo and in vitro efficacy trials of FBT performed using rainbow trout infected with *Gyrodactylus* species showed that anthelmintic activity was not observed in vivo test and signs of toxicity were reported at a high concentration of 10 mg/L for 3 h. However, in vitro test showed that all parasites *of Gyrodactylus* species could be killed by treatment with FBT for a prolonged exposure time (i.e., 1 h) [28].

In vivo test on the efficacy of FBZ and OXF in rainbow trout demonstrated that FBZ treatment was uniquely effective to eliminate *Gyrodactylus* species at a dose ranging from 1.5 to 25 mg/L for 3 h. However, in vitro test of both compounds confirmed that they had no anthelmintic activity against *Gyrodactylus* species [29].

In a pharmacodynamic study in which Japanese pufferfish (*T. rubripes*) were administered 25% formulation of FBT via feed at a dose of 25 mg/kg bw consecutively for 5 days, the T_{max} of FBT was 4 h with a C_{max} of 0.58 μg/*g*. Plasma levels of FBZ were constant (approximately 4 or 5 μg/*g* over 24 h before cessation), although those of FBT, OXF, or $OXFSO_2$ were maintained at below 1, 0.5, or 0.5 μg/*g*, respectively [27].

When Japanese pufferfish (*T. rubripes*) were administered a single dose of 25 mg/kg bw/day FBT, FBT was only detectable at below 1.8 μg/g at 4 h after administration and was absent thereafter. The T_{max} of the total residues (FBT, FBZ, OXF, and $OXFSO_2$) in the tissues (muscle, skin, and the kidneys) was 12 h, and C_{max} ranged from 1.8 to 5.0 μg/*g*. The T_{max} of the total residue in the liver was 4 h with a C_{max} of 29.0 μg/*g*. The total residues, excluding FBT, were still detectable up to 24 h post-administration in various tissues and 72 h post-administration in the plasma [27].

An efficacy test using two amberjacks species, *S. quinqueradiata* and *S. dumerili* [30], demonstrated that FBT treatment was effective against infection by the gill flukes *H. heterocerca* and *Z. japonica* in two fish species, and the effective regimen was confirmed to be 10 mg/kg bw/day for 5 days. Moreover, there were no obvious signs of toxicity, and all treated animals showed good feeding activity [20]. Another study on the efficacy of FBT using the *S. quinqueradiata* and *S. dumerili* showed that infection with *M. seriolae*, a causative agent of beko disease, was prevented appropriately by oral FBT treatment at a dose of more than 3 mg/kg bw/day for 3–10 days [31]. In field efficacy trials of FBT, amberjack-susceptible parasites such as *H. heterocerca*, *Z. japonica*, and *M. seriolae* were successfully removed through oral FBT administration. The frequency of infected fish decreased, and the progression of cyst formation was delayed [18, 22].

An analysis regarding the antiparasitic effects of FBZ in stickleback fish that was naturally infected *G. anomala* highlighted that the number of infected fish was markedly reduced and mature parasites' polaroplast was completely damaged by multi or single applications through bath at a concentration up to 50 μg/mL for 6 h [32].

Research on the efficacy of FBZ in juvenile rohu fish infected with *Dactylogyrus* species, which are considered critical gill parasites causing severe economic damage to the aquaculture industry, showed that multiple applications of FBZ at a dose of 20 mg/kg bw/day for 7 days

Table 2 Pharmacological studies of febantel and fenbendazole

Compound	Study design (species, dosage, and admin. regime)	Target parasites	Results	References
FBT	Tiger puffer (*T. rubripes*); 25 mg/kg bw/day for 5 day; feed	–	T_{max} of FBT (4 h); C_{max} (0.58 μg/*g*); FBZ concentration in plasma was constant (i.e. 4–5 μg/*g*) until cessation; FBT, OXF, and $OXFSO_2$ in plasma with negligible quantities (i.e., < 1 μg/*g*)	FSCJ [27]
FBT	Tiger puffer (*T. rubripes*); 25 mg/kg bw/day (Single); feed	–	FBT was only detectable at below 1.8 μg/*g* at 4 h and absent thereafter; T_{max} of total residues (FBT and its metabolites) in muscle, skin and kidney was 12 h with C_{max} (~5.0 μg/*g*); T_{max} of total residues (FBT and its metabolites) in liver was 4 h with C_{max} (29.0 μg/*g*); residues were detectable until 72 h in plasma; 24 h in organs	FSCJ [27]
FBT	Japanese Amberjack (*S. quinqueradiata* & *S. dumerili*); 0–20 mg/kg bw/day for 5 day; feed (different three trials)	*H. heterocerca* and *Z. japonica*	No apparent avoidance to medicated feed, and no signs of toxicity in all groups; effective dose and duration of FBT were demonstrated: 10 mg/kg bw/day for 5day	Shirakashi et al. [20]
FBZ	Juvenile Rohu (*Labeo ronita*) infected with *Dactylogyrus* sp.; 20 mg/kg bw/day (single) or for 7 day (e.g. three times; 1st, 3rd, and 7th day); feed	*Dactylogyrus* sp.	Effective to infection of target parasite via oral admin. of FBZ at 20 mg/kg bw/day on 1st, 3rd, and 7th day	Gupta et al. [3]
FBT	Tiger puffer (*T. rubripes*); 0–100 mg/kg bw/day; single or 2 day, 3 day, or 5 day; feed (three experiments)	*H. okamotoi*	Time to peak concentration of FBT at 4 h after administration and steadily decreased after 8 h; time to peak concentration of OXF sulfone at 12 h and detected in plasma until 3d	Kimura et al. [5]
FBZ	Silver perch (*Bidyanus bidyanus*); bath at 10 mg/L for 48 h or feed at 75 mg kg bw/day for 6day	*Lepidotrema bidyana*	Significant decrease in the number of adult *L. bidyana* following bath (81–100%) and oral admin. (84%–98%); juvenile *L. bidyana* following bath (31%–68%) and oral administration (28–76%)	Forwood et al. [36]
FBT	Tiger puffer (*T. rubripes*); 25 mg/kg bw/day for 5 day; feed	*H. okamotoi*	Main metabolite in plasma is FBZ followed by OXF and OXF SO_2; peak concentration (10.28 μg/g at 12 h), $T_{1/2}$ (12.17 h), and peak concentration of FBZ sharply decline thereafter; no. of target gill fluke was significantly decreased at 4–5d after treatment; Effective dose and duration of treating immature and mature worms were demonstrated: 25 mg/kg bw/day for 5 days and WHP for 3 weeks	Kimura et al. [34]
FBZ	Rainbow trout (*O. mykiss*); 25 mg/L for 3 or 12 h; 0.77, 1.5, 6.2, or 12.5 mg/L for 12 h; WB (noncirculating system)	*Gyrodactylus* sp.	No emergence of parasites at dosage from 1.5 to 25 mg/L	Tojo et al. [29]
OXF	Rainbow trout (*O. mykiss*); 25 or 200 mg/L for 3 h; WB (non-circulating system)	*Gyrodactylus* sp.	No anthelmintic activity at the highest concentration	Tojo et al. [29]
FBZ	*Gyrodactylus* sp. obtained from infected rainbow trout (*O. mykiss*); in vitro, 12.5 mg/L for 1 h, medium (petri dish)	*Gyrodactylus* sp.	No death of target parasite	Tojo et al. [29]
OXF	*Gyrodactylus* sp. obtained from infected rainbow trout (*O. mykiss*); in vitro, 200 mg/L for 1 h, medium (petri dish)	*Gyrodactylus* sp.	No death of target parasite	Tojo et al. [29]
FBT	Juvenile Japanese Amberjack (*S.quinqueradiata* or *S. dumerili*); 0.5–25 mg/kg bw/day for up to 10 day; WB (total seven trials)	*M. seriolae*	Dose of 3 mg/kg bw/day or greater for 3d is effective when FBT orally admin. at early stage of infection for preventing cyst formation and multiplication of parasites	Yanagi et al. [31]

Table 2 (continued)

Compound	Study design (species, dosage, and admin. regime)	Target parasites	Results	References
FBT	*Gyrodactylus* sp. obtained from infected rainbow trout (*O. mykiss*); in vitro, 1000 mg/L for 0.5 h or 1 h; medium (petri dish); In vivo, 2.5 or 10 mg/L for 3 h; WB (noncirculating system)	*Gyrodactylus* sp.	100% efficacy observed when FBT treated for 1 h in vitro; no anthelmintic activities at both concentration in vivo	Santamarina et al. [28]
FBZ	Young and adult three-spined sticklebacks *(G. aculeatus)*; 0–50 µg/mL for 2 day or 6 day; bath *tolerance test, 1–100 µg/mL for 100 h; bath *infectivity test, 50 µg/mL for 6 h (single) or 3 × 2 µg/mL for 6 h (36 h intervals); bath	*G. anomala*	Infectivity test, spore infectivity was drastically lowered (no. of infected fish from 5–7 to 1–2); deep invaginations in the anterior or posterior pole of mature spores	Günter Schmahl and Jochen Benini, [32]
FBT	Japanese Amberjack (*S. quinqueradiata* & *S. dumerili*); 0–10 mg/kg bw/day for 5 day; feed	*M. seriolae*	Cyst detection rate and progression of cyst formation in both species	Kawakami et al. [18]
FBT	Japanese Amberjack (*S. quinqueradiata, S. dumerili*); 0, 10 mg/kg bw/da for 5 day; feed (different four locations, total four trials)	*H. heterocerca* and *Z. japonica*	Decreased infection prevalence of both fish species against gill flukes	Shirakashi et al. [30]
FBT	Tiger puffer (*T. rubripes*); 0, 12.5, or 25 mg/kg bw/day for 5 day; feed (total six trials)	*H. okamotoi*	Gill fluke was eliminated up to 80% by treatment, but there was no difference between concentrations	Kimura et al. [35]
FBT	Juvenile Japanese Amberjack (*S.quinqueradiata* or *S. dumerili*); ① 0–10 mg/kg bw/day for 5day; WB (three trials) ② 10 mg/kg bw/day for (5 days + 2 days interval, 1 cycle), total 15 cycles	*M. seriolae*	Concentration of FBT depends on cumulative mortality at the end of experiment; Significant decrease in cyst detection rate and progression of cyst formation after treatment; no adverse effects observed in both tests	Kawakami et al. [18]

FBT febantel, *FBZ* fenbendazole, *BL* Bilirubin, *TG* triglyceride, *CRE* creatine, *hpf* hours post-fertilization, *SOD* superoxide dismutase, *GST* glutathione S-transferase, *CAT* catalase activity, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *OXF* oxfendazole, *OXF* SO_2 oxfendazole sulfone, *Vd* volume of distribution, *WHP* withdrawal period

Table 3 Results of febantel exposure assessment

Commodities	MRLs	MR/TRR ratio*	Corrected value	Intake (kg/day)		Exposure (mg/day)	
				Average	High	Average	High
Fish	0.05	1.00	0.05	0.0292	0.2191	0.0015	0.0110
Cattle muscle	0.10	1.00	0.10	0.0220	0.2623	0.0022	0.0262
Cattle liver	0.50	1.00	0.50	0.0001	0.1194	< 0.0001	0.0597
Cattle kidney	0.10	1.00	0.10	< 0.0001	0.0004	< 0.0001	< 0.0001
Cattle fat	0.10	1.00	0.10	0.0013	0.0007	0.0001	0.0001
Pig muscle	0.10	1.00	0.10	0.0471	0.4319	0.0047	0.0432
Pig liver	0.50	1.00	0.50	0.0001	0.0946	< 0.0001	0.0473
Pig kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Pig fat	0.10	1.00	0.10	< 0.0001	0.0010	< 0.0001	0.0001
Horse muscle	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Horse liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Horse kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Horse fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sheep muscle	0.10	1.00	0.10	< 0.0001	0.0015	< 0.0001	0.0001
Sheep liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sheep kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sheep fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Goat muscle	0.10	1.00	0.10	< 0.0001	0.2184	< 0.0001	0.0218
Goat liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Goat kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Goat fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer muscle	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Chicken muscle	0.05	1.00	0.05	0.0238	0.5438	0.0012	0.0272
Chicken liver	0.50	0.29	1.72	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Chicken fat	0.05	1.00	0.05	< 0.0001	0.0044	< 0.0001	0.0002
Chicken kidney	0.05	0.18	0.28	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Eggs	1.30	1.00	1.30	0.0335	0.0449	0.0436	0.0584
Milk	0.10	0.20	0.50	0.0963	0.5533	0.0481	0.2766
Sum of exposure (mg/day)						0.3300	
ADI = 0.007 mg/kg bw/day × 60 kg						0.42	
Hazard Index (%)						78.6	

* Ratios of marker to total radioactive residue (MR:TRR) were obtained from EMA (2013)

could reduce the number of young fish infected with *Dactylogyrus* species [33].

Several studies aimed at evaluating the efficacy of FBT against *H. okamotoi* and the pharmacokinetics of FBT in tiger puffer fish demonstrated that FBZ was accepted as the main metabolite [34]. The T_{max} of FBT was approximately 4 h and gradually decreased after 8 h. In contrast, the T_{max} of $OXFSO_2$ was three times higher than that of FBT, and $OXFSO_2$ was detectable until 3 days after suspension [5]. Following FBT treatment at a dose of 25 mg/kg bw/day for 5 days via feed, the number of *H. okamotoi* substantially reduced after 4–5 days [34]. In addition, the efficacy did not differ with exposure concentration [35].

In an investigation of the pharmacological activities of baths and orally administered FBZ against the monogenean gill parasite *L. bidyana* of silver perch (Mitchell), the efficacies of bath and oral administration against mature *L. bidyana* were 91% and 95%, respectively, without any toxicological concerns, such as behavioral abnormalities or adverse physical signs and mortalities. The efficacies of both treatments against immature *L. bidyana*

Table 4 Results of fenbendazole exposure assessment

Commodities	MRLs	MR/TRR ratio*	Corrected value	Intake (kg/day)		Exposure (mg/day)	
				Average	High	Average	High
Fish	0.05	1.00	0.05	0.0292	0.2191	0.0015	0.0110
Cattle muscle	0.10	1.00	0.10	0.0220	0.2623	0.0022	0.0262
Cattle liver	0.50	1.00	0.50	0.0001	0.1194	< 0.0001	0.0597
Cattle kidney	0.10	1.00	0.10	< 0.0001	0.0004	< 0.0001	< 0.0001
Cattle fat	0.10	1.00	0.10	0.0013	0.0007	0.0001	0.0001
Pig muscle	0.10	1.00	0.10	0.0471	0.4319	0.0047	0.0432
Pig liver	0.50	1.00	0.50	0.0001	0.0946	< 0.0001	0.0473
Pig kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Pig fat	0.10	1.00	0.10	< 0.0001	0.0010	< 0.0001	0.0001
Horse muscle	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Horse liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Horse kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Horse fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sheep muscle	0.10	1.00	0.10	< 0.0001	0.0015	< 0.0001	0.0001
Sheep liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sheep kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Sheep fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Goat muscle	0.10	1.00	0.10	< 0.0001	0.2184	< 0.0001	0.0218
Goat liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Goat kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Goat fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer muscle	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer liver	0.50	1.00	0.50	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer kidney	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Deer fat	0.10	1.00	0.10	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Chicken muscle	0.05	1.00	0.05	0.0238	0.5438	0.0012	0.0272
Chicken liver	0.50	0.29	1.72	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Chicken fat	0.05	1.00	0.05	< 0.0001	0.0044	< 0.0001	0.0002
Chicken kidney	0.05	0.18	0.28	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Eggs	1.30	1.00	1.30	0.0335	0.0449	0.0436	0.0584
Milk	0.10	0.20	0.50	0.0963	0.5533	0.0481	0.2766
Sum of exposure (mg/day)						0.3300	
ADI = 0.007 mg/kg bw/day × 60 kg						0.42	
Hazard Index (%)						78.6	

* Ratios of marker to total radioactive residue (MR:TRR) were obtained from EMA (2013)

were substantially lower than those against mature ones (i.e., efficacy of 28%–76%) [36].

In summary, previous pharmacological studies have shown that FBT treatment is remarkably effective against blood-sucking parasites responsible for gill fluke disease, such as *H. okamotoi*, *M. sebastis*, and *Dactylogyrus sp.* across various fish species. Specifically, *M. sebastis* is recognized as a prominent pathogen isolated from Korean farmed fishes like rockfish *Sebastes schlegelil*, blackhead seabream *Acanthoparus schlegelii*, and Red seabream *Pagrus major* [37].

Praziquantel is the only approved anthelmintic drug for aquatic animals in Korea, widely used in human medicine, veterinary practice, and aquaria. However, the development of praziquantel resistance has been documented in numerous studies [38]. Significantly, a reduction in efficacy was noted when treating praziquantel to salmon infected with *Eubothrium* in Norway [39, 40].

Considering the emergence of praziquantel resistance and the outstanding efficacy of FBT and its active metabolite FBZ, we anticipate that FBT and FBZ could serve as

excellent alternatives to praziquantel in the Korean aquaculture industry.

Exposure assessment

Tables 3 and 4 show that the estimates of chronic dietary exposure are calculated as 0.3300 mg/person/day and the values are divided by 0.42 mg/person/day (60 kg of body weight). Hazard indices are shown up to 78.6%, suggesting that the residues from using FBT and FBZ will pose negligible consumer health risks.

This study confirms that FBZ and its metabolites are more frequently detected in the skin than in muscle after FBT and FBZ treatment in fish. Furthermore, residues that can be metabolized into $OXFSO_2$ have been observed in the liver and kidneys in large quantities for a prolonged period compared with those in muscle. The beneficial effects of treating gill and skin diseases were demonstrated without any significant signs of toxicity in various fish species, including Japanese amberjacks, Indian carp (i.e., rohu), and pufferfish, through the application of FBT and FBZ. The effective dose and duration of FBT ranged from 10 to 50 mg/kg bw/day consecutively for 5 days without any signs of toxicity. Feeding or bath treatment was more effective than gavage or injection.

As a result of the exposure assessment, the primary source of FBT and FBZ exposure was milk, with 0.2766 mg capita per day, corresponding to 83.8 percent of the total exposure. The estimated exposure from fish was 0.0015 mg capita per day, accounting for 0.45 percent. The Hazard Index (HI) is calculated by dividing the estimated total exposure by the acceptable daily intake. Therefore, when the Hazard Index, as in the case of FBT and FBZ, is below 100 percent, it is considered that the human health risk from the consumption of food items, including veterinary drug residues, would be negligible. Consequently, it is concluded that the tentative Maximum Residue Limit (MRL) of FBT and FBZ for fish was acceptable.

Most research identifying residue levels in fish has focused on muscle. In contrast, residue investigations of potential edible tissues in fish, such as other visceral organs (i.e., the intestine, ovaries, or eggs), are limited. However, in several countries, these organs are generally consumed in salted form [41, 42].

Additionally, an investigation in which aquatic animals were fed antimicrobials over a long period demonstrated that antimicrobial residues could negatively affect the intestine (i.e., altered intestinal enzyme activities and imbalanced relative abundance of gut intestinal microflora) [43–45].

Considering the great diversity of fish consumption patterns and the effects of veterinary drugs on the intestine, further depletion or metabolism studies on potential edible tissues in fish are warranted.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13765-024-00879-6.

Additional file 1: Table S1. ADI and rationales for febantel recommended by international regulatory agencies. **Table S2.** ADI and rationales for fenbendazole recommended by international regulatory agencies. **Table S3.** ADIs for target chemicals and rationales.

Acknowledgements

The authors sincerely express their gratitude to applied biological chemistry, editors, and peer reviewers. Their comments and suggestions enhanced the findings discussed within this Contemporary Review.

Author contributions

MJK: Investigation, writing—original draft, review & editing. JYK, DWS and H-KK: Supervision and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding

This study was supported by a grant from the Ministry of Food and Drug Safety of Korea for 2023 (No. 23191MFDS279).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Received: 26 September 2023 Accepted: 16 February 2024
Published online: 30 March 2024

References

1. Orobets V, Lisovets E, Zabashta S, Ermakov A (2019) Control of fish parasites in aquaculture. IOP Conf Ser: Earth Environ Sci 403:012065. https://doi.org/10.1088/1755-1315/403/1/012065
2. OECD/FAO (2016) OECD-FAO Agricultural Outlook 2016–2025. OECD Publishing, Paris. https://doi.org/10.1787/agr_outlook-2016-en
3. Gupta G, Chatterjee A, Kumar M, Sardar P, Varghese T, Srivastava PP, Gupta S (2020) Efficacy of single and multiple doses of fenbendazole against gill parasites (Dactylogyrus sp.) of Labeo rohita (Hamilton, 1822) and its physio-metabolic effects on the fish. Aquac Res 51(3):1190–1199. https://doi.org/10.1111/are.14470
4. Sommerville C (2009) Controlling parasitic diseases in aquaculture: new developments. In: Burnell G, Allan G (eds) New technologies in aquaculture. Woodhead Publishing Series, Cambridge, pp 215–243. https://doi.org/10.1533/9781845696474.2.215
5. Kimura T, Sameshima M, Nomura Y, Morita J, Mizoguchi H, Ishihara M (2006) Efficacy of orally administered febantel against monogenean Heterobothrium okamotoi infection of cultured tiger puffer Takifugu rubripes. Fish Pathol 41:147–151. https://doi.org/10.3147/jsfp.41.147
6. Gharavi-nakhjavani MS, Niazi A, Hosseini H, Aminzare M, Dizaji R, Tajdar-oranj B, Mirza Alizadeh A (2023) Malachite green and leucomalachite green in fish: a global systematic review and meta-analysis. Environ Sci Pollut Res. https://doi.org/10.1007/s11356-023-26372-z

7. Kebirungi P, Nyombi A, Omara T et al (2022) Oxytetracycline residues in bovine muscles, liver and kidney tissues from selected slaughter facilities in South Western Uganda. Bull Natl Res Cent 46:17. https://doi.org/10.1186/s42269-022-00702-68
8. Pokrant E, Yévenes K, Trincado L, Terraza G, Galarce N, Maddaleno A, Martín BS, Lapierre L, Cornejo J (2021) Evaluation of antibiotic dissemination into the environment and untreated animals, by analysis of oxytetracycline in poultry droppings and litter. Animals 11:853. https://doi.org/10.3390/ani11030853
9. Leal JF, Santos EB, Esteves VI (2019) Oxytetracycline in intensive aquaculture: water quality during and after its administration, environmental fate, toxicity and bacterial resistance. Rev Aquac 11(4):1176–1194. https://doi.org/10.1111/raq.12286
10. Papich MG (2015) Saunders handbook of veterinary drugs-e-book: small and large animal. Elsevier Health Sciences, Amsterdam, pp 312–316
11. European Medicines Agency (EMA). 2013. European public MRL assessment report (EPMAR) for fenbendazole (extension to chicken and extrapolation to all food pro ducing species) EMA/CVMP/914694/2011. 15 January 2013.
12. Food and Drug Administration (FDA). 2022. Animal & Veterinary NADA 131–675 Safe-Guard®-supplemental new animal drug application-summary. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/11816. Accessed 28 Mar 2024
13. Food and Drug Administration (FDA). 1991. Animal & Veterinary NADA 140–912 (original) RINTAL (febantel) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/526. Accessed 28 Mar 2024
14. The European Agency for the Evaluation of Medicinal Products (EMEA). 1997. Febantel (summary report 3). EMEA/MRL/192/97-FINAL. The European Agency for the Evaluation of Medicinal Products, London, UK. https://www.ema.europa.eu/en/documents/mrl-report/febantel-summary-report-3-committee-veterinary-medicinal-products_en.pdf. Accessed June 1997
15. European Medicines Agency (EMA). 2011. Panacur AquaSol fenbendazole. European Medicines Agency, London, UK. https://www.ema.europa.eu/en/documents/overview/panacur-aquasol-epar-summary-public_en.pdf. Accessed 17 March 2020
16. Kim MJ, Kim JY, Choi JD, Moon G (2022) Establishment of acceptable daily intakes (ADIs) and risk assessment for ephedrine, Menichlopholan, Anacolin, and Etisazole Hydrochloride. Korean J Environ Agric 41(4):261–275. https://doi.org/10.5338/kjea.2022.41.4.32
17. Arcella D, Boobis A, Cressey P, Erdely H, Fattori V, Leblanc J-C, Lipp M, Reuss R, Scheid S, Tritscher A, Velde-Koerts TV, Verger P (2019) Harmonized methodology to assess chronic dietary exposure to residues from compounds used as pesticide and veterinary drug. Crit Rev Toxicol 49(1):1–10. https://doi.org/10.1080/10408444.2019.1578729
18. Kawakami H, Ishii Y, Nakajima K, Yanagi S, Satoh J (2021) Field trials of febantel for the treatment of the beko disease in Seriola spp. Fish Pathol 56:71–78. https://doi.org/10.3147/jsfp.56.71
19. Shirakashi S, Miwa S, Katsuki T, Harakawa S, Kawakami H, Nakayasu C, Mori K (2021) Evaluations of lethal and sub-lethal toxicity of febantel in the juvenile Japanese amberjack Seriola quinqueradiata. Fish Pathol 56:79–88. https://doi.org/10.3147/jsfp.56.79
20. Shirakashi S, Nishikawa S, Ishii Y et al (2021) Efficacy of Febantel against Gill Monogeneans of Amberjacks II: field trial assessment. Fish Pathol 56(4):212. https://doi.org/10.3147/jsfp.56.212
21. Carlsson G, Patring J, Kreuger J, Norrgren L, Oskarsson A (2013) Toxicity of 15 veterinary pharmaceuticals in zebrafish (Danio rerio) embryos. Aquat Toxicol 126:30–41. https://doi.org/10.1016/j.aquatox.2012.10.008
22. Shirakashi S, Asai N, Satoh J, Nakayasu C (2021) Persistence assessment of febantel and its effects on blood profile in juvenile Japanese amberjack Seriola quinqueradiata. Fish Pathol 56:97–100. https://doi.org/10.3147/jsfp.56.97
23. Iosifidou EG, Haagsma N, Tanck MWT, Boon JH, Olling M (1997) Depletion study of fenbendazole in rainbow trout (Oncorhynchus mykiss) after oral and bath treatment. Aquaculture 154(3–4):191–199. https://doi.org/10.1016/S0044-8486(97)00051-3
24. Soukupova-Markova Z, Doubkova V, Marsalek P, Svobodova Z, Papezikova I, Lang S, Palikova M (2015) Degradation rate of praziquantel and fenbendazole in rainbow trout following oral administration. Neuro Endocrinol Lett 36(1):64–67
25. Kitzman JV, Holley JH, Huber WG et al (1990) Pharmacokinetics and metabolism of fenbendazole in channel catfish. Vet Res Commun 14:217–226. https://doi.org/10.1007/BF00347741
26. Short CR, Flory W, Hsieh LC, Barker SA (1988) The oxidative metabolism of fenbendazole: a comparative study. Journal of Veterinary Pharmacology and Therapeutics 11(1):50–55. https://doi.org/10.1111/j.1365-2885.1988.tb00120.x
27. Food Safety Commission of Japan (FSCJ). 2020. Oxfendazole, Febantel and Fenbendazole. 2nd edn. Veterinary Drugs Assessment. Food Safety Commision of Japan [In Japanese]. https://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20092511601&fileId=201. Accessed 20 Oct 2020.
28. Santamarina MT, Tojo J, Ubeira FM, Quinteiro P, Sanmartin ML (1991) Anthelmintic treatment against Gyrodactylus sp. infecting rainbow trout Oncorhynchus mykiss. Dis Aquat Org 10(1):39–43
29. Tojo J, Santamarina MT, Ubeira FM, Estevez J, Sanmartin ML (1992) Anthelmintic activity of benzimidazoles against Gyrodactylus sp. infecting rainbow trout Oncorhynchus mykiss. Dis Aquat Org 12:185–189
30. Shirakashi S, Nishikawa S, Kawakami H, Ishihara M, Fukui T, Hirose K (2021) Efficacy of febantel against gill monogeneans of amberjacks I: laboratory assessment for effective dose and administration period. Fish Pathol 56:205–211. https://doi.org/10.3147/jsfp.56.205
31. Yanagi S, Satoh J, Mekata T, Sakai T, Kawakami H, Harakawa S, Mori KI (2021) Chemical treatment of beko disease in Seriola fishes: laboratory trials of commercially available fishery and veterinary medicines. Fish Pathol 56(2):62–70. https://doi.org/10.3147/jsfp.56.62
32. Schmahl G, Benini J (1997) Treatment of fish parasites. 11. Effects of different benzimidazole derivatives (albendazole, mebendazole, fenbendazole) on Glugea anomala, Moniez, 1887 (Microsporidia): ultrastructural aspects and efficacy studies. Parasitol Res 84:41–49. https://doi.org/10.1007/s004360050354
33. Gupta G, Kumar M, Sardar P, Varghese T, Srivastava PP, Gupta S (2021) Pharmacokinetics and physio-metabolic response of single and multiple dose of fenbendazole in Labeo rohita (Hamilton, 1822) fingerlings. Aquac Res 52(1):260–272
34. Kimura T, Morita J, Nomura Y, Enomoto J, Mizoguchi H, Ishihara M (2007) Concentration-time profile of febantel in cultured tiger puffer takifugu rubripes. Aquac Sci 55(2):279–284. https://doi.org/10.11233/aquaculturesci1953.55.279
35. Kimura T, Nomura Y, Kawakami H, Itano T, Iwasaki M, Morita J, Enomoto J (2009) Field trials of febantel against gill fluke disease caused by the monogenean Heterobothrium okamotoi in cultured tiger puffer Takifugu rubripes. Fish Pathol 44:67–71. https://doi.org/10.3147/jsfp.44.67
36. Forwood JM, Harris JO, Deveney MR (2013) Efficacy of bath and orally administered praziquantel and fenbendazole against L epidotrema bidyana Murray, a monogenean parasite of silver perch, B idyanus bidyanus (M itchell). J Fish Dis 36(11):939–947. https://doi.org/10.1016/j.aquaculture.2013.08.034
37. Kang GH, Cha SJ (2019) Monitoring of pathogens detected in cultured fishes of Gyeongnam in 2018. Korean J Fish Aquat Sci 52(5):539–546. https://doi.org/10.5657/kfas.2019.0539
38. Norbury LJ, Shirakashi S, Power C, Nowak BF, Bott NJ (2022) Praziquantel use in aquaculture—current status and emerging issues. Int J Parasitol Drugs Drug Resist 18:87–102. https://doi.org/10.1016/j.ijpddr.2022.02.001
39. FHF (The Norwegian Fishery and Aquaculture Industry Research Fund) 2006. Bendelorm (Eubothrium sp.) hos laks (Salmo salar): Utprøving av nye behandlingsmidler og utvikling av et in vitro bioassay for måling av resistens overfor praziquantel—Rapport fra et pilotprosjekt [Tapeworm (Eubothrium sp.) in salmon (Salmo salar): trial of new therapeutics and development of an in vitro bioassay to measure praziquantel resistance—Report]. https://www.fhf.no/prosjekter/prosjektbasen/551024/. Accessed 28 Mar 2024
40. FHF (The Norwegian Fishery and Aquaculture Industry Research Fund) (2008). reportResistens hos bendelorm (Eubothrium sp.) Sluttrapport 2008 [Resistance in tapeworm (Eubothrium sp.) Final Report 2008]. https://www.fhf.no/prosjekter/prosjektbasen/552024/. Accessed 25 Aprl 2020
41. Lee JS, Park JM, Kim AJ, Lee JS, Park JM, Kim AJ (2022) The history of salted-seafood consumption and an evaluation of its nutritional and functional value. Asian J Beauty Cosmetol 20(2):273–284. https://doi.org/10.20402/ajbc.2022.0035

42. Koo O, Lee S, Chung K, Jang D, Yang H, Kwon D (2016) Korean traditional fermented fish products: Jeotgal. J Ethnic Foods 3(2):107–116. https://doi.org/10.1016/j.jef.2016.06.004
43. Sáenz JS, Marques TV, Barone RSC et al (2019) Oral administration of antibiotics increased the potential mobility of bacterial resistance genes in the gut of the fish Piaractus mesopotamicus. Microbiome 7:24. https://doi.org/10.1186/s40168-019-0632-7
44. Sun S, Korheina DK, Fu H, Ge X (2020) Chronic exposure to dietary antibiotics affects intestinal health and antibiotic resistance gene abundance in oriental river prawn (Macrobrachium nipponense), and provokes human health risk. Sci Total Environ 720:137478. https://doi.org/10.1016/j.scitotenv.2020.137478
45. Shi F, Huang Y, Yang M, Lu Z, Li Y, Zhan F, Lin L, Qin Z (2022) Antibiotic-induced alternations in gut microflora are associated with the suppression of immune-related pathways in grass carp (Ctenopharyngodon idellus). Front Immunol 13:970125. https://doi.org/10.3389/fimmu.2022.970125

Publisher's Note