

# Review of AMDUCA and Extra-Label Drug Use in Food Animals

Ronald E. Baynes, DVM, PhD

Food Animal Residue Avoidance Databank, North Carolina State University College of Veterinary Medicine, 1060 William Moore Drive, Raleigh, NC 27607

## Abstract

This presentation will review the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 and how the Food Animal Residue Avoidance Databank (FARAD) provides scientifically-based residue withholding information within the context of extra-label drug use guidelines. Several beef and dairy cases will be presented to demonstrate FARAD's successes and challenges to minimize violative drug residues in animal-derived food products. Finally, several of the research initiatives developed by FARAD scientists that have improved withdrawal time estimation will be reviewed within the context of extra-label drug use in food animals.

## Résumé

Cette présentation va discuter le *Animal Medicinal Drug Use Clarification Act* (AMDUCA) de 1994 et montrer comment le *Food Animal Residue Avoidance Databank* (FARAD) fournit de l'information à caractère scientifique sur le retrait des résidus dans le cadre des directives d'utilisation hors homologation des drogues. Plusieurs exemples tirés de l'industrie laitière et du bœuf seront présentés pour illustrer les succès et les défis de FARAD afin de minimiser la violation des normes pour les résidus de drogues dans les produits d'animaux de consommation. Finalement, plusieurs initiatives de recherche, développées par des chercheurs du FARAD, qui ont amélioré l'estimation du temps de retrait seront discutées dans le contexte de l'emploi non-conforme des drogues chez les animaux de consommation.

## AMDUCA, the Law!

The passage of the Animal Medicinal Drug Use Clarification Act (AMDUCA) amended the Federal Food, Drug, and Cosmetic Act to allow veterinarians to prescribe extra-label uses of approved animal drugs and human drugs in animals with various stipulations and guidelines, among which was that an extended withdrawal time be proscribed following extra-label drug use in food animals. The Food Animal Residue Avoidance Databank (FARAD) has been recognized as the primary resource (Figure 1) from which food animal veterinarians can obtain extra-label information when

treatment modalities require extra-label drug use. The passage of AMDUCA further placed the burden on FARAD to acquire more and accurate pharmacokinetics data that would improve its scientific estimates of a safe withdrawal time following extra-label drug use.

A final word of caution is that there are families of drugs and substances listed in Table 1 below that, in accordance with AMDUCA, are prohibited<sup>2</sup> from use in food-producing animals, and it is not the policy of FARAD to provide withdrawal estimates for these drugs.

## FARAD Cases

It is not surprising that the majority of calls to FARAD are related to extra-label drug use in food animal species. The majority of these cases are related to dairy and beef cattle exposures followed by small ruminants and swine. This unique database and algorithms enable FARAD to recommend safe withdrawal times as stipulated by AMDUCA, thus reducing the risk of contaminated meat, milk or eggs from entering the human food supply.

FARAD has a long history of over 25 years of risk/crisis communication and management. This is evidenced from several of the many high-profile cases below that have relied on FARAD's expertise and unique database to resolve chemical food safety crises on the basis of sound science and analysis by its team of pharmacologists, toxicologists, veterinarians, and computational specialists. FARAD continues to serve as a source of information for stakeholders in the livestock and pharmaceutical industries as they strive to increase US meat exports to Asia and Europe. Because FARAD serves as an academic and independent non-governmental organization (NGO), its computations and simulations contribute significant transparency on issues that can influence international trade. FARAD's value to US animal agriculture and trade has been difficult to quantify, simply because its primary role is to provide information and guidance to producers, veterinarians, and other stakeholders that has prevented dumping/condemning of animal products as well as protecting the public from exposure to hazardous drugs and chemical contaminants. There are numerous examples of recent high-profile cases (e.g., melamine, radionuclides) where FARAD has served as a "silent collaborator" or "invisible

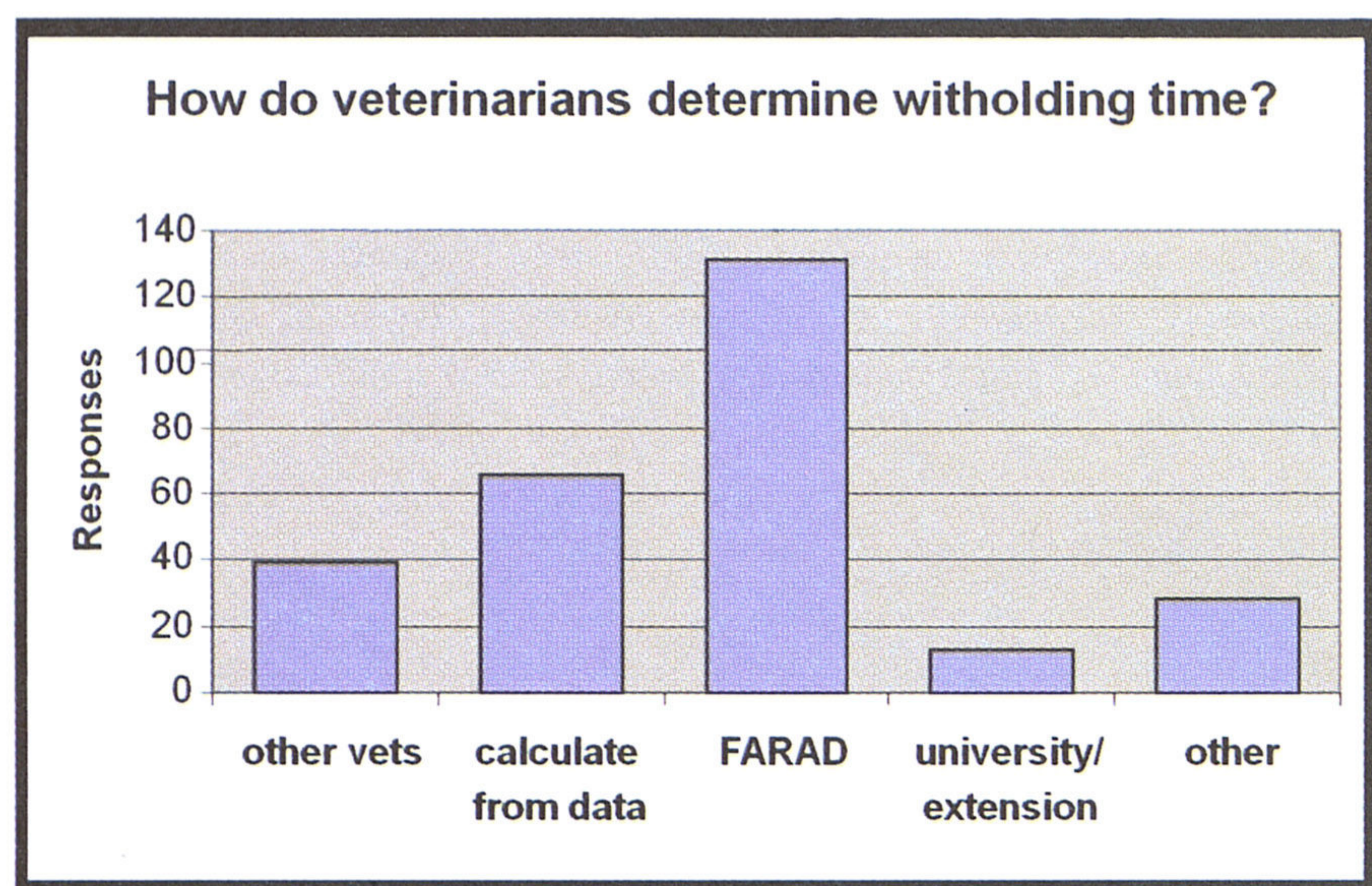


Figure 1. Sources of withdrawal time information.

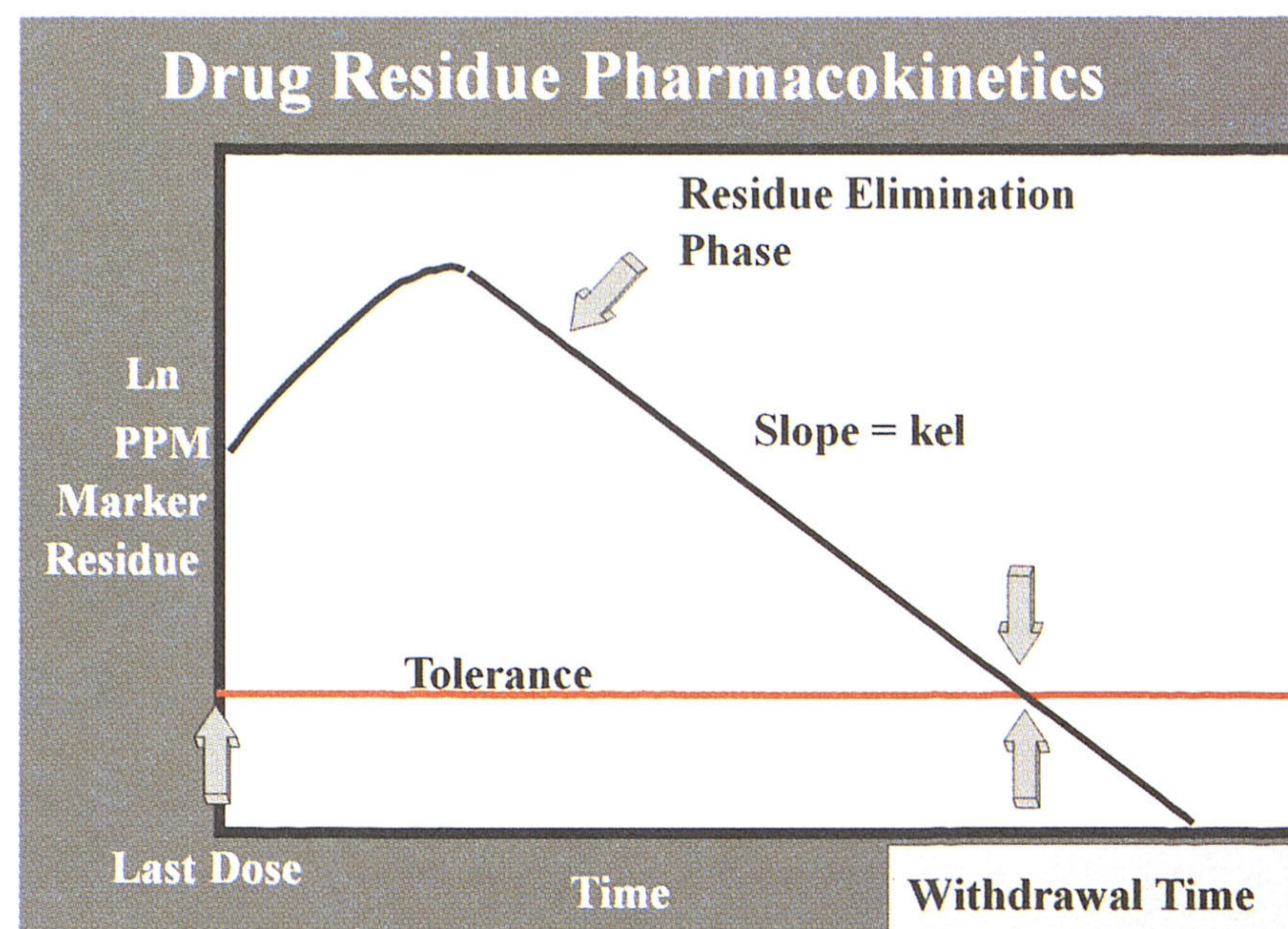


Figure 2. Data elements required for derivation of a label withdrawal time

Table 1. Drugs prohibited from extra-label use in food-producing animals.

Chloramphenicol
Clenbuterol
Diethylstilbestrol (DES)
Nitroimidazoles
Furazolidone, nitrofurazone, and other nitrofurans
Sulfonamide drugs in lactating dairy cattle (only label use allowed)
Fluoroquinolones (only label use allowed)
Glycopeptides (vancomycin)
Adamantane and neuraminidase inhibitor classes of drugs
Feed additives (except for some minor species indications, which must follow the FDA CPG)
Phenylbutazone can be used in an extra-label manner EXCEPT for dairy cattle > 20 months

FARAD have insufficient pharmacokinetic information, and FARAD has to recommend a very conservative withdrawal time<sup>1</sup> estimate based on toxicological risk assessments (Figure 4) or limit of detection of the chemical assay. In the case of milk residue concerns, FARAD will provide an extended withdrawal interval (WDI) with the added recommendation of continued testing. Only in cases where there is no data and the chemical is a known human carcinogen or suspected to be of toxicological concern to human health does FARAD recommend that the carcass be condemned. Future work is aimed at validation of estimated withdrawal intervals for extra-label drug use in food-producing animals. In spite of limited funds, FARAD continues to support international data acquisition to ensure that the US food supply remains residue-free.

shield” in mitigating drug and chemical contamination of US meat and milk. The absence of FARAD in many of these cases would have resulted in a more severe economic loss and reduced consumer confidence.

### Research Initiatives

If there are extensive kinetic data (time-tissue concentration data), FARAD scientists will conduct a pharmacokinetic analysis of the data to determine the time at which the meat or milk concentration would be expected to reach the approved tolerance (Figure 2). The dose, route, disease, species differences, and other factors related to population variance can influence drug disposition, and thus estimating a safe withdrawal time requires data analyses of varying complexity (Figure 3). We often have cases where the literature and

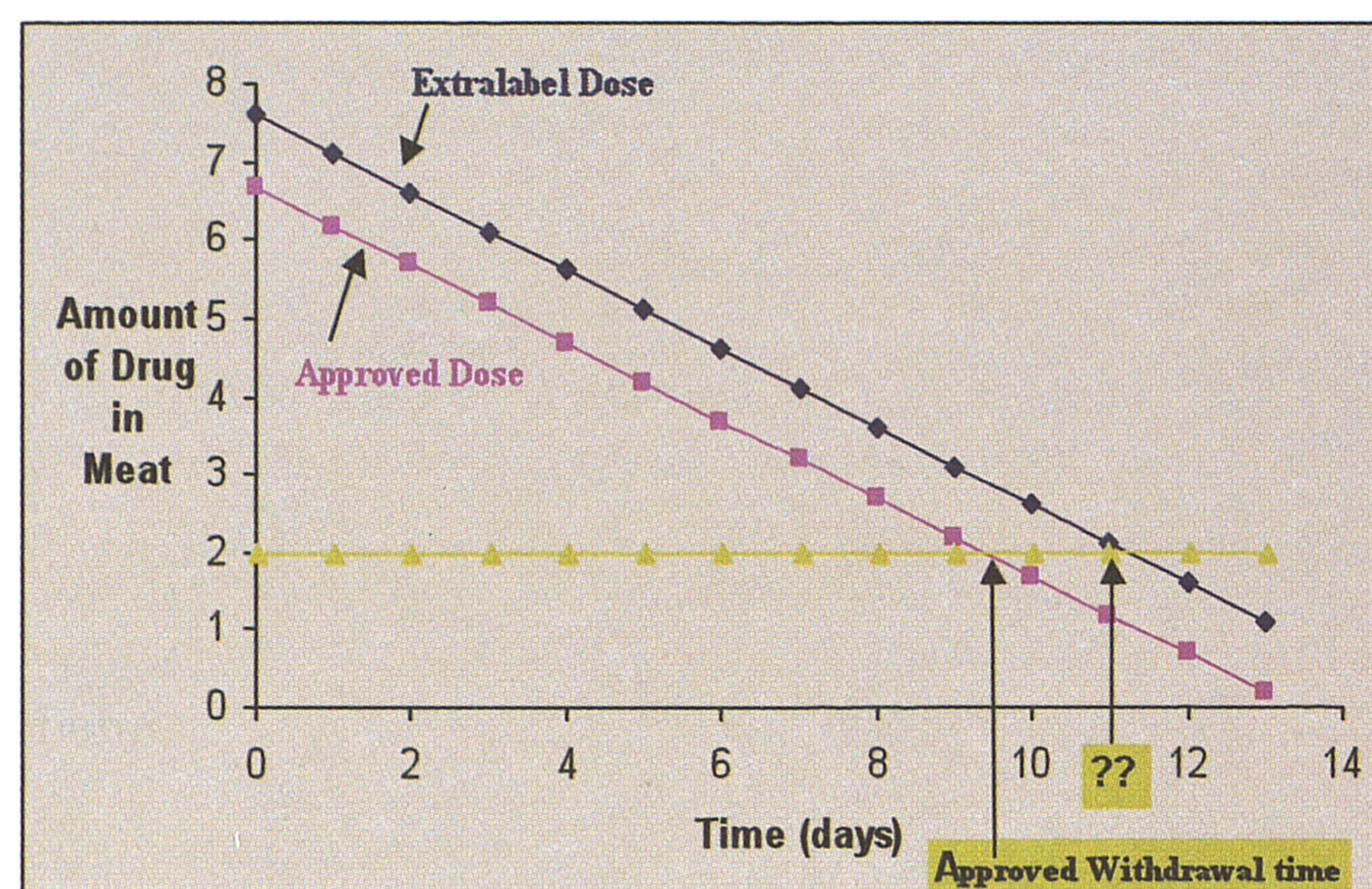
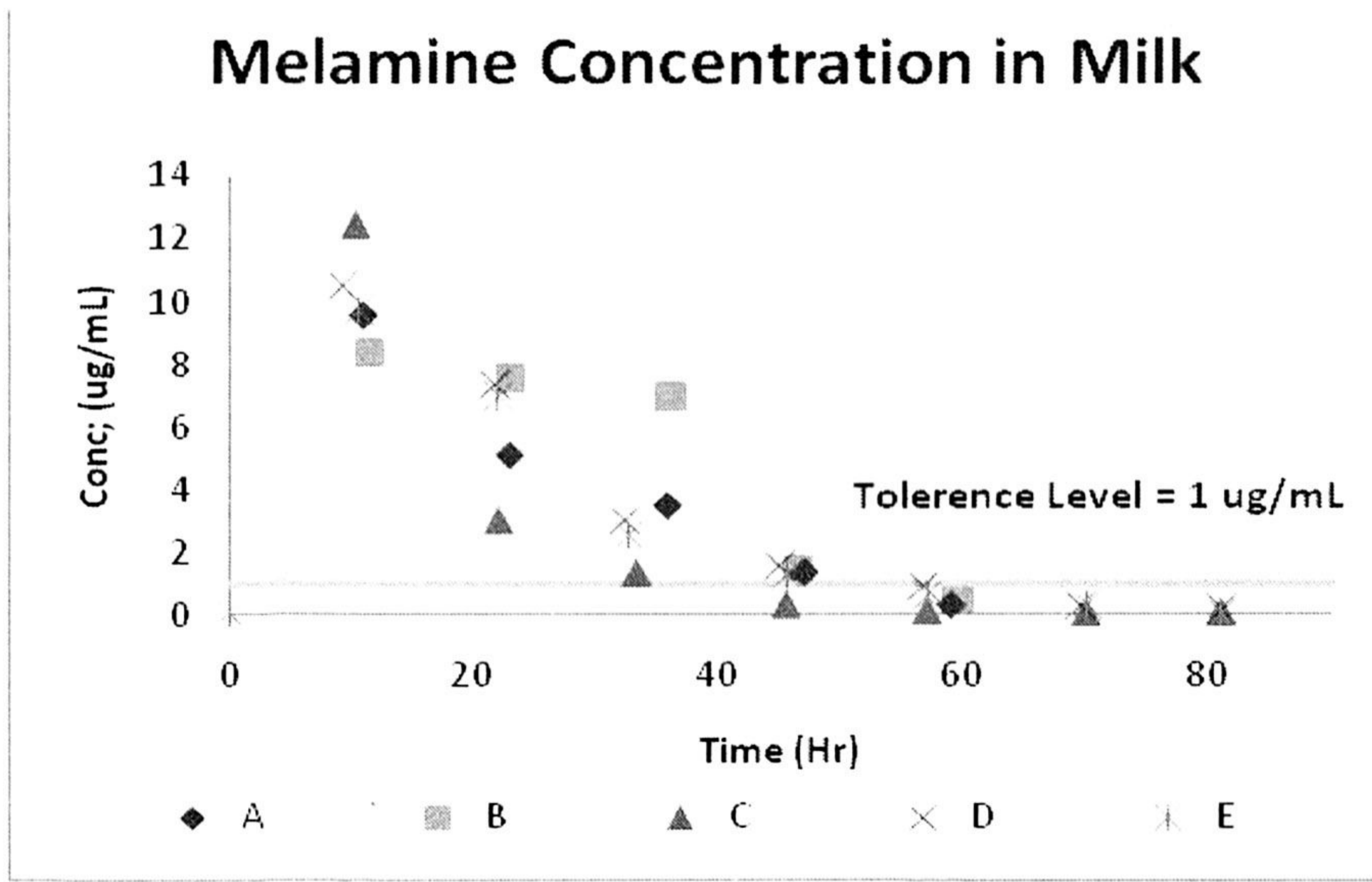


Figure 3. Estimation of a safe withdrawal time following an extra-label dose.



**Figure 4.** Estimation of a safe withdrawal time of contaminant exposure in dairy.

## References

1. Baynes RE, Barlow B, Mason SE, Riviere JE: Disposition of melamine residues in blood and milk from dairy goats. *Food Chem Toxicol* 48:2542-2546, 2010.
2. Davis JL, Smith GW, Baynes RE, Tell LA, Webb AI, Riviere JE: FARAD Digest: Update on drugs prohibited from extralabel use in food animals. *J Am Vet Med Assoc* 235:528-534, 2009.

# SEE IMPROVEMENT IN AS LITTLE AS 6 HOURS



© Copyright American Association of Bovine Practitioners; open access distribution.



See a Difference in One Dose  
[www.resflorgold.com](http://www.resflorgold.com)

Broad-spectrum Resflor Gold goes to work fast on BRD. It offers the dual activity of an antibiotic and a non-steroidal anti-inflammatory drug in one. Calves show improvement in as little as six hours. See for yourself in a 60-second time-lapse video you can access on your mobile device. You'll be surprised to see how quickly calves improve on Resflor Gold.



Download a FREE QR code reader app and scan this code with your smartphone to see Resflor Gold get results.

**To see the difference one dose and as little as six hours can make, see your Merck Animal Health sales representative or animal health supplier for more information.**

For subcutaneous use in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal. The effects of florfenicol and flunixin on bovine reproductive performance, pregnancy, and lactation have not been determined. When administered according to the label directions, RESFLOR GOLD may induce a transient local reaction in the subcutaneous and underlying muscle tissue. Full product information on page 12.

## PRODUCT INFORMATION

NADA 141-299, Approved by FDA.



(Florfenicol and Flunixin Meglumine)  
Antimicrobial/Non-Steroidal Anti-Inflammatory Drug

**For subcutaneous use in beef and non-lactating dairy cattle only. Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.**

**BRIEF SUMMARY:** For full prescribing information, see package insert.

**INDICATION:** RESFLOR GOLD® is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, and control of BRD-associated pyrexia in beef and non-lactating dairy cattle.

**CONTRAINDICATIONS:** Do not use in animals that have shown hypersensitivity to florfenicol or flunixin.

**WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.** This product contains material that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service or to obtain a copy of the MSDS, call 1-800-211-3573. For technical assistance or to report suspected adverse reactions, call 1-800-219-9286.

Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Toxicity studies in dogs, rats, and mice have associated the use of florfenicol with testicular degeneration and atrophy. NSAIDs are known to have potential effects on both parturition and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. The effects of flunixin on imminent parturition have not been evaluated in a controlled study. NSAIDs are known to have the potential to delay parturition through a tocolytic effect.

RESFLOR GOLD®, when administered as directed, may induce a transient reaction at the site of injection and underlying tissues that may result in trim loss of edible tissue at slaughter.

**RESIDUE WARNINGS:** Animals intended for human consumption must not be slaughtered within 38 days of treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

**ADVERSE REACTIONS:** Transient inappetence, diarrhea, decreased water consumption, and injection site swelling have been associated with the use of florfenicol in cattle. In addition, anaphylaxis and collapse have been reported post-approval with the use of another formulation of florfenicol in cattle.

In cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported, primarily following intravenous use of flunixin meglumine.

Made in Germany  
Intervet Inc. Roseland, NJ 07068  
©2009, Intervet Inc. All Rights Reserved.  
Mav 2009

US 3448 IV