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SHORT COMMUNICATION

Ecotoxicity of Aquaculture Chemotherapy-A Case Study in Chile

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Abstract

Aquaculture has experienced rapid growth in Chile over the past three decades, currently ranking first in America in terms of production. The use of chemotherapy, involving chemical drugs to prevent and treat disease outbreaks, has been widespread in salmon aquaculture for managing fish population diseases. To mitigate the negative environmental impacts of aquaculture chemotherapy, an analysis of the current legal framework governing Environmental Impact Assessments (EIAs) for veterinary medicinal products was conducted, referencing the Chilean regulatory framework and international guidelines. The analysis revealed a need to enhance the Chilean legal framework to align with international standards, thereby facilitating sustainable aquatic production. The study identified a legal framework that permits high ecotoxicity acceptance parameters, resulting in elevated environmental risk due to the use of Florfenicol in seawater-phase aquaculture, as indicated by a risk quotient (RQ) value exceeding 100.

Introduction

Aquaculture is a significant economic activity in Chile, ranking as one of the largest producers and exporters of aquaculture products globally. In 2022, the country produced 758,953 tons of Atlantic salmon, 241,904 tons of Coho salmon, and 73,315 tons of Rainbow Trout (SERNAPESCA 2022). Chile leads aquaculture production in the Americas, contributing 34.21% of the total production, with a total output of 1,505.5 thousand tons of live weight, as reported by the Food and Agriculture Organization (FAO 2024). Although Chilean aquaculture has successfully generated economic growth, concerns persist regarding its environmental impact. In 2023, the industry used 5,840.45 tons of hydrogen peroxide and 5.47 tons of other antiparasitics for 1,076,627.69 tons of harvested biomass, resulting in 51,438.24 tons of dead biomass. This translates to a usage rate of 5,150.84 g/t for hydrogen peroxide and 4.85 g/t for other antiparasitics.

Sixteen antibiotics are used in animal treatments in Chile, compared to three in the United States (US) and four in Norway (Cabello 2003). In the case of aquaculture in Chile, antibiotics have been mainly used in sea water (Lozano et al. 2018). The excessive use of antibiotics in the salmon industry remains a significant issue, with 98% of the total antibiotics used in salmon farming in Chile being applied during the seawater phase. Florfenicol accounted for 98.22% of this amount. In 2023, Chile's total antibiotic usage was 338.9 tons for a total biomass production of 1,107,109 tons (SERNAPESCA 2024).

Chemotherapy has been widely used to prevent and treat disease outbreaks, resulting in multiple adverse effects on the environment and human health (Reverter et al. 2014). The presence of chemotherapy drugs in aquatic ecosystems can have ecotoxicological effects at various biological levels (Li et al. 2021). Ecotoxicological risks refer to the harmful effects that a compound or physical agent can have on both the environment and organisms, including fish, microorganisms, wildlife, and plants. The study of a pharmacological or immunological product's ecotoxicity aims to assess the harmful effects associated with the administration of the product on the environment, estimate the risk, and define the necessary measures to reduce this risk (SAG 2011; Tihulca 2013; CENMA 2014). The VICH guidelines, developed through international cooperation, provide guidance on environmental impact assessments for veterinary products. These guidelines serve as a reference for countries, including Chile, in the regulation of veterinary products.

For the registration of drugs in Chile, an analysis of environmental risk information must be presented to the Chilean Ministry of the Environment of the Agricultural and Livestock Service (SAG), based on the methodology "International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products" (VICH) (SAG 2010; Tihulca 2013; Ministerio de Medio Ambiente, Gobierno de Chile 2015). The aim of this study is to compare the Chilean regulatory framework for environmental impact assessments (EIAs) for veterinary chemical products with the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products guidelines in order to make a contribution to sustainable aquaculture production.

Methods

A comparison was performed between the Chilean regulatory framework for Environmental Impact Assessments (EIAs) of veterinary medicinal products (SAG 2011), and international guidelines (VICH 2000, 2004; EMA 2016). An environmental risk assessment was conducted to evaluate the potential risks associated with the use of Florfenicol in the marine environment, in accordance with VICH 2000 and 2004 guidelines (VICH 2000, 2004).

Results

Environmental Risk Assessment For Florfenicol 50% Oral Powder For Aquatic Use In Chile, In Accordance With Vich (Vich 2000, 2004).

Phase I Environmental Impact Assessment (VICH 2000)

Legislation requires an environmental impact assessment for this drug, as it is not a natural substance and its use does not alter the concentration or distribution in the environment. Florfenicol, an antibiotic of the Phenicoles family, derived from chloramphenicol, acts as a bacteriostatic agent by inhibiting bacterial protein synthesis through reversible binding to the 50S subunit of the ribosome, preventing polypeptide chain elongation (Horsberg et al. 1996). This product will be used in fish intended for human consumption. As there are no environmental impact studies for smaller species treated and raised similarly to larger species, this assessment focuses on the latter. The antibiotic will be used to control disease outbreaks in 100% of susceptible animals. Since the product is not completely metabolized in treated animals, it is a neutral, liposoluble compound that is widely distributed throughout the animal organism, reaching significant concentrations within cells and transcellular fluids 12 hours after treatment initiation. The product is primarily excreted through the feces and urine of treated animals (Horsberg et al. 1996). As the product will be used to treat aquatic species, releasing it into the aquatic environment, and there is no waste

disposal matrix in place, the calculation of the risk coefficient (QR) must be performed. The initial environmental concentration (EIC Aquatic) of the product released from aquaculture facilities is not less than 1 mcg/l, and there is no method or technology to reduce its environmental release.

Phase II Environmental Impact Assessment (VICH 2004)

Florfenicol, a widely utilized antibiotic in aquaculture, exhibits bacteriostatic activity against both gram-positive and gram-negative pathogens, including *Aeromonas*, *Vibrio*, *Yersinia*, *Flavobacterium*, and *Photobacterium* (Horsberg et al. 1996). Following intestinal absorption, Florfenicol is distributed to tissues, with peak concentrations detected in muscle tissue at 12 hours post-treatment, corresponding to the Minimum Inhibitory Concentrations (MIC). The antibiotic is subsequently excreted in urine and feces. Both Florfenicol and its metabolites can enter marine sediment and water columns through leaching of unconsumed food and excreta from treated animals. With a molecular weight of 358.21 Daltons, a water solubility of 1.32 g/L at pH 7, and a partition coefficient of 0.37, Florfenicol has a low bioaccumulation potential and a half-life of 4.5 days in marine sediment (Hektoen et al. 1995).

To evaluate the potential environmental risks associated with this product, an experimental model is employed, utilizing various species across different trophic levels. However, this model does not incorporate data from marine environment species in southern Chile (No data from marine environment species in southern Chile were found).

Formulas and abbreviations (VICH 2004)

Predicted Environmental Concentration (PEC) = (Total Florfenicol / mg /day) / total liters per farm
Predicted No Effect Concentration (PNEC)= LC50 o EC50 o NOEC / AF
Risk Quotient (RQ) = PEC/PNEC
LC50 = represents the Lethal Concentration 50, a standardized measure of the toxicity of a surrounding medium that is expected to cause the death of 50 percent of a sample population of a specific test animal within a specified exposure period.
EC50 = denotes the concentration of an agonist necessary to elicit a response halfway between the baseline and maximum response.
NOEC= The No Observed Effect Concentration, is the concentration at which no adverse effect is observed.
AF= Assessment Factors.

PEC Calculation involves the determination of the Predicted Environmental Concentration (Table 1), using average data for a salmon farming center in Chile (SERNAPESCA 2012) for further calculation of Predicted No Effect Concentration (PNEC) and risk quotient (RQ) (Table 2.)

Table 1. PEC Calculation (VICH 2004)

Average data for a salmon farming center in Chile (SERNAPESCA 2012)	**Values**
Standard cage dimensions (m^2)	30 x 30
Depth (m)	15
Cage volume (m^3)	13.500
Nº cages per center	20
Total volume per center (m^3)	270.000
Liters per (m3)	1.000
Total liters per center	270.000.000
Atlantic salmon density (kg/m3)	17
Average harvest weight (kg)	4
Kg of salmon per center	4.590.000
Florfenicol dose (mg/kg/day) (Horsberg et al. 1996)	10
Days of treatment (Horsberg et al. 1996)	10
Florfenicol total amount /mg/day	45.900.000
PEC=	1.67

Table 2. Predicted No Effect Concentration (PNEC) and Risk Quotient (RQ) Calculation

Type	Species	LC50 (mg/l)	Exposition time	AF	PNEC	PEC	RQ	Reference LC50
Fish	*Hyphessobrycon eques*	>100	48 h	100	>1	0,17	**<0,17**	(Carraschi et al. 2015)
	Piaractus mesopotamicus	>100	48 h	100	>1	0,17	**<0,17**	(Carraschi et al. 2015)
Snail	*Pomacea canaliculata*	>100	48 h	100	>1	0,17	**<0,17**	(Carraschi et al. 2015)
Aquatic plant	*Lemna minor*	97,03	7 days	100	>1	0,17	**<0,17**	(Carraschi et al. 2015)
Crustacean planktonic	*Daphnia magna*	>100	48 h	100	0,97	0,17	**0,18**	(Carraschi et al. 2015)
Crustacean planktonic	*Daphnia magna*	1,9	21 days	100	0,02	0,17	**8,95**	(Martins et al. 2013)
Phytoplankton (Unicelular algae)	*Skeletonema costatum*	5,93	96 h	100	0,06	0,17	**2,87**	(Liu et al. 2012)
Phytoplankton (Unicellular algae)	*Tetraselmis chui*	1,03	96 h	100	0,01	0,17	**13,08**	(Lai et al. 2009)

The Risk Quotient (RQ) is evaluated against a value of one. If the value is less than one, further testing is not recommended. However, an RQ of less than one may not necessarily imply that the risk is acceptable, as this determination must be made on a scientific basis. Metabolites excreted in quantities of 10% or more of the administered dose, which do not participate in biochemical pathways, should be added to the active substance to permit recalculation of the Predicted Concentration (PC), as stated by the European Medicines Agency in 2016 (EMA 2016). In contrast, Chile's regulations for RQ classification diverge from international standards. According to the Servicio Agrícola y Ganadero (SAG) 2010 regulation (SAG 2010), pharmaceutical products for veterinary use are considered environmentally safe when the national ecotoxicity evaluation indicates an RQ Risk Coefficient of 100 or less. If the RQ falls between 100 and 1,000, the drug registrant must propose environmental monitoring.

The Risk Quotient results from the analysis (Table 2) are exceeded for crustacean planktonic and phytoplankton (Unicelular algae) evaluated against a value less than one , when evaluating against a value of 100 (SAG 2010) the values are not exceeded .

Conclusions

Differences exist between Chile's regulatory framework for Environmental Impact Assessments of veterinary medicinal products (SAG 2011) and international guidelines, and these discrepancies should be addressed. In Chile, pharmaceutical products exclusively for veterinary use are deemed environmentally safe when the ecotoxicity assessment result under national conditions indicates a Risk Quotient (RQ) of 100 or less (Exempt Resolution No. 665, SAG), whereas the Environmental Impact Assessment for Veterinary Medicinal Products Phase II VICH Guidance compares the RQ to a value of one, and values less than one indicate no further testing is required.

The ecotoxicity analyses approved by the SAG for registered products must be based on scientific evidence. It is essential that Chile conducts these studies incorporating habitat species from national salmon farming areas, preferably endemic species associated with sea farming, and considers chronic toxicity studies in invertebrates of Chile's salmon farming marine sediment, incorporating NOEC parameters (SAG 2011; Tihulca 2013), given that the Risk Quotient results from the analysis exceed one (*Tetraselmis chui*, *Skeletonema costatum*, and *Daphnia magna*).

Ethical approval

The authors declare that this study complies with research and publication ethics.

Informed Consent

Not Applicable

Conflict of interest

There is no conflict of interests for publishing this study.

Data availability statement

The authors declare that the data from this study are available upon request.

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Author contributions

Patricio de Los Rios-Escalante: Conceptualization, Editing. Veronica Barra: Editing. Cristina Kretschmer: Conceptualization, Analyses, Writing, Editing. Ivonne Lozano-Muñoz: Conceptualization, Analyses, Editing.

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