The tetracyclines are often used in pork production to control or treat health problems such as respiratory disease. To achieve therapeutic success, the antimicrobial agent must reach the site of the infection. For tetracyclines administered orally, this means the drug must first be absorbed from the gastrointestinal tract into the blood stream, and then distributed to the target tissue. The following overview of published research reviews and compares the main pharmacokinetic parameters of feed-administered chlortetracycline (CTC) and oxytetracycline (OTC) in swine (though the clinical relevance of these data is not known).

**Absorption**

One measure of absorption is a pharmacokinetic parameter called bioavailability. Absolute bioavailability (F) represents the rate and extent of drug absorption from the intestinal lumen, and is a strong determinant of drug concentrations in the blood. CTC and OTC have been found to greatly differ in their levels of absorption, with F determined to be 13% for CTC compared to only 4% for OTC (Figure 1). Bioavailability is 3-fold greater for CTC than for OTC.

**Distribution**

Once absorbed into the bloodstream, an antimicrobial must then be distributed to the tissues, a process highly affected by two factors: the lipid solubility of the drug, and the extent of protein binding.

High lipid solubility helps the drug cross the blood vessel wall and move into the target tissue, and also helps the drug reach ribosomes inside...
bacterial cells, thus increasing bacteriostatic efficacy. CTC has been demonstrated to be more lipid-soluble than OTC.\textsuperscript{1,2} Protein binding is important because only free tetracycline molecules are able to cross through the blood vessel and move into the tissue. However, protein binding significantly impacts clinical efficacy only when the degree of binding exceeds 85\% to 90\%, and both CTC and OTC have protein binding levels less than this threshold.\textsuperscript{1,2}

Drug distribution is described by a pharmacokinetic parameter called the apparent volume of distribution (Vd), an estimator of drug diffusion to tissues. The Vd of CTC is about 24\% greater than that of OTC (Figure 2), meaning that CTC distributes more readily in tissues.\textsuperscript{2}

**Drug Levels in Blood and Lungs**

The superior bioavailability and distribution characteristics for CTC in swine help to explain why blood and lung levels are consistently higher for CTC than for OTC. In one study, pigs averaging 30 lb body weight (BW) were fed 364 g/ton of either CTC or OTC.\textsuperscript{3} Blood and lung tissue samples were collected at 1, 3, 6, 12, and 24 hours after initiation of treatment. CTC blood levels averaged 50\% higher than OTC (Figure 3), and CTC lung tissue levels averaged 80\% higher than OTC (Figure 4).
In another pharmacokinetics study, Swedish researchers\textsuperscript{4} fed 55-lb barrows CTC or OTC at a dosage of 50 mg/kg BW (23 mg/lb BW) (approved dosage for OTC and CTC is 10 mg/lb BW). Blood and lung tissue levels were assessed after 1 day and 4 days of treatment, with the samples collected 6 hours post-meal. CTC generated blood levels 17- to 20-times higher than OTC blood levels, and CTC lung tissue concentrations were 7- to 11-times higher than OTC (Figure 5).

Researchers at South Dakota State University conducted a study evaluating blood levels of grower and finisher pigs fed CTC of OTC at 3 feeding levels (200, 400, or 800 g/t) with dietary calcium at either NRC (low) levels or NRC+ 50% (high) levels.\textsuperscript{5} Pigs averaged 69 lb at the finisher phase. Grower diets contained 16% protein and 0.6 or 0.9% calcium; finisher diets contained 14% protein and 0.5 or 0.75% calcium. In general, feeding excessive calcium decreased CTC and OTC blood levels compared to pigs fed calcium at NRC levels (Figures 6 and 7). At each dosage and calcium level fed (except for one), grower and finisher pigs fed CTC demonstrated higher blood levels than pigs fed OTC.
Therapeutic Efficacy

Therapeutic distinctions between tetracyclines were investigated in a study where 85-lb pigs fed therapeutic 10 mg/lb BW levels (600 g/t) of either CTC or OTC were challenged with *Pasteurella multocida*. A challenged, non-medicated control group was also evaluated. Treatments were initiated 2 days before challenge on day 0 and continued through day 10. The MIC of the challenge organism was the same for all groups.

Results reveal that blood levels for CTC-fed pigs were 70% higher than the blood levels achieved in animals fed OTC (Figure 8). Average lung lesion score (percentage of abnormal lung tissue relative to healthy tissue) of pigs fed CTC was significantly reduced 54% ($P \leq 0.05$) compared to non-mediated controls (Figure 9). While numerical lesion reduction was observed in OTC-fed pigs compared to controls, the difference was non-significant ($P > 0.05$).

Performance outcomes during the 10-day challenge period are summarized in Figure 10. Average daily gain (ADG) of pigs fed CTC was significantly improved 61% (0.34 lb, $P \leq 0.05$) compared to non-mediated controls, while ADG improvement in OTC-fed pigs compared to controls was non-significant ($P > 0.05$). Feed conversion efficiency (feed/gain) was numerically improved 51% for pigs medicated with CTC compared to controls, but only a modest 7% improvement was observed for the OTC-fed group.
Clear distinctions in pharmacologic and efficacy parameters exist between CTC and OTC.

Conclusions
The results of these studies show clear distinctions in pharmacologic and efficacy parameters between CTC and OTC when used in swine feeds.

- Bioavailability is 3-fold greater for CTC than for OTC, indicating better absorption of drug from the gut of pigs.
- CTC is more lipid-soluble than OTC and protein binding for both drugs is clinically insignificant, so the volume of distribution of CTC is 24% greater than that of OTC (CTC more readily distributes into body tissues).
- One study found that CTC blood levels averaged 50% higher than OTC while CTC lung tissue levels averaged 80% higher than OTC.
- In another study, CTC generated blood levels 17- to 20-times higher than OTC blood levels, and CTC lung tissue concentrations were 7- to 11-times higher than OTC.

In pigs challenged with Pasteurella multocida:

- Blood levels for CTC-fed pigs were 70% higher than the blood levels achieved in animals fed OTC. The clinical relevance of this finding is unknown.
- Lung lesion scores were reduced by 54% (P ≤ 0.05) in pigs fed CTC compared to controls. Lesion scores in OTC-fed pigs were not statistically different than controls.
- ADG was improved by 61% (P ≤ 0.05) for pigs fed CTC while ADG for pigs fed OTC was not statistically different than controls.
References