

Meta-analysis of the effects of monensin in beef cattle on feed efficiency, body weight gain, and dry matter intake¹

T. F. Duffield,*² J. K. Merrill,[†] and R. N. Bagg[†]

*Department of Population Medicine, University of Guelph, ON, Canada N1G 2W1; and [†]Elanco Animal Health, Elanco Division of Eli Lilly Canada, Inc., 120-150 Research Lane, Guelph, ON, Canada N1G 4T2

ABSTRACT: A meta-analysis of the impact of monensin on growing and finishing beef cattle was conducted after a search of the literature. A total of 40 peer-reviewed articles and 24 additional trial reports with monensin feeding in beef cattle were selected, after meeting apriori quality criteria. Data for each trial were extracted and analyzed using meta-analysis software in STATA. Estimated effect size of monensin was calculated for feed efficiency (FE), ADG, and DMI. Monensin use in growing and finishing beef cattle reduced DMI ($P < 0.001$) and improved both ADG ($P < 0.001$) and FE ($P < 0.001$). The average concentration of monensin in feed across studies was 28.1 mg/kg feed (100% DM) and this resulted in approximately a 6.4% (but only 2.5 to 3.5% in the last 2 decades) increase in FE, 3% decrease in DMI, and 2.5% increase in ADG. All 3 outcomes displayed moderate and significant heterogeneity of monensin response (I^2 , which is a measure of variation beyond chance, = 29% for FE, 42% for DMI, and 23% for ADG); therefore, random effects models were used for those outcomes. There were no single influential studies that overweighted the

findings for any outcome. Meta-regression analysis of the effect sizes obtained from these data showed that dietary factors, dose, and study design were influential in modifying effect size of monensin treatment. Use of corn silage in the diet influenced the effect size of monensin for DMI and FE, with diets containing corn silage resulting in a greater improvement in FE and a larger effect on reducing DMI. Studies conducted to assess multiple doses of monensin showed similar effects to the use of corn silage in the diet. Studies conducted in the United States or with higher ADG in control animals (>1.17 kg/d) showed less effect of monensin on ADG. Pen-level studies showed a greater monensin increase on ADG than did those conducted on individual animals. Linear effect of monensin dose was observed for FE, DMI, and ADG outcomes, with greater effects on improving FE and reducing DMI with larger doses of monensin but lesser improvement in ADG with increasing dose. These findings confirm that monensin improves FE in growing and finishing beef cattle, and that this effect is linear with dose.

Key words: beef cattle, feed efficiency, meta-analysis, monensin

© 2012 American Society of Animal Science. All rights reserved.

J. Anim. Sci. 2012.90:4583–4592
doi:10.2527/jas2011-5018

INTRODUCTION

Monensin is a carboxylic polyether ionophore (Haney and Hoehn, 1967) provided to cattle orally as a sodium salt. Monensin selectively inhibits Gram-positive bacteria, thereby impacting ruminant metabolism by increasing efficiency of energy metabolism, improving nitrogen metabolism, and reducing bloat and lactic acidosis risk (Schelling, 1984). Monensin changes the ratio of VFA in the rumen, increasing propionic acid produc-

tion and reducing molar percentages of butyric and acetic acids (Richardson et al., 1976; Prange et al., 1978), thus providing more energy from feed to the animal through increased glucose supply. Increased production of propionic acid from the rumen increases hepatic gluconeogenic flux (Lomax et al., 1979; Baird et al., 1980).

The reported impacts of monensin since its approval for feedlot cattle in the mid-1970s on feed efficiency (FE), ADG, and DMI have not always been consistent. For example, many studies have found monensin to significantly improve FE (Steen et al., 1978; Horton et al., 1981), whereas some studies have not found significant effects on FE (Horton, 1984; Yang et al., 2010). Meta-analysis can be used to both summarize effects of treatment across studies and investigate

¹We acknowledge Mary-Anne Kenny and Devin Nobert for their assistance with the literature review.

²Corresponding author: tduffiel@ovc.uoguelph.ca

Received Dec. 12, 2011.

Accepted June 15, 2012.

factors explaining potential heterogeneity of response. Meta-analysis has been extensively used to assess treatment effects in human health care (Egger et al., 2001). Recent examples of meta-analysis used in animal science and veterinary literature include a meta-analysis of dietary predictors of milk fever (Lean et al., 2006), impact of bovine ST on production and health (Dohoo et al., 2003a), and impact of monensin in dairy cattle (Duffield et al., 2008a,b,c). The purpose of this study was to describe the effect of monensin on DMI, ADG, and FE in growing and finishing beef cattle, using meta-analytic methods to describe its impact and help explain differences in responses among studies.

MATERIALS AND METHODS

A literature search and screening process was initially conducted using Pubmed, Agricola, CAB, and Google Scholar search engines to create a data set of monensin articles using the keywords: “monensin and cattle” or “monensin and cow or monensin and steer.” No date restrictions were placed on the search engines, thus encompassing the entire time monensin has been available for research in cattle (since 1972). In addition, Elanco Animal Health was asked for unpublished reports that might be used for this analysis. All trial reports (**reports**) and peer-reviewed articles (**papers**) were initially screened for acceptability by determining whether the research was conducted on growing and finishing beef cattle. Initial screening of trial reports and papers was conducted by 2 individuals. All other rejections and inclusions were reviewed by 1 of the authors and confirmed by the other 2 authors. There were 360 peer-reviewed papers and 600 trial reports (searched through the Elanco archive of research reports) that were initially identified. After discarding papers that were obviously not beef research, a starting data set of 114 peer-reviewed papers was achieved. In addition, 203 eligible trial reports were retrieved from the Elanco database.

Selection for Inclusion and Exclusion Criteria

For inclusion, papers or reports must have been conducted on weaned growing and finishing beef cattle. Either steers or heifers were included, but bulls and cows were excluded. Thus, all review papers and reports ($n = 19$), and nontarget species papers and reports, such as research on dairy cows, dairy heifers, and preweaned calves ($n = 30$), were excluded. An extensive number of research reports ($n = 101$) and some peer-reviewed studies ($n = 15$) did not contain sufficient information to conduct a meta-analysis from the data. Each treatment (control and monensin) required reporting of the number of units of concern per treatment, mean for the treatment, and either

a measure of dispersion or a P -value. Many of the rejected studies did not provide measures of dispersion associated with the study outcomes that would have allowed inclusion of data in the analysis. If there was no measure of dispersion reported but a P -value was included, these papers were retained and SE were estimated. Similarly, many of the rejected Elanco archive trial reports were summary reports of several trials and, therefore, contained insufficient statistical data to extract for analysis. Studies were initially required to be randomized trials (completely randomized, complete block, or factorial designs) to be eligible for analysis but not necessarily blinded. However, there were several older trial reports ($n = 4$) and 2 peer-reviewed papers that were otherwise acceptable but randomization of treatments was not indicated in the methods. These data were included in analysis and because their inclusion was not found to be significantly different from their omission in the final regression model for FE, we elected to retain them for the analysis. There were 4 occurrences of duplicate data that were excluded. This data screening process left 148 papers or trial reports to evaluate study quality for inclusion in the meta-analysis. Trials with cross-over and Latin square designs were excluded, due to small sample size and potential problems with rumen adaptation periods and sufficient time for washout. Trials with a direct comparison of monensin treatment to another treatment (positive control), but without a negative control group, were excluded. Studies with only one replication per treatment or studies that were conducted at the pen level, but analyzed at the individual level, were also considered flawed and excluded. There were 84 of these design flaws or inappropriate design for the purpose of this meta-analysis that were equally split between papers and trial reports. There were 64 papers and reports (40 papers and 24 trial reports) of 148 eligible studies (43%) that provided useable data and appropriate measures of variance on the outcomes of interest. It was determined that in 61 out of 64 papers, Rumensin (Elanco Animal Health, Greenfield, IN), which contained the active ingredient monensin, was the product used.

A template for data extraction was drafted; the template included number of animals and/or number of pens per treatment group, mean, and SE. If the standard error was not published, it was either estimated from the exact P -values (Mederos et al., 2012) or other measures of variance, or the data were excluded. When a P -value was reported as less than a number (i.e., <0.05), the number was used as the P -value for the SE calculation. Other factors that influenced the outcomes of interest were included in the data extraction process, including type of study (factorial or not; multiple or single dose), treatment dose (mg/kg feed of DM), treatment duration, days on feed, breed, basic diet information (corn silage, corn, barley, forage percentage in diet), season at start

of trial, type of paper (peer-reviewed or not: **Y/N**), use of tylosin in the feed, sex (steers, heifers, or mixed), and starting BW on the study. Data for all the analytes measured in each study were extracted and entered into a spreadsheet.

Statistical Analysis

A meta-analysis was conducted on the extracted outcomes using Stata (Intercooled Stata V. 9.0, College Station, TX). A fixed effect model was first conducted for each parameter to estimate the effect size (**ES**), 95% confidence intervals (**CI**), and statistical significance of ES. The ES estimate analysis was conducted using a standardized z statistic (also called a standardized mean difference) and allowed analysis that was independent of differences in unit measurement (e.g., pounds vs. kilograms), is more robust when there is heterogeneity, and weights individual studies using SD for each treatment and sample size. More details on ES calculations have been published (Lean et al., 2009). Still, for all significant outcomes, unit of measurement was converted to kilograms to allow the calculation of weighted mean differences (**WMD**) of treatment relative to control, where the weights used were the inverse of the variance in the differences in means.

Variation in experiment-level ES was assessed with a χ^2 test for heterogeneity (Egger et al., 2001). An α level of 0.10 was used because of the relatively low power of the χ^2 test to detect heterogeneity among the experiments. Heterogeneity of results among trials was quantified using the I^2 statistic (Higgins et al., 2003). The I^2 statistic describes the percentage of total variation across studies, which is due to heterogeneity rather than chance. Where Q is the χ^2 heterogeneity statistic and k is the number of trials, I^2 was calculated as:

$$I^2 = \frac{Q - (k - 1)}{Q} \times 100$$

Uncertainty intervals for I^2 (dependent on Q and k) were calculated. Negative values of I^2 were put equal to 0. Consequently, I^2 lie between 0% and 100%. A value greater >50% may be considered substantial heterogeneity.

If there was evidence of heterogeneity, a random effects model was used. A meta-regression analysis was subsequently used to explore the sources of heterogeneity of response, using the individual ES for each trial as the outcome and the associated SE of ES as the measure of variance. Meta-regression was conducted by first screening individual variables, such as study characteristics, dose, days on feed, or diet factors, in a univariate regression with a liberal P -value cutoff of $P = 0.25$. Variables, such as dose and days on feed, were treated as continuous variables.

Other variables were coded as present or absent, and were dichotomous. All variables meeting the first screening criteria were entered into a backward stepwise regression method until all variables that remained were significant at $P < 0.05$. Forest plots were used to visually display the ES, 95% CI, and study weights. Publication bias was investigated both graphically with funnel plots and statistically, using both Begg's (Begg and Manumdar, 1994) and Egger's test (Egger et al., 1997). In the case of significant publication bias, the number of studies needed to reverse the reported findings (**Fail-Safe n**) was calculated based on Rosenthal's methods (Rosenthal, 1979). Finally, the influence of individual studies was assessed with the use of an influence plot to determine the impact of removing individual studies on the ES estimate (Dohoo et al., 2003b).

RESULTS

A summary of the studies used for the various meta-analyses is provided in Table 1. There were 64 papers and reports containing 169 trials with monensin and performance outcomes. Of these, 51 papers reported on FE as kilograms of DMI per kilogram of BW gain, 10 papers reported on FE as kilograms of BW gain per kilogram of DMI (FE inverse), and 3 papers did not report FE but provided either DMI or ADG. The FE value reported in the majority of studies was the parameter calculated, excluding any removed animals. Some studies contained a summary of 1 trial conducted on multiple trial sites, whereas other studies reported multiple trials conducted at a single trial site. The mean dose of monensin was 28.1 mg/kg feed, with a range of 3 to 98 mg/kg feed (Figure 1). A summary of all meta-analysis findings for each outcome is presented in Table 2. Over all the trials analyzed, monensin decreased DMI (WMD = -0.268 kg, ES = -0.72, $P = 0.001$) and increased ADG (WMD = +0.029 kg/d, ES = +0.29, $P = 0.0001$). Monensin improved FE marked by a reduction in kilograms of DMI per kilogram of gain (WMD = -0.53 kg DMI per kilogram BW gain, ES = -0.93, $P = 0.001$). The meta-analysis of the 32 trials reporting FE inverse showed an increase in kilograms of BW gain per kilogram of DMI. (WMD +0.002 kg BW gain per kilogram DMI, ES = +0.212, $P = 0.048$) Although forest plots are often a useful graphic display of data for meta-analysis, the number of trials involved in the majority of this analysis precluded providing readable graphics for presentation.

There was heterogeneity in the response of monensin from trial to trial on FE. The $Q \chi^2$ statistic indicated that this heterogeneity was significant ($\chi^2 = 183.11$, $df = 129$, $P = 0.002$). Thus, the model for FE was evaluated, using a random effect, and possible sources of heterogeneity were explored with meta-regression. Subsequent meta-regression analysis conducted to explore reasons

Table 1. Summary of papers used for meta-analysis of monensin performance effects in growing and finishing cattle

First author, yr	Source type: J = journal, T = trial report ¹	Location	Trial	Dose of monensin (mg/kg DM)	TMR ²	Pens, n	No./ pen	Corn silage	Outcomes measured
Klett, 1972	T	Texas	5	6.1 to 48.9	Yes	4	10	No	DMI, ADG, FE
Klopfenstein, 1972	T	Nebraska	5	6.1 to 48.9	Yes	2	8	No	DMI, ADG, FE
Potter, 1974a	T	United States	5	12.2 to 48.9	Yes	5	25	No	DMI, ADG, FE
Farlin, 1974	T	Nebraska	6	6.1 to 36.7	Yes	2	24	No	DMI, ADG, FE
Hatfield, 1974	T	Illinois	6	6.1 to 36.7	Yes	4	6	No	DMI, ADG, FE
Sherrod, 1974	T	Texas	6	6.1 to 36.7	Yes	2	10	No	DMI, ADG, FE
Potter, 1974b	T	Indiana	8	7.17 to 60.7	No	5	15	No	DMI, ADG, FE
Linr, 1975	T	United States	1	40.4	No	4	7	Yes	DMI, ADG, FE
Garrett, 1975	T	California	2	6.1, 36.7	Yes	2	10	No	DMI, ADG, FE
Hurst, 1975a	T	Beverley, UK	1	33.3	Yes	3	19	No	DMI, ADG, FE
Osmond, 1975	T	Devon, UK	2	11.1, 33.3	Yes	3	7	No	DMI, ADG, FE
Potter, 1975	T	Indiana	3	7.3 to 46.9	No	5	15	No	DMI, ADG, FE
Hurst, 1975b	T	Beverley, UK	2	11.1, 33.3	Yes	2	14	No	DMI, ADG, FE
Utley, 1976	J	Georgia	1	29.3	No	18	1	No	DMI, ADG, FE
Farlin, 1976	T	Nebraska	2	6.1, 36.7	Yes	3	35	Yes	DMI, ADG, FE
Osmond, 1976	T	Cornwall, UK	1		No	4	11	No	DMI, ADG, FE
Mayes, 1976	T	Cornwall, UK	1		No	4	11	No	ADG
Raun, 1976	J	Indiana	7	3 to 97.8	Yes	13	5	No	DMI, ADG, FE
Lesperance, 1976	T	Nevada	4	6.1 to 24.4	No	4	4	No	DMI, ADG, FE
Wells, 1976	T	NSW, Australia	1	30	Yes	3	30	No	DMI, ADG, FE
Boling, 1977	J	Kentucky	3	13 to 43.5	No	3	8	Yes	DMI, ADG, FE
Potter, 1977	T	Indiana	6	6.1 to 36.7	Yes	2	10	No	DMI, ADG, FE
Garrett, 1977	T	California	2	6.1, 36.7	Yes	2	12	No	DMI, ADG, FE
Steen, 1978	J	Kentucky	3	12.2 to 32.6	No	3	8	Yes	DMI, ADG, FE
Dartt, 1978	J	Kentucky	2	200 mg/cow	No	3	8	Yes	ADG
Johnson, 1979	J	Washington	1	28 to 36.7	Yes	5	6	No	DMI, ADG, FE
Hanson, 1979	J	Nebraska	6	33	Yes/No	2	6	Yes	DMI, ADG, FE
Pendlum, 1980	J	Kentucky	1	32.8	No	6	8	Yes	DMI, ADG, FE
Mowat, 1977	J	Ontario, Canada	3	29.3 to 32.5	No	4 to 12	3 to 5	No	DMI, ADG, FE
Byers, 1980	J	Ohio	2	30.6, 33.4	No	3	10	Yes	DMI, ADG, FE
Wagner, 1981	J	Oklahoma	2	36.7	Yes	4	4	No	DMI, ADG, FE
Thonney, 1981	J	New York	1	22.3	No	6	36	No	DMI, ADG, FE
Berger, 1981	J	Nebraska	3	16 to 36.7	No	3 to 4	6 to 16	Yes	DMI, ADG, FE
Horton, 1981	J	Saskatchewan, Canada	2	36.7	Yes	2	6 to 25	No	DMI, ADG, FE
Perry, 1983	J	Indiana	2	33	Yes	7	12	Yes	DMI, ADG, FE
Utley, 1982	J	Georgia	1	35.9	Yes	41	1	No	ADG, FE
Horton, 1984	J	Florida	1	36.7	Yes	4	8	Yes	DMI, ADG, FE
Beacom, 1988	J	Saskatchewan, Canada	1	33	Yes	5	10	No	DMI, ADG, FE
Burrin, 1988	J	Nebraska	6	11, 33	Yes	9	9	Yes	DMI, ADG, FE-INV
Zinn, 1988	J	California	2	33	Yes	8	6	No	DMI, ADG, FE
Garrett, 1989	J	Morocco, Africa	3	22.1 to 23.6	No	3 to 4	1	No	DMI, ADG, FE
Loerch, 1990	J	Ohio	3	26.5 to 39.6	Yes	6 to 12	8	Yes	DMI, ADG, FE
Stock, 1990	J	Nebraska	3	27.5	Yes	10	11	No	DMI, ADG, FE-INV
Collins, 1992	J	South Dakota	2	37.7, 48.9	No	4	8	No	DMI, ADG, FE-INV
Zinn, 1993	J	California	2	36.7	Yes	8	5	No	DMI, ADG, FE
Fontenot, 1993	J	Virginia	4	32.1 to 41.4	No	3	8	Yes	DMI, ADG, FE
Zinn, 1994	J	California	2	31.1	Yes	4	5	No	DMI, ADG, FE
Stock, 1995	J	Texas	1	27	Yes	12	60	No	DMI, ADG, FE
Casey, 1994	J	Pretoria, S. Africa	1	37.5	Yes	15	7	No	DMI, ADG, FE
Lana, 1997	J	New York	4	11, 22	Yes	3	7	Yes	DMI, ADG, FE-INV
Steele, 2001	J	Oklahoma	1	15.9	No	4	12	No	DMI, ADG, FE
Gibb, 2001	J	Alberta, Canada	1	26	Yes	12	1	No	DMI, ADG, FE
Lana, 2001	J	New York	4	22	Yes	5	1	Yes	DMI, ADG, FE-INV
Wang, 2003	J	Alberta, Canada	2	25	Yes	12	15	No	DMI, ADG, FE

Table 1. Continued.

First author, yr	Source type: J = journal, T = trial report ¹	Location	Trials	Dose of monensin (mg/kg DM)	TMR ²	Pens, n	No./ pen	Corn silage	Outcomes measured
Benchaa, 2005	J	Nova Scotia, Canada	1	33	No	10	5	No	DMI, ADG, FE-INV
Lefebvre, 2006	J	Quebec, Canada	4	33	Yes	2	5	Yes	DMI, ADG, FE-INV
Swingle, 2007	T	Texas	2	36.5	Yes	4	94	Yes	DMI, ADG, FE
Arelovich, 2008	J	Argentina	2	35	Yes	5	1	No	DMI, ADG, FE
Depenbusch, 2008	J	Kansas	2	38	Yes	9	7	No	DMI, ADG, FE-INV
Erickson, 2008	T	Nebraska	1	40.3	Yes	8	20	Yes	DMI, ADG, FE
Hunsaker, 2008	T	Colorado	1	40.3	Yes	4	70	Yes	DMI, ADG, FE
Koers, 2008	T	Oklahoma	1	40.3	Yes	4	71	No	DMI, ADG, FE
Salinas-Chavira, 2009	J	California	1	28	Yes	6	6	No	DMI, ADG, FE-INV
Yang, 2010	J	Alberta, Canada	1	41.7	Yes	14	5	No	DMI, ADG, FE

¹All trial reports were supplied by Elanco Animal Health, Greenfield, IN. FE = feed efficiency (kilogram of DMI per kilogram of BW gain), FE-INV = inverse feed efficiency (kilogram BW gain per kilogram of DMI).

²TMR = total mixed ration.

for heterogeneity resulted in 4 significant variables that influenced ES for FE: 1) studies assessing multiple vs. single doses of monensin; 2) dose (milligrams per kilogram of feed, 100% DM); 3) total mixed ration (TMR) delivery vs. top dress; and 4) presence of corn silage in the diet (Table 3). Effects of monensin on FE were more consistent in multidose studies with nonsignificant ($P = 0.443$) heterogeneity, whereas single-dose studies displayed significant heterogeneity ($P = 0.001$). Studies that included monensin in a TMR showed less heterogeneity and less of an effect, compared with studies with dose included in a supplement top dress, which showed significant heterogeneity but a greater average effect. Studies in which corn silage was fed displayed a greater effect for monensin on FE compared with studies not using corn silage. However, heterogeneity was significant for both. A weighted mean difference meta-analysis was used to estimate the overall effect of monensin on FE, which was -0.53 kg of feed per unit of BW gain. The regression coefficients generated from the modeling, us-

ing this meta-analysis, were then used to illustrate the linear effect of dose. A 0.008-kg reduction in DMI per kilogram of BW gain was identified per 1 mg/kg feed increase in dose of monensin in the feed. This translates into estimated FE improvements of -0.55 , -0.64 , and -0.73 kg DMI per kilogram of gain for doses of 22, 33, and 44 mg/kg feed increase in TMR diets with estimates derived from multidose studies. A stratified meta-analysis of monensin effect (Table 4) shows effects on FE that are linear and statistically significant at lesser and greater dose ranges (3 to 15 mg/kg feed increase, and >44 mg/kg feed). This would support the current U.S.-approved dose range of Rumensin for FE of 6 to 49 increase mg/kg feed. Analysis of FE was also stratified by year of research (using decades of 1970s, 1980s, 1990s, and 2000+, as strata) to explore differences in response by decade (Table 5).

The Begg's test for publication bias was significant for the FE analysis ($P = 0.0001$) and the associated funnel plot (Figure 2) illustrates a bias toward smaller studies that reported responses when FE was improved with monensin treatment and a lack of small studies that may have found an increase in FE with monensin. Nevertheless, the estimated Fail-Safe n (Rosenthal, 1979) indicated that it would require 8,000 trials with opposite results to those available to reverse the findings that monensin treatment improved FE.

Monensin reduced DMI, improved ADG, and improved BW gain per unit of feed (Table 2). A forest plot for inverse FE (BW gain per unit feed:kilograms ADG per kilogram of DMI) is illustrated in Figure 3. Similar meta-regression analyses were attempted for each of these variables (DMI, ADG, and inverse FE), as was conducted for FE (Table 3). However, there were an insufficient number of studies with inverse FE to conduct meta-regression for that outcome. Even though monensin positively affected ADG, this effect was reduced with

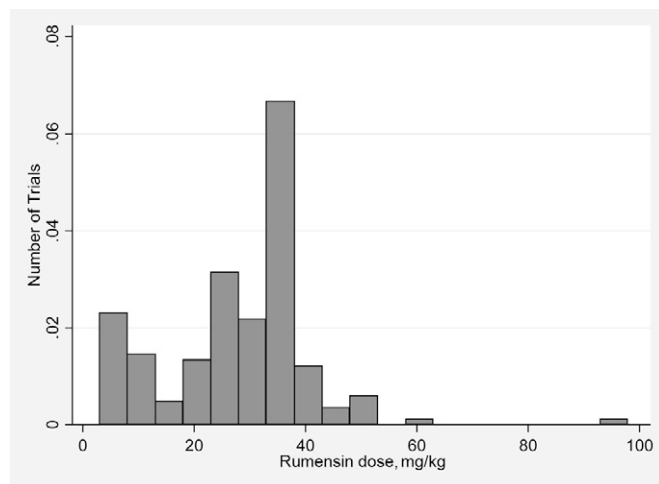


Figure 1. Histogram monensin dose in feed across all trials used for meta-analysis of feed efficiency, DMI, and ADG, in growing and finishing cattle.

Table 2. Summary of effect size estimates of monensin on performance outcomes in growing and finishing cattle, derived from meta-analysis

Outcomes measured	Weighted mean difference for monensin control (95% CI) ¹	Change, %	Pens or cattle per treatment	Trials	Effect size ² (95% CI)	I ² (95% uncertainty interval) ³	Effect size P
FE, kg feed/kg BW gain	-0.53 (-0.61, -0.45)	-6.4	634	130	-0.934 (-1.09, -0.77)	29 (11, 23)	<0.001
DMI, kg	-0.268 (-0.32, -0.21)	-3.1	854	151	-0.716 (-0.88, -0.55)	42 (28, 53)	<0.001
ADG, kg/d	+0.0291 (0.019, 0.040)	+2.5	799	156	+0.292 (0.16, 0.42)	28 (5, 38)	<0.001
FE, kg gain/kg BW gain	+0.0021 (-0.0001, 0.0043)	+1.3	186	32	+0.212 (0.0016, 0.42)	0 (0, 40)	0.048

¹Weighted mean difference is estimate of actual effect of treatment in units measures; CI = confidence interval.

²Effect size is a standardized z-value to statistically compare treatment vs. control differences between studies.

³I² is a measure of variation beyond chance.

increasing dose. Based on extrapolation from a simple plot of ADG ES for monensin by dose of monensin (data not shown), monensin effect on ADG would be expected to be negative (<0 vs. control), beginning at ~46 mg/kg feed of monensin. The impact of influential studies on all models was tested, using influence analysis. Even though there were influential studies, especially those with larger sample sizes, inclusion or removal of these studies did not change the direction of effect in any analysis and caused little change in the overall ES estimates.

Table 3. Summary of significant meta-regression variables influencing the effect size (ES) of monensin on feed efficiency (FE), DMI, and BW gain in growing and finishing cattle

Variables	Coefficient	95% confidence interval	P
FE			
Intercept	-0.453640	(-0.921, 0.014)	0.057
Multiple-dose studies	-0.671687	(-0.949, -0.394)	<0.001
Monensin by TMR delivery ¹	0.33731	(-0.0234, 0.698)	0.067
Corn silage in diet	-0.60844	(-0.949, -0.267)	<0.001
Dose of monensin, mg/kg DM	-0.09531	(-0.019, -0.0002)	0.044
DMI			
Intercept	0.51393	(0.1001, 0.9277)	0.012
Corn silage in diet	-0.32844	(-0.6008, -0.0560)	0.004
Multiple-dose studies	-0.53848	(-0.8184, -0.2586)	<0.001
Dose of monensin, mg/kg DM	-0.03086	(-0.0420, -0.0197)	<0.001
ADG			
Intercept	1.65019	(0.9639, 2.336)	<0.001
U.S. origin studies	-0.71498	(-1.0554, -0.3745)	<0.001
Pen studies (vs. individual)	0.52098	(0.232, 0.810)	<0.001
Control cattle ADG	-0.4746	(-0.846, -0.103)	0.012
Dose of monensin, mg/kg DM	-0.02179	(-0.0308, -0.0128)	<0.001

¹TMR = total mixed ration.

DISCUSSION

The impact of monensin on improving FE was not surprising and was verified by the finding of reduced DMI and improved ADG with monensin. Given the diversity of studies, the presence of significant heterogeneity in response for FE was expected. Based on the meta-regression analysis, this was largely explained by differences in study design, delivery of monensin, dose, and diet. Cattle fed in feedlots would be expected to receive a more consistent concentration of monensin when delivered in a TMR. However, topdressing with liquid or grain on top of feed in a pen setting would likely result in variable concentration of monensin by individual animals. Stratifying on this factor (TMR delivery) eliminated the heterogeneity for the TMR group (data not presented). Similarly, studies that involved multiple doses of monensin showed less heterogeneity and single-dose studies showed more. This might be explained by the fact that many single-dose studies had objectives to investigate other factors influencing FE (e.g., days on feed, diet, and sex of cattle), whereas investigating dose effects of monensin were frequently the main objective of multidose studies. Dose of monensin showed a lin-

Table 4. Stratified meta-analysis of feed efficiency in growing and finishing cattle, across dose ranges of monensin in feed

Monensin dose range, mg/kg feed 100% DM	No. trials	Weighted mean difference for feed efficiency, ES		
		for feed	for feed	ES
<16	30	-0.532	-0.938	0.0001
16-30	36	-0.628	-0.817	0.0001
31-44	56	-0.455	-0.989	0.0001
>44	8	-1.153	-1.280	0.0001

¹ES is a standardized z-value to statistically compare treatment with control differences between studies.

Table 5. Stratified meta-analysis of monensin effects on feed efficiency in growing and finishing cattle, across 4 decades of research (1970s to 2000s)

Decade, year strata for studies	No. trials	Mean monensin dose, mg/kg feed	Weighted mean difference for feed efficiency, kg feed/kg BW gain	Control mean feed efficiency, kg feed/kg BW gain	Change in feed efficiency, %	ES for feed efficiency ¹	ES <i>P</i> -value
1970s	85	26	-0.715	8.79	+ 8.1	-1.0279	0.0001
1980s	21	31.7	-0.539	8.39	+6.4	-1.1591	0.0001
1990s	13	33.9	-0.148	6.39	+2.3	-0.4505	0.0001
2000+	11	32.3	-0.229	6.38	+3.5	-0.9498	0.0001

¹Effect size (ES) is a standardized z-value to statistically compare treatment with control differences between studies.

ear effect of greater FE observed with increasing dose in mg/kg feed of ration DM. The dose range in these data was 3 to 98 mg/kg feed, with a mean of 28.1 mg/kg feed. Because there were fewer studies at the larger doses of monensin, meta-regression was conducted, excluding the 2 largest doses (61 and 98 mg/kg feed) and 8 largest doses (>44 mg/kg feed). A linear effect of dose was still identified with a slightly increased regression coefficient (0.011 and 0.014 vs. 0.009), with corresponding significance values of $P = 0.09$ and $P = 0.06$ for the 2 largest doses and 8 largest doses removed, respectively, compared with $P = 0.04$ for the full data set analysis. The linear dose effect was much more apparent within TMR studies or within multidose studies. This seems to make sense because the multidose studies were largely designed to measure dose titration of effect on FE. Also, non-TMR studies would likely deliver variable dose concentrations in DM depending on individual animal intake, whereas TMR studies have a fixed concentration of monensin. Corn silage in the diet may have simply

served as a marker for identifying studies that used finishing diets vs. growing diets. As such, the greater ES estimates of FE in corn silage-based diets would seem to make sense. Effects of monensin on these parameters are most likely driven by increased propionate supply to the liver. In greater forage-based, grower-type diets, one might hypothesize greater effects on ADG but perhaps less effect on reducing DMI. However, in finishing diets, already greater in energy concentration, the increased propionate created by monensin might have less effect on gain and more effect on reducing DMI. It would have been useful to explore potential dietary interactions of monensin on FE in greater detail; however, the data used in this paper span nearly 40 yr and there was an inconsistent reporting of useable feed data to be able to reconstruct diets with any degree of reliability.

There were several variables that were significant influencers of the effects of monensin on FE in the univariate regression but did not remain significant in the final regression model. These included decade of study ($P = 0.032$), days on feed ($P = 0.009$), control FE ($P = 0.022$), and starting BW ($P = 0.022$). Some other variables that were explored for effects of monensin on FE but were not found to have significant influence included: use of tylosin in the diet, use of either corn or barley as the primary grain, forage:concentrate ratio, and breed (British vs. other). Despite decade not remaining in the final model, the impact of monensin improving FE has decreased over the past 40 yr from an 8.1% improvement in the 1970s to a 2.3 to 3.5% improvement in the 1990s to 2000s, respectively (Table 5), as FE has improved from 8.79 kg of feed per kilogram of BW gain to the most recent (2000s) value of 6.39 kg of feed per kilogram of BW gain. One can assume from this that management factors (unmeasured in this meta-analysis) are likely the reason for this dramatic improvement in FE of 27%. Furthermore, although the average effect of monensin on FE across all studies evaluated in this analysis was found to be 6.4%, current management factors have led to vast improvements in FE values in modern feedlots. Thus, the expectation for monensin in these management systems would be to improve FE by 2.5 to

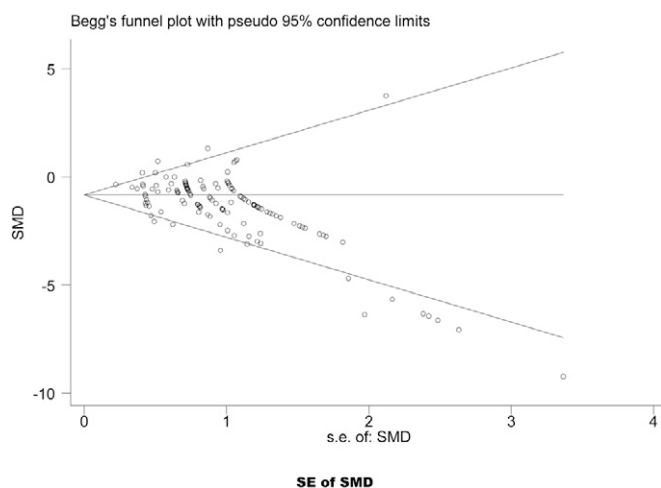


Figure 2. Funnel plot of monensin effect on feed efficiency in growing and finishing cattle, for assessing publication bias. SMD = standardized mean difference. The relative size of the circles represents the relative weighting of the study with the larger circles representing greater weight. The horizontal line represents the overall effect size estimate. The 2 diagonal lines indicate an estimate of the 95% confidence interval of the effect size estimate. Interpretation: Publication bias may be present if there is an unequal number of studies (particularly, smaller weight studies) on 1 side of the horizontal line.

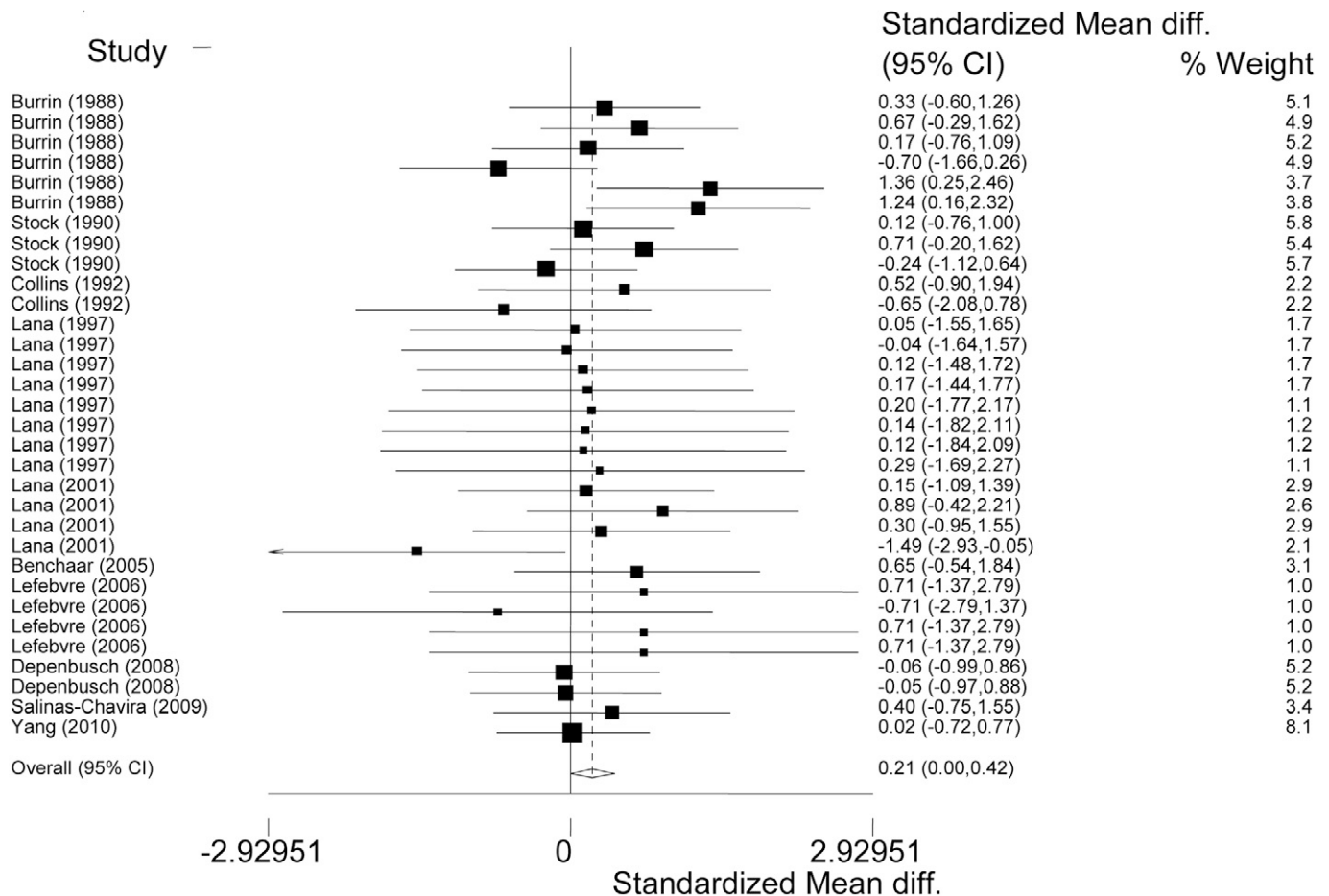


Figure 3. Forest plot of the effect of monensin on feed efficiency in growing and finishing cattle, measured in unit of gain per unit of feed intake. Study refers to the first author and year of the publication. Standardized mean diff. (difference) was standardized using the z-statistic. Thus, points to the left of the line represent a reduction in the trait and points to the right of the line indicate an increase in the variable. Each square represents the mean effect size for that study. The upper and lower limit of the line connected to the square represents the upper and lower 95% confidence interval (CI) for the effect size. The size of the square reflects the relative weighting of the study to the overall effect size estimate, with larger squares representing greater weight. The dotted vertical line represents the overall effect size estimate. The diamond at the bottom represents the 95% CI for the overall estimate. The solid vertical line represents a mean difference of 0 or no effect.

3.5%, depending on dose and dietary energy.

In the meta-regressions of monensin ES for DMI and ADG, trials with corn silage diets showed a greater ES for monensin on reducing DMI but was not a significant factor in the regression model for ADG. Other factors that influenced DMI included study design factors (multidose vs. single-dose studies) and dose. The effect on DMI was greater in multidose studies and the effect of monensin on reducing DMI increased with increasing dose.

Factors influencing ES of monensin on ADG included study location (United States vs. other countries), ADG in the control group, type of animal feeding (pen vs. individual), and dose. Studies conducted in the United States showed less of an effect on improving ADG compared with non-U.S. studies, but all studies showed considerable heterogeneity. Studies conducted with individual vs. pen feeding situations showed increased heterogeneity and reduced effect on ADG. This may be a function of environmental impacts, such as tethering and adapting to Calan headgates, which may restrict po-

tential ADG response. Studies with greater ADG in control animals showed lesser ADG response with monensin. This finding is consistent with the expectation that monensin would give greater ADG responses on higher forage, lower grain diets. Greater doses of monensin were associated with lesser impacts on ADG.

Conclusions

This meta-analysis shows that monensin improves FE in growing and finishing cattle, both in studies reporting feed:gain ratio and studies reporting gain:feed ratio. Monensin reduces feed:BW gain by 0.53 kg of feed/kg BW gain. Monensin reduced DMI by 0.27 kg and improved ADG by 0.029 kg/d. The average concentration of monensin in feed across all studies was 28.1 mg/kg feed. This was in a data set with average daily DMI of 8.6 kg, ADG 1.15 kg, and average FE of 8.33. Thus, FE is improved by 6.4% (but only 2.5 to 3.5% in the last 2 decades). Linear effects of monensin dose in feed were

found for FE (greater dose improving efficiency), DMI (greater dose reducing DMI), and ADG (greater dose reducing ADG response).

LITERATURE CITED

- Arelovich, H. M., H. E. Laborde, M. I. Amela, M. B., Torrea, and M. F., Martinez. 2008. Effects of dietary addition of zinc and (or) monensin on performance, rumen fermentation and digesta kinetics in beef cattle. *Sp. J. Agric. Res.* 6:362–372.
- Baird, G. D., M. A. Lomax, H. W. Symonds, and S. R. Shaw. 1980. Net hepatic and splanchnic metabolism of lactate, pyruvate and propionate in dairy cows in vivo in relation to lactation and nutrient supply. *Biochem. J.* 186:47–57.
- Beacom, S. E., Z. Mir, G. O. Korsrud, W. D. G. Yates, and J. D. MacNeil. 1988. Effect of the feed additives chlortetracycline, monensin and lasalocid on feedlot performance of finishing cattle, liver lesions and tissue levels of chlortetracycline. *Can. J. Anim. Sci.* 68:1131–1141.
- Begg, C., and M. Manumdar. 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50:1088–1101.
- Benchaar, C., J. L. Duynisveld, and E. Charmley. 2005. Effects of monensin and increasing dose levels of a mixture of essential oil compounds on intake digestion and growth performance of beef cattle. *Can. J. Anim. Sci.* 86:91–96.
- Berger, L. L., S. C. Ricke, and G. C. Fahey. 1981. Comparison of two forms and two levels of lasalocid with monensin on feedlot cattle performance. *J. Anim. Sci.* 53:1440–1445.
- Boling, J. A., N. W. Bradley, and L. D. Campbell. 1977. Monensin levels for growing and finishing steers. *J. Anim. Sci.* 44:867–871.
- Burrin, D. G., R. A. Stock, and R. A. Britton. 1988. Monensin level during grain adaptation and finishing performance in cattle. *J. Anim. Sci.* 66:513–521.
- Byers, F. M. 1980. Determining effects of monensin on energy value of corn silage diets for beef cattle by linear or semi-log methods. *J. Anim. Sci.* 51:158–169.
- Collins, R. M., and R. H. Pritchard. 1992. Alternate day supplementation of corn stalk diets with soybean meal or corn gluten meal fed to ruminants. *J. Anim. Sci.* 70:3899–3908.
- Dart, R. M., J. A. Boling, and N. W. Bradley. 1978. Supplemental protein withdrawal and monensin in corn silage diets of finishing steers. *J. Anim. Sci.* 46:345–349.
- Depenbusch, B. E., J. S. Drouillard, E. R. Loe, J. J. Higgins, M. E. Corrigan, and M. J. Quinn. 2008. Efficacy of monensin and tylosin in finishing diets based on steam-flaked corn with and without corn wet distillers grains with soluble. *J. Anim. Sci.* 86:2270–2276.
- Dohoo, I. R., K. Leslie, L. DesCoteaux, A. Fredeen, P. Dowling, A. Preston, and W. Shewfelt. 2003a. A meta-analysis review of the effects of rBST. 1. Methodology and effects on production and nutrition related parameters. *Can. J. Vet. Res.* 67:241–251.
- Dohoo, I., W. Martin, and H. Stryhn. 2003b. Meta-analysis. Page 706 in *Veterinary Epidemiologic Research*. AVC Inc., Charlottetown, PEI, Canada.
- Duffield, T. F., Rabiee, A. R., and Lean, I. R. 2008a. A meta-analysis of the impact of monensin in lactating dairy cattle. Part 3. Health and reproduction. *J. Dairy Sci.* 91:2328–2341.
- Duffield, T. F., A. R. Rabiee, and I. R. Lean. 2008b. A meta-analysis of the impact of monensin in lactating dairy cattle. Part 2. Production effects. *J. Dairy Sci.* 91:1347–1360.
- Duffield, T. F., A. R. Rabiee, and I. R. Lean. 2008c. A meta-analysis of the impact of monensin in lactating dairy cattle. Part 1. Metabolic effects. *J. Dairy Sci.* 91:1334–1336.
- Egger, M., G. Davey Smith, and D. Altman. 2001. Systematic reviews in health care. Meta-analysis in context. BMJ Books, London.
- Egger, M., G. Davey Smith, M. Schneider, and C. Minder. 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–634.
- Fontenot, J. P., and H. M. Huchette. 1993. Feeding sorbitol alone or in combination with monensin to finishing cattle. *J. Anim. Sci.* 71:545–551.
- Garrett, J. E., F. Guessous, and A. Eddebbarh. 1989. Utilization of sugar beet molasses and monensin for finishing dairy bullocks. *Anim. Feed. Sci. Tech.* 25:11–21.
- Gibb, D. J., S. M. S. Moustafa, R. D. Wiedmeier, and T. A. McAllister. 2001. Effect of salinomycin or monensin on performance and feeding behaviour of cattle fed wheat- or barley-based diets. *Can. J. Anim. Sci.* 81:253–261.
- Haney, M. and M. Hoehn. 1967. Monensin, a new biologically active compound. I: Discovery and isolation. *J. Antimicrob. Chemother.* 349:349.
- Higgins, J. P. T., S. G. Thompson, J. J. Deeks, and D. G. Altman. 2003. Measuring inconsistency in meta-analyses. *BMJ* 327:557–560.
- Horton, G. M. J. 1984. Performance of growing steers fed lasalocid or monensin in a high silage diet. *Nutr. Rep. Intl.* 29:1427–1435.
- Horton, G. M. J., J. G. Manns, H. H. Nicholson, and G. A. Harrop. 1981. Behavioral activity, serum progesterone and feedlot performance of heifers fed melengesterol acetate and monensin. *Can. J. Anim. Sci.* 61:695–702.
- Johnson, R. J., M. L. Herlugson, L. B. Ojikutu, G. Cordova, I. A. Dyer, P. Zimmer, and R. DeLay. 1979. Effect of avoparcin and monensin on feedlot performance of beef cattle. *J. Anim. Sci.* 48:1338–1342.
- Lana, R. de P., and D. G. Fox. 2001. Interactions between monensin sodium, oil and soybean nitrogen sources in the performance of aberdeen angus bulls in confinement. *Rev. Bras. Zootec.* 30:247–253.
- Lana, R. P., D. G. Fox, J. B. Russell, and T. C. Perry. 1997. Influence of monensin on Holstein steers fed high-concentrate diets containing soybean meal or urea. *J. Anim. Sci.* 75:2571–2579.
- Lean, I. J., P. J. DeGaris, D. M. McNeal, and E. Block. 2006. Hypocalcemia in dairy cows: Meta-analysis and dietary cation anion difference theory revisited. *J. Dairy Sci.* 89:669–684.
- Lean, I. J., A. R. Rabiee, T. F. Duffield, and I. R. Dohoo. 2009. Invited review: Use of meta-analysis in animal health and reproduction: Methods and applications. *J. Dairy Sci.* 92:3545–3565.
- Lefebvre, B., F. Malouin, G. Roy, K. Guiguere, and M. Diarra. 2006. Growth performance and shedding of some pathogenic bacteria in feedlot cattle treated with different growth-promoting agents. *J. Food Prot.* 69:1256–1264.
- Loerch, S. C. 1990. Effects of feeding growing cattle high-concentrate diets at a restricted intake on feedlot performance. *J. Anim. Sci.* 68:3086–3095.
- Lomax, M. A., G. D. Baird, C. B. Mallinson, and H. W. Symonds. 1979. Differences between lactating and non-lactating dairy cows in concentration and secretion rates of insulin. *Biochem. J.* 180:281–289.
- Mederos, A., L. Waddell, J. Sanchez, D. Kelton, A. S. Peregrine, P. Menzies, J. Vaneeuwen, and A. Rajic. 2012. A systematic review-meta-analysis of primary research investigating the effect of selected alternative treatments on gastrointestinal nematodes in sheep under field conditions. *Prev. Vet. Med.* 104:1–14.
- Mowat, D. N., J. W. Wilton, and J. G. Buchanan-Smith. 1977. Monensin fed to growing and finishing cattle. *Can. J. Anim. Sci.*

- 57:769–773.
- Pendlum, L. C., J. A. Boling, and N. W. Bradley. 1980. Nitrogen sources and monensin levels for growing steers fed corn silage. *J. Anim. Sci.* 50:29–34.
- Perry, T. W., D. R. Shields, W. J. Dunn, and M. T. Mohler. 1983. Protein levels and monensin for growing and finishing steers. *J. Anim. Sci.* 57:1067–1076.
- Prange, R. W., C. L. Davis, and J. H. Clark. 1978. Propionate production in the rumen of Holstein steers fed either a control of monensin supplemented diet. *J. Anim. Sci.* 46:1120–124.
- Raun, A. P., C. O. Cooley, E. L. Potter, R. P. Rathmacher, and L. F. Richardson. 1976. Effect of monensin on feed efficiency of feedlot cattle. *J. Anim. Sci.* 43:670–677.
- Richardson L. F., A. P. Raun, E. L. Potter, C. O. Cooley, and R. P. Rathmacher. 1976. Effect of monensin on rumen fermentation in vitro and in vivo. *J. Anim. Sci.* 43:657.
- Rosenthal, R. 1979. The “file drawer problem” and tolerance for null results *Psychol. B.* 86:638–641.
- Salinas-Chavira, J., J. Lenin, E. Ponce, U. Sanchez, N. Torrentera, and R.A. Zinn. 2009. Comparative effects of virginiamycin supplementation on characteristics of growth-performance, dietary energetic, and digestion of calf-fed Holstein steers. *J. Anim. Sci.* 87:4101–4108.
- Schelling, G. 1984. Monensin mode of action in the rumen. *J. Anim. Sci.* 58:1518–1527.
- Steele, J. D., D. L. Lalman, J. G. Kirkpatrick, and R. P. Wettemann. 2001. Performance of beef heifers fed ad libitum soybean hulls and hay with or without a monensin-containing mineral supplement. *Okla. Agric. Exp. Sta. Res. Rep.*
- Steen, W. W., N. Gay, J. A. Boling, N. W. Bradley, J. W. McCormick, and L. C. Pendulum. 1978. Effect of monensin on performance and plasma metabolites in growing-finishing steers. *J. Anim. Sci.* 46:350–355.
- Stock, R. A., S. B. Laudert, W. W. Stroup, E. M. Larson, J. C. Parrott, and R. A. Britton. 1995. Effect of monensin and monensin and tylosin combination on feed intake variation of feedlot steers. *J. Anim. Sci.* 73:39–44.
- Stock, R. A., M. H. Sindt, J. C. Parrott, and F. K. Goedecken. 1990. Effects of grain type, roughage level and monensin level on finishing cattle performance. *J. Anim. Sci.* 68: 3441–3455.
- Thonney, M. L., E. K. Heide, D. J. Duhaime, R. J. Hand, and D. J. Perosio. 1981. Growth, feed efficiency and metabolite concentrations of cattle fed high forage diets with lasalocid or monensin supplements. *J. Anim. Sci.* 52:427–433.
- Utley, P. R., R. E. Hellwig, W. C. McCormick, and J. L. Butler. 1982. The effect of treating coastal bermudagrass pellets. *Can. J. Anim. Sci.* 62:499–505.
- Utley, P. R., G. L. Newton, R. J. Ritter, and W. C. McCormick. 1976. Effects of feeding monensin in combination with zeranol and testosterone-estradiol implants for growing and finishing heifers. *J. Anim. Sci.* 42:754–760.
- Wagner, D. G., and S. C. Ostlie. 1981. Finishing heifers on high vs low roughage feedlot diets with and without monensin. Pages in 189–192 in *Okla. Agric. Exp. Sta. Res. Rep.*
- Wang, Y., T. A. McAllister, J. Baah, R. Wilde, K. A. Beauchemin, L. M. Rode, J. A. Shellford, G. M. Kamande, and K. J. Cheng. 2003. Effects of Tween 80 on in vitro fermentation of silages and interactive effects of Tween 80, monensin and exogenous fibrolytic enzymes on growth performance by feedlot cattle. *Asian-Aust. J. Anim. Sci.* 16:968–978.
- Yang, W. Z., B. N. Ametaj, C. Benchaar, M. L. He, and K. A. Beauchemin. 2010. Cinnamaldehyde in feedlot cattle diets: intake, growth performance, carcass characteristics, and blood metabolites. *J. Anim. Sci.* 88:1082–1092.
- Zinn, R. A. 1988. Comparative feeding value of supplemental fat in finishing diets for feedlot steers supplemented with and without monensin. *J. Anim. Sci.* 66:213–227.
- Zinn, R. A., and J. L. Borques. 1993. Influence of sodium bicarbonate and monensin on utilization of a fat-supplemented high-energy growing-finishing diet by feedlot steers. *J. Anim. Sci.* 71:18–25.
- Zinn, R. A., A. Plasencia, and R. Barajas. 1994. Interaction of forage level and monensin in diets for feedlot cattle on growth performance and digestive function. *J. Anim. Sci.* 72:2209–2215.