A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR PREDICTING THE WITHDRAWAL PERIOD OF OXYTETRACYCLINE IN CULTURED CHINOOK SALMON (ONCORHYNCHUS TSHA WYTSCHA)

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1. ABSTRACT

Oxytetracycline (OTC) is an antibiotic used widely to prevent or treat bacterial diseases in cultured salmon. In the present study, a physiologically based pharmacokinetic (PBPK) model of OTC was coupled with the Monte Carlo technique in predicting the withdrawal period (WP) of OTC for a population of cultured chinook salmon (Oncorhynchus tshawytscha). Since the PBPK model was implemented with ranges rather than fixed parameter values, it also could be used to account for the inter-individual variability across the population. The model-predicted WP, defined as the post-dosing time when the OTC residue was at or below 0.1 ppm with 95% certainty for the 99th percentile salmon population, were 60 days and 49 days at 9°C and 15°C seawater, respectively. These WP were very close to those determined by a currently used empirical method for the same data sets. However, the population based physiological model is a more useful tool than the empirical method of WP determination since treatment specific information such as fish weight, bioavailability, dose regime, and water temperature can be incorporated into the simulation.

2. INTRODUCTION

Oxytetracycline (OTC), a broad-spectrum antibiotic, is used widely as a prophylactic or treatment for bacterial diseases in aquaculture (Ahmad and Matty, 1989). OTC
is often administered to cultured salmon as medicated feed at a rate of 50–100mg/kg body weight per day for 3–14 days depending on the severity of infection. After treatment with OTC, the salmon must be kept for a minimum time before harvesting of the stock can take place. Observation of the withdrawal period (WP) ensures that edible tissues of salmon are free of residues and are safe for human consumption.

Several empirically based methods are currently used to determine the WP of drugs in cultured finfish. These include the statistical tolerance limit method of the U.S. Food and Drug Administration (FDA, 1994), the 90% upper prediction limit method (Salte and Liestøl, 1983), and the degree day method of the European Union (Schnick, 1992). Because the empirical method derives its WP directly from the drug residue elimination data, it has at least three major limitations: First, a drug depletion study must be performed at several water temperatures (Brown, 1992) since fish are poikilothermic and the elimination of the drug from fish varies with the water temperature. Second, the estimated WP is useful only for interpolation i.e., the WP is valid only for the fish species and exposure conditions used in the depletion study. Third, the effects of inter-individual variability on the WP are not considered although it is assumed that the variability associated with the fish used in the depletion profiles of the tolerance method (FDA, 1994) may provide an adequate approximation of the inter-individual variability of a population. The limitations of the empirically based approach can be minimized or overcome by a physiologically based pharmacokinetic (PBPK) model which describes the absorption, distribution and elimination of a drug in terms of identifiable anatomical spaces and physiological and biochemical processes of the fish.

A single PBPK model has been used successfully to describe the pharmacokinetics of OTC in both trout and salmon (Law, 1992; Broklebank et al., 1997) because the salmonids have similar anatomy, physiology (Thorarensen, 1994) and OTC pharmacokinetic profiles (Abedini et al., 1998; Namdari et al., 1998; Namdari et al., 1999). The same PBPK model also has been used to describe the pharmacokinetics of OTC in the tissues of cattle after i.v. or i.m. administration (Achenbach et al., 1998). Currently, the PBPK model of OTC is deterministic i.e., a set of fixed values are used as model input parameters and the outputs of the model also are fixed values. Therefore, the model does not have the benefits of a formal statistical procedure and is not designed to describe or understand individual variability in a fish population.

The purposes of this paper were (a) to describe a novel, theoretical approach of WP determination by implementing the PBPK model with the Monte Carlo technique (Rubenstein, 1981) for a population of cultured chinook salmon, (b) to validate the population based physiological model with experimental data, (c) to identify key PBPK model parameters to which the predicted WP is particularly sensitive, and (d) to study the extent to which inter-individual variability in the population confers variability on the predicted WP.

3. MATERIALS AND METHODS

3.1. Model Concepts

3.1.1. Model Structure. We reported a 9-compartment PBPK model which described closely the pharmacokinetics of OTC in the tissues of salmon after multiple OTC-medicated feed treatments (Law, 1992; Broklebank et al., 1997). The original PBPK model was developed with little or no basic information on the skin and the bone com-