

## An oxytetracycline residue depletion study to assess the physiologically based pharmacokinetic (PBPK) model in farmed Atlantic salmon

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Oxytetracycline (Terramycin Aqua, Pfizer Canada, Calgary, Alberta) is licensed in Canada for the treatment of certain bacterial diseases of farmed fish at 75 mg active ingredient per kg fish, PO, for 10 d, without a veterinary prescription (1). The withdrawal time for edible tissue (flesh, skin) is 40 d after the last day of treatment if the ambient water temperature is greater than 10°C, and 80 d if the ambient water temperature is below 10°C (1). The maximum tolerance limit for oxytetracycline (OTC) in edible tissue is 0.1 ppm (1). Veterinarians in Canada may prescribe higher levels of OTC than permitted on the label. However, it is the veterinarian's responsibility to prescribe the safe withdrawal time.

We compared the OTC concentrations predicted by a physiologically based pharmacokinetic (PBPK) model (2) with the OTC concentrations actually measured from salmon tissues sampled during and at the end of the prescribed withdrawal time. The model envisages the salmon as a network of compartments, each representing individual organ or tissue groups interconnected by the arterial and venous blood flow. Uptake, distribution, and excretion of OTC are described in terms of quantitative interrelationships among the physiological, biochemical, and physicochemical parameters derived from the average fish body weight in the pen, the dosing regimen, and the range of water temperatures for the sea farm. The OTC PBPK model does not include statistical analysis, so interpretation of the data relies on "eyeball" comparison by the user.

The study site contained 90 000 salmon, weighing on average 1.5 kg, divided evenly amongst 30 cages, measuring 15 m at the surface and extending to a depth of 17 m. Two different but commonly used OTC dosage

regimes were tried at the same time. In the 1st dosing regime, the salmon in 3 randomly chosen pens were treated twice with OTC-medicated feed at an inclusion rate of 100 mg active ingredient/kg fish/day for 10 d, separated by a 10-day feeding period of nonmedicated feed. In the 2nd dosing regime, the salmon in 3 other randomly chosen pens were treated with OTC medicated feed at an inclusion rate of 100 mg active ingredient/kg fish for 14 d.

Three fish were arbitrarily dip-netted from each seacage at specific postdosing times for each dosing regimen. Three fish sampled per pen was the smallest number of fish required to calculate the mean and standard deviation of a sample group without making the study too expensive. Control fish were sampled for both dosing regimes prior to OTC medication. The fish were labelled, frozen whole, and transferred to Simon Fraser University for OTC analysis.

The average ambient water temperature, recorded 3 m beneath the surface, throughout the study period was 9°C. It ranged from 6.5°C at the start to 11°C at the end of the study.

Oxytetracycline was not detected in the tissues of the control fish. There was considerable fish-to-fish variation in the empirical tissue OTC residue levels. The highest OTC concentration was found in the liver and the lowest in the muscle. Oxytetracycline concentrations decreased in the order of liver > kidney > skin > muscle.

For the 1st dosing regime, at 77 d postdosing, 7 out of 9 fish had detectable OTC residues in muscle. Oxytetracycline was not detected in the tissues of salmon sampled at 118 d postdosing. For the 2nd dosing regime, at 93 d postdosing, 4 out of 9 fish had OTC residues in muscle. Oxytetracycline was not detected in any salmon tissues at 134 d postdosing. The PBPK model predicted that OTC residues in muscle would fall below the targeted tolerance level of 0.1 ppm at 108 d postdosing for the 1st dosing regime, and at 100 d postdosing for the 2nd dosing regime. Currently, the method used for determining drug withdrawal time in farmed fish is based on fitting empirical data to obtain the withdrawal time (classical pharmacokinetic approach) (3), and, in general, the withdrawal times are very conservative and keep salmon in the seacages much longer than may be required. In this case, they were 180 d for the 1st dosing regime, and 145 d for the 2nd dosing regime.

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The PBPK model is a deterministic model (no statistical analysis) and provides simulation or prediction of OTC residues independent of the empirical data. Consequently, the withdrawal times predicted may not be as conservative as those predicted by the pharmacokinetic approach.

Refinement of the PBPK model could lead to the reasonably accurate prediction of tissue residue depletion times under the changing dosages, temperatures, ages, severity of disease, and species of fish, in which case, aquaculture clinicians could employ it (using a drug off-label) to estimate withdrawal periods or improve therapeutic efficacy by estimating drug concentration in a particular tissue.

## References

1. Agriculture and Agri-Food Canada. Compendium of Medicating Ingredients Brochure, Section 35A. Feeds and Fertilizer Division, Canada Department of Agriculture and Agri-Food. 5th ed, 1984. Available from Supply and Services Canada, Canadian Government Publication Centre, Ottawa, Ontario K1A 0S9.
2. Law FCP. A physiologically based pharmacokinetic model of oxytetracycline for salmonids. Proc 8th Symp Vet Pharmacol Ther, Guelph, Ontario 1992: 33-43.
3. Salte R, Liestol K. Drug withdrawal from farmed fish. Depletion of oxytetracycline, sulfadiazine and trimethoprim from muscular tissue of rainbow trout (*Salmo gairdneri*). Acta Vet Scand 1993; 24: 418-430.

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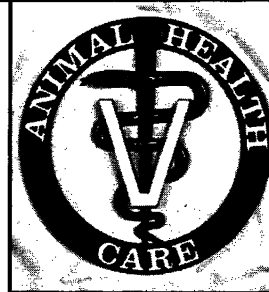
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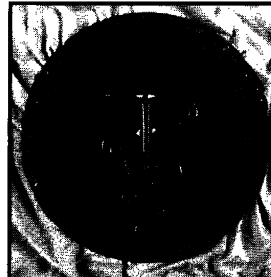
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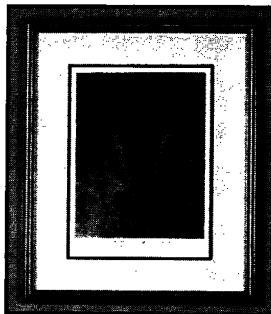
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