

K-1424 Risk Assessment of Macrolide Use in Fed Cattle on the Treatment of Human Food-borne Illness

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AMENDED ABSTRACT

Background: Tylosin and tilmicosin (T-T) are commonly used in feedlot cattle for respiratory disease treatment and prevention of serious illness such as liver abscesses. Some believe this use increases the risk of human food-borne illness with resistant bacteria from beef consumption. The FDA-CVM regulatory Guidance 152 document (www.fda.gov/cvm) advises veterinary antimicrobial sponsors to conduct a qualitative risk assessment (RA) on the hazard of antimicrobial use in food animals.

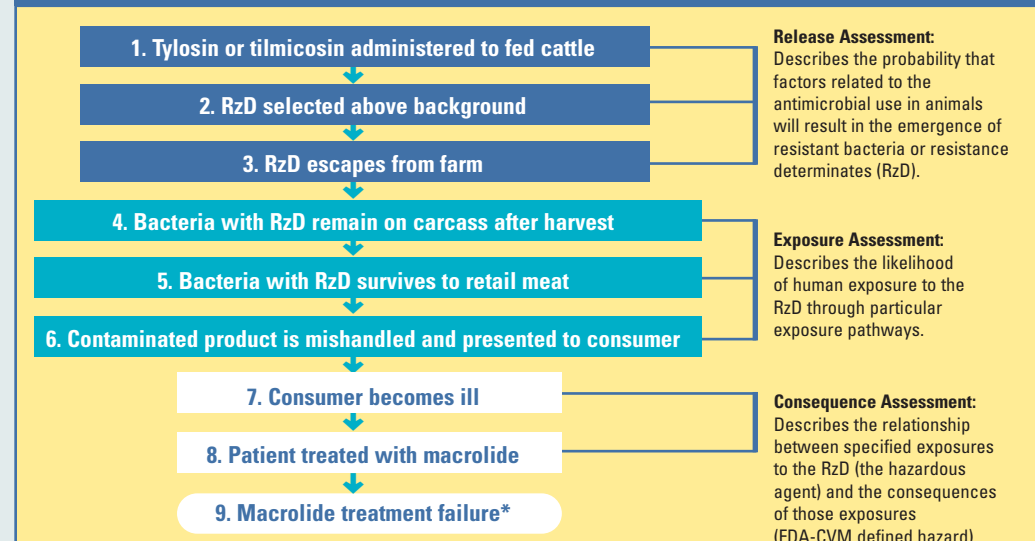
Methods: The FDA-CVM definition of hazard was used; illness 1) caused by food-borne bacteria with a resistance-determinant (RzD; RELEASE component); 2) attributed to specified animal-derived commodity (EXPOSURE component); and 3) treated with human-use drug of the same class (CONSEQUENCE component). A binomial fault tree model was used to determine Pr of *Campylobacter* spp. [CAMPY] and *E. faecium* [ENT] hazard occurring in the USA/year. Parameter estimates were derived from industry drug use surveys, scientific literature, published medical guidelines, and government documents (CDC, USDA, NARMS, FoodNet). Generally, the more conservative (higher risk) estimates were used to calculate risk.

Results and Conclusions: This FDA-CVM (Guidance 152) based RA demonstrates a very “Low” qualitative risk, with an analyzed Pr of < 1 in 236 million, and < 1 in 29 billion (USA population) for food-borne illness in CAMPY and ENT, respectively. This RA was a unique farm-to-fork semi-quantitative analysis that indicates current uses of macrolides in cattle appear to create a risk much lower than the potential benefit to food safety, animal welfare, and public health.

INTRODUCTION

There is continued concern regarding antimicrobial resistance in human pathogens, particularly those assumed to be of food-borne origin. To address this concern, a majority of government regulatory authorities, industry associations and other organizations are proposing that risk assessment methods be applied to the issue of antimicrobial resistance associated with food-producing animals (US FDA, 2002a; Vose, 2001; APVMA, 2000; WHO, 2001). A risk assessment combines information on the consequence of an event with the probability of occurrence of that event, within the current state of technology and common practice. The United States Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) has issued risk assessment guidelines in their Regulatory Guidance Document 152 (US FDA, 2002a) that can be used to guide a new animal drug sponsor in preparing the overall pre-approval risk estimate and corresponding risk management options to ensure that public health is not compromised. However, it can also be useful for evaluating the risk from currently approved food animal drugs and provide input for science-based decision making. The objective of this study was to conduct a risk assessment for the administration to beef cattle of two macrolide veterinary antibiotics, tylosin and tilmicosin (T-T) consistent with the methodologies proposed by the FDA-CVM.

Figure 1. Pathway of events leading to the risk of food-borne human illness with resistant organism due to antibiotic treatment of fed cattle



* 1) death attributable to the episode,
2) persistence of presenting symptoms and laboratory test abnormalities, or
3) lack of bacteriological evidence of pathogen eradication at designated evaluation intervals.

Tylosin is used in cattle and administered via medicated feed or by injection for disease treatment or prevention. Tilmicosin is a semi-synthetic derivative of tylosin approved for treatment and control of respiratory disease in cattle only by injection. The scope of this risk assessment included all label claim uses for both macrolides (T-T) in the US.

MATERIALS AND METHODS

For this assessment, the hazard was defined in accord with Guidance Document 152 as “human illness” that is: 1) caused by macrolide-resistant *Campylobacter* spp. (CAMPY) or *Enterococcus faecium* (ENT), 2) attributable to consumption of contaminated beef, and 3) treated with a human antimicrobial drug from the macrolide class (US FDA, 2002a). Infection caused by *Salmonella* spp. was not addressed because this organism is neither routinely susceptible to nor widely treated by macrolide agents in human practice. *Enterococci* were modeled, not because they cause food-borne illness, but because they are generally regarded as a reservoir of macrolide resistance genes. These genes may reside in commensal bacteria that colonize food animals and may possibly serve as a reservoir of resistance for microbes that are pathogenic for humans (Chung, 1999; Khan, 2002; Nawaz, 2000; Rollins, 1985). The risk was defined and modeled as the yearly probability that an average individual in the US population would be affected by the defined hazard and would experience an adverse therapeutic event (i.e., poorer efficacy than usual as manifested by longer duration of diarrhea, progression to more severe disease, or mortality).

The FDA-CVM has recommended what has been termed a “qualitative” risk assessment. This method uses High, Medium, and Low estimates for each of the three analyzed components: release-, exposure- and consequence-assessment. However, we used the “event fault tree” approach (NRC, 2003), recognizing that some data might be limited and may need to be approximated, thus meeting a definition of “semi-quantitative” analysis. This approach describes all the necessary events that must occur to create the modeled risk. It provides greater transparency regarding calculations and assumptions at each point in the chain of events.

Model. Figure 1 graphically summarizes the modeled chain of events necessary to lead to the defined hazard. Parameters were derived from industry drug use surveys, scientific literature, medical guidelines, and government documents. For most events, the most likely probabilities or frequencies were modeled. When numbers were uncertain, the most conservative, or highest risk, estimates were used to avoid underestimating potential risk. Uncertainty distributions of inputs and resulting outputs were not modeled, since this study was meant to be an initial evaluation following the Guidance 152 document for a qualitative risk assessment. Each event or “Node” was represented in a separate worksheet of an Excel® spreadsheet software program (Microsoft, Redmond, WA). Quantities or probabilities associated with each Node were entered into the worksheet, combined with output or calculations from the previous sheet and carried forward to the next sheet.

Node 1. Tylosin or Tilmicosin administered to food animals. All uses of T-T were considered, e.g., therapeutic, disease prevention, and disease control relevant to CVM-approved label claims for cattle. Although some animals might have received both medicated feed and an injection of a macrolide, they could not be easily distinguished in the database and thus were counted as two exposures. Furthermore, even a single dose was considered an exposure, even though sixty days of feed medication most likely do not have the same effect on resistance selection as a single injection.

An annual estimate of the number of fed cattle (92.6% of total cattle) that were harvested in 2001 was 32.9 million (USDA, 2003a). The estimate of T-T use, based on the number of animals treated for any purpose as reported from quarterly national mail surveys of producers, was 49% of fed cattle (Doane, 2000).

Node 2. Resistance selected above background. After an animal is treated with T-T, there is some chance that macrolide resistance may be selected above background levels in resident ENT and/or CAMPY. This probability is a function of three factors: A) presence of ENT and/or CAMPY in treated animals, B) intrinsic or background susceptibility of these bacteria, and C) mutation or RzD acquisition with survival of newly resistant strains. These probabilities were separately estimated for CAMPY and ENT by multiplying together the 1) reported prevalence of CAMPY and ENT in animals, 2) pre-existing background levels of resistance measured in animal sources of CAMPY and ENT, and 3) probability that resistant organisms will develop and thrive in those treated animals. Our final estimates for these parameters are shown in Table 1.

Table 1. Assessment of the Adverse Human Health Impact Attributable to the Use of Macrolides in Fed Cattle: Key Parameters and Results.

Components/Binomial Events	Beef Cattle	
	CAMPY	ENT
RELEASE		
1. Animals exposed to tylosin and tilmicosin (millions) ^a	16.1	16.1
2. Pr that RzD develops in exposed animals as a function ^b of:	1%	89%
a) Bacteria present in animals	50%	100%
b) Susceptible bacteria in population	99%	89%
c) Resistance in human isolates	3%	100%
3. Pr that RzD escapes from farm ^c	100%	100%
EXPOSURE		
4. Pr that bacteria with RzD remain on carcass after slaughter ^d	4%	8%
EXPOSURE and CONSEQUENCE		
5.-7. Ratio (β) that contaminated carcass leads to human illness ^e	8.6x10 ⁻⁶	8.6x10 ⁻⁶
CONSEQUENCE		
8. Pr of cases of diarrhea treated with a macrolide ^f	3%	0.0001%
9. Pr that treatment fails if infection by bacteria with RzD is treated with a macrolide ^g	50%	100%
RISK		
Annual Pr of adverse health events in US due to treatment of RzD-caused food-borne infection with a macrolide	< 1 in 236 million	<1 in 29 billion
^a Based on industry usage surveys (treatment, control, prevention, performance) ^b Function of human-R measured, expected prevalence and susceptible organism population in cattle ^c Assume all animals will carry RzD to slaughter ^d CAMPY based on FSIS data, assuming all have some fecal (ENT) contamination ^e Based on comparisons of FSIS data for all CAMPY relative to CDC FoodNet data for human illness. Over-estimated for ENT ^f Based on FDA fluoroquinolone RA interpretation of disease reporting, treatment, etc. ^g Clinical response publications show <50% failures		

Node 3. Resistant determinant escapes from the farm. Resistant determinants can theoretically leave the farm or place of drug administration via a variety of routes. However, since the hazard was defined as food-borne illness, the model focused on RzD leaving the farm in market animals. However, it was conservatively assumed that any treatment resulting in the development of RzD would have a 100% probability of leaving the farm in cattle.

Node 4. Bacteria with resistant determinant remain on carcass after harvest. Food Safety and Inspection Service (FSIS) data derived from surveys from 1992 through 1997 (CAMPY) appeared to provide the most relevant data on the percentage of contaminated beef carcasses in slaughter facilities. These data indicate that approximately 4% of beef carcasses were contaminated with CAMPY (Table 1) (USDA, 2003d). *E. coli* was used as an indicator of contamination from intestinal contents and ENT prevalence. FSIS data similar to that reported for CAMPY indicated that approximately 8% of beef carcasses were contaminated with *E. coli* (USDA, 2003d).

For this analysis, we assumed that all ground meat coming from contaminated dressed beef (43%) carcasses would be contaminated (Jay, 2000). We did not consider imported beef products and we assumed all beef produced in the US was consumed in the US.

Ratio Method (Applied to Nodes 5-7). Due to weaknesses and data gaps for 1) organism prevalence at retail sale, 2) probability of consumer mishandling, 3) dose presented to consumer, and 4) probability of illness (Nodes 5, 6, and 7), a ratio method that collapses the output from these three nodes into a single calculation was employed. The FSIS data (Node 4) provided a reliable national estimate of wholesale carcass contamination. The CDC FoodNet data (CDC, 2003) provides a reasonable national estimate of human CAMPY illness. The latter data are equivalent to the output from Node 7 ignoring the RzD issue, i.e., modeling all CAMPY cases from meat. In other words, even though enough information is not available to accurately estimate the individual probabilities for Nodes 5, 6 and 7, the combined probability of these three nodes can be estimated. Therefore, the probability of human campylobacteriosis from a meal that originated from a contaminated

carcass can be determined. Briefly, the number of all human CAMPY cases is simply divided by the number of CAMPY-contaminated servings. The resulting ratio (β) was then used with the results from Node 4 to produce the number of human illnesses due to Rzd-bearing CAMPY. The data used and the resulting proportionality constants are described in more detail in equation 1.

$$\text{Equation 1: } C / [\sum (NC_i * CW_i * CR_i) / SS] = \beta.$$

Where:

C = annual number of human cases “attributable” to foods of animal origin (FoodNet), regardless of Rzd

NC_i = number of animal carcasses produced annually for beef

CW_i = average weight of dressed carcass

CR_i = carcass contamination rate per serving of beef based on FSIS data

SS = average serving size (~1/4 lb)

β = ratio, equivalent to the probability that a contaminated carcass will produce illness, after wholesale and retail processing, consumer preparation, and consumption.

For CAMPY, the 2002 FoodNet rate of 13.37 laboratory-diagnosed cases per 100,000 was multiplied an estimate of 38-fold under-reporting and the US population of 280 million to produce a national estimate of 1.42 million cases (Mead, 1999). However, not all those cases should be attributed to beef consumption. CAMPY infections can occur due to contact with infected pets, raw milk, contaminated water and other sources (Franco, 1988; Barber, 2003; US FDA, 2003b). Therefore, for this analysis, a conservative estimate of 90% (n = 1.28 million) of total cases was attributed to consumption of the specified meat products. The resulting ratio was estimated as 8.6 X 10⁻⁶. A similar method was used by the FDA for CAMPY from chicken with a resulting value for β of 7 X 10⁻⁵ (US FDA, 2003b). Although not a food-borne disease, the same parameter was used for ENT.

Node 8. Ill patient is treated with macrolide class antibiotic. The output from Node 8 could be considered as the probability of the FDA-CVM defined hazard. For this hazard to be realized, the illness must be treated with a macrolide-class agent. The probability of this event for CAMPY was estimated from FDA-FQ (CVM, 2003b) and results from the probabilities of 1) the patient seeking medical care (23.5%), 2) submission of a culture (17.7%), 3) positive test for CAMPY (94.5%), 4) accurate diagnosis (75%), and 5) use of a macrolide (100%). The probability of changing therapy from the empiric regimen to a macrolide after CAMPY diagnosis was conservatively assumed to be 100% (standard of practice). However, in routine practice, the initial therapy would only infrequently be changed in the absence of frank clinical failure.

It is likely that routine practice would not result in macrolide use for diarrhea. Examination of published “practice guidelines” (Guerrant, 2001) shows that infectious diarrhea is a complex series of disorders requiring a thorough clinical and epidemiological evaluation that includes, among many other considerations, the possibility of consumption of mishandled food products. Infectious Disease Society of America (IDSA) guidelines for community-acquired or traveler’s diarrhea (especially accompanied by significant fever or blood in stool) dictate that samples should be cultured or tested for key pathogens including CAMPY (Guerrant, 2001), and therapy should consider a fluoroquinolone or a macrolide (if “resistant” CAMPY is suspected). Surveys show infrequent and decreasing use of the stool culture (Cheney and Wong, 1993), driven by the self-limited course of illness and routine delays in the available results, thus providing little guidance to immediate therapeutic choices. This situation leads physicians to consider antimicrobial and/or supportive treatments. The commonest drugs selected are fluoroquinolones and trimethoprim/sulfamethoxazole rather than macrolides (Guerrant, 2001; Mandell, 2000; Gilbert, 2003; Adachi, 2000). Therapy for CAMPY, if known from diagnosis or positive culture, would be erythromycin (500 mg bid x 5 days), but this course usually will not be prescribed unless a fluoroquinolone-treated case worsens possibly because of resistance or severe underlying disease. However, some experts (Gilbert, 2003) still recommend a fluoroquinolone (ciprofloxacin) or possibly azithromycin for “first-line” therapy of CAMPY gastroenteritis.

Node 9. Infection with a resistant organism results in clinical treatment failure. The overall risk was defined as the probability of the defined hazard (Node 8) times the consequence, defined as treatment failure. Treatment failure can have numerous definitions including: 1) death attributable to the episode, 2) persistence of presenting symptoms and laboratory test abnormalities, or 3) lack of bacteriological evidence of pathogen eradication at designated evaluation intervals. The probability of CAMPY treatment failure was conservatively estimated at 50% (Table 1), realizing that fatalities are very rare and that numerous alternative agents are available. The probability of treatment failure in case of macrolide treatment of ENT infection was conservatively set at 100%.

RESULTS

This FDA-CVM (Guidance 152) based RA demonstrates a very “Low” qualitative risk, with an analyzed Pr of < 1 in 236 million, and < 1 in 29 billion (USA population) for food-borne illness in CAMPY and ENT, respectively (Table 1).

■ **Changes in parameters still show minimal risk.** Some parameters had a large degree of associated uncertainty and we evaluated their effect with a simple sensitivity analysis. The results for various settings in Node 9 (probability of treatment failure), and Node 2 (probability of Rzd development) for CAMPY are shown in Table 2. This table shows that for the overall risk to reach 1 in 7 million, one must assume a 50% probability of resistance development in the treated animals (Node 2, Factor C), and assume a 100% probability of

treatment failure. This result is not the probability that one mutation will occur, but that the mutant population will compete with the wild-type population of the same species to a degree that will present a sufficiently infectious dose when consumed as a mishandled food product. Table 2 also shows that changes in other parameter estimates will cause linear changes in resulting risk.

■ **Semi-quantitative method improves transparency.** One goal of a risk assessment is transparency, implying that the approach taken and results obtained are clear to all who study it. We consider this semi-quantitative approach to be more transparent and interpretable than a qualitative analysis because the calculations and parameter estimates are explicitly stated and refutable. A qualitative analysis, using High, Medium and Low estimates, adds non-refutable subjectivity.

■ **Highly conservative assumptions were made.** Many of the assumptions and parameter estimates made in this model were very conservative, thus increasing the risk estimate. For example, we assumed:

- 100% of the carcasses, if contaminated, would produce contaminated infective servings (43% of carcass weight).
- all therapeutic uses of tylosin or tilmicosin produced the same risk.
- that a single treatment was equivalent to long-term feeding.
- 100% probability of Rzd escape from the farm.
- 50% failure rate for treatment of a macrolide-resistant CAMPY infection with a macrolide.
- 90% of CAMPY cases were due to meat consumption.
- a strong link of causality between contaminated carcasses and human illness (ratio method).

The ratio procedure that we used to derive β incorporates simplifying and possibly incorrect assumptions of causality. For example, it assumes that all cases that are deemed “attributable to foods of animal origin” are caused specifically and uniquely by food-borne contamination, even though attributed risk estimates typically reflect statistical associations rather than causation. It assumes there is no background contribution in the creation of human cases attributed to foods of animal origin, even though other sources such as water probably account for some proportion of such cases (Gillespie, 2002).

■ **The risk must be weighed against animal and public health benefits.** Assessment of any policy will enter into the greater public debate which, overtly or inherently, must consider the cost (risk) and benefit relationship. The macrolide products (T-T) have been beneficial to animal health, which most likely translates into beneficial effects on both food quality and food safety.

Table 2. Sensitivity analysis of various parameters about treatment failure and probability of resistance development to macrolides from fed cattle exposed to tylosin or tilmicosin on the risk of human campylobacteriosis.

Probability of treatment failure if treated with macrolide (Node 9)	Probability of significant resistance development in treated animal (Node 2)	Resulting risk 1 in X million ^{a,c}
25%	3% ^a	473
50% ^a	3% ^a	236
100%	3% ^a	118
25%	15%	94
50% ^a	15%	47
100%	15%	23
25%	30%	47
50% ^a	30%	23
100%	30%	12
50% ^a	100%	7

^a parameter used for best estimate

^b beef only

^c compare to FDA FQ of 1 in 0.03 million (US FDA, 2001)

CONCLUSIONS

In summary, this FDA-CVM Guidance 152-based risk assessment has produced a unique farm-to-patient, semi-quantitative analysis using extensive scientific and governmental numerical data. It demonstrates that T-T use in fed cattle presents an extremely “Low” qualitative risk illness from CAMPY and ENT, respectively. These results indicate that current uses of macrolides in fed cattle appear to create a risk much lower than the potential benefit to food safety, animal welfare, and public health.

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