Kansas Agricultural Experiment Station Research Reports

Volume 0
Issue 10 *Swine Day (1968-2014)*

Article 611

1995

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Recommended Citation

Herrman, T; Behnke, Keith C.; and Loughin, T (1995) "Mixing and clean-out properties of sulfamethazine and carbadox in swine feed," *Kansas Agricultural Experiment Station Research Reports*: Vol. 0: Iss. 10. https://doi.org/10.4148/2378-5977.6451

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Abstract

Results of this study suggest that carbadox was incorporated uniformly in the feed by mixing. However, the two medicated feed additives containing sulfamethazine did not incorporate uniformly in the feed. The causal mechanism for the poor mixing performance of sulfamethazine was not discovered; however, assay variability was eliminated as a primary source of variation. Flushing the feed mixing, conveying, and sack-off systems twice with ground corn did not eliminate drug carryover. Further investigation of the mixing and clean-out properties of medicated feed additives is warranted.; Swine Day, Manhattan, KS, November 16, 1995

Keywords

Swine day, 1995; Kansas Agricultural Experiment Station contribution; no. 96-140-S; Report of progress (Kansas State University. Agricultural Experiment Station and Cooperative Extension Service); 746; Swine; Feed; Mixing; Clean-out; Drugs

MIXING AND CLEAN-OUT PROPERTIES OF SULFAMETHAZINE AND CARBADOX IN SWINE FEED

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Summary

Results of this study suggest that carbadox was incorporated uniformly in the feed by mixing. However, the two medicated feed additives containing sulfamethazine did not incorporate uniformly in the feed. The causal mechanism for the poor mixing performance of sulfamethazine was not discovered; however, assay variability was eliminated as a primary source of variation. Flushing the feed mixing, conveying, and sack-off systems twice with ground corn did not eliminate drug carryover. Further investigation of the mixing and clean-out properties of medicated feed additives is warranted.

(Key Words: Feed, Mixing, Clean-Out, Drugs.)

Introduction

Concern over the safety of the food supply in the United States is paramount among consumers. The current good manufacturing practices (cGMPs) used to regulate animal feed production outline procedures to help assure that meat, milk, and eggs produced from animals receiving medicated feeds contain no violative drug residues.

Food and Drug Administration (FDA) cGMPs specify that "Equipment shall be capable of producing medicated feed of intended purity and potency"; this includes proper mixer performance. Mixer testing procedures are outlined by the American Society of Agricultural Engineers. This procedure entails describing feed uniformity by calculating the coefficient of variation (CV) using salt assays from 10 feed samples collected from the mixer. The cGMPs also specify that "Adequate procedures shall be established and used for all equipment used in the production and distribution of medicated feeds to avoid unsafe contamination of medicated and non-medicated feeds".

Sulfamethazine and carbadox are two antibacterial drugs widely used in swine production. Residue tolerances for these two products in uncooked tissue are 0.1 ppm and 0.0 ppm, respectively. Both products are classified as category II drugs under the cGMPs; withdrawal times are 15 days for sulfamethazine and 10 weeks for carbadox. Both products are used to improve weight gain and feed efficiency, as well as control or prevent bacterial diseases.

The high rate of violations for tissue residues of sulfamethazine has concerned FDA personnel for years. The FDA has identified that a lack of sequencing, flushing, and cleaning of mixer equipment accounted for 25% of sulfamethazine violations. As little as 1 ppm of sulfamethazine in feed, or 1/4 teaspoon of sulfa in a 1-ton batch of feed, can cause violative sulfa residues. Evaluating the performance of these two medicated feed additives in terms of their flushing and clean-out properties may help explain the cause for cross-contamination of feed.

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Studies examining the cause of cross-contamination in feed manufactured on-farm revealed that powdered sulfamethazine increased this risk compared to the granular form of the drug. The drug manufacturing industry developed granular and pellet forms of sulfamethazine to help reduce cross-contamination. This effort, combined with a strong education campaign by USDA and FDA, reduced the violation rate in pork from 13% prior to 1978 to about 5% from 1980 to 1987. For sulfamethazine in swine, the current residue violation rate is less than 1%.

Improper mixing and incorrect inclusion rates of medicated feed additives create the potential for tissue-residue violations. The FDA has established assay limits of 20% and 25% for complete feed containing sulfamethazine and carbadox, respectively. Exceeding these tolerances presents a potential source of violative tissue residue, whereas inclusion rates below the established tolerance may reduce the efficacy of the drug to control disease and allow development of microbial resistance.

This study was conducted to examine the mixing and clean-out properties of two forms of sulfamethazine and one carbadox product to better understand the role that product form, mixing performance, and flushing/clean-out properties may play in producing quality feed.

Procedures

Medicated swine feed was produced in 1,000 lb batches at the feed mill of the Department of Grain Science and Industry, Kansas State University (Table 1). The study was replicated three times for each of three medicated feed additives:

1) 10 g per lb sulfamethazine in extruded pelleted form (pelleted sulfa),

2) 10 g per lb sulfamethazine in granular form (granular sulfa), and

3) 2.5 g per lb carbadox (carbadox).

Table 1. Swine Grower Ration Used to Test Mixing and Clean-Out Properties of Sulfamethazine and Carbadox

Ingredient	Percent
Corn	73.45
Soybean meal (48% CP)	22.20
Monocalcium phosphate	1.45
Limestone	1.05
L-lysine·HCl	.10
Vitamin premix	.20
Trace mineral premix	.15
Salt	.30
Drug[1]	1.00

[1]Inclusion rate for sulfamethazine products, only 5 lb of the carbadox product was added to feed and an additional 5 lb of ground corn was used.

Sulfamethazine was included in the feed at a rate of 110 ppm of feed, and carbadox was used at 55 ppm of feed. Treatments were arranged in a completely randomized design with repeated measures taken at three mixing times and after transferring feed to 50 lb sacks.

Corn conforming to U.S. Grain Grading Standards for number 2 yellow corn was ground to a particle size ranging between 550 and 700 microns using a Jacobson hammermill with a 1/8 in diameter screen. A 400 lb ground corn placebo was passed through the mixing and sack-off system, and the mixer, leg, and sack-off bin then were cleaned prior to mixing feed for the study. Feed consisting of corn (73.5% by weight) and soybean meal (22.2% by weight) was batched with a Wisconsin Electric Manufacturing, Inc. system and emptied into a Sprout Waldron horizontal double-ribbon mixer. The micro-ingredients (monocalcium phosphate, limestone, lysine, vitamins, trace minerals, and salt) were added to the mixer by an Able micro-ingredient system.

Mixing properties of the medicated feed additives were evaluated by sampling the

mixer using a Seedburo Grain Probe after 1.5, 2.5, and 4 min of mixing time. In order to reduce costs for incorporating replications, the CVs were computed based on eight rather than 10 samples. Following the mixing treatment, feed was conveyed to the sack-off bin and packaged into 50 lb capacity sacks, of which eight were sampled. Two flush treatments with 200 lb of corn followed each batch of feed. The feed system was cleaned by the same procedures used in mill preparation.

Samples from the mixer, packaging, flush, and clean-out were split using a riffler and analyzed separately for salt and drug content. Salt analyses were performed using Quantab titrators. Assays for sulfamethazine and carbadox were performed by a commercial lab. The lowest detection limits for these assays are 5 ppm and 2 ppm, respectively. Triplicate assays were performed on all samples that were 30% outside the desired medication level following the first assay results.

Coefficient of variation (CV), standard deviation, and mean measurements taken across the locations were calculated for each drug, replication, and mixing time using the Univariate procedure in SAS. Drug levels were analyzed on a proportional basis, because the carbadox inclusion rate was half of the sulfamethazine inclusion rate. The GLM procedure in SAS was used to evaluate treatment effects for both the mixing and clean-out portions of the study. Main effects were separated using Fisher's least significant difference (LSD) technique, and interactions were analyzed using the least significant difference among the least squares means produced by the GLM procedure. Variance components in the general linear model were evaluated using the VARCOMP procedure of SAS. A paired-comparison t-test was performed on the mean difference between drug mixing uniformity and salt mixing uniformity.

Results and Discussion

Mixing Properties. Mixing properties compared among drugs were different ($P < .01$), whereas mixing time did not differ ($P > .05$). Carbadox mixed well, as indicated by an average CV of 11.4% (Table 2). The CV for pelleted sulfa was 30.4%, and the CV for granular sulfa was 25.6%.

Increased mixing time after 1.5 min did not significantly improve the uniformity of drug distribution in the swine feed ($P > .10$). This suggests that some factor other than mixing time hindered sulfamethazine distribution in the feed. Electrostatic properties of feed ingredients are reported to occur; however, a paucity of information is available regarding the influence of static charge on mixing properties. Ingredient carriers, oil, and grounding the mixer are used to reduce static cling. However, ingredients not directly in contact with the mixer may possess electrostatic charge. If static charge was the cause for non-uniform distribution of sulfamethazine in the feed, additional mixing would not rectify this problem. Further investigation to explain the cause for poor mixing performance should include measuring various physical properties of sulfamethazine, salt, and corn, such as density, particle size, hygroscopicity, conductivity, and static charge during mixing or movement.

Mean assay values for each drug × mixing time combination (Table 2) indicate that the pellet form of sulfamethazine was present at a lower concentration (87.1 ppm) than the granular form (108.4 ppm) in the complete feed. Both sulfamethazine products were packaged as a Type-B premix at a concentration of 10 g per lb, and assays of the premixes for drug level indicated that the granular and pellet forms contained 114% and 104% of the label amount, respectively. The higher mean for the granular sulfamethazine explains why its CV was smaller than that of the pellet form. The standard deviations for both products were similar, and the range between assays was about 27 ppm greater for the granular product.

The statistical components of variability for the two sulfamethazine products and carbadox were analyzed using data from

samples subjected to triplicate drug assays. Assay variability was small relative to other components of variability in the experiment. The greatest variability occurred between replications for the same sample site within each drug treatment.

The paired-comparison t-test between salt and drug CVs revealed that carbadox did not differ significantly ($P > .05$) from salt with respect to distribution uniformity in the feed, whereas both forms of sulfamethazine displayed mixing properties that were significantly different ($P < .05$) than those of salt.

Clean-out Properties. We observed a drug × location interaction in feed clean-out/flush material ($P < .01$; Figure 1). Drug concentrations in both the ground-corn flush treatments did not vary ($P > .05$) among products. A trend for sulfamethazine to be present but carbadox not to be present at detectable concentrations was established for both corn flush treatments.

The mixer clean-out samples displayed a similar trend with respect to drug carryover. Sulfamethazine contents in mixer clean-out samples did not differ ($P > .05$) between the pellet (8.1 ppm) and granular (12.6 ppm) product, However, carbadox (<2.0 ppm) differed from the granular form of sulfamethazine ($P < .05$). The highest sulfamethazine concentration (16.2 ppm) found in 1.1 kg of mixer clean-out material could result in a contamination of 32 parts per billion in the subsequent 1,000 lb batch of feed. This is below the 1 ppm level that can lead to violative tissue residues.

The feed collected from the boot of the leg contained significantly ($P < .05$) higher drug levels than the flush and mixer clean-out material. No significant difference was present between the three drug products. The highest level of sulfamethazine carryover (37.8 ppm pellet and 39.9 ppm granular) occurred in the material collected from the boot of the leg. Because this is a dead spot in the feed conveying system, the only way to remove carryover material is to clean the boot (physical removal). A high concentration of drug at this location is not undesirable, because the pellet and granular products were designed to flush from the system.

The concentrations of drugs in material collected from the sack-off bin varied dramatically between products. The concentration of carbadox in the sack-off bin was approximately 86% of the inclusion rate (43 ppm) compared to the sulfamethazine products, which were present at 7 ppm and 23.5 ppm for the pellet and granular forms, respectively. Clean-out material from the sack-off bin consists of fine, dust-like particles. Perhaps carbadox possesses similar dust-like properties and separates from the feed at the sack-off bin. The presence of a high drug concentration in the sack-off bin appears particularly hazardous, because it relates to product cross-contamination. The high concentration of carbadox in the sack-off bin also may explain why it was not present in the ground corn flush.

Veterinarians, swine producers who manufacture their own feed, and commercial feed processors should be aware of the different properties that medicated feed additives possess with respect to mixing and clean-out performance. In light of these results, it is imperative that the cGMPs are followed to avoid cross-contamination and violative tissue residue. Veterinarians and commercial feed companies who supply producers with premix, basemix, or supplement products containing drugs can play an integral role in educating producers about the importance of good manufacturing practices and how to avoid cross-contamination.

Table 2. Coefficient of Variation (CV) Percentages and Means, Ranges, and Standard Deviations (in ppm) for Two Sulfamethazine Forms and Carbadox at 1.5, 2.5, and 4 Minutes Mixing Time and after Bagging Feed

		Assay results, ppm		
Treatment	CV %	Mean	Range	Std. Dev.
Sulfa pelleted				
1.5 min. mix	28.2	73.6	86.9	20.8
2.5 min. mix	32.4	90.2	126.9	29.2
4.0 min. mix	30.8	98.6	122.6	30.4
bags	30.4	85.9	103.1	26.2
Average	30.4	87.1	109.9	26.6
Sulfa granular				
1.5 min. mix	25.1	109.8	125.0	27.6
2.5 min. mix	25.9	112.7	150.5	29.2
4.0 min. mix	28.2	104.5	149.5	29.5
bags	23.4	106.6	121.8	25.0
Average	25.6	108.4	136.7	27.8
Carbadox				
1.5 min. mix	14.3	48.1	30.5	6.9
2.5 min. mix	5.7	44.5	10.7	2.6
4.0 min. mix	10.6	45.2	18.6	4.8
bags	14.9	44.7	31.0	6.7
Average	11.4	45.6	22.7	5.2

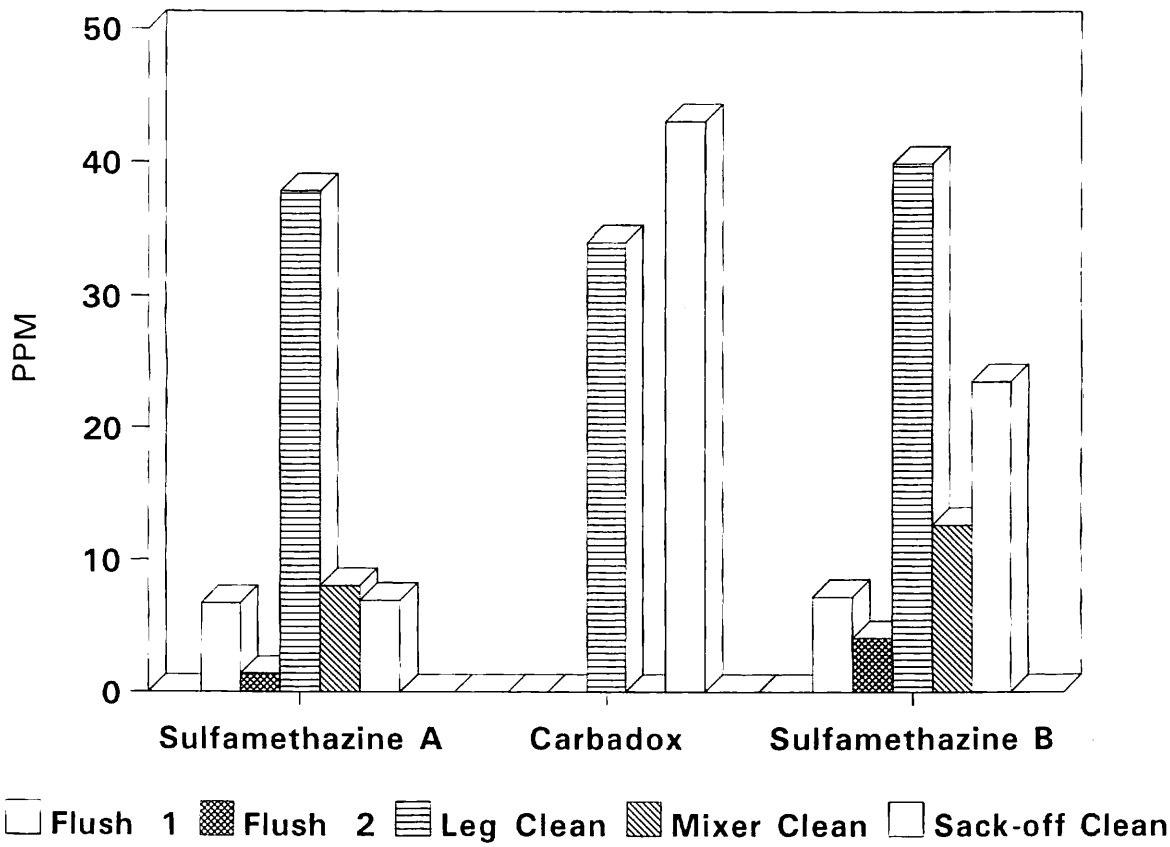

Figure 1. Interactions among Three Medicated Feed Additives and Five Sources of Clean-Out Material.