Ionophores for growing and finishing beef cattle: History, benefits, challenges, and global warming

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Take-Home message

Monensin, an ionophore feed additive, initially was approved by the FDA in 1975 to improve the feed to gain ratio of cattle that today is fed to most feedlot cattle in the US.
Monensin alters the relative population or activity of microbes within the rumen.
Feed efficiency benefits from monensin feeding are correlated with an increased ruminal yield of propionate and reduced yield of methane, a global warming waste gas produced during ruminal fermentation.

At 40 g per ton of feed, added monensin decreases the incidence of digestive and metabolic disorders of feedlot cattle by inhibiting certain deleterious of ruminal microbes; this in turn allows beneficial microbes to thrive.

At a low dietary concentration (5 g per ton) monensin increases rate of gain, perhaps due to greater ruminal escape of dietary protein, but concentrations above 20 g per ton reduce feed intake, likely due to an increased ruminal energy yield.

Compared with the feed to gain improvements reported with monensin 30 years ago, benefits today from feeding monensin appear smaller, likely due to changes in the nutrient content of diets, more extensive grain processing, and changes in methods used to express feed efficiency.

Because including monensin in ruminant diets can improve feed efficiency by up to 5 percent while decreasing ruminal yield of methane substantially, use of this feed additive has an economic advantage for livestock producers while often reducing the environmental impact of ruminant production by reducing the yield of a greenhouse gas produced during ruminal fermentation.

Abstract

Ionophores are included in the diets being fed to 92% of the receiving cattle and 97% of the finishing cattle based on a survey of feedlot consultants in the US and Canada (Samuelson et al., 2016). That survey indicated that among the ionophores that are fed to receiving cattle, monensin had 77% of the market share with 22% going to lasalocid; for finishing cattle, monensin had the entire share of the US market among the consultants surveyed.

Monensin falls into a class of lipid-soluble chemicals called ionophores. By transporting ions through cell membranes of microbes, ionophores inhibit survival of certain bacterial strains and coccidia. Through altering the relative populations or the metabolism of bacteria in the digestive tract of ruminants, most ionophores alter the fermentation end-products; this shift can alter the rate and/or efficiency of production as well as the health of ruminants. Classified as drugs for livestock, the registration, distribution, and use of ionophores is regulated by the Food and Drug Administration (FDA). All ionophores marketed in the US are derived from Streptomyces bacteria but the specific strain will differ among ionophores (cinnamonensin for monensin first approved first marketed in 1975 as Rumensin by Elanco; lasaliensis for lasalocid first marketed in 1982 as Bovatec by Zoetis; Eurocidicus for laidlomycin first marketed in 1993 as Cattylst by Zoetis). Because the ions transported differs among ionophores (Na for monensin; K for

salinomycin; mono- and divalent ions for lasalocid), ruminal effects and performance responses will differ. This presentation will discuss the performance and ruminal effects primarily for monensin.

Because ionophores, declared to be safe and effective by the FDA, can increase the efficiency of converting feed energy into ruminant products (milk and meat) while often decreasing methane production in the rumen, worldwide addition of ionophores to ruminant diets should have beneficial effects not only on ruminant productivity but also for reducing emission of methane, a gas that contributes to the global warming of our fragile atmosphere.

Discovery. Animal scientists from Elanco, the animal research arm of Eli Lilly located in Greenfield, IN, assisted by Dr. Werner Bergen of Michigan State, devised a process to screen compounds for their ability to alter the ratios among the major volatile fatty acids (VFA) produced during ruminal fermentation. This screening was based on the concept summarized by Wolin (1960) that the carbon and energy available from fermentation of glucose (derived from either starch or cellulose) were converted to and retained within three major VFA - acetate (2 carbons), propionate (3 carbons) and butyrate (4 carbons) in addition to one primary waste product – methane (one carbon). The fraction of glucose energy that remains in these three VFA that is absorbed and metabolized by ruminants differs markedly. Of the energy initially present in glucose, acetate retains only 62% of the energy, propionate retains 109%, and butyrate retains 91%; all the energy transferred to methane is lost as gas when ruminants eructate (belch). The extra-caloric efficiency (109%) for propionate is the result of transfer of excess hydrogen electrons from acetate and butyrate to propionate.

To screen various feed additives, drugs, herbs, and spices for their impact on the ratios of VFA produced during fermentation in the rumen, the Elanco group added numerous compounds at various concentrations individually or in combination to rumen fluid fermenting in tubes; propionate concentrations or the propionate to acetate ratios were measured after the samples had fermented for hours or days. Compounds that increased the propionate to acetate ratio were re-tested and later were dosed into the rumen of cattle equipped with rumen cannulas to check if the response observed in vitro could be replicated within the rumen of live ruminants. One of the compounds found to increase the proportion of propionate proportion by this screening procedure was the widely used poultry coccidiostat already being produced and marketed by Eli Lilly that had been approved for poultry in 1991 by the FDA, a product called Co-Ban. Already having experience with this compound, its safety data, and the capacity to produce Co-Ban and analyze its concentrations in mixed diets, the research team began to pursue an FDA clearance for feeding this compound to feedlot cattle. The initial FDA approval for ruminants in 1975 was for increasing feed efficiency of feedlot cattle when included in ruminant diets within the range of 5 to 30 mg monensin sodium per ton of feed (Elanco, 1975). Later research (Nagaraja et al., 1981; Branine and Galyean, 1990) and field observations revealed that the incidence of digestive disorders of feedlot cattle was reduced by feeding up to 40 mg per ton of feed; monensin subsequently was approved at this level. Later trials with lactating dairy cows detected improvements in milk production efficiency (McGuffey et al., 2001); monensin subsequently was approved for including in diets for lactating dairy cows.

To verify that feeding monensin could improve performance of growing and finishing feedlot cattle, the effects of supplemental monensin on rate and efficiency of gain as well as health, ruminal VFA concentrations, some carcass characteristics, and meat quality indicators were tested in 19 individual feeding trials at various locations throughout the US (Elanco, 1975). In these trials, diverse feedlot diets were supplemented with various monensin concentrations (usually 0, 5, 10, 15, 20, and 30 g/ton of feed). The animal performance data from those feedlot trials were re-analyzed for this presentation. Although Elanco coordinated and analyzed the trial data, these feeding trials were conducted across the US using local feeds; cattle were fed under the supervision of animal science research and extension personnel. Needed health information was gathered locally, and carcass data were collected at various packing plants. Coordination with animal scientists familiarized animal science research and extension personnel and graduate students across the country with monensin and with skilled Elanco representatives. This working relationship enhanced the trust between university personnel and Elanco that proved useful to achieve widespread and acceptance of monensin by commercial feedlot operators and owners once it received FDA approval. Using a similar approach, expansion of the clearance of monensin at higher concentration than initially tested, and clearance for feeding monensin to lactating cows helped to move

product testing smoothly through the research and testing channels needed for FDA clearance, and accelerated the commercial acceptance of monensin among consultants and ruminant livestock producers within the U.S.

Impact of monensin on efficiency of production by lactating dairy cows and feedlot cattle

Two meta-analyses concerning efficacy of monensin were published recently. Meta-analysis summarizes production responses across numerous studies – in this case feeding and research trials 1) with lactating dairy cows and 2) on performance of growing and finishing beef cattle. Responses from dozens of individual trials where pens or groups of animals had been fed a control diet or that identical diet with monensin added were compiled and merged so mean response and variance of that response could be tested statistically. By meta-analysis, consistency of the responses across trials, diets, and locations is tested with much greater power and across a broader range of diets and locations than is detected in individual trials where the range in diets and the number of pens of animals per treatment is limited.

In trials with lactating cows (Duffield et al., 2008), responses to addition of monensin to the diet in 71 separate trials were merged. Measurements and mean responses indicated that daily dry matter intake was decreased an average of 2.3% while daily milk yield increased 2.3% by adding monensin. Percentages of both fat and protein in milk decreased with feeding of monensin, but daily yield of protein was increased by 1.9% due to the increase in daily milk production. Body condition scores and weight gains by cows also were increased indicating that cows receiving monensin were obtaining more net energy per unit of feed than cows fed the identical diet but with no monensin added.

For growing-finishing beef cattle, responses to supplementing diets with monensin were estimated based on meta-analysis of 40 peer-reviewed articles and 24 additional trial reports published between 1975 and 2012 (Duffield et al., 2012). As noted with lactating cows, daily dry matter intake was reduced (3.2%) while daily liveweight gain was increased (2.3%); this led to a mean reduction in the amount of feed needed per unit of gain of 6.4% when monensin was included in the diet across all the levels and years that monensin was fed (Table 1). Recalculated from the initial trials with monensin, the feed to gain ratio was decreased by 5.3, 5.2, 6.8 or 7.5% by adding 5, 10, 20, or 30 g per ton of feed (Table 2). These efficiency responses by both lactating cows and feedlot cattle clearly demonstrate a consistency in production responses and the potential economic advantages of including monensin in a wide variety of diets for cattle.

Table 1. Responses of growing/finishing cattle to monensin supplementation[a]

Measurement	Mean response	Change, %	Response range	Significance
Dry matter intake, kg/d	-0.268	-3.1	-0.32 to -.21	0.001
Average daily gain, kg/d	-0.0291	2.5	.019 to 0.040	0.001
Gain/feed	0.0021	1.3	-.0001 to .0041	0.048
Feed/gain	-0.53	-6.4	-0.61 to -0.45	0.001

[a] From Duffield et al., 2012.

With feedlot cattle, the reduced feed to gain ratio of the Elanco (1975) report tended to be linear with a slightly greater benefit from higher dietary concentrations of monensin but numerically matching the linear and quadratic direction of response noted in re-analysis of the initial trials with monensin (Table 2). This change is attributable to two factors: a linear decrease in feed intake plus a quadratic response in daily gain in which cattle fed 5 mg monensin made significantly faster gains than cattle fed either 0 or 30 g monensin per ton (Table 2). In the meta-analysis of Duffield et al. (2012), significant advantages in the feed to gain ratio were detected across each of the decades that trial results were published. However, the numeric benefit in the feed to gain ratio decreased with decade from 8.1% in the 1970's to 6.4 in the 1980's to a plateau in the 1990's and 2000's of 2.3% and 3.5%, respectively. Because microbial

resistance to monensin is not anticipated as it interferes with the energy conversion process in microbes, this decrease presumably reflects numerous dietary and management changes over time that also have decreased the feed to gain ratio. These changes would include the use of higher concentrate diets and more extensive grain processing, both of which increase the ruminal propionate proportion and decrease the feed to gain ratio, slick bunk management to stabilize dry matter intake and reduce the variation in feed intake from day-to-day that unchecked can lead to acidosis, and higher dietary protein levels. Reexamination of the 1975 data set revealed that feed intakes therein probably were expressed based on wet weight, not feed dry matter, and that final weights presumably were live weights. not adjusted for differences in digestive tract fill based on carcass weights and dressing percentage. Among the trials from 1975, those with the highest feed to gain advantages typically contained substantial amounts of moisture (from silages) that invariably lead to increased fill of the digestive tract when cattle are marketed. In contrast research reports published since 1990 generally express efficiency on feed dry matter basis, preferably as gain to feed rather than feed to gain, (to avoid infinite values when gain is zero), and final weights are calculated from carcass weights to correct for differences in digestive tract fill. Finally, the feed to gain ratio for the control diets in trials from the 1970's averaged 8.79; in the 2000's, it averaged 6.38, a 27% reduction. Increasing speed by a given percentage takes less additional energy if the starting speed is low than if one is travelling at a high rate of speed. The difference in the baseline feed efficiency rather than a reduced biopotency of monensin most likely explains the lower feed to gain ratios for monensin in the more recent decades; this points out the need to scrupulously examine data from the individual trials that are being merged for meta-analysis.

Table 2. Influence of monensin level on feedlot cattle performance and shape of the response

Monensin, g/ton feed	0		5		10		20		30		Linear	Quadratic
Dry matter intake/gain	7.58	a	7.15	b	7.16	b	6.98	b	6.97	b	0.01	0.01
Decrease in feed:gain ratio, %	0	a	5.71	b	5.29	b	7.31	b	7.36	b	0.01	0.10
Dry matter intake, lb/d	17.42	a	17.01	ab	16.79	ab	16.18	c	15.73	c	0.01	0.55
Decrease in DMI, %	0	a	2.26	ab	3.51	b	6.79	c	9.34	c	0.01	0.55
Daily gain, lb.	2.33	b	2.41	a	2.37	ab	2.34	abc	2.28	b	0.02	0.05
Propionate, % of VFA	40.6	b	44.1	a	43.1	a	44.3	a	44.9	a	0.01	0.16
Increase in propionate, %	0	b	10.56	a	7.37	a	11.13	a	12.85	a	0.01	0.21
Diet ME, Mcal/kg DM	2.78	c	2.87	b	2.87	b	2.92	ab	2.94	a	0.01	0.05
Increase in ME, %	0	c	3.04	b	3.22	b	5.16	a	6.02	a	0.01	0.44

[a,b,c] Means in a row sharing a superscript do not differ ($P < 0.05$).

Various indicators have been used to reflect efficiency of production. These include gain to feed ratio, feed to gain ratio, and metabolizable or net energy content of a diet. Gain to feed ratio is the index most

useful for calculating economic benefit based merely from the cost of feed, but gain to feed normally increases when feed intake increases and thereby is responding to factors beyond energy content of the diet. Secondly, both feed to gain and gain to feed are imprecise indicators of energy content of a feed; this is because a substantial but variable proportion of feed energy consumed is used for maintenance whereas gain in the equation reflects only the portion of energy that has been retained by the animal, not the total amount of energy used by an animal for maintenance plus gain. Like an idling car, animals expend energy even if they are not gaining weight or are losing weight. Feed to gain ratios also respond in a surprising and peculiar fashion as rate of gain reaches zero or animals lose weight. With zero weight gain, one is dividing feed supply by 0; division by 0 results in infinite values. In addition, the variability in the feed to gain ratio increases markedly as gain decreases. Gain to feed ratios avoid these two problems. However, as an indicator of energy value of a diet, metabolizable energy (ME) and net energy (NE) values that can be calculated directly from ME can be calculated directly from animal performance measurements (feed intake, mean weight, and rate of gain) are preferable; these automatically adjust for differences in both feed intake and in maintenance requirements and thereby are preferable as an index of the energy value of a diet that has been obtained by growing-finishing animals. The ME value of a diet can be used to predict performance for starting cattle of a specific initial weight from predicted feed intake whereas feed to gain or gain to feed ratios, because they vary with starting weight and intake, cannot be used to predict performance. Feed additives or management factors can improve the feed to gain ratio or the gain to feed ratio in two ways: by altering feed intake or by altering the energy value of a diet. Only when these two are separated can the response to the combination of two additives or management factors be predicted. For example, estrogenic implants and some additives decrease the feed to gain ratio primarily through increasing feed intake, ionophores and more extensive grain processing increase the feed to gain ratio by increasing the fraction of dietary energy that is available for an animal, and slick bunk management improves feed to gain ratio by decreasing feed waste. Knowledge of how a given management factor or feed additive alone is influencing productivity can help one determine whether multiple management or feed additive factors when combined will or will not prove beneficial to increase production economics.

Modes of action of monensin

Broader knowledge about the mode(s) of action of monensin should help producers and consultants to formulate diets that will avoid interactions that may reduce the benefits from feeding monensin. In 1984, Shelling as well as Bergen and Bates listed several points in rumen metabolism or function whereby monensin might improve energetic efficiency.

Modification of ruminal VFA production. During fermentation, glucose (derived from ruminal digestion of either starch or cellulose) is converted to acids. More of the energy from glucose is conserved if the fermentation products absorbed from the rumen are propionate, valerate, isovalerate, lactate, or ethanol rather than methane, hydrogen, acetate, butyrate, or isobutyrate. Because increases in ruminal propionate served as the original target for selecting monensin, one would expect that feeding monensin should increase the ruminal propionate concentration. As expected, when adjusted for trial differences, the proportion of ruminal propionate increased significantly from a mean of 39.2 to 42.6% of VFA as monensin level was increased from 0 to 5 g per ton; thereafter the propionate proportion plateaued (42.1, 43.3, and 44.0 at 10, 20, and 30 g per ton of feed, respectively) as shown in Table 2. To check if diet energy content was altered by monensin feeding, diet ME values were calculated based on cattle performance and feed intake from the multiple original feedlot trials (Elanco, 1975). Addition of monensin at all levels significantly increased ME content of the diet with addition at 5 and 10 g per ton of feed increasing diet ME values by 3.2% and addition at 20 and 30 g per ton increasing ME by 5.0 and 5.8%, respectively (Table 2). These results could be interpreted to suggest that the energy benefit from feeding monensin at a low level could be explained by an increased ruminal propionate concentration, but above 10 g per ton of feed, beneficial effects must be ascribed to other some other factor(s). This conflicts with the suggestion that an increased propionate proportion can fully explain the mode of action by which monensin improves production efficiency. Additional effects may relate to changes in the population of ruminal microbes or in animal behavior or physiology. As paternity lawyers always tell the accused, a casual relationship does not prove causality or cause and effect – that requires further evidence!

To estimate how much energy could be saved by altering the VFA ratio, relative concentrations of VFA in the rumen from the 19-trial feedlot summary from Elanco (1975) were employed to predict the energetic efficiency of converting glucose from either starch or cellulose to the mean ruminal VFA ratios measured (and presumably produced in the rumen) based on fermentation energy balance equations summarized by Wolin (1960). Energetic efficiency for converting glucose to VFA for the control diets averaged 81.7%; supplementation with 5, 10, 20, and 30 g monensin per ton of feed increased this value by 1.46, 1.46, 1.68 and 2.55%, respectively. With diets containing 65% carbohydrate of which 60% may be fermented in the rumen, this means that at 30 g monensin per ton, conservation of energy should be increased by less than 1% by this VFA change alone! This compares with the 9% improvement in feed to gain ratio noted with this level of supplementation. Some additional energy would be saved if the efficiency of metabolism of absorbed VFA is lower for acetate than for propionate or butyrate as some studies from the Rowett Institute in the 1960's suggest. Nevertheless, the observation that observed energetic efficiency of animal growth is greater than the calculated potential energy savings from a VFA change alone supports the suggestion that efficiency of converting sugars to VFA in the rumen cannot fully explain the performance benefits that have been measured with monensin supplementation. Indeed, the relationship of the feed to gain ratio to the molar propionate fraction from the Elanco summary of trials (Table 2) indicates that the addition of 5 or 10 g of monensin per ton of feed decreased the feed to gain ratio across individual studies but adding monensin above 10 g produced only limited responses in either the ruminal propionate or the feed to gain ratio.

Regardless of the level of butyrate produced, when the ruminal propionate concentration reaches 66% of the ruminal VFA, propionate would be absorbing all the excess reducing equivalents generated during production of acetate plus butyrate. Even below this level, some free hydrogen may be released if the supply of other hydrogen acceptors in the rumen (valerate, nitrate, sulfate, unsaturated fatty acids) is insufficient to use the excess hydrogen generated during acetate and butyrate production. Furthermore, ruminal propionate levels are considerably lower with diets that contain higher amounts of forage diets. This in turn indicates that the potential benefit from increasing propionate with monensin is much greater with high forage than with high concentrate diets merely because the starting propionate fraction is much lower with high forage diets. This in turn supports the NRC (2000) contention that the energetic benefit from feeding monensin should be greater for lower energy, higher fiber diets. As a result, they proposed that addition of monensin to a diet should decrease "*the net energy requirement for maintenance by 12% with no change in the net energy requirement for gain."* This conflicts with the BCNR (2015) conclusion that the "*dietary ME value should be increased by 2.3% for monensin"* which implies that the energetic benefit of monensin should increase as diet energy content increases. If maintenance requirements are reduced by monensin, benefits from monensin should be greater late during the finishing period when maintenance requirements are greater due to heavier body weights, not merely when higher forage levels are being fed.

As a sidelight, based on fermentation balance equations, the observed alterations in VFA concentrations and gas production indicate that adding 30 g of monensin per ton of feed should decrease total gas (carbon dioxide plus methane) production by 8.3% and methane production by 9% per unit of glucose fermented. Note that an increase in propionate decreases production of both methane and carbon dioxide. Surprisingly, some researchers have depended upon methane as a percentage of rumen headspace gases as an index of methane production. Such reasoning is faulty. If both total gas and methane are reduced in parallel as propionate concentration increases, methane as a fraction of total gas will NOT be altered even though total yield of methane in the rumen is reduced. Because in vivo measurements analyze total expired gases, not simply ruminal gases, such measurements also are imprecise estimates of the full ruminal change in methane production that can be achieved with inhibitors or methane production. Indeed, if the propionate fraction in absorbed VFA is increased, carbon dioxide production by tissues will be increased; that in turn will lead to an overestimate of the methane production per unit of total gas produced in the rumen plus ruminant tissues. Realistically, if milk or beef production is limited by supply of energy, methane yield must be calculated on a milk or beef production basis and thereby per unit of glucose fermented, not merely on the amount of methane produced by an animal. Feeding monensin alters two factors related to production of methane by ruminants, first by decreasing the yield of methane from the rumen by increasing the capture of reducing equivalents as propionate and secondly by increasing in gain per unit of feed beyond that attributable to propionate alone. Ultimately

this means that less feed is used and less methane should be generated per unit of milk or beef produced.

The degree that monensin will decrease methane production was measured directly in trials with steers by Vyas et al. (2018). They found that addition of monensin at 30 g per ton to a high forage diet (32% starch) based on barley silage reduced methane yield by 27% while increasing ruminal propionate concentration. But with a high concentrate diet (54% starch) based on barley grain, monensin failed to increase propionate, as it already was high, and failed to decrease methane production. This supports the concept that effects of monensin will vary with the level of forage and the potential for monensin to increase the ruminal yield of propionate.

Inhibition of methane and gas production with monensin has found applications beyond ruminants. Monensin often is added to swine waste storage units to prevent formation of foams and froths that can lead to gas explosions associated with methane accumulation. Similarly, ionophores depress the methane yield from ruminant livestock wastes, much to the chagrin of developers of bioenergy systems. The antimicrobial activity of monensin remains active temporarily in feces from cattle fed monensin and continues to reduce methane production from wastes produced by ruminants and nonruminants; this factor often is overlooked when calculating total methane production associated with livestock production.

Modification of the population of ruminal or gut microbes. Metabolic activity of monensin and other ionophores can been explained through its impact on ATP production by different species of bacteria. Through permitting ions to leak through the cell membranes, especially for Gram+ bacteria, their competitive survival in the rumen is reduced when compared with Gram– bacteria, whose thicker cell membrane helps protect them from ion leakage (Russell and Strobel, 1989). Many of the Gram+ ruminal bacteria are deleterious to rumen function and ruminant health. Bacteria inhibited by monensin include Streptococcus bovis and lactobacillus that often are involved with ruminal acidosis (Russell, 1987; Russell and Strobel, 1989) and certain methanobacteria that increase ruminal energy loss as methane and increase ruminal gas production that may increase the incidence of bloat. However, Eubacterium ruminantium, a fiber-digesting microbe, also is inhibited by monensin; this depresses ruminal fiber digestion when monensin is first fed (Slyter et al., 1992); fortunately, other fibrolytic species take up the slack to restore fiber digestibility within a week or two. Monensin resistant microbes, those that are favored by feeding monensin, include several bacterial strains responsible for starch digestion, the selenomonads, and the megasphera involved with deactivating lactic acid by converting it to propionate, thereby avoiding lactate accumulation that is responsible for acute ruminal acidosis (Nagaraja et al., 1981). Whether acting through an altered ruminal population or by altering surface tension of floating legume proteins, monensin feeding also reduces the incidence of frothy bloat associated with legumes and wheat pasture (Branine and Galyean, 1990). Finally, even at low concentrations, monensin acts as a coccidiocide to prevent coccidiosis that can be a serious health problem, particularly with newly received calves.

Altered site and extent of digestion. In the short term, ruminal and total tract digestion of NDF are reduced despite a decrease in ruminal liquid dilution rate (Lemenager et al., 1978) that would be expected to increase extent of fiber digestion. Adverse effects on activity of certain fiber-digesting microbes (Slyter et al., 1992) may be involved in short-term trials though following several weeks of adaptation to monensin, no depressions in NDF and ADF digestibility remain evident. No effects on total tract nutrient digestibility were detected in a summary of 6 trials in the Elanco (1975) report, but increases in total tract digestibility of dry matter, energy, and surprisingly, acid detergent lignin as well as decreases in ruminal starch digestion have been reported by others (Rust et al., 1978; Muntifering et al., 1981; Beede et al., 1986); increases in digestibility might be attributed to reduced ruminal mixing and a slight reduction in DMI, both of which should increase retention time for digestion either in the rumen or the large intestine.

The most striking change in site of digestion relates to protein. Ruminal ammonia concentrations typically are significantly lower when monensin is fed (Poos et al., 1979; Perry et al., 1983; Hanson and Klopfenstein, 1984; Faulkner et al., 1985; Rodriguez et al., 1986); yet total outflow of non-ammonia N from the rumen may not be changed (Poos et al., 1979; Zinn et al., 1994) despite a decreased yield of

microbial mass (by 8 to 33%). This decrease in microbial protein is compensated by increases in the duodenal supply of plant N due to greater ruminal escape of dietary protein. When calculated as a fraction of dietary plant portion, ruminal escape of dietary plant protein has been reported to be increased with feeding monensin at 30 g per ton from a mean of 9% to a mean of 55%. The decreases observed in both yield and efficiency of synthesis of microbial protein (Zinn et al., 1994) might be ascribed to a deficiency of peptides, amino acids, or amino acid derivatives that microbes otherwise could use but are not available due to the reduced ruminal degradation of plant proteins from the diet.

The reduction in ruminal degradation of plant proteins can be attributed to inhibition of certain proteolytic bacteria in the rumen by monensin (Russell and Martin, 1984), especially in the population of hyper-ammonia producing (HAP) bacteria found in the rumen (Chen and Russell, 1988, 1989a, 1989b). Most of the ruminal degradation of amino acids and peptides and the rapid production of ammonia after a protein meal has been attributed to monensin-sensitive Peptostreptococcus (Chen and Russell, 1988; Wang et al. 2015). This increase in the duodenal supply of dietary plant protein associated with feeding monensin may explain why monensin consistently improves the feed to gain ratio of cattle fed low levels of dietary protein (Perry et al., 1979) and has helped to retain performance following withdrawal of supplemental protein from the diet (Dartt et al., 1978). If addition of monensin to the diet decreases yield of microbial protein, which is rich in lysine, but increases ruminal escape of dietary protein, which often is rich in methionine, such changes would be expected to substantially alter the supply of and need for supplemental rumen escape protein or amino acids. As a result, benefits from supplementing diets with specific bypass protein sources or amino acids treated to escape ruminal digestion should be altered when monensin is included in the diet. In addition to increasing the supply of amino acids for the ruminant's growth or milk production, an increased postruminal supply of dietary protein also provides additional amino acids that can be readily converted to glucose. This in turn should reduce the need to mobilize body protein when the demand for glucose is high as occurs early in lactation. Because microbial crude protein is comprised partly of nucleic acid N, the proportion of protein comprised of digestible amino acids also should be considerably greater for the dietary protein that escapes ruminal digestion than for microbial crude protein synthesized in the rumen.

Altered feeding behavior. With lactating cows and feedlot cattle, including monensin in the diet reduced daily feed intake by averages of 2.3 and 3.1%, respectively (Duffield et al., 2008, 2012); with feedlot cattle, this intake reduction appears to be linear with increasing dietary concentrations of monensin level (Table 2). Based on the increase in daily gain, available energy supply per unit of feed was increased despite only a slight reduction in feed intake at the lowest level of monensin (5 g/ton); at higher monensin levels, feed intakes rebounded back down to baseline values.

Several explanations have been proposed for the reduced DMI by lactating cows and feedlot cattle fed higher levels of monensin. Initially hypophagia was blamed on distaste of the commercial product (Baile et al., 1979). Indeed, feed sorting and rejection of the coarse pellets that carried monensin was apparent in one of our early feedlot trials with steers. Fortunately, reducing the diameter of the pellets readily solved this problem by reducing the potential for cattle to sort, but with lactating cows, the prevalent sorting and selection of feed components remains of concern. Extent of feed sorting appears to be minimized by slick bunk management as used in many feedlots today. As a substitute for adding high amounts of added salt to repress consumption of a pasture or range supplement, monensin has been used. A temporary reduction in rate of NDF digestion when cattle are first exposed to monensin (Slyter, 1992) also could increase ruminal fill and depress feed intake of fiber-rich pasture diets. Certainly, feed intake by newly arrived feedlot cattle typically is reduced when monensin is first included in the diet. By increasing the dietary concentration of monensin in a stepwise fashion rather than abruptly, the impact of this depression in DMI is reduced. To avoid intake depression, some consultants recommend selecting lasalocid as the ionophore to use in starting diets waiting to switch to monensin once cattle are adapted to their feedlot diets. But because the activity of lasalocid against coccidia is much lower than of monensin, including some coccidiostat together with lasalocid is recommended for starting cattle on feed. Because different ionophores target different microbial populations within the rumen, rotational use of ionophores might prove useful. An altered vagal nerve activity that reduces salivary flow or decreases ruminal motility also could explain the decreased dilution rate of ruminal liquid among cows fed monensin (Lemenager et al., 1978). An increase in the energy content of the diet typically decreases feed intake,

as is obvious from substitution of grain for forage or from substitution of dietary fat for dietary carbohydrate, even when production of beef or milk remains unchanged. This “set point” energy intake control system, wherein feed intake is regulated by energy usage, seems logical; it readily explains the yoyo weight changes apparent among humans that strive to lose weight by trying every new fad diet in a futile attempt to lose weight only to learn that their weight eventually rebounds to its “set point” value. Based on this reasoning, when energy content of the diet is increased by monensin supplementation, one logically would expect feed intake to decrease. Finally, specific hypophagic (intake depressing) effects of propionate could be involved. Blood infusions of propionate depress feed intake and meal size more than isocaloric infusions of acetate in studies (Anil and Forbes, 1980; Allen, 2000); this matches with the decreased meal size often observed with feedlot cattle fed monensin. However, the physiological relevance of this observation remains questionable; the liver typically removes all the propionate from the portal blood and does not allow propionate to reach the peripheral blood stream. Consequently, abrupt postprandial spikes in propionate in the peripheral blood stream would not be expected during a meal to abruptly halt a meal. Perhaps some propionate, like ammonia, may escape liver uptake by traveling via the lymphatic system; this could allow a limited amount of propionate to appear eventually in peripheral blood. Ultimately, alteration in supply of absorbed nutrients or effects of propionate on blood NEFA or insulin concentrations (DiCostanzo et al., 1999), components of the hepatic oxidation theory advanced by Allen et al. (2009), or interactions with leptin or ghrelin release or stability, might be involved.

Like the impact of urea on meal pattern characteristics, monensin generally decreases meal size and day-to-day fluctuations in DMI but in turn increases meal frequency (Stock et al., 1995). Though apparent in trials where intake can be measured with individual animals, fluctuations in DMI by individual animals remain undetected in feedlots where many cattle share a bunk; population effects readily overshadow intake patterns of individual animals. Reducing meal size and daily fluctuation in DMI helps to avoid wide swings in energy supply for ruminal microbes that can result in ruminal and postruminal acidosis in feedlot cattle, the release of endotoxins associated with gut permeability and sudden death, and perhaps even precipitate the hemorrhagic bowel syndrome of lactating cows. But in contrast with this effect, availability of the substrate for endotoxin formation, the cell walls of Gram– bacteria, should increase with feeding of monensin due to an increased ruminal prevalence of Gram- bacteria. Reduction in the incidence of bloat may be expected as clearly illustrated by Bartley et al. (1983). As frothy bloat has been attributed to an altered surface tension provided by uncoiled legume proteins, the reduction in ruminal proteolysis with monensin feeding might be reducing the bloat incidence. Likewise, prevention of pulmonary damage involved with high tryptophan feeds and reduced release of indoles might be attributed to a reduction in ruminal proteolysis or to some alteration in indole metabolism associated with monensin feeding. In total, these changes in feeding behavior as well as changes in ruminal metabolism attributable to monensin can help to explain the reduced death losses of feedlot cattle associated with digestive disorders and certainly justifies FDA approval of the higher monensin dose level (40 g per ton of feed) than was approved initially (5 to 30 g per ton) based on the reduction in feed to gain ratio.

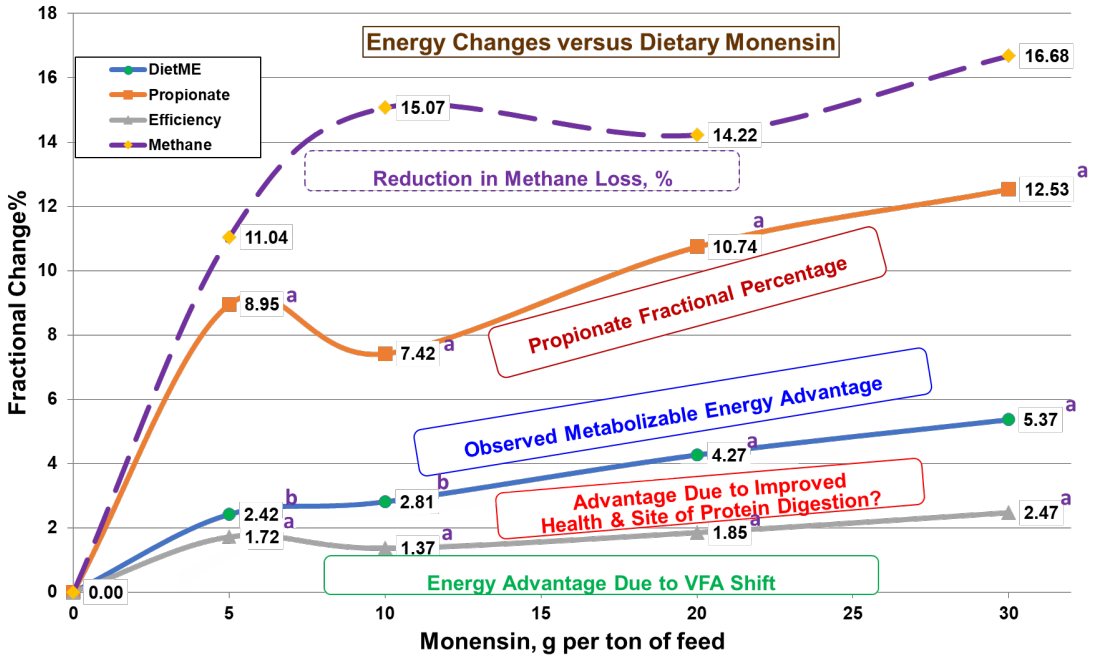

Figure 1. Energy changes in response to dietary monensin inclusion.

Applications, Researchable Questions, Summary, and Philosophy.

1. A summary of the effects of monensin feeding on ruminant productivity is outlined in Figure 1. With high concentrate feedlot diets, addition of monensin decreases the feed needed per unit of gain by over 3% and metabolizable energy content of diets by over 5%. This is more than twice the energy conservation that should become available from an increase in propionate as a fraction of VFA formed in the rumen. However, at a low level of monensin supplementation (5 g per ton of feed) some 70% of the advantage in ME could be explained by the VFA shift. The missing improvement in available energy presumably can be attributable to health benefits and increased ruminal escape of dietary protein associated with an altered ruminal microbiome. Based on the VFA changes alone, ruminal methane production should be decreased up to 15%. **Thus, monensin supplementation of ruminant diets should be of interest not only for increasing productivity but also for reducing the environmental footprint of ruminant production.**

2. At low monensin concentrations, rate of gain is increased, but advantages in feed efficiency slightly favor higher dietary concentrations of monensin where feed intake is reduced by 2 to 4%. ***[Might lowering the monensin level during the final month on feed, when maintenance requirements are highest, permit feed and energy intake to increase at this stage of finish and avoid late-finishing slumps in performance?]***

3. By reducing ruminal degradation of dietary protein, the intestinal supply of dietary amino acids is increased. ***[Does monensin reduce the need for dietary protein, particularly with younger cattle where dietary protein needs are greatest? Does it increase performance particularly for the lighter, less mature cattle in a pen making final pen weights within a pen less variable? Might monensin replace the need for and benefit from rumen bypassed protein sources and amino acids?]***

4. By reducing meal size, the incidence of digestive disorders of cattle is reduced, particularly at higher monensin concentrations. ***[Has monensin helped to avoid digestive problems often***

attributed to intermittent feeding? Have management changes such as restricted feed intake and slick bunk management reduced this benefit from monensin feeding?]

5. Effectiveness of various ionophores can be reduced by high concentrations of sodium or potassium according to Newbold et al. (2013). ***[Does source or level of intake of rumen-buffering minerals influence ruminal activity of ionophores? Might the reduced methane production from bio-waste fermenters that use waste from cattle fed monensin be restored by adding specific minerals that can inhibit ionophore activity?]***

6. Through increasing the propionate yield, production of both methane and carbon dioxide is reduced, especially when diets contain more fiber. Can global warming be reduced and ruminant productivity be increased by worldwide feeding of monensin as proposed by Tedeschi et al. (2003)? ***[By grazing, ruminants harvest and digest unused, unharvested forages in both developing and developed countries. This in turn increases the supply of desired ruminant products (protein, fiber) and uses energy from fiber-rich feeds and surplus products and byproducts that otherwise would be wasted. Monensin both reduces methane production and increases the efficiency with which dietary energy is used. Combined, these effects theoretically should reduce production of global warming gases by ruminants by up to 20% while maintaining or enhancing animal production. If monensin were provided through a feed supplement for pen-fed animals or from a slow-release bolus for grazing ruminants, it seems both logical and feasible that reductions in global warming could be achieved using an FDA approved product with a proven safety and efficacy record. If armed with quantitative information, global warming scientists worldwide and international health and nutrition specialists should counter pressures from governmental and environmental groups that seek to prohibit use of ionophores based on unfounded concerns about microbial resistance to ionophores. Unlike other antibiotic classes used routinely in human medicine and therapeutics where antibiotic resistance is a major concern, ionophores have not and presumably will not be used routinely in human medicine. Like the addition of iodine to salt, the addition of fluoride to water, the fortification of bread with vitamins and iron to prevent deficiencies that can be debilitating, the use of antibiotics to treat infections, and vaccination for prevention of numerous diseases of animals and humans, worldwide supplementation of ruminant diets with monensin should prove beneficial for both animal and human health and well-being as well as for our fragile planet.]***

Views expressed in this paper may not represent those of the sponsor, producers of monensin, or individuals involved with organizing this conference.

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