DISSERTATION

DAIRY MANAGEMENT DECISIONS UTILIZING AVAILABLE EVIDENCE AND INFORMATION

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ABSTRACT

DAIRY MANAGEMENT DECISIONS UTILIZING

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Animal agriculture in today's economic environment is often complex and the uncertainties involved in the decision process make being profitable a challenge. Serving as business consultants, veterinarians can aid producers in helping to make profitable decisions by utilizing available decision tools that enable a better understanding of the economic risk for decisions. Scientific studies that examine the biological response to health or management interventions on dairy farms, while valuable for understanding biology are sometimes limited in their ability to aid in the making good decisions for interventions in agriculture. Adding economics as well as incorporating the variance associated with point effect estimates of biological effect may be a way to decrease the uncertainty or better understand the risk surrounding a management decision.

One decision tool available for understanding possible interventions is the use of cross sectional surveys and longitudinal observational studies. A longitudinal study was designed to evaluate various management factors and feed additives and their association with undifferentiated diarrhea events on dairy farms. Based on data from 76 farms, our research team found that a fermented *Saccharomyces* cerevisiae yeast culture (**SCFP**) reduced the risk of a cow having a diarrhea event by 30% (IR = 0.707 (P = 0.043, CI = 0.505, 0.989). In addition, having a herd located in the Eastern US versus the Western US was associated with more diarrhea events (IR= 2.036 P = 0.066, CI = 0.953, 4.39).

In striving to find the best literature and studies available to help guide the decision process, published studies may differ in estimates of the magnitude of herd response to various

management inputs (actions). One key tool that is gaining scientific prominence is the use of meta-analytic techniques to combine multiple studies into a single entity to predict the effect of certain interventions on certain indices of herd health and productivity. A meta-analysis of thirty-six separate studies on a *Saccharomyces* cerevisiae yeast culture fermentation product was conducted. A total of 69 comparisons met the criteria for inclusion in a random-effects meta-analysis and a sub-group analysis of peer reviewed studies of feeding a SCFP showed an estimated raw mean difference between treated and untreated cattle of 1.18 kg/d (95% CI, 0.55 to 1.81), 1.61 kg/d (95% CI, 0.92 to 2.29), and 1.65 kg/d (95% CI, 0.97 to 2.34) for milk yield, 3.5% fat corrected milk and energy corrected milk, respectively. Milk fat yield and milk protein yield showed an increase in the raw mean difference of 0.06 kg/d (95% CI, 0.01 to 0.10) and 0.03 kg/d (95% CI, 0.00 to 0.05). Estimated raw mean difference in dry matter intake during early lactation (< 70 DIM) and non-early lactation were 0.62 kg/d (95% CI, 0.21 to 1.02) and a decrease of 0.78 kg/d (95% CI, -1.36 to -0.21), respectively from feeding SCFP.

Another meta-analysis of active dry yeast (**ADY**) products was performed; this included 22 papers with 25 comparisons that met the final criteria for inclusion. These studies, conducted in 13 different countries, evaluated active dry yeast products from 7 different companies. This random-effects meta-analysis, showed there was high heterogeneity in the study outcome for milk yield, making it an unreliable outcome to report. One sub-group analysis identified an area of heterogeneity to be study location (in North America versus outside North America). Milk yield for the 7 studies conducted in North American were 0.49 kg/d versus 0.96 kg/d for 13 studies conducted outside North America. The raw mean difference in milk fat yield was 0.05 kg/d and there was a numerical difference in milk protein yield of 0.02 kg/d. No difference in dry matter intake was observed.

Utilizing the information in meta-analysis of products can be improved by the use of stochastic analysis by incorporating the variance from the point estimate parameters into a partial budget of the production changes. Software programs exist that can perform Monte Carlo simulations on partial budgets, factoring in both the biological effects and their variance from the meta-analysis result as well as the economics of the biological change for the producer's business. ModelRisk 5.1.1 (Vose Software BVBA, Belgium, 2015) was used to generate 10,000 iterations of a partial budget, utilizing the mean outcome and variance parameters from the SCFC meta-analysis. The resulting stochastic partial budget calculation showed a risk of not having above a break-even response as 0.27%; in addition, the cost of making a Type 1 error versus a Type 2 error would be less than $0.001 versus $0.38 per cow/d. This means that based on the information contained in the meta-analysis the producer is left with the probability of 0.27% of losing <$0.001 / cow /d by feeding SCFP versus the decision to not feed SCFO and have a 99.8% chance of not earning $0.38 per cow/d. Based on the meta-analysis data, a Monte Carlo simulation of the ADY products in early lactation showed a risk of not having a break-even response as 38.87%.

This dissertation demonstrates the use of direct fed microbials may have a benefit in nutrition programs on dairies. Specifically, the use of SCFP was associated with a decrease in diarrhea events as well as increases in milk production when analyzed using meta-analytic methodology. To aid in decision making the use of stochastic analysis utilizing the variance from the meta-analysis along with the associated point effects is a useful tool to graphically and numerically demonstrate the uncertainty of the outcome. Integrating the biological variation and it associated economic values into a distribution of outcome along with their associated conditional probabilities can be used to calculate the cost of Type 1 and Type 2 components of the decision helping to frame the decision in quantifiable units possibly more useful to a diary producer.

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EXECUTIVE SUMMARY

Dairy Management Decision Making Utilizing Available Evidence and Information

Animal agriculture in today's economic environment is often complex and profitability can be difficult as indicated by the changing dairy sector. The dairy industry illustrates these problems well. In 2003, there were 70,375 registered dairy herds in the US, but by 2015 there were only 43,584 (Gould 2016b), a reduction of 38%. Although some dairies may go out of business because people retire or no longer wish to farm, many of these dairies cease to exist because other, more profitable dairies take their place in producing milk. As farm numbers have declined, dairy cow inventory has increased, changing from 9.08 million cows to 9.32 million cows over this time period (Gould 2016a). During the same time period milk production per cow has climbed from 18,759 lbs. / cow / year to 22,393 lbs. / cow / year (Gould 2016c). Clearly, herds have gotten bigger and per-cow milk production is higher in the dairies that remained in business over this period. This suggests that the dairies that left the industry were not all voluntary exits from animal agriculture but farms that failed to adapt to a more efficient or profitable form of business enterprise.

Veterinarians can be key advisors to dairies and other animal agricultural enterprises, as they often have the ability and training to provide more than simple technical services (e.g. pregnancy diagnosis, surgery). Veterinarians have the opportunity to function in a valuable advisory role for making economic decisions that involve herd and enterprise management. The practice of management itself is a discipline similar to practicing medicine, in that decisions are made in the face of uncertainty (Drucker 1973). Being able to make the best informed decision based on relevant information is key to being a successful business; this principle includes

agriculture. Many decisions are made using intuition and business people that have been successful in business in the past often have had success because they are very good at making decisions based on intuition. As decisions become more complex and the need to make economically optimizing decisions consistently increases, the need for business advisors to help gather and quantify the needed information becomes more valuable to the business manager in the decision-making role. The best advisor will seek evidence that improves the probability the economic decision being made is the best possible. For veterinarians, these business decisions have two key parts: The biological decision (we make a diagnosis based on some type of test or we recommend use of a certain product) and the economic decision, which can be simplified to be the economic outcome that results from the biological decision. Both portions of the decision have uncertainty associated with them. For example, we can conduct a physical examination to diagnose a health problem in a cow. Treating the cow has a cost, and the outcome of the treatment possesses its own degree of uncertainty. The cow could die and the farm receives no money or has to pay for disposal, or it could be culled at an uncertain price for instance the cull cow could sell for $0 or for $2000 or more dollars. The cow could return to production and provide a net return of $300 to $600 per year for the next 10 years or 1 year. The more we can reduce the uncertainty within such scenarios, the less risky becomes the treatment decision. Risk can be defined as the probability of achieving an outcome that is less than the expected (or desired) outcome (Backus, Eidman, and Dijkhuizen 1997). Decision makers must have a grasp of the probabilistic nature of the uncertainties in the decisions, as well as the inherent economic impact of these uncertainties (Howard 1966) to be able to understand the potential outcomes or the true choices of the decision they are making.

The purpose for this dissertation is to evaluate several methods for improving our understanding of informing decisions, in the context of decision making regarding the use of direct fed microbials in dairy cattle. In Chapter 1, a review of the economic decision models and history of their development and use in the agriculture focusing on dairy decision models will be discussed. Because adequate information to describe the potential outcome of decisions is not always available and methods for gathering information from populations without the ability to conduct a random controlled experiment is often needed, in Chapter 2 the design of an observational study is described for one such dairy question. This chapter involves an observational study to estimate the effect of the addition of several common feed additives and farm management practices on the risk of the occurrence of herd-level diarrhea in dairy operations. The utilization of cross sectional surveys and observational study designs maybe the only methods to find this type of management information out for the farm manager because randomly controlled, prospective studies may not be possible due to cost or ethical concerns.

Randomized, controlled studies often do exist for the purpose of informing decision makers about the biological outcome of a farm intervention decision; unfortunately, these studies may provide conflicting conclusions or and / or lack significance, the latter of which could be due to the lack of power to detect a difference in the intervention owing to small sample size. In Chapter 3, we use meta-analytics to estimate the effects of a yeast culture fermentation product on milk production and feed intake on dairy farms. The use of meta-analysis is a statistical method to combine many studies to better inform us of the mean and uncertainty surrounding the mean based on all relevant information from the literature (DerSimonian and Laird, 1986; Lean et al., 2009). In Chapter 4 a meta-analysis is again presented but differs in evaluating the intervention of adding active live yeast products to feeding programs in dairy cattle. Because the

dairy decision maker is interested in more than just the point estimates of the proposed intervention in Chapter 5 we utilize the uncertainties found in the meta-analyses to develop an economic model for dairy decision making using a partial budget model that incorporates the use of Monte Carlo simulation. The use of stochastic software to build a Monte-Carlo partial budget will allow the use of the point estimates and associated variance to better inform the decision maker of the comprehensive view of the possible outcomes for the decision surrounding the intervention for yeast culture or active dry yeast in a dairy diet.

CHAPTER 1

DECISION ANALYSIS MODELS

Introduction

Making decisions in the face of uncertainty is the function of management in any enterprise (Drucker, 1973). Being able to make the best informed decision based on relevant information is key to being a successful business. What tools are available to reduce uncertainty around information that goes into making those decisions? As veterinarians working in animal health and agricultural production, there is often a distinction made between risk and uncertainty. Risk is often being defined as a situation or state where the decision maker knows the possible alternative outcomes and can attach a probability to them, whereas in uncertainty, the decision maker has less information on the outcome(s) and cannot attach probabilities to them (Dijkhuizen et al., 1997a, Rushton, 2009b).

Risk can also be defined as the probability of achieving an outcome less than the expected (or desired) outcome. In complex production situations, mathematical decision models can help us quantitate multiple linked probabilities together to give us a more accurate estimate of the true risk, thereby reducing at least some of the overall uncertainty in decision making. The use of a model or some type of simplified mathematical representation of a business function has probably been used since the middle ages (DeGroot and Schervish, 2014). This is true in agriculture, whether in farming, dairy, or beef operations.

In veterinary medicine, the outcome of health-related and dairy management decisions typically has a biological component coupled with the economics of the outcome. Understanding the multiple variables that go into a decision-making process may be harder in

agriculture than in other fields of business because many of our decisions are based on biological factors that have inherent biological variation typically absent from manufacturing environments. Further, measurement errors, sampling errors, or other forms of bias can complicate the decision-making process. One of the principle jobs of veterinarians in agricultural practices is to provide information to agricultural owners, the client, in which to make informed decisions. Veterinary medicine encourages evidence based medicine (EBM) which can be summarized as locating the best available evidence, critically appraising the evidence for validity, impact, and applicability, and integrating the findings with the clinical need of the client (Slater, 2010). In practical terms, the clinical needs of the patient in an agricultural environment must include the biological outcome; further, the uncertainties inherent in both biological systems and economics must be formally included. Without these, the veterinarian's clients are left to using intuition.

Veterinarians, although trained in biological systems, are often less knowledgeable regarding data analysis and decision making tools. While it is common to use intuition, often with good results, as valued advisors to the dairies, veterinarians need to help the decision maker with the analysis of best evidence available. A review of the available tools have been available and development of new tools can aid practitioners in searching and applying the most current analytic methods, thereby fulfilling the concept of EBM.

Purpose

The purpose of this literature review is to review mathematical modelling used to support decision-making in veterinary medicine. The review will focus on tools described in the literature for production medicine, primarily in dairy production and from 1970 to present. This review will categorize and summarize the common models available in the peer-reviewed literature. First will be a review and critique of the foundational models; subsequently, the

review will describe how these models have developed from foundational to contemporary models.

The decision tools reviewed in this chapter are forms of mathematical modeling that originally were developed using hand calculations and slide rulers, but as computer technology advanced the utilization of computers to rapidly allow alternative variables and their mathematical relationship of the underlying disease or production system in question to be analyzed in a much more complex manner (McGrayne, 2011). Mathematical modeling is useful for the study of complex phenomena, like the population dynamics of infectious agents or biological process, because models show how separate measurements can be seen as a manifestation of the same underlying processes (deJong, 1995).

Cost-Benefit Models

Decision tools had a rapid increase in development in the mid-1970s and the tools developed in two primary categories, which were regional or national level models and models that were applied at the herd- or individual animal-level. The regional or national model development was driven by animal health and disease eradication such as foot and mouth disease (FMD) (Ellis and James, 1978) and classical swine fever (Ellis et al., 1977) that impacted health over a large area and multiple farms where implementation at a national level was needed to for success. These researchers adapted and utilized cost-benefit analysis (CBA) developed from classical economics used in making public policy decisions, and the benefit they bring to the country or region (Ellis, 1972; James and Ellis, 1978). These models, also often termed benefit-cost models, were primary deterministic (having only a single input or output value) and were extremely complex models. For instance, the models were built to evaluate changes in disease rates, the cost of eradication (McInerney, 1991) impacts at the farm, community, regional and

national level (Putt et al., '88), while the benefits that were evaluated were primarily economic. Additionally, these models have been used to evaluate issues in food safety, nutrition, or food security (McInerney, 1996). These models continue to be developed today for evaluation of surveillance and intervention strategies for BSE, FMD, and anthrax, (Verstegen et al., 1998, Tomassen et al., 2002, Kivaria et al., 2007, Rushton, 2009a, Hausermann et al., 2010). The aim of economic analysis is to indicate whether more or fewer resources should be allocated to influence the level of disease experienced, in what form, and in which specific combinations. In short, the purpose is to inform decisions on the management of disease, not simply to document its frequency of occurrence (McInerney et al., 1992).

All rational decision-making involves an evaluation of relevant pros and cons so that the logic of making a decision between the benefit derived and the cost of implementing the program is unarguable. CBA is simply a formalized technique for doing this, assembling a complicated pattern of positive and negative aspects of a decision, expressing them in monetary units, summarizing them in two composite values, and then examining the balance between them (McInerney, 1991). Unlike models that are built around individual animal- or herd-level models, one of the key distinguishing feature of regional or national cost-benefit models is their incorporation of change in supply-demand curves as well as discounted future value calculations for changes in productivity at the national or regional level which subsequently induces change in prices or costs at the herd level over time (Dijkhuizen et al., 1995; Rushton, 2009c). While these complex cost-benefit models are useful decision making tools at the regional or national level, they are not useful for day-to-day decision making on the farm level, the place where field veterinary practitioners interface with clients. This review will focus on the development and

availability of models and papers that specifically address individual animal- or herd-level decisions.

Models used on Farm

Veterinarians and farm advisors are often called on dairy farm managers (or managers of other animal agricultural enterprises) on the implementation of herd health or production practices. The dairy owner/manager has typically operated successfully in the past (otherwise they would not still be in business) often using intuition without the input of specific decision modeling tools. These managers have had a long period of trial and error and are often able to select the optimum use of inputs from information and knowledge from past mistakes and successes. As dairies (or other enterprises) become larger and more complex, the need for outside consultants and tools for optimizing decisions and the integration of biological outcomes with the economic value of these outcomes increases in importance. As dairies grow and decision inputs change such as new products or disease risk or change in economic markets (i.e. change in milk price, coupled with larger cow numbers), these more complex problems lead to the need for adoption of decision tools (Rushton,2009c). The key portions of the decision making tools are a consideration of the underlying biological function of the farm process that are the underlying drivers of the enterprise, the difference in the mean outcome of the proposed change along with the variance and standard error represented in the literature. These models are simplified idealized models of a complex world that involve reductionism – they hold several factors constant and abstract from the real world (Tisdell, 1995). While the simpler the model the less it can incorporate all the possible complexities, there is a trade-off to the end user either veterinarian or dairy operator to utilize the model for specific use on an enterprise, targeted to their unique characteristic variables.

As computers developed in the 1970s, decision models developed by individuals pioneering these decision analysis tools in all fields. Decision tools such as decision trees, stochastic analysis, Markov chains and Bayesian analysis were first developed for military use and paralleled the computer development in the mid-70s (McGrayne, 2011). As the industry developed these decision tools they were also being adopted with increasing frequency into parallel business uses, of which agriculture production and business farm enterprise was one such business application.

Partial Budgets

The first basic model category is the partial budget. The partial budget is a simple comparison of the current economical state of the production or disease state compared to the predicted economic state after a proposed intervention. The partial budget is useful as it states the production question in terms of money. Partial budgets are optimizing models, although the output does not intuitively tell us where the change from a positive marginal economic input to a negative marginal input occurs, they do show if the change in costs is equal to or greater than the increase in profit. Partial budgets eliminate all input variables - such as fixed costs - that are not part of the decision. While there is no specific time function nor need to define a probability distribution for input variables, the partial budget is very useful to making a binomial decision (i.e., should we implement the intervention or not?). It requires a relatively small amount of data collection and is useful for making changes in the production system that do not involve several simultaneous changing variables (Rougoor et al., 1994, Dijkhuizen et al., 1995). The simplicity of partial budgets makes them especially easy to be used on the farm for specific input output problems (Figure 1.1). The partial budget, while often simple in structure, can be attached to much more sophisticated models. Rougoor et al. (1994), in her consideration of Caesarean

sections on dairies, used data from the retention payoff model (RPO) to create a partial budget for culling animals which uses Markov chain modeling to understand the cost and probabilities of culling. Because partial budgets involve defining costs of input and value of outputs, these are inherently built into almost all models other than analytical (inferential) models.

Benefits		Costs	
(1) Additional returns (heavier weights of calves)	US$ 25	Returns foregone (drop in milk production)	US$ 30
(2) Reduced costs (less feed)	US$ 10	Extra costs (surgery and culling)	US$160
Total	US$ 35		US$190
Net result (US$35 – US$190)	US$ – 155		

Figure 1.1. A partial budget of the economics of caesarean section in Frisian dairy cattle adapted from Rougoor et al., 94. Number (1) is additional returns realized from the change, (2) is the reduced costs as a result of the change, (3) returns foregone as a consequence of the change and (4) extra costs incurred due to the implementation of the change. The change should be adopted if the sum of (1) and (2) is greater than that of (3) and (4). (A.A. Dijkhuizen, et al., 1995)

Categorization of Mathematical Models

Analytical vs. Theoretical Models.

Many types of models began to develop as computers and their software become more user friendly. The core features of many later decision models were analytical models. Analytical models are used to develop and characterize the underlying process or function and associated variance as often observed through the use of random controlled experimentation. Analytic models are built to understand the underlying biological function and incorporate this biological function into the model structure. Analytical models are normally used as data input into theoretical models, they would not normally be useful for on farm decision analysis. One early analytical model that has - and continues to have - a high impact on farm decision models is the Woods lactation curve (Wood, 1967) which described mathematically the shape of the lactation curve for the Friesian cow (Figure 1.2). While the analytical model is designed to describe the current state of the working

system, the theoretical model is designed to take the current state and compare it to the state after an intervention has occurred. The theoretical model can be an optimization model that looks for what point of a series of inputs optimizes or maximizes the output, such as maximizing the marginal profit in a partial budget. A theoretical model can also be a simulation model that is not being used to optimize output, but rather simulates the changes that occur in various parameters with changes in another parameter. There are obviously many overlaps between the actual models and descriptions, and many models have simulation and optimization components.

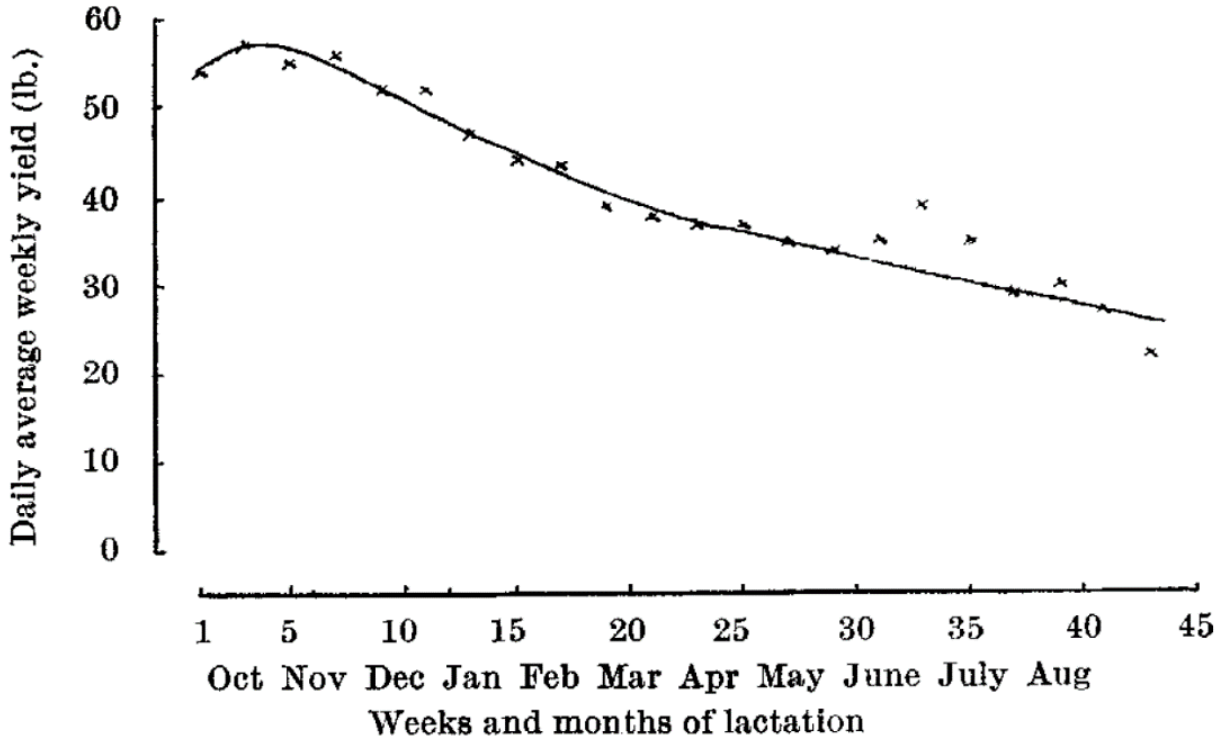


Figure 1.2. Regression curve $y = 56.62\ n^{0.396} \exp(-0.00942\ n)$ fitted to a single Friesian lactation. (Woods, 1967).

Optimization Models

The goal of optimization is to identify the best outcome from a variety of options. The assumption made for optimization models is that the desired "optimal state" is known (i.e., it is one of a fixed set of choices under consideration). The assumption is that the farm

managers/owner would desire to maximize economic value over a time horizon. This is not always a valid assumption as other payoffs of value as alternatives to money are found (Dijkhuizen et al., 1997b). Normally these models are discrete in time and designed to look at a specific event over a specific period.

Decision Tree Analysis. Decision tree analysis is one specific type of theoretical model that would generally be considered an optimization model. In 1980, the use of decision tree analysis was described for treatment of ovarian cysts in cattle (White and Erb, 1980). The question, "At what day post-partum does it become cheaper to treat a cystic cow rather than to wait for spontaneous recovery" was modeled as a series of decisions, each represented by a node with a specific decision which each has a probability outcome (Figure 1.3). The decision tree branches left to right. The branch splits with each branch representing a different possible event that has a distinct probability. The probability related to each decision is written on the branch, which is derived from literature or expert opinion. The point at which decisions branch is called a chance node and is represented by a circle on the tree. The previously calculated outcomes (monetary or non-monetary values) are on the right side of the tree. Probabilities of outcomes at chance nodes are multiplied by outcome values. The total expected value at a chance node is the sum of these products. This sum is written over the chance node and is circled. A decision can then be made at the preceding decision node to choose the path with optimum value. One moves left to right taking the more optimum chance node branch until the outcome value is reached (White and Erb, 1980). The accuracy of the decision tree rests on the probability assumptions that the modeler uses in the model. The practitioner can use local costs and values to enhance the model and also use high and low values in a system of sensitivity analysis to look at what key probabilities would significantly change the outcome.

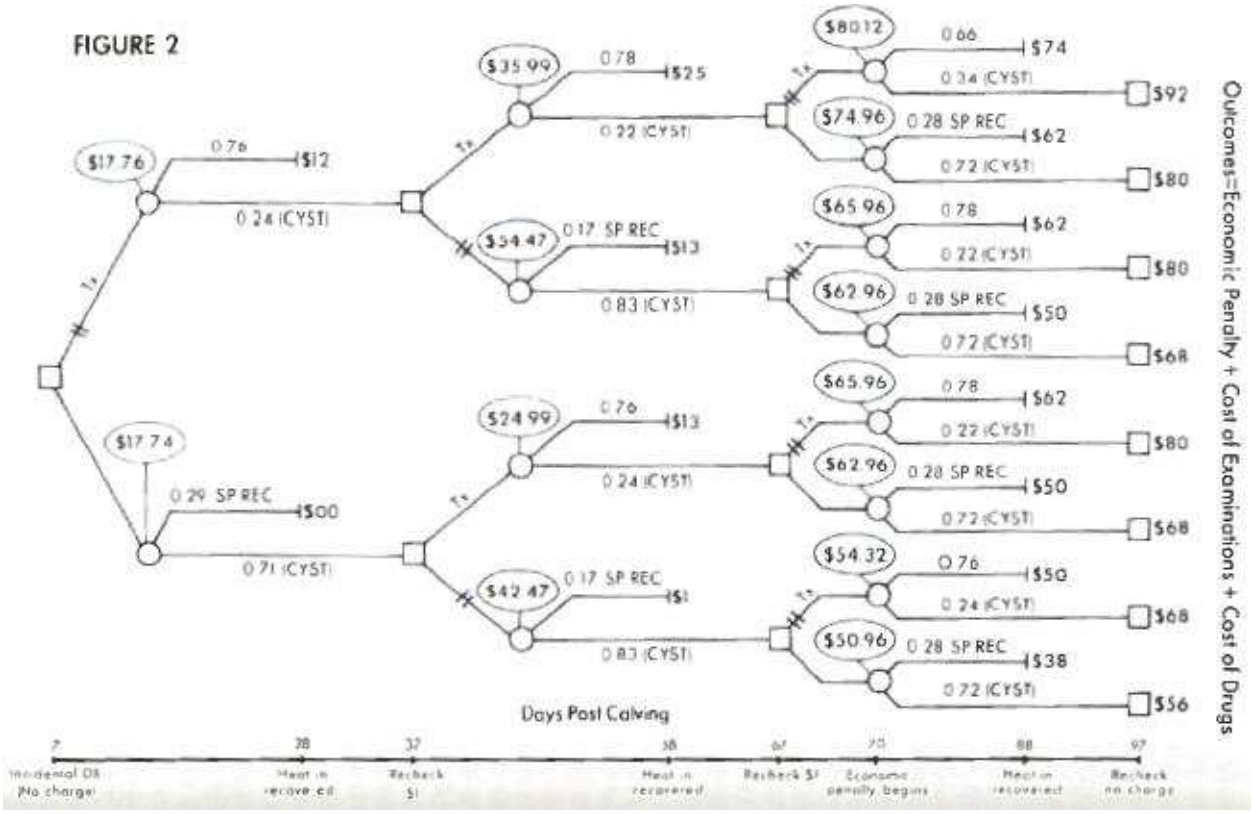


Figure 1.3. Decision tree; to treat or not treat cystic ovaries. The circles are chance nodes and the square is an outcome on the right side of the tree. Probabilities following a chance node follow a chance on the appropriate branch. The total expected value at a chance node are the sum of the products, probabilities multiplied by the outcome values (Erb and White, 1980).

In 1984, a decision tree model (Madison et al., 1984) was published in which the authors built a graphical model that contained lines of indifference created for the probability of success versus the cost of treatment. Using the model the producer or veterinarian could look at the salvage value of the animal versus the probability of success and cost of treatment and see if an intervention was warranted. A similar model (Fetrow et al., 1985) was published the following year for use in salvage decisions that plotted the choice between 2 different interventions, instead of a single choice. The hyperbole on the chart was the line of indifference between the interventions. One limitation of the Fetrow model was the decision could only take the form of two mutually exclusive and exhaustive outcomes, one favorable and one unfavorable. These

papers introduced an indifference curve into the decision making process for animal disease interventions graphing the difference in the value of the outcomes and the difference in the probabilities of the outcomes (Figure 1.4). This uses the probability of a correct outcome against the difference in the cost of the procedure. If the intercept point is to the left of the curve that procedure would be favored, if to the right of the curve the alternative intervention would be favored. If the intervention falls on the line, the producer would be indifferent as to which procedure is used.

Further expanding the idea of the choice between 2 expected outcomes in a decision tree developed by Galligan, Marsh, and Madison (Galligan et al., 1987). In this paper, the authors described how to utilize the standard deviation of the expected outcome to help producers who may or may not be risk adverse to be able to choose between 2 procedures that have different risks using the decision tree. Building further on the value of utilizing risk in the decision model, Galligan, and his co-authors brought portfolio theory into the decision tree model (Galligan et al., 1991b). Building on a previous model, Galligan and Marsh (1988), describe how they could use portfolio theory with a decision tree in which the decision involves selection of one of 3 different reproductive programs. Galligan and Marsh adapted this to combinations of interventions on the dairy because there are typically combinations of interventions that practitioners can employ on dairies. By using a combination of treating with prostaglandin and observing for estrus as well as timed artificial insemination (AI), they showed that there was less risk (lower variance) with a higher expected value than prostaglandin and observation alone and almost as much expected value with much less risk than timed AI alone (Figure 1.5). Ngategize developed a model to look at the treatment of cystic follicles using 7 different combinations of GNRH or HCG combination or no treatment (Ngategize et al., 1987). Another model developed

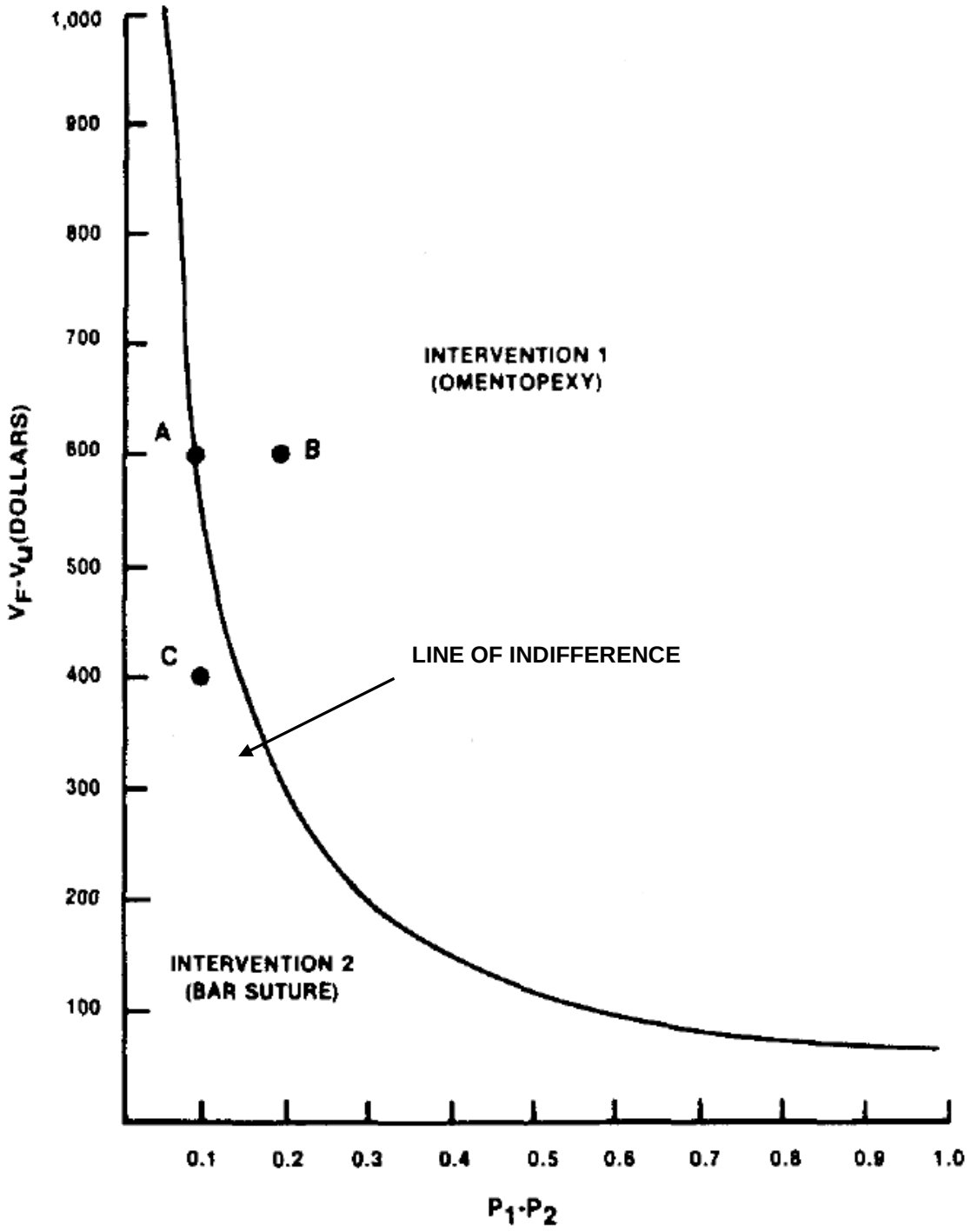


Figure 1.4. Graphic solution for a hypothetical choice between 2 treatments for left displaced abomasum. Treatment 1 minus Treatment 2=$100. VF-VV is the difference in value for the two outcomes and P1-P2 is the difference in probabilities Point B is more expensive with higher probability for success. Point C is less expensive but with lower chance of success. A producer would be indifferent to which surgery is used if it falls on the line of indifference (used with permission) (Fetrow et. al, 1985).

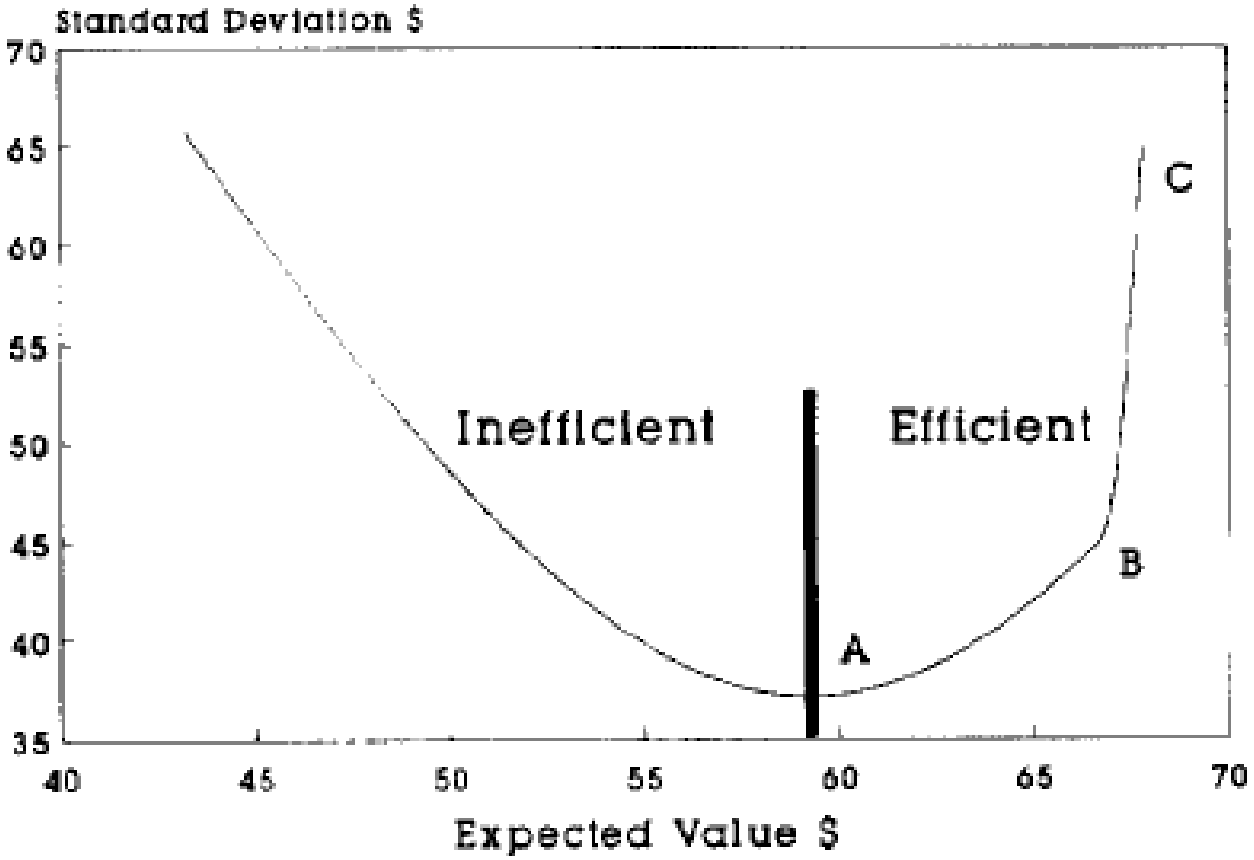


Figure 1.5. The expected return and risk (standard deviation) of intervention combination using portfolio theory. Point A is using no prostaglandin, Point B is using prostaglandin and observing for estrus and Point C is using timed AI. Point A is less efficient because its expected value is lower although the risk is lower. Point B is more optimum because for very little additional risk a much better expected value is obtained (used with permission). (Galligan et al. 1991).

in 2004 evaluated the potential economic benefits of using intermammary antibiotics or an internal teat sealant at dry-off for herds in the UK (Berry et al., 2004). The use of a computerized decision tree analysis was published by Dorhorst as an aid in regarding management decisions for Paratuberculosis (Johne's) in dairy herds. The program called Precision Tree, an add on for Excel (Palisade Corporation, Ithaca, NY) allowed them to evaluate 960 different decision permutations (Dorshorst et al., 2006). A different software program called TreePlan was used in a model to look at treatment and testing alternative options (Pinzon-Sanchez et al., 2011) which had 144 terminal values evaluated. A New Zealand paper (Reichel

et al., 2008) was published using TreeAge software for its decision tree to evaluate BVDV infections and vaccination protocols. While simple in concept, the use of personal computers have increased the complexity and use of incorporating more decisions into the models than originally used in the early 1980's, facilitating identification of optimal outcomes.

Linear Programing. Linear programing is another type of optimization model that is specific to the mathematical process for finding the optimal solution. The essential characteristics of a linear program are (1) there is a function to be maximized or minimized, (2) there are limited resources that can be used to satisfy the objective and (3) there are several ways to use resources (Jalvingh et al., 1997). While Jalvingh described the linear models very well in Animal Health Economics, strictly linear models were not used in any published papers. They were used within sub-models for bigger projects.

Simulation Models

Contrasting with optimization models in which there is an optimum solution given the objective function with the restrictions, is simulation modeling. As in other models, the simulation model is a mathematical model that can be changed by manipulating a set of predefined input variables. While being able to demonstrate the effect of various interactions of parameters, simulation models can also be used to identify a better, or even optimal, solution than the present state, if different interventions were implemented. In *Animal Health Economics*, a seminal book in veterinary decision-making, Dijkhuizen categorizes simulation models into static and dynamic models. Static models do not contain time as a variable, whereas dynamic models do. The key usefulness of dynamic models is to incorporate time as a variable, as opposed to a point in time decisions such as in the decision tree. Most farm systems where models are being applied will change over time, and these changes influence decisions affecting optimization (Dijkhuizen et al.,

1997c). An example might be changing the health of a heifer operation resulting in fewer heifers dying and more heifers making it to the freshening string. In the long run, this might improve the farm's income by supplying less expensive replacement animals and superior milk production, but this effect will not occur for at least 2 years, and in the meantime, will cost more money for feed and housing, while at the same time impacting other facets of the system which also impact cash flow.

Another category of models that can be both static and dynamic is the category of deterministic versus stochastic models. Deterministic models use and predict a specific point effect. For example, 70 pounds of milk or 2.2 pounds per day average daily gain or 52 pounds of dry matter intake. Stochastic models, on the other hand recognize that there is uncertainty regarding the specific values for all inputs and outputs, which can frequently be represented as probability distributions with standard deviations. These probability distributions can take various statistical forms such as triangle, rectangle, normal, log normal, or gamma distributions for continuous variables or binomial, Poisson, or multinomial for discrete variables. The simulation model can sample these distributions at each iteration of the simulation model thereby giving a risk distribution for the outcome parameters from the model.

Dynamic Programming

Dynamic Programing (DP) (versus Linear programing) takes its name from the fact that the functional equation and its associated computational techniques are derived from and adapted to a process changing over a discrete or continuous time interval. The dynamic program is a series of or sequence of decisions that are made as the animals or system moves through time (Huirne et al., 1997). Each "state" has its own mathematical calculation with its objective function that is defined for each stage and all subsequent stages. If the subsequent outcomes are known for certain, this is a deterministic dynamic model whereas a stochastic dynamic program uses a probability distribution

to describe the state. Although linear programing can be adapted to several time periods by the addition of a new set of restrictions, reflecting the constraints in each time interval (Dreyfus, 1956), limited resources are allocated to various activities. In comparison, dynamic programming resources are allocated at each of several time periods. In linear programing, the inputs and outputs of various actives are assumed to be proportional to the activity. Because dynamic programing divides activities and resources into smaller time intervals it has the ability to model much larger and more complex problems than linear programing. The Markov chain would be considered a type of dynamic program. The Markov chain is a random process that undergoes transitions from one state to another state through time. It must possess a property that is usually characterized as "memorylessness" in which the probability distribution of the next state depends only on the current state and not on the sequence of events that preceded it. This specific kind of "memorylessness" in the Markov chain is what defines it from other dynamic programing models (https://en.wikipedia.org/wiki/Markov_chain).

One early dynamic programing model analyzed a 10 year planning horizon looking at changes in milk, beef and feed prices, replacement costs, and interest rate for changes in profitability on the farm (Stewart and Burnside, 1977). As in the description of dynamic programing, they divided the multi-stage problem into a series of independently solvable single-stage problems or state variables that are a set of parameters such as age and production in the case of the dairy cow that consist of a number of distinct values (Vanarendonk, 1984). They had 2695 state variables over the 10-year planning horizon, which was very large for computers of that day. Because of the size, they had to condense input. They assumed that all culling decisions were made at 60 days in milk prior to breeding and they used estimated standardized 305-day milk production for the cumulative production output.

Dynamic programming was used in a more-narrow sense in several studies wherein replacement programs for dairies were evaluated; each model was built on some aspect of the earlier models. Renkema and Stelwagen (1979) produced a model of the economic changes for changing culling rates due to improved overall herd health. Their assumption was that a cow should be kept in the herd as long as her expected marginal profit is higher than the expected average profit during a replacing young cow's life. He teamed up with Korver then with an extended model for looking at culling strategies during the first lactation (Korver and Renkema, 1979), and then with Dijkuhizen (Dijkhuizen et al., 1984; Dijkhuizen et al., 1985b) for a model that looked at reproductive failure in the dairy herd. Notably, Dijkhuizen (Dijkhuizen et al., 1985b) modeled the increase in milk production for lengthening lactations for total milk, but also that this milk was produced at a lower than average milk production for the herd. This was also different for each lactation in the herd. This was made in 20-day increments as opposed to Renkema's model that made the culling decision once per lactation. In a follow up article using the same model, the authors looked at how long was it profitable to continue to inseminate a cow or heifer with poor fertility (Dijkhuizen et al., 1985c). In 1986 Dikhuzien and coauthors developed a similar model for reproduction in swine (Dijkhuizen et al., 1986). In this model, they introduced the concept of the Retention Pay-Off index (RPO). The key idea behind the RPO was to calculate on an individual sow basis, was it profitable to retain the sow and breed her again or replace her with an average replacement. They utilized discounting to compensate for the value of time as an investment versus replacement. This concept was later used in dairy models such as DC305 for ranking cows using the ECON command for herd management programs.

Other early dynamic programming models were constructed (Vanarendonk, '84) that incorporated the changes in seasonality in the model. The Dutch dairy farms use grass grazing

during specific parts of the year, so the cost structure changes during this time. Calving during different seasons and the change in labor and feed can have significant changes in the profitability of the dairy. A subsequent model was developed that was extended to allow variation in conception. Three alternatives were looked at: inseminating the cow with some calculated probability of success, leaving her open or replacing her immediately on a monthly interval from 2 to 7 months. As long as the future value of the cow lactating which depended on her production and persistency was greater than the value of a replacement animal the decision was made to keep her in the herd. (Vanarendonk and Dijkhuizen, 1985). This model appears to have been a very foundational model for reproduction to initially developed many of the ideas later used to construct the RPO index.

Stochastic Programing

Models incorporating stochastic programing versus deterministic programing utilize the distributions of possible inputs to incorporate risk or the variance of the parameters into the model. Utilizing computers to sample from a defined distribution allows the modelers to determine standard deviations and means of outcomes. Dijkhuizen et al., (1985a) developed a model to stochastically simulate decision models on the farm including reproduction and culling. Another early model that incorporated stochastic inputs was a Reed-Frost model (Carpenter, 1988) that simulated the spread of a generic virus versus immunity from vaccination. Other early examples of stochastic models that were used were one for optimizing replacement selection in dairy herds (Bergner and Hubner, 1981), a model to simulate the yield of a dairy cow (Goodall and Sprevak, 1984), the reproductive performance of the dairy herd (Morant, 1985) a model to predict rates and the economics of dairy disease in the herd (Hurd and Kaneene, 1987), and a model of multiple ovulation and embryo transfer breeding schemes (Jeon et al., 1990).

Models using Spreadsheets

With the development of more sophisticated spreadsheet capabilities on personal computers, decision models have been developed that more closely align with the concept of on-farm decision tools. Many of the previously described programs were run on university main frames using programing language. Using spreadsheets for model building made models more easily adaptable for in field usage. One key example of this was a model that utilized the concept of RPO originally developed by Dijkhuizen and Renkema to build a spreadsheet to make breeding and replacement decisions on farm (Groenendaal et al., 2004). This model calculated the RPO values, the future production, revenues, and costs of dairy cows at different levels of milk production with different numbers of days open. This was determined, utilizing marginal net revenue instead of dynamic programing. The optimum time for replacement of the dairy cow was determined by comparison of the marginal net revenue of the current cow versus the discounted future annuity anticipated from the replacement animal. In Groenendaal (Figure 1.6) one can see how the RPO changes both within the lactation, with the future value just prior to calving, and a decrease through around 7 to 9 months post-calving; the future value then increases as the cow successfully approaches the next lactation and the probability of culling decreases. One can also observe that the future value decreases as the lactation number increases, reflecting the decrease in future production annuity from the cow. If a cow would fail to become pregnant, the RPO curve would continue downward, eventually becoming a negative value. Another benefit of the model is the ability to calculate the cost of days open compared to replacing or not replacing the cow.

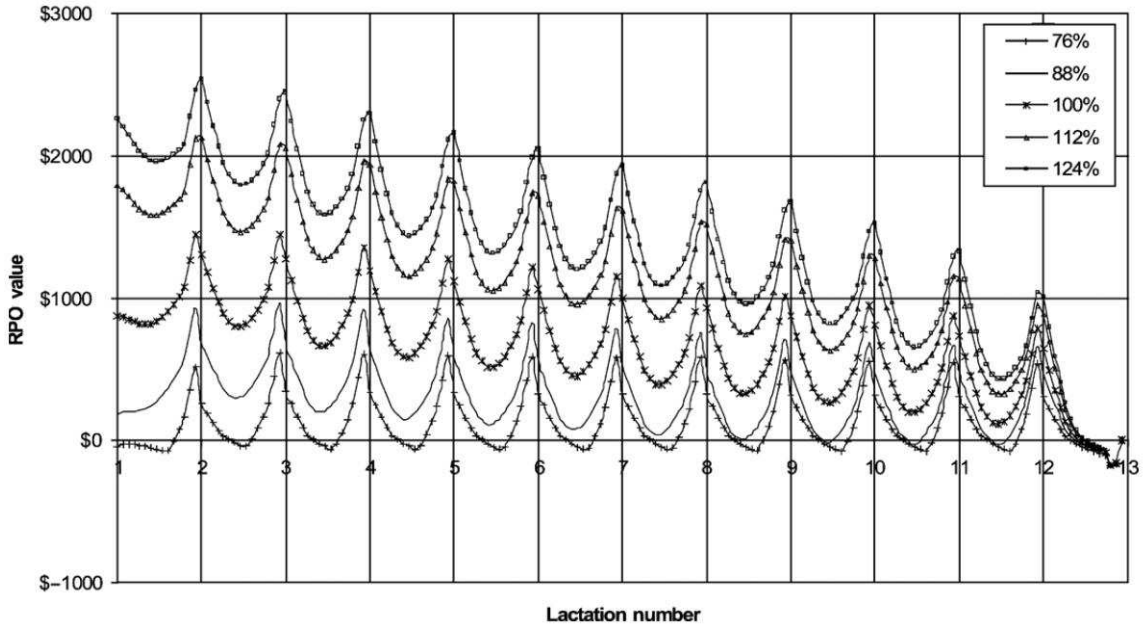


Figure 1.6. Retention pay-off (RPO) values for different milk production levels (relative to the herd average milk production) for cows with an average 15 month calving interval. (Vetical lines indicate the calving event; a successful breeding occurs 9 month before) (used with permission) (Groenendaal et al., 2004).

Spreadsheet and HTML Partial Budget Type Interactive Decision Tools

Many tools are available that target decision making areas of dairy production and dairy veterinary production consulting. The University of Wisconsin Dairy Management Department has several tools available on line for download, dealing with a variety of production decisions. Some of these tools are the Optigen Evaluator (Inostroza et al., 2009), a replacement cow model that examines the future economic value of a cow (Cabrera, 2010a), the value of sexed semen for heifers (Cabrera, 2009) and a retention pay-off model on an excel spreadsheet (Shahinfar et al., 2014).

There are many other decision making tools and papers listed on the University of Wisconsin website, *Http://dairymgt.info/tools.php* along with associated papers for most of the models. A listing of some of these models are, Income over Feed Costs, Dairy Ration Break Even Analysis, Heifer Pregnancy Rate, Cost-Benefit of Accelerated Liquid Feeding Programs for Dairy Heifers, Heifer Break-even, Herd Structure Simulation, Exploring Timing of

Pregnancy Impact on Income Over Feed Cost, Dairy Reproductive Economic Analysis, The Economic Value of a Dairy Cow, Value of a Springer, LGM-Dairy Analyzer, Working Capital Decision Support Tool, Decision support System Program for Dairy Production and Expansion, and many more tools. Of note in a more tradition model, Cabrera published a Markov linear program to optimizing replacement animals (Cabrera, 2010b) and along with Kalantari added stochastic analysis (Kalantari and Cabrera, 2015) to the dynamic programing Markov chain model to look at changes in economics due to changing 21 day pregnancy rates.

Other recent decision models that have been published since 2006 that are relevant to production medicine are a DP model for understanding how the value of a pregnancy depends on lactation number, milk yield, persistency of lactation, prices, breeding and preplacement decisions (de Vries, 2006). The purpose of this model was to maximize the profit per slot per year with the cow that is currently being milked versus a possible preplacement animal. The model had 3 different modules: the first module that was used to calculate cow performance data; second, an optimization module that used dynamic programing to determine inputs for the replacement program for individual cows; and third, a Markov chain module to calculate data for monthly subgroups of cows. The key idea of this program was to make culling vs retention decisions, e.g. if the Retention Pay Off of the current cow is less than zero, then her slot in the herd should be replaced with a replacement heifer. "The RPO is the discounted future cash flow from trying to keep the cow until the optimal time to cull her and her future replacement heifers minus the discounted future cash flow from immediately culling the cow and her future replacement heifers" (de Vries, 2006). de Vries found that the value of the pregnancy depended largely on the shape of the lactation curve used to predict future milk production for the cow (Figure 1.7). The cost of losing the pregnancy increased with things that would have made the lactation more valuable such as length of gestation, increased

persistency, and increased probability of getting pregnant. Decreasing the purchase price for a heifer used to replace the cow greatly decreased the value of the pregnancy.

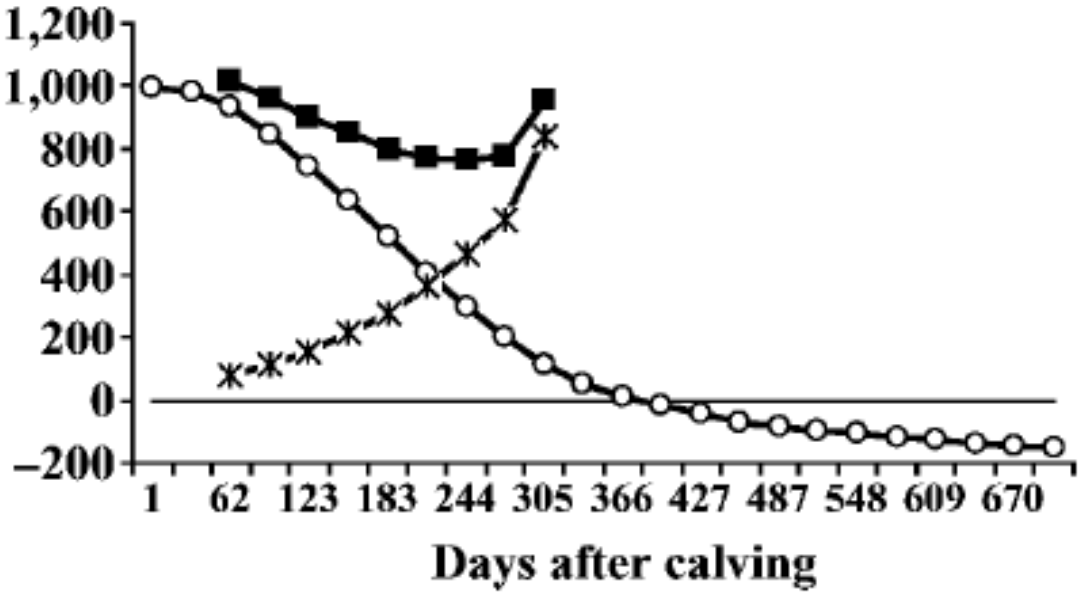


Figure 1.7. Retention payoffs (RPO) (X) for a non-pregnant cow (0) and a cow that became pregnant on d 61 after calving (•) by day after calving. Cows are in their first lactation with average lactation curves. Value of pregnancy is equal to the difference between the RPO of the pregnant and non-pregnant cow on the same days after calving because both RPO are greater than $0 (de Vries, 2006).

Within the de Vries model, there is considerable opportunity for consideration of variance around the "getting pregnant" factors. One model (Giordano et al., 2011) that was produced looked at the partial budget values and the sensitivities associated with a farm using only estrus detection, timed AI and a combination of timed AI and estrus detection. This model was developed using a Markov chain simulation deterministic model with partial budgeting to obtain the net present value per cow per year of the different models. This author found that both timed AI programs were superior to estrus detection using values obtained from some representative Wisconsin herds. The 100% timed AI program with a 1% increase in conception rate was superior to a less expensive program with shorter interbreeding intervals. This demonstrated how

this model could be used for making targeted changes on the herd. Contrasting to the Giordano study, Galvao developed a model (Galvao et al., 2013) using stochastic dynamic Monte-Carlo simulation to look at these same reproduction programs. This model compared the economic outcome of reproductive programs using estrus detection, timed artificial insemination (**AI**) or a combination of both at high and low estrus detection (**ED**) levels as well as different AI compliance levels for injections of drugs to synchronize the cow for AI. In contrast to Giordano's model, this model found high accuracy of heat detection to result in more pregnancies than programs that had low compliance for injecting cows for AI synchronization, demonstrating that the variability of the underlying parameters is a valuable tool with in models as well as the model outcome is sensitive to the absolute values of the underlying model as in high and low ED. Galvao's group only used stochastic modeling for the animal's estrus, but used deterministic values for all the underlying subgroups losing much of the value of the stochastic modeling to incorporate variance that would expect to be seen on the dairy.

Type 1 and Type 2 Models

One of the most interesting models for aiding in decision-making on the dairy is one that places more emphasis in incorporating the underlying variation of the biological response along with our inability to know the true outcomes of research on biological responses. These are the models that incorporate analysis of both the cost to the dairy of Type 1 and Type 2 errors calculated from the statistical model. A Type 1 error would be when a producer decided to use an intervention and found out he had made a mistake and his returns were actually below breakeven. A Type 2 error would be when a producer decided not to implement a proposed intervention when doing so would have made him an above breakeven return on his investment. One such model examined the value of accurate estrus detection (Williamson, 1975). Williamson observed that the mean interval in the model of time

from calving to conception that a change in heat detection might influence is actually a sample of observations from a normally distributed variable with a true mean and a standard deviation. Because the true mean is unknown, there is inherent error regarding the observed (estimated) value. Each of the resultant outcomes has a cost or profit to the outcome based on frequency of the outcome. The experimental mean in his study was 99.4 days for the interval. The true breakeven for using the KMar Heat Mount detector (KMAR Inc., Steam Boat Springs, CO) intervention (a pressure-activated marker for the backs of cows to visibly show the cow was mounted by another cow indicating estrus) was 102.2 days, using the dairy-specific value for reduction of calving interval. The risk of erroneously concluding the outcome is less than 102.2 days when it was really greater than that based on the sample mean (Type 1 error) or, conversely, concluding the true mean is greater than 102.2 days when it was really less. The resultant cost of this outcome, can be plotted in a risk graph which shows the economic cost of the Type 1 and Type 2 error (Figure 1.8). Galligan et al., (1991a) published a model similar to Williamson where he described a more useful method for incorporating many of the concepts of the previous paper, but in a model that could be used more easily. In the Galligan Type 1 - Type 2 model, the authors summarized the mean and variance for the increase in milk production versus the cost of the product from 16 published papers regarding decision for use of bovine somatotropin. Another option in the model was made using 12 papers that modeled the value of feeding bicarb in the ration for increased milk production. Their model produce the same type of risk curves as Williamson (Figure 1.9). Galligan then built a stand-alone model that could be run on a personal computer or on a web based program utilizing the concepts in his paper that allowed users to input different interventions. The inputs required were means and variances from random controlled trials of the intervention that was being questioned. This program and other useful tools to aid in decision-making are available on Galligan's website (http://dgalligan.com/; (Galligan,2008).

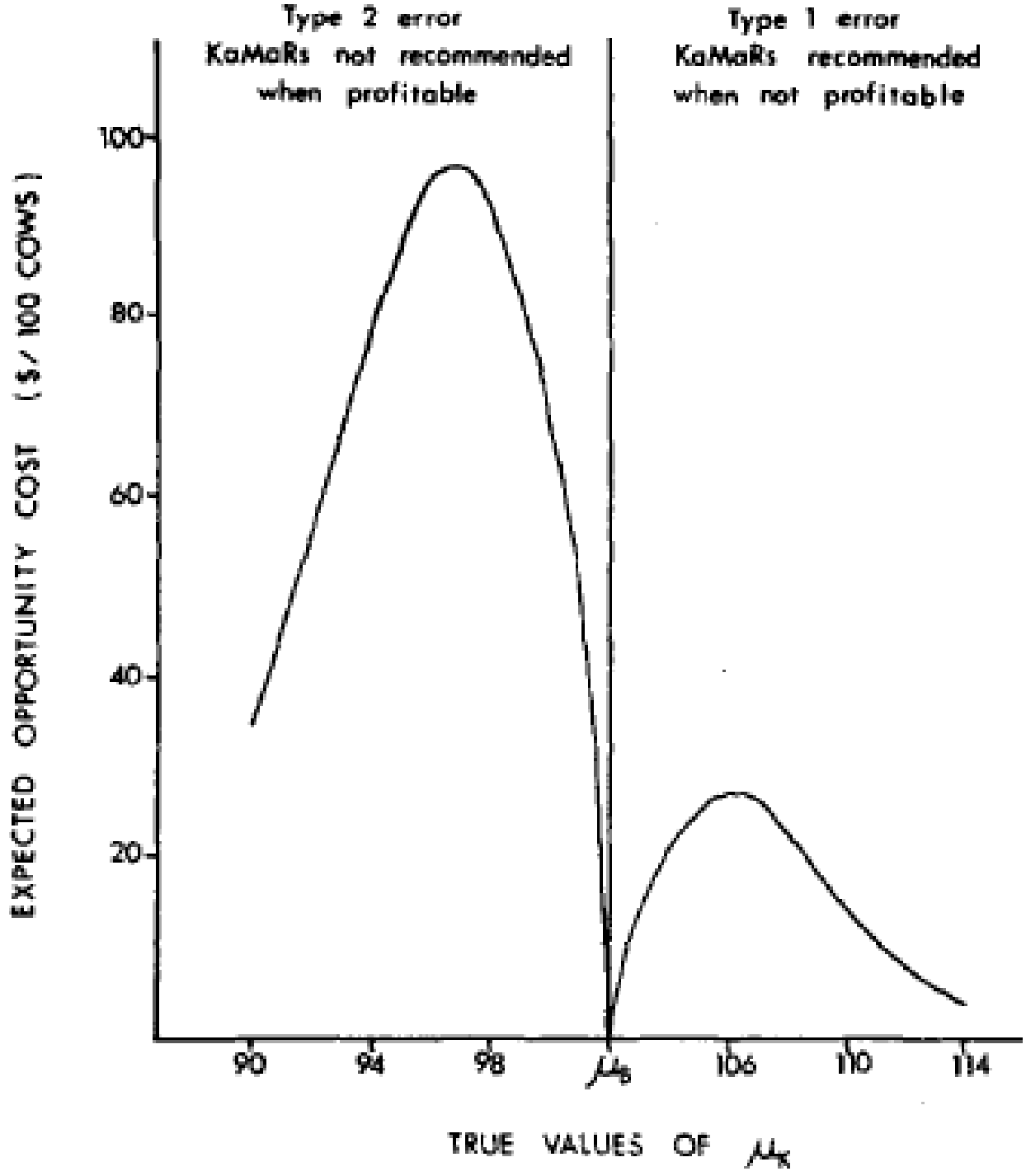


Figure 1.8. Risk curves show the expected opportunity costs of Type 1 and Type 2 errors for the decision to use K-Mar heat detectors in a specific farm (Williamson, 1975).

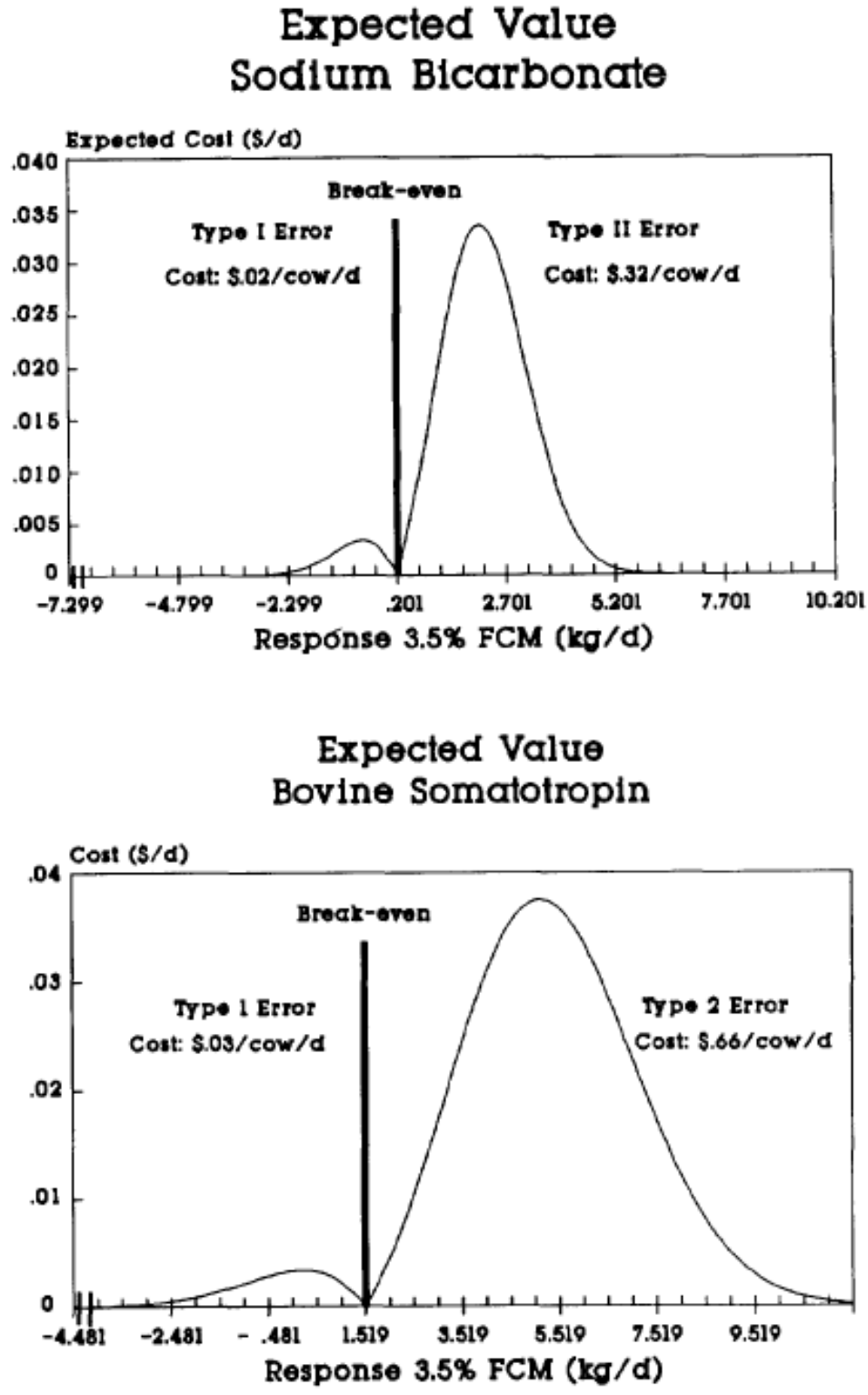


Figure 1.9. Risk curves show the expected opportunity costs of Type 1 and Type 2 errors for the use BiCarb or the use of Bovine Somatotropin from a literature review with multiple trials. (Used with permission) (D. T. Galligan, et al., 1991).

A further development of using the Type 1 and 2 statistical definition to bring clarity to decision making at the farm level was brought forth by Overton, wherein he utilized stochastic inputs from a commercial Monte Carlo simulation program called @Risk (Overton 2006). The author evaluated a simulated farm that used timed AI vs. a simulated farm that used visual estrus detection program and that had a pregnancy rate (**PR**) of 16%. The PR used is a calculation of the cows that became pregnant divided by the cows that were at risk of becoming pregnant during each 21 day period after the cow passes the voluntary wait period for breeding to commence. The farms PR is the average for all cows available for each 21 day period for a 12 month period. Overton simulated input distributions for the AI compliance along with milk price, milk production, and replacement costs. The risk curve output from the Monte Carlo simulation is the result of the computer sampling each distribution as it calculates the partial budget for the change due to the AI intervention. The output reports showed in this simulation there was an 8.6 % chance of the intervention being below break-even and conversely a 91.4% chance that a profit would result from this intervention with utilizing this set of variance and cost structure. The difference in this case is the realization in the model that the amount of money lost if AI had been used when it should not have been, (Type 1 error) is not a single deterministic number. Instead, the loss might have been barely below break-even, perhaps just losing $0.05 per/cow/d. Within the distribution curve, this has a frequency. Conversely, the AI intervention might have lost $1.00 per cow which is less likely in the simulation than losing $0.05 per cow. This also has a frequency in the distribution. Conversely, the AI intervention might have lost $20 per cow. This is not very likely and occupies a point on the frequency distribution far to the left tail. Through repeated sampling, a frequency distribution is obtained, and this frequency distribution can be broken down into very small segments with each segment of frequency

multiplied by the amount lost at this frequency. If the categories are broken down into an infinite number of categories, the loss becomes a continuous function. All of these frequencies multiplied by the cost of the Type 1 intervention can be added together to account for the total estimated cost for the Type 1 error. The same process can be used for the Type 2 error; the AI intervention is not used, when it should have been because mistakenly it is assumed it is of no benefit. This would be the case if the producer was afraid of causing a Type 1 error. Again, the lost income from not using AI is multiplied times the frequency from the sample of the hypothetical population. This lost income (income that wasn't earned) might have been only $0.05. This would be a fairly high frequency because there is higher probability the AI intervention was effective but not greatly effective. Conversely the lost income opportunity might have been $60 per cow, although this is fairly unlikely and occupies a point far to the right-hand tail of the Gaussian distribution curve. Again, as in the Type 1 error calculation, each lost income (cost) amount is multiplied by the frequency this is simulated to occur at, and all the frequency X costs are added up to come up with a total cost of a Type 2 error. These distributions are possible because the outcome is a sample of an unknown population with an unknown true mean, but possessing a set standard deviation based on primary research. If this calculation was made after the program had been used and measured on the farm, we would have known the true mean and the true net profit (Figure 1.10).

Value of Information VOI

Potentially a new area of analysis that has been developing in the human medical literature since the early 1990s is the area of Value Of Information (VOI) (Yokota and Thompson, 2004). This field is directed at the amount of uncertainty in the current research around a specific intervention (drug or practice) and then evaluated for the cost of gathering

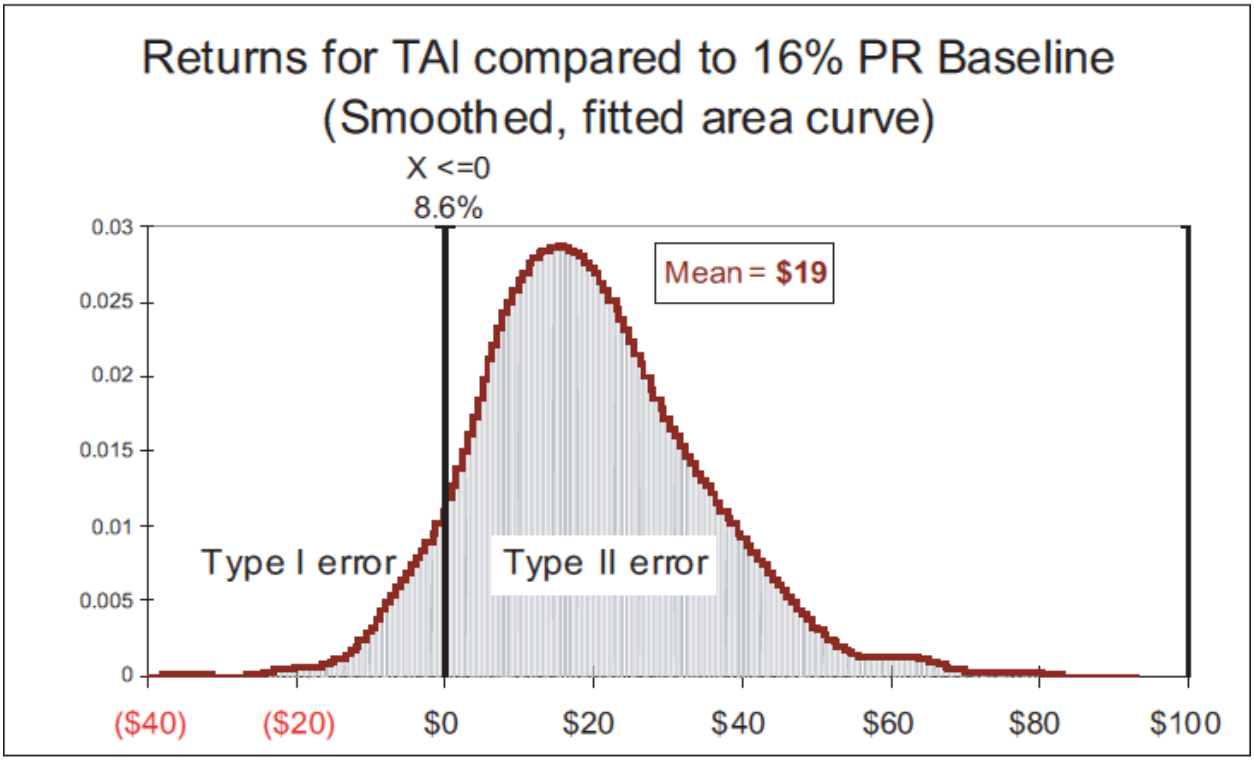


Figure 1.10. Fitted area curve of modeled economic returns and the breakeven point for timed artificial insemination (TAI) as compared to an estrus detection-based program with a 16% baseline pregnancy rate (Overton, M.W, 2006).

more information to reduce the uncertainty versus the value or utility of the intervention or practice. The focus on the VOI models targets a theoretical perfect information in which no uncertainty exists. The value of making a decision based on having no uncertainty is called the Expected Value of Perfect Information (EVPI). EPVI can be calculated by having the outcome of the model under uncertainty or under prior knowledge in a Bayesian statistical model subtracted from the value of the decision under no uncertainty. In some cases, resolving uncertainty before making decisions might have little value to the outcome, while at other times resolving the uncertainty with further information might provide great value that is not intuitively obvious. VOI provides guidance on how decision makers might reduce uncertainty before selecting a course of action (Keisler et al., 2014) The outcomes of the uncertainty can be

plotted as Overton (Overton, 2006) and Galligan (Galligan et al., 1987) did in their models of uncertainty versus the economic outcomes discussed above and then be plotted into efficient frontiers for the values and compared for the best expected utility given the cost of obtaining more information (Eckermann et al., 2010). An early paper in which the author compared the bidding for a construction job and the value in obtaining the bid or losing the bid with and without "clairvoyance" or perfect knowledge of the other firms bid, demonstrated a method for putting a subjective value for improving the knowledge of the outcome or reducing uncertainty by decreasing the uncertainty in bidding for the job (Howard, 1966). His goal was to maximize the expected value of his companies profit or value from a contract. He felt that only when one knows what it is worth to reduce uncertainty do we have a basis for allocating resources in experimentation designed to reduce the uncertainty. While this methodology is increasingly being used in human medicine, the value or utility of the benefit of additional information is difficult to assess. For example what is the value of decreasing gastro-oesophageal reflux disease (GERD) (Eckermann et al., '10) or Alzheimer's disease (Karl Claxton, 2001) in human patients? In contrast to human medicine, in food animal medicine, because the cost of intervention is already taken into account in our decision models, the value of additional information could be readily applied. A literature search in dairy and beef found only one manuscript utilizing VOI currently in these fields (Cox et al., 2005). This model was developed to describe the value of further testing on the US cattle herd to find cases of bovine spongiform encephalitis (BSE) versus the potential lost income from market loss if additional BSE cases were found in the US. Based on the rise in published models that utilized VOI from 11 between 1990 to 92 up to over 65 in 2008-10 (Keisler et al., 2014), it would be expected to see more of these models being developed in animal agriculture in the future.

Summary

Decision analysis is greatly aided by the use of quantitative models that explore the cost-benefit and probabilistic outcomes of decision-making. Prior to the early 1970's there were few models built to explore decisions regarding agriculture. As computers became more accessible, many models were developed. Pioneer developers such as Van Arendonk, Renkema, Dijkhuizen and Galligan along with others originated many of the early models and set the stage for most of the modeling that is being explored today. Many of the early models used rather simplistic, albeit useful partial budgets and decision trees. However, more complex models using dynamic models, Markov chains or linear programing were also among the earliest models. Recent published models have included greater sophistication and complexity, but primarily build on the early models and use the same underlying concepts. The newest group of models built using spreadsheets are gaining in popularity. While these newer models have become increasingly refined and focus on more specific and precise questions, they are more accessible to the decision-makers, as the inputs can be used at the farm level. Additionally, the most recent advancements have benefited from off-the-shelf stochastic programs that aid the decision makers in considering uncertainty and variances that are a key to the inputs and outputs of intervention questions. New stochastic methods incorporating VOI models are increasingly being used in human medicine and other industrial fields and are just now beginning to be used to reduce uncertainty in applying economically justified research in animal agriculture.

CHAPTER 2

OBSERVATIONAL LONGITUDINAL STUDY OF FEED ADDITIVES AS RISK FACTORS FOR HERD DIARRHEA INCIDENTS ON US DAIRY FARMS

Chapter 2 Executive Summary

As measures are enacted to reduce antimicrobial use in agriculture, finding management, feeding practices, and feedstuffs that could decrease diarrhea on dairy farms would be of benefit to animal and human health. Due to the difficulty in performing randomized controlled trials with to test different treatment exposure is difficult in the commercial herd setting, utilizing an observational study design technique may be a valuable means to study diarrhea on commercial dairies. A longitudinal observational study was conducted to assess the incident rate of undifferentiated diarrhea events by month on the farm and study the impact of exposure to different direct fed microbial dietary additives and also to assess the impact of different common farm management practices, and farm design to impact the incidence rate of diarrheal disease. The study design was stratified by region, to target 150 farms in 10 different regions that corresponded to somewhat distinct management and environmental examples. The regions were East, East Plains, Mid-West, Northern California, Northwest, Plains, Southern California, the Southeast, the Southwest, and Wisconsin. A cross sectional survey instrument was administered to collect data relating to disease incident risk factors. Only 76 farms completed both the surveys and supplied electronic backups that provided information on incidents of diarrhea recorded in the herd records system. Sixty-nine farms either did not provide electronic dairy records with the survey, or there was no evidence they electronically recorded diarrhea events.

The remaining 76 herds were analyzed for risk factors for incident of diarrhea using Proc Glimmix in SAS (version 9.4, SAS Institute., Cary, NC), both as a Poisson distribution and as a negative binomial distribution. The final multivariable negative binomial included a yeast culture fermentation product of *Saccharomyces cerevisiae*, whether the farm vaccinated for BVD, and whether the herd was located in the Eastern or Western US. Feeding yeast culture had an Incident Risk Ratio (*IR*) of 0.707 (P = 0.043, CI = 0.505, 0.989). Having a herd in the eastern US was associated with an increased *IR* 2.036 (P = 0.066, CI = 0.953, 4.39). Vaccinating the herd with a BVD vaccine was associated with a decreased *IR* of 0.213 (P = 0.186, CI = 0.022, 2.111). The study shows there is a small association with feeding a yeast culture based additive and lower incidence of diarrhea on farms. This association although small, (a decrease of 2 cases per 1000 cows per month), indicates that further research should be conducted in this area.

Introduction

Similar to many other animal-based agricultural units, a common problem affecting dairy herds is diarrhea. There are few studies of diarrheal disease published where treatment exposure for diarrhea occurrence was a primary outcome of interest in adult dairy cattle. Some of the reasons for this is the relatively low prevalence of acute diarrheal disease (less than 14 days duration) in experimental herd settings, making random control trials difficult. The other issue making experimental settings difficult is there are a variety of etiologic causes that can lead to symptomatic diarrhea in the adult dairy cow of lactating age. Some of these causes are viral (Houe 2003) or bacterial infection (Nielsen 2013), feeding spoiled feed, mycotoxins in the feed (Whitlow and Hagler 2008), or an imbalance in the ration (rapidly fermenting starch or too little effective fiber) (Plaizier et al. 2008, Dijkstra et al. 2012). In the National Animal Health Monitoring Survey conducted in 2007, herd owners were reported as providing information that

35.7% of the dairies had experienced cases of diarrheal disease (lasting longer than 48 hour duration) in their dairy herd and that it affected approximately 2.5% of cows over the course of a year. (NAHMS, 2007). Many herd-level risk factors have been identified that are correlated with diagnostic testing for a bacterial cause of diarrhea in cattle of all ages, of which *Salmonella* is high on the rule-out list for causative factors (Fossler et al. 2005), (Loneragan et al. 2012). In the author's experience, diagnostic testing to confirm *Salmonella* spp. as well as other potentially infectious agents as the cause of diarrhea may be conducted inconsistently. Many dairies have treatment protocols for managing diarrheal disease in calves as well as adult cattle, and some protocols include the use of antimicrobial drugs. However, with increasing concerns over antimicrobial resistance, alternative methods should be considered to treat and/or prevent diarrhea in dairy cattle. One alternative method that has begun to be used more frequently is the use of direct fed microbial products (**DFM**) which we will group under this title for both bacterial derived as well as yeast derived products.

Direct fed microbial products are often added to dairy rations both adult and young stock as an intervention intended to reduce the incidence and severity of diarrheal disease (McAllister et al. 2011), although scientific support for this practice is sparse. In one study calves that were fed a particular DFM in a Salmonella challenge study had a reduction in mortality and diarrhea (Brewer et al., '2014), but there is little published data for adult dairy cows regarding its impact on diarrheal incidence.

Direct fed microbials may be composed of bacteria or products of bacterial growth, as well as live yeasts, yeast cultures and yeast cell wall extracts (Brewer et al. 2014, Di Francia et al. 2008, Seo et al. 2010). The use of certain DFM on farm is purported to positively influence the microbial environment of the gastrointestinal tract and/or the immune system of dairy cattle.

Because the etiology of diarrhea in dairy cattle is not consistently determined, treatment protocols for diarrhea differ among farms, and because different dairy farmers may choose to add DFM to rations for different reasons, developing and conducting well-controlled prospective experiments on the effect of DFM on the incidence and severity of naturally-occurring diarrhea would be difficult on commercial dairies. In addition, misclassification of diarrheal disease by farm workers and lack of diagnostics due to the expense of using laboratory testing to confirm a specific case definition for diarrheal disease, makes ascertaining both the incidence and therefore the treatment effect very difficult.

Epidemiologic principles using an observational longitudinal design have been used in human public health to ascertain risk factors that impact the frequency of many diseases (Mahmood et al. 2014). Applying the use of an observational longitudinal study for diarrheal disease may enable detection of changes in the incidence rate of diarrheal disease among dairy farms that do or do not include DFM in the ration. Therefore, an observational longitudinal study was conducted to determine if the use of DFM in the feed rations was associated with the incidence of undifferentiated diarrheal disease in adult dairy cows in US dairy farms.

Materials and Methods

Overview

A longitudinal observational study was conducted on herds enrolled from a listframe. The farms were stratified by geographical region, and randomly selected from the list using a randomized number generated in a spreadsheet and assigned to each herd. The herds were then listed in order by randomized number and the first 30 herds selected. Herd management was characterized by an interview using a standardized questionnaire. Recorded diarrheal disease occurrence was collected from an on-farm computerized commercial management software

program (DC305, PCDart, DHI Provo) for two different time windows, retrospectively for twelve months prior to the interview and then for six months following the initial interview. The population of cows at risk for each month was obtained from the herd management software, and the adjusted incident rates were estimated using negative binomial regression and compared among cattle exposed to different DFM products.

Study Population

The list frame of herds eligible for inclusion in the study was obtained from the CRM (Customer Relations Management Software, Microsoft) database established by Diamond V (Cedar Rapids, IA). The database was developed from the list of all dairies in each state with grade A milk permits. It was a large comprehensive database of a majority of the dairy herds in the US. All herds in the database with greater than 500 cows were included in the initial list frame for randomization. The sample size of 150 dairies each accounting for 12 months of cows at risk assuming 50% of the farms were exposed to the DFM of interest resulting in a change of incidence rate of 2% to 1% or a 50% change due to the exposure of interest was thought to be a meaningful biological and economic change to the dairy and to achieve statistical significance with the associated variability in the population. The population was stratified into ten regions based on perceived regional differences in management style and production strategies. The list frame consisted of the following regional strata: Northern California, (Fresno area north (North of Hwy 180)), Southern California, (Fresno area South of Hwy 180), the Pacific-Northwest, (Washington, Oregon, Idaho, Utah), Southwest (New Mexico, Texas, Arizona), East Plains, (Iowa, Minnesota, North and South Dakota), Plains (Colorado, Kansas, Oklahoma), East (all states east of Ohio and north of Georgia), Southeast, (Florida, Georgia, Alabama, Tennessee, Kentucky, Mississippi), Midwest, (Michigan, Ohio, Indiana, Illinois, Missouri), and Wisconsin

with a target of enrollment of 15 herds from each region. The herds within each cluster were randomly chosen by electronic randomization and listed in order.

A cross-sectional survey instrument was reviewed and approved by the Colorado State University Institutional Review Board. The survey instrument was tested on a small group of nine farms and changes were made to improve the clarity. The first 36 herds in each stratum were sent a letter from Colorado State University asking for their participation in the survey. The Diamond V Mills technical sales staff was trained to administer a survey instrument (Appendix B) in April 2013. Farm enrollment occurred from June 2013 to August 2013, with a second visit to the dairy scheduled to occur between January 2014 and March 2014, but not less than 6 months between visits to collect the prospective 6 months' data. Each farm was visited by one of the technical sales team members from Diamond V within two months starting in June 2013 and asked to participate in the survey. Enrollment was to continue until 15 herds from each region agreed to participate. The survey was conducted verbally with the owner or herdsman. The surveyor made a determination of who the appropriate person was on the farm with sufficient knowledge to answer the questions. A copy of the data recorded in the electronic recording system was obtained at the time of the survey on a USB stick and transferred to a central location for analysis.

During the survey visit, first, the owner or herdsman was asked questions that qualified the herd as meeting the criteria for the survey and the study goals and methods were explained. If the dairy did not meet the criteria, the interviewer did not collect electronic health event information. To be included in the study, the farm must have used either PC Dart, DC305, or DHI-Provo as their management software at the time of enrollment. Health events must have been recorded electronically with the recording of some event for diarrhea incidence. If no

diarrhea designations were recorded, the farm was asked and the farm had to agree to begin recording diarrhea health events up until the next set of records was obtained. The dairy herdsman, owner, or dairy nutritionist must have been able to successful recall if and when a DFM was fed to the herd regime. A DFM was only designated to having been fed if greater than half the milking cows were being fed the DMF on a continual basis. If only the dry cows or cows in the fresh pen were fed the additive, the additive was counted as not being fed at the herd level. If the farm representative declined to participate in the survey and data collection, or the farm did not meet the criteria, the interviewer moved to the next farm on the random herd list and continued to recruit farms until 15 herds were enrolled in a region or the list for the region was exhausted, i.e. no further herds were available from the list frame for that region. The enrolled farm was revisited to pick up another record backup 6 months after the first visit which would provide a total of 18 months of health events for each farm.

The purpose of the management questionnaire (cross sectional survey) was primarily to characterize the exposure information on DFM products used. The secondary goal was to characterize factors that could affect diarrheal disease occurrence, or could otherwise serve as confounding factors in diarrheal disease incident rate. The DFM categorical variables included in the questionnaire were *Saccharomyces cerevisiae* fermentation products, (SCFP, Diamond V, Cedar Rapids, IA), Bovamine, (division of Chr. Hansen Holding A/S, Demark), Celmanax, (Arm and Hammer Animal Nutrition, Princeton, New Jersey), Amax, (Arm and Hammer Animal Nutrition, Princeton, New Jersey), Amaferm (Biozyme Inc., St. Joseph, MO), Omnigen, (Philbro Animal Health Corporation, Teaneck, NJ), and any active dry yeast (**ADY**), or other DFM products. Other categorical variables captured in the survey included breed, (i.e. Holstein, Jersey or other breeds), type of facility, (dry lot, traditional free stall barn, cross ventilated, tunnel

ventilated, Saudi style barns or tie stall barn), type of milking parlor, (rotary, parallel, herringbone parlor), and diet type, (TMR or grazing), (there were no grazing dairies). The survey included questions to determine what vaccinations were given (yes or no) to the cows that might lead to a difference in diarrhea rates. These included vaccinations for Bovine Viral Diarrhea, (**BVD**) (any brand of vaccine that include BVD), *Salmonella* Newport Bacterial Extract SRP CattleVaccine, (**SRP**) (Zoetis Animal Health, Parsippany, NJ), Enviracor J-5 E. Coli Bacterin Cattle Vaccine, (**J5**) (Zoetis Animal Health, Parsippany, NJ), Endovac-Bovi, (IMMVAC, Columbia MO), any autogenous vaccine for *Salmonella* or *Escherichia* coli, or the use of Rumensin, (Elanco, Greenfield, ID). The type of DFM fed on the farm along with the dates the farm started and stopped feeding the DFM were documented and included in the analysis. If the DFM being fed was changed, or if the farm started feeding a DFM during the months for which the health events were obtained, recorded health events were not used in the study for a period of 4 weeks rounded to the nearest month after the change was initiated. If the farm stopped feeding the DFM, recorded health events were also not included in the month the change in feeding took place. For the farm to be considered as feeding a DFM, more than 50% of the herd had to be fed the additive for a minimum of one month (30 consecutive days) prior to the date of enrollment

Analysis

The case definition was undifferentiated diarrhea severe enough to be recorded in the electronic data base. The assumption was that severe diarrhea would be moved to a hospital pen for treatment and therefore be recorded for move and treatment. The data regarding farm management and diarrheal diseases were collated into single database and descriptive statistics were analyzed. The data were analyzed at the herd level, with outcome, population at risk, and exposures quantified for each month that herds provided data. Associations between monthly

diarrheal disease occurrence and exposures that may have affected disease incidence were analyzed using a mixed linear model (Dohoo, Martin, and Stryhn 2009a). The model was built using Proc Glimmix of SAS (Version 9.4, SAS Institute, Cary, NC, 2002-2012) with both a Poisson and negative binomial link function. If the dispersion parameter generated from the Poisson regression was different from 1.0, indicating there was significant over dispersion, then the negative binomial model was used. The outcome variable for these models was the count of reported diarrheal disease occurrence per month on a farm; the offset was the natural log of the herd population count for the same month. Farm was analyzed as a random intercept, and data for different months were specified as a repeated measure for each farm. The primary exposure variable of interest was exposure to different DFM products. Each product was specified as a different binary (yes/no) variable. Region was analyzed as a single fixed effect variable with 10 categories, and also as a binary (East/West) variable. Month was analyzed as a multivariable model with each month separately and then collapsed into Quarters Q1 = January, February, March, Q2 = April May June, Q3 = July, August, September, and Q4 = October, November, December), to see if Quarters were significant determinant of a change in frequency of diarrhea. Exposure to the nine vaccines of interest were analyzed as separate binary (yes/no) variables. Breed was analyzed as two binary (yes/no) variables, one for Holsteins, and another for Jerseys; there were no other breeds represented in the study population. Facility type was analyzed as two binary variables for farms that were constructed with dry lots (yes/no) and those with free stalls (yes/no). Other management/construction features were also analyzed as binary variables for rotary milking parlors (yes/no), parallel parlors (yes/no), herringbone parlors (yes/no), tunnel ventilated barns, and cross-ventilated barns (yes/no). Each of these exposure variables was used to create a univariable model. Variables that had *P* values < 0.2 were included in multivariable

model development, and backward selection was used to remove variables until all variables included in the final multivariable model using a critical alpha for retention of 0.1. Region was analyzed as a binary (East/West) variable for multivariable model building. Variables that were removed during multivariable model building were reintroduced singly into the final model to identify potential confounding; variables demonstrating substantial confounding were evaluated to determine an appropriate method for modelling or removed (Dohoo, Martin, and Stryhn 2009b).

If the farms failed to have diarrhea in their events health table, the farm records were analyzed to find if diarrhea events were recorded under other variables such as "scours". Many farms did have diarrhea recorded under different names or as comments in the tables. These were manually extracted for each of the farm's records and coded as diarrhea in the database. If the computer records contained records of at least 1 diarrhea events for the farm, the months following the diarrhea event were included in the analysis even if there were zero (0) incidents for subsequent months.

The Incidence Rate Ratio (*IR*) was calculated from the parameter estimate in the GLIMMIX model by taking the anti-log of the 2 Res Log Pseudo Likelihood estimate. The base herd with the reference values was calculated from the antilog of the intercept multiplied by 1000 to calculate the estimated incident rate of diarrheal disease per 1000 cows per month. The effect of the exposure variable on the incident rate was calculated by multiplying the *IR* of that parameter times the *IR* of the base herd (the intercept parameter). The change in incidence is the difference in these values.

Results

One hundred and forty-five dairies agreed in the study. Of the 145 dairies, 69 herds either did not record diarrhea incidents on their farm or refused to provide the dairy records. Only 76 of the dairies provided dairy records that contained diarrhea events for at least 1 month in which there was a recorded diarrhea event.

The strata for the regions did not occur as originally planned. The original plan was to include data from 15 of the 36 herds approached for each region. However, 8 of the regions still did not achieve 15 herds that agreed to participate or qualified to participate prior to exhausting all of the herds for that region in the listframe. Two of the regions, the Southwest and the East Plains were able to collect more than the first 15 herds on the list. Due to the lack of response in some regions, the extra records from the regions with extra responses were used in the analysis (Table 2.1). Region was analyzed as a multivariable regression using all 10 regions regressed against diarrheal events. Although there were more farms used in some regions than others, there was no effect of region with East Plains being the lowest ($P < 0.19$) for the outcome diarrhea events.

Table 2.1. Dairy farms responding to a cross sectional survey for the impact of Direct Fed Microbials on incident of diarrhea, stratified by region. For each dairy with a response to the survey, this table shows which ones provided any diarrhea information and of the farms that provided information, how many months of data were included.

Region[1]	No Diarrhea[2]	Diarrhea[3]	Months of Data [4]
East	24	3	23
East Plains	6	28	410
Mid-West	4	8	98
N. California	16	4	54
Northwest	1	4	61
Plains	4	3	39
S. California	2	1	14
Southeast	1	0	0
Southwest	8	24	302
Wisconsin	3	1	10
Grand Total	**69**	**76**	**1019**

[1] Regions for East = MD, ME NC, NH, NY, PA, SC, VA, VT. East Plains = IA, MN, NE, SD. Mid-West = IL, IN, MI, MN, MO, ND, OH. N. California = Fresno addresses north. Northwest = ID, OR, UT, WA. Plains = CO, KS, OK, WY. S. California = addresses S of Fresno. Southeast = AL, FL, GA, KY, MS TN. Southwest = AZ, NM, NV, TX. Wisconsin = Wisconsin.

[2] Number of dairies by region that responded to the survey but the farm lacked any information in the herd record data set that indicated they recorded diarrhea in any form.

[3] Number of dairies by region that responded to the survey questions that had records of diarrhea incident recorded for at least 1 month.

[4] Months of incident rate data for each region that contributed information. The monthly data was a repeated measure in the analysis.

The average size of the dairies participating in the study was 2,886, with the smallest dairy having 510 cows in the herd and the largest dairy 12,291 cows (Table 2.2). The number of months of recorded data was very variable due to some farms only providing the previous 12 months of records and not records during the follow-up visit (the additional 6 months). Some of the farms were new start-ups and did not have 12 months of data. Also, some farms started using a new record keeping system within the year previous to the initial survey or did not record diarrhea for

the entire 12 to 18 month study period. In addition, not all the surveys had complete sets of information for each data point. Surprisingly, many farms indicated they fed more than one DFM at the same time (Table 2.3). In the statistical analysis, each predictor variable was analyzed as a separate variable in the univariable analysis. No interactions for the different combinations were analyzed because there were insufficient numbers of the combinations of additives.

The dataset was analyzed both as a Poisson distribution and as a negative binomial distribution. The negative binomial distribution was used as a better model fit based on the -2 Res Log Pseudo-Likelihood fit of 2870.0 versus 4492.64, and a generalized Chi-Square/Df close to 1 (1.13).

Table 2.2 Herd size statistics for herds responding to cross sectional survey and longitudinal study of the impact of DFM on diarrheal incident in 2013.

Number of Dairy Cows	
Min	510
Max	12,291
25th Q	1,275
50th Q	2,245
75th Q	3,897
Average	2,886
Median	2,245

Table 2.3 Number of farms with individual categories of variables from cross sectional survey and longitudinal study of the impact of different DFM and their impact on diarrheal disease in dairy herds in the US in 2013.

	Number of Farms[1]	**% of Farms**
Breed		
Holstein	68	89.5%
Jersey	12	15.8%

		Number of Farms[1]	% of Farms
Housing Type			
	DryLot no freestalls	18	23.7%
	Conventional Freestall	49	64.5%
	Cross Ventilated	8	10.5%
	Tunnel Ventilated	3	3.9%
	Saudi Style	1	1.3%
Parlor Type			
	Rotary	13	17.1%
	Parallel	54	71.1%
	Herringbone	9	11.8%
Feeding Method			
	Total Mixed Ration	76	100.0%
	Graze	0	0.0%
Vaccinations			
	Infectious Bovine Rhinotracheitis	73	96.1%
	Bovine Viral Diarrhea	73	96.1%
	Any Diarrhea Vaccine	72	94.7%
	SRP Salmonella Newport Extract Bacterin	56	73.7%
	Enviracor J-5 E. Coli Bacterin	57	75.0%
	Any Autogenous Vaccine	8	10.5%
	Endovac Bovi	17	22.4%
	Any Ecoli Scours Vaccine	23	30.3%
Direct Fed Microbial			
	DV SCFP	48	63.2%
	Bovamine	11	14.5%
	Celmanax	11	14.5%
	Amax	3	3.9%
	Amaferm	1	1.3%
	Active Dry Yeast	2	2.6%
	Omnigen	11	14.5%
	Any other DFM	5	6.6%
Rumensin			
		62	81.6%

[1] Farms that were analyzed with this variable.

In the univariable model, (Table 2.4) each outcome variable reported the effect measure which was the Log Pseudo Likelihood estimate of the incident (**ln*I***) of the number of diarrhea incident for herd of 1 cow per month. In each case of the predictor variable for DFM the reference case was the control or herds not fed the DFM and the table reports the effect of feeding the product. Likewise, in the farm management analysis, not using this particular farm design or parlor type is the reference and the effect represents the management in question. For example, in (Table 2.5), Drylot represents herds that primarily used a drylot system versus all other type of systems, (Freestall, Cross Ventilated, and Tunnel Ventilated Barns). Likewise, for vaccination type, the VaccBVD represents herds that declared they used some brand of vaccination for BVD.

Table 2.4. Dairy Farms responding to a cross sectional survey performed in 2013 for diarrheal incident relationship to what feed additives (Direct Fed Microbials) were fed. The responses are broken into East and West Region showing how many farms responded for each additive or additive combination, whether or not they provided records on diarrhea incident.

Direct Fed Microbials [1]	**East** [2]	**West** [3]
Amax [4]	13	12
Bovamine [5]	27	34
Celmanax [6]	2	0
DV SCFP [7]	242	229
Other DFM [8]	26	0
Bovamine + Celmanax +_Amax	1	0
Bovamine + DFM	0	1
Celmanx + Amax + Omnigen[9]	0	10
Celmanax + Amaferm[10] + Omnigen	12	0
Celmanax + Omnigen	30	11
DV SCFP + ADY[11]	0	18
DV SCFP + Bovamine	25	36
DV SCFP + Bovamine + Amax	0	1
DV SCFP + Bovamine + Amax	1	0
DV SCFP + Bovamine + Celmanax + ADY + Omnigen	18	0

Direct Fed Microbials [1]	East [2]	West [3]
DV SCFP + Bovamine + Celmanax + Omnigen	20	0
DV SCFP + Celmanax	6	1
DV SCFP + Celmanax + Omnigen	46	12
DV SCFP + DFM	13	19
No Data	0	15
No Feed Additive	105	103

1. Direct Fed Microbials reported to be fed for each month of data per farm. Rows with multiple products indicate the farms that reported to feed multiple product simultaneously.

2. Regions for East = MD, ME NC, NH, NY, PA, SC, VA, VT, IA, MN, NE, SD, IL, IN, MI, MN, MO, ND, OH.

3. Regions for the West= CA, ID, OR, UT, WA, CO, KS, OK, WY AZ, NM, NV, TX.

4. Amax is a yeast culture of *Saccharomyces cerevisiae* fermentation manufactured by Arm and Hammer Animal Nutrition of Princeton, NJ.

5 Bovamine, a bacterium of *Lactobacillus acidophius* NP51 and *Propionibacterium freudenreichii* NP24 fed as a direct fed microbial is manufactured by Nutrition Physiology Company, a division of Chr. Hansen Holding A/S, Demark.

6 Celmanax is a combination *Saccharomyces cerevisiae* fermentation product and yeast cell wall carbohydrates (MOS). It is manufactured by Arm and Hammer Animal Nutrition, Princeton, NJ.

7 Diamond V is yeast culture, *Saccharomyces cerevisiae* fermentation product manufactured by Diamond V, Cedar Rapids, IA.

8 Other DFM is any direct fed microbial, either bacterial or yeast based that was reported fed not included in the list of branded products.

9 Omnigen is manufactured by Phibro Animal Health Corp, Teaneck, NJ.

10 Amaferm is a fermentation product of *Aspergillus oryzae* manufactured by BioZyme, St. Joseph, MO.

11 ADY is Active Dry Yeast by any manufacturer.

Table 2.5. Univariable Table**.** Direct Fed Microbials fed to dairy farms analyzed as of categorical univariate variables [1] when analyzed for "not treated =(ref)" vs. treated on the log of the incidence of diarrhea in an observational longitudinal study.

Predictor Varialble[2]	2 Res Log Pseudo Likelihood (Estimate [3])	SE	*P* value	Lower CL	Upper CL	Incident Rate Ratio [4]	*IR* Lower CL	*IR* Upper CL
Direct Fed Microbial								
DV SCFP [5]	-0.352	0.172	0.041	-0.691	-0.014	0.703	0.501	0.986
Bovamine [6]	-0.526	0.555	0.343	-1.615	0.562	0.591	0.199	1.755
Celmanax [7]	0.602	0.532	0.257	-0.441	1.645	1.826	0.644	5.183
Amax [8]	-0.639	0.961	0.506	-2.525	1.246	0.528	0.080	3.476
Amaferm [9]	2.160	1.621	0.183	-1.022	5.341	8.669	0.360	208.763
ADY [10]	0.416	1.167	0.722	-1.875	2.707	1.516	0.153	14.984
OtherDFM [11]	1.138	0.763	0.136	-0.360	2.636	3.121	0.698	13.954
Rumensin [12]	0.678	0.484	0.161	-0.271	1.628	1.971	0.763	5.092
Omnigen [13]	0.606	0.547	0.268	-0.467	1.680	1.834	0.627	5.364
Breed								
Holstein [14]	-0.145	0.620	0.816	-1.361	1.072	0.865	0.256	2.920
Jersey [15]	0.441	0.518	0.395	-0.575	1.457	1.554	0.563	4.291
Facility type								
DryLot [16]	-0.471	0.453	0.299	-1.360	0.418	0.625	0.257	1.519
Freestall [17]	0.692	0.394	0.079	-0.081	1.464	1.997	0.923	4.325
Farm Management							**1.000**	**1.000**
CrossVent [18]	-0.278	0.629	0.659	-1.512	0.957	0.758	0.220	2.603
Tunnel [19]	0.245	0.973	0.801	-1.665	2.156	1.278	0.189	8.634
Rotary [20]	0.780	0.494	0.115	-0.189	1.750	2.182	0.828	5.754
Parallel [21]	-0.407	0.418	0.330	-1.226	0.413	0.666	0.293	1.511

Predictor Varialble[2]	2 Res Log Pseudo Likelihood (Estimate [3])	SE	*P* value	Lower CL	Upper CL	Incident Rate Ratio [4]	*IR* Lower CL	*IR* Upper CL
Vaccination								
VaccBVD [22]	-1.951	1.159	0.093	-4.225	0.323	0.142	0.015	1.381
VaccSRP [23]	0.555	0.449	0.217	-0.327	1.436	1.742	0.721	4.205
VaccJ5 [24]	0.480	0.450	0.287	-0.404	1.363	1.615	0.668	3.906
EndoVac [25]	-0.284	0.462	0.539	-1.191	0.623	0.753	0.304	1.864
VaccEcoliOther [26]	0.192	0.422	0.649	-0.636	1.020	1.212	0.529	2.773
Anydiavac [27]	1.108	0.788	0.160	-0.439	2.654	3.027	0.645	14.207
Region [28]								
East	0.973	1.660	0.558	-2.285	4.230	2.645	0.102	68.731
East Plains	1.603	1.230	0.193	-0.811	4.016	4.966	0.445	55.473
Mid-West	1.682	1.321	0.203	-0.910	4.274	5.377	0.403	71.823
N. California	1.594	1.443	0.270	-1.238	4.427	4.924	0.290	83.647
Northwest	-0.377	1.451	0.795	-3.224	2.469	0.686	0.040	11.814
Plains	1.745	1.513	0.249	-1.225	4.714	5.724	0.294	111.486
S. California	-0.751	2.055	0.715	-4.784	3.281	0.472	0.008	26.597
Southwest	0.628	1.236	0.611	-1.797	3.054	1.874	0.166	21.194
Wisconsin	0.000					1.000		
Catagorical Region [29]								
East	0.825	0.376	0.028	0.087	1.564	2.283	1.091	4.776
West	0.000					1.000		
Quarter [30]							**1.000**	**1.000**
1	-0.108	0.068	0.114	-0.242	0.026	0.898	0.785	1.026
2	-0.052	0.069	0.452	-0.188	0.084	0.949	0.828	1.088

Predictor Varialble[2]	2 Res Log Pseudo Likelihood (Estimate [3])	SE	*P* value	Lower CL	Upper CL	Incident Rate Ratio [4]	*IR* Lower CL	*IR* Upper CL
3	0.004	0.065	0.950	-0.124	0.132	1.004	0.884	1.141
4	0.000					1.000		

[1] The coefficients from the negative binomial regression model are given in terms of the log of the incident (ln*I).* The coefficient represents the amount (ln*I*) is expected to change with a unit change in the predictor (Dohoo, Martin, and Stryhn 2009b). Modeled using SAS 9.4 GLIMMIX. SAS Institute Inc., Cary, NC.,. Farm is a random intercept. This model is a negative binomial model to account for over dispersion in the Poisson model. The natural log of the herd cow numbers is the offset variable.

[2] Categorical treatment variables were modeled as univariable "treated" or "not treated" in the model.

[3] For the estimate coefficient the non-treated effect is the reference. The coefficient is the ln*I* for the unit change in cases of for being or using the categorical variable.

[4] The incident rate ratio (*IR*) is the natural antilog of the ln*I*. The *IR* represents the proportional increase in *I* for a unit change in the predictor. An *IR* of 1 is no change. An *IR* of 1.5 would be a 50% increase. In the case of the DFM predictors the proportional change for feeding the product.

[5] Diamond V is yeast culture, *Saccharomyces cerevisiae* fermentation product manufactured by Diamond V, Cedar Rapids, IA.

[6] Bovamine, a bacterium of *Lactobacillus acidophius* NP51 and *Propionibacterium freudenreichii* NP24 fed as a direct fed microbial is manufactured by Nutrition Physiology Company, a division of Chr. Hansen Holding A/S, Demark.

[7] Celmanax is a combination *Saccharomyces cerevisiae* fermentation product and yeast cell wall carbohydrates (MOS). It is manufactured by Arm and Hammer Animal Nutrition, Princeton, NJ.

[8] Amax is a yeast culture of *Saccharomyces cerevisiae* fermentation manufactured by Arm and Hammer Animal Nutrition of Princeton, NJ.

[9] Amaferm is a fermentation product of *Aspergillus oryzae* manufactured by BioZyme, St. Joseph, MO.

[10] The category ADY is any active dry yeast as identified in the dairy survey.

[11] Any DFM was any DFM not specifically identified in another category in the dairy survey.

[12] Rumensin is monensin a feed additive antibiotic that targets gram positive rumen bacteria manufactured by Elanco, Greenfield, ID.

[13] Omnigen is manufactured by Phibro Animal Health Corp, Teaneck, NJ.

[14] The categorical predictor variable Holstein is tested against the reference value of any other breed of cows "not Holstein" which would be Jersey, cross-breds and others.

[15] The categorical predictor variable Jersey is tested against the reference value of any other breed of cows "not Jersey" which would be cross-breds, Holstein and others.

[16] Drylot is farm management system where cows are not kept indoors but are housed out of door in dirt lots, not in pasture with or without shades.

[17] Freestall barns are farm management systems in which the cows are kept indoors with or without access to exercise lots where the cows are bedded in freestalls and naturally ventilated. The reference for this predictor variable would be any other type of management system including drylot, crossvent, or tunnel ventilated barns.

[18] Crossvent is a farm management system in which cows are housed in cross ventilated barns. They are typically in freestalls and the air is moved under pressure across the narrow access of the rectangular barn. The reference for this predictor variable would be any other type of management system including freestall, drylot, or tunnel ventilated barns.

[19] Tunnel is a farm management system in which cows are housed in tunnel ventilated barns. They are typically in freestalls and the air is moved under pressure down the long axis of the rectangular barn. The reference for this predictor variable would be any other type of management system including freestall, drylot, or cross ventilated barns.

[20] Rotary is farm systems in which cows are milked on a rotary platform. The reference for this predictor variable would be any other type of milking system which is herringbone or parallel parlors.

[21] Parallel is farm systems in which cows are milked in a parallel milking parlor. The reference for this predictor variable would be any other type of milking system which is herringbone or rotary parlors.

[22] VaccBVD is a predictor variable yes or no if farm vaccinated cows with vaccine containing any brand with antigens against BVD.

[23] VaccSRP is a predictor variable yes or no if farm vaccinated cows with Salmonella Newport Bacterial Extract SRP CattleVaccine. It is a vaccine containing SRP technology (siderophorne receptors and porins). This vaccine is manufactured by Zoetis Animal Health, Parsippany, NJ.

[24] VaccJ5 is a predictor variable yes or no if farm vaccinated cows with Enviracor J-5 E. Coli Bacterin Cattle Vaccine. This vaccine is specific of ecoli mastitis but some people feel it may reduce diarrhea as well. This vaccine is manufactured by Zoetis Animal Health, Parsippany, NJ.

[25] EndoVacc is a predictor variable yes or no if farm vaccinated cows with Endovac-Bovi which is a gram negative mastitis vaccine manufactured by IMMVAC of Columbia MO. Many people feel it may cross protect against diarrhea in the cows as well.

[26] VaccEcoliOther is a predictor variable yes or no if farm vaccinated cows with any other brand of ecoli vaccine as well as bactrins.

[27] Anydiavac is a predictor variable yes or no if farm vaccinated cows with any vaccine directed against a diarrhea type outcome.

[28] Region was a multivariable predictor variable consisting of the region wherein the farm was located. Regions for **East** = MD, ME NC, NH, NY, PA, SC, VA, VT. **East Plains** = IA, MN, NE, SD. **Mid-West** = IL, IN, MI, MN, MO, ND, OH. **N. California** = Fresno addresses north. **Northwest** = ID, OR, UT, WA. **Plains** = CO, KS, OK, WY. **S. California** = addresses S of Fresno. **Southwest** = AZ, NM, NV, TX. Wisconsin = WI was the reference value.

[29] West or East was a collapsing of the regions into either western herd (N. California, S. California, Pacific NW and Plains), vs the eastern herd (East, East Plains, Wisconsin, and the Midwest). The west was the reference value.

[30] Quarter is a multivariable categorical predictor variable for the quarters of the year. 4th quarter is the reference quarter.

The results of the univariable analysis for parameter estimates with *P* values less than 0.20 which were included for backward selection using a critical alpha for retention of 0.1 were, DV SCFP (*IR* = 0.703, *P* = 0.041), Amaferm (*IR* = 8.669, *P* = 0.183), Other DFM (*IR* = 3.121, *P* = 0.136), Rumensin (*IR* = 1.197, *P* = 0.161), Freestall (*IR* = 1.997, *P* = 0.079), Rotary (*IR* = 2.182, *P* = 0.115), Vaccinate with BVD (VaccBVD) (*IR* = 0.142, *P* = 0.093), Any diarrhea vaccination (Anydiavac) (*IR* = 3.027, *P* = 0.160), East Plains (*IR* = 4.966, *P* = 0.193), East Region (*IR* = 2.283, *P*=0.028), 1st Q (*IR* = 0.898, *P* = 0.114). When region was collapsed into East (East, East Plains, SE, Wisconsin, and the Midwest) or West (N. California, S. California, Pacific NW, SW, and Plains), the category was significant (*P*=0.028) with West used as the reference region. A herd in the East had an *IR* of 2.28 showing an increased risk of >200% for diarrhea incidents per month /1000 cows over the base herd in the West region represented by the intercept.

The final model (Table 2.6) results showed feeding DV SCFP had an *IR* = 0.707 when controlling for herds that vaccinated for BVD and if the herd was in the East or West which represents about a 30% decrease in risk versus a herd not feeding DV SCFP or a decrease of 2.03 diarrhea events / 1000 cows per month when compared to the base (intercept) herd. The increase in diarrhea events for a dairy being in the east while controlling for the other parameters was an *IR* of 2.036 or about a 200 % increase. This tells us that herds in the east reported about 14 cases per 1000 cows per month with a CI of 6 to 30 cases (Dohoo, Martin, and Stryhn 2009b). Vaccinating for BVD while not significant in the final model was forced in due to the high IR and its near significance in the univariable model (*IR* = 0.213).

Table 2.6. The final multivariable model for the risk due to certain categorical variables on diarrheal incident on US dairy farms from and observational longitudinal study.

Predictor Varialble[2]	-2 Res Log Pseudo-Likelihood (Estimate [3])	SE	*P* value	Lower CL	Upper CL	Incident Rate Ratio [4]	*IR* Lower CL	*IR* Upper CL
Intercept	-4.972	1.202	<.0001	-7.370	-2.575	0.007	0.001	0.076
DV SCFP[5]	-0.347	0.171	0.043	-0.684	-0.011	0.707	0.505	0.989
VaccBVD[6]	-1.545	1.168	0.186	-3.837	0.747	0.213	0.022	2.111
East[7]	0.711	0.387	0.066	-0.048	1.470	2.036	0.953	4.349

[1] The coefficients from the negative binomial regression model represent the log of *I* (incident) (ln*I*) is expected to change with a unit change in the predictor (Dohoo, Martin, and Stryhn 2009b). Modeled using SAS 9.4 GLIMMIX. SAS Institute Inc., Cary, NC., 2016. Farm is a random intercept. This model is a negative binomial model to account for over dispersion in the Poisson model. The natural log of the herd cow numbers is the offset variable.

[2] Categorical treatment variables were modeled as control or treated with control being the reference.

[3] For the estimate coefficient the non-treated effect is the reference. The coefficient is the ln*I* for the unit change in cases of for being or using the categorical variable.

[4] The incident rate ratio (*IR*) is the natural antilog of the ln*I*. The *IR* represents the proportional increase in *I* for a unit change in the predictor. An *IR* of 1 is no change. An *IR* of 1.5 would be a 50% increase. The control is the reference.

[5] Diamond V is yeast culture, *Saccharomyces cerevisiae* fermentation product manufactured by Diamond V, Cedar Rapids, IA.

[6] Herd not receiving vaccination for Bovine Viral Diarrhea of any brand.

[7] Herd are located in the east region versus the west. These regions were West equals Northern California (Fresno area north) Southern California, (Fresno area south), the Pacific-Northwest, (WA, OR, ID, UT), Southwest (NM, TX, AZ), and Plains (CO, KS, OK). The East region was East Plains (IA, MN, ND and SD), East (MD, ME NC, NH, NY, PA, SC, VA, VT), Midwest (IL, IN, MI, MN, MO, ND, OH.

Discussion

Diarrhea is a major health problem on dairy farms, but the exact extent is not known because farms might not always record diarrhea incidents. According to the 2007 National Animal Health Monitoring System (NAHMS 2007) Dairy Study about 10% of cow deaths were attributed to diarrhea or other digestive problems and farmers report about 2.5% of all cows have diarrhea events per year. In this survey using dairy records the overall average rate of a recorded diarrhea event was 1.1% / month. This would equate to around 13% / year for of cows in dairy herds having at least one case of diarrhea. In the NAHMS study the actual dairy records are not used to analyze the diarrhea rates. The data in this study may be more a more accurate assessment although much higher. In 2009 looking at herds with clinical diarrhea and specifically looking at salmonellosis, Cumming and colleagues found an incident density at the animal level of 1.8 cases or cows testing positive for *Salmonella* per 1000 animal years in the Northeastern US (Cummings et al. 2009). Cummings was reporting only cows that tested positive for salmonellosis, while the diarrhea recorded on farm in this study was undifferentiated and could have been from a variety of causes. The incident density in the current study was 83.1 per 1000 cow years which is 80 times the level in the Cummings study. This large increase might be due to many other causes of diarrhea on farm but also might be due to undifferentiated misclassification of the diarrhea event itself.

While feeding DFMs may decrease diarrhea from infectious causes, (Cernicchiaro et al. 2014, Magalhaes et al. 2008, Seo et al. 2010), there is evidence that some DFMs may also decrease the risk of problems of feed contaminated with mycotoxins (Whitlow and Hagler 2008) or decrease the risk of sub-clinical acidosis, both of which can induce diarrhea (Seo et al. 2010). Another risk factor examined in this study was immunization for BVD, which is an important cause of diarrhea in US dairy herds (Hochsteiner et al. 2002, Houe 2003). While many risk

factors were examined in this survey, only DV SCFP, vaccinating for BVD, being from the East region, and freestall barns were close to significant, Fossler (2005) found a decrease of Salmonella shedding in herds using freestall barns. We found more events of diarrhea in freestall barns in the univariate model but this was dropped as confounding with the variable WestorEast region. Although shedding of Salmonella and events of diarrhea are related there are many other risk factors associated with undifferentiated diarrhea. Events of diarrhea may be more associated with rations, weather, as well as region and some of these factors could be more associated with region. For example feeding higher corn silage rations in the Midwest might be more associated with rumen acidosis leading to diarrhea. We had freestall barns and region confounded in our study. This could be due to more diarrhea in the east and freestall barns are more common in the east.

The finding for some impact on diarrhea events for DV SCFP is in keeping with Brewer's finding that calves had less diarrhea than control after calves were inoculated with *Salmonella* while being fed a *Saccharomyces* fermentation product (Brewer et al. 2014). In addition SCFP has been shown to decrease ruminal acidosis (Li et al. 2016) which is a possible risk factor for diarrhea (Plaizier et al. 2008, Dijkstra et al. 2012). While this study only showed only 1 DFM associated with a decrease in diarrhea events, this is more likely due to the sampling size associated with different feeding regimes. The number of farms targeted in the sample was not achieved (76 vs 150) resulting in low power for many of the less commonly fed DFM products and therefore could represent a Type 2 error for many other the other products variables, therefore no conclusion can be drawn from the lack of significance in the other variables.

Other possible issues that may lead to bias within this study are possible errors in classification. One large misclassification is what constitutes the case definition of diarrhea in the opinion of the dairy, and what gets recorded in the database. There were many months where 0 cases diarrhea were reported whereas the maximum incidences of reported diarrhea was 384 cases per 1000 cows. It is obvious from the data that some farms record many more incidents of all diseases in their data. Some large farms with 2000 or more cows had fewer than 1 or 2 cases of diarrhea per month recorded (these tended to be in the west) whereas some smaller dairies with fewer than 1000 cows had more than 100 cases in a month. This could reflect more intensive monitoring depending on farm sizes but could be a management cultural practice in the West; in other words, diarrhea may not be considered as a recordable health event on western versus eastern dairies. Overall the higher incident density than for example Cummings could represent a much higher specificity for identifying diarrheal disease which could be the result of non-differential misclassification. The effect of non-differential misclassification would be to bias the estimated effect toward the null. This nullifying effect could indicate that in the final model what appears as a rather small effect due to DV SCFP could actually be larger than 2 cases per 1000 cows per month.

There are many treatments that are used on farm to treat diarrhea (e.g. oral or parenteral electrolyte solutions, astringent boluses, antibiotics). For the dairy industry to provide good decision analysis to farms, accurate recording, and standardized case definitions would need to become the norm for the dairy industry. With the exact number of cases being unknown, being able to provide good solutions for treating diarrhea while combating antimicrobial resistance resulting from treatment of diarrhea incidents will be a difficult undertaking. Identifying possible feed additives or management practices that could lead to lower levels of diarrhea and

therefore antibiotic treatments is a possible alternative that holds great promise for the future. In this study, the only feed additive to show improvement in diarrhea incidents was SCFP. The feeding of SCFP only accounted for approximately 2 cases in 1000 cows per month. Much of the qualitative data available on feeding DFM to dairy cattle indicate a milk production effect (Poppy et al. 2012) which may be more important to a dairy producer than the economics of a reduction in diarrhea cases.

The study used Diamond V employees to conduct the survey, which could create a selection bias in the survey data possible making herds using DV SCFP more likely to answer the survey. A larger proportion of study herds (67%) used DV SCFP alone or in combination with another brand of DFM. Another selection bias was that the survey responders volunteered for filling out the survey and providing the herd electronic records. Surprisingly many herds used combinations of 2 to 4 different DFM products at the same time. If this is true, it represents an opportunity for dairies to limit their choices, as there is no evidence that multiple products have an additive effect. It is possible that the survey responder didn't actually know what is being fed on the farm and answered they fed DV SCFP as one of their feed ingredients because it was a DV representative asking them the question.

It is possible that the Diamond V employees could have inadvertently chosen herds to participate that fed Diamond V products and also had low incidents of health events while herds that were not fed Diamond V products or herds being fed other products or management characteristics such as barn design or parlor design had higher diarrhea incidents, however, this was not apparent when the herd information was reviewed. Also, the farms visited were from a list of randomized farms. Farms were visited according to this list until approximately 15 farms

agreed to participate or the list was exhausted. Having a higher herd participation rate from the randomized list of herds would have minimized this possible bias.

Conclusions Chapter 2

Utilizing a broad survey of herds across the United States, many different feed additives, and management practices were identified. Of the different management practices surveyed, only feeding of DV SCFP was significantly associated with a decrease in recorded diarrhea events. Due to possible misclassification, the result showing a decrease of 2 cases per 1000 cows per month could be underreported. Vaccinating with a BVD vaccine was also associated with a trend toward decreased incidents as well as herd location East vs. West. A lack of accurate records for health events being documented on the farm may decrease the ability to accurately make inferences based on observational studies. In order to be able to utilize data collected on farms, data collection guidelines may need to be established to make data collection more consistent. Possibly paying farms to participate in a study of this nature where they would see a tangible return for the effort of keeping more accurate records could benefit a more accurate assessment of the DFM exposure. For this type of study, more farms would need to be included in the study to help minimize the inherent variation sometimes seen in smaller studies and to potentially have enrollment of farms that utilize a wider variety of DFM products to minimize diarrhea incidents.

CHAPTER 3

A META-ANALYSIS OF THE EFFECTS OF FEEDING YEAST CULTURE PRODUCED BY ANAEROBIC FERMENTATION OF SACCHAROMYCES CEREVISIAE, ON MILK PRODUCTION OF LACTATING DAIRY COWS

Chapter 3 Executive Summary

The purpose of this study was to use meta-analytic methods to estimate the effect of a commercially available yeast culture product on milk production and other production measures in lactating dairy cows through the use of a meta-analysis of randomized controlled trials. A total of 61 research publications (published journal articles, published abstracts, and technical reports) were identified through a review of the literature provided by the manufacturer and search of published literature using 6 computer search engines. Thirty-six separate studies with a total of 69 comparisons met the criteria for inclusion in the meta-analysis. The fixed effect meta-analysis showed substantial heterogeneity for milk yield, energy corrected milk, 3.5% fat corrected milk, milk fat yield, and milk protein yield. Sub-group analysis of the data showed much less heterogeneity in peer reviewed studies versus non-peer reviewed abstracts and technical reports, and tended to show higher, but not significantly different, treatment effects. A random-effects meta-analysis showed estimated raw mean difference between treated and untreated cattle reported in peer reviewed publications were 1.18 kg/d (95% CI, 0.55 to 1.81), 1.61 kg/d (95% CI, 0.92 to 2.29), and 1.65 kg/d (95% CI, 0.97 to 2.34) for milk yield, 3.5% fat corrected milk and energy corrected milk, respectively. Milk fat yield and milk protein yield for peer reviewed studies showed an increase in the raw mean difference of 0.06 kg/d (95% CI, 0.01 to 0.10) and 0.03 kg/d (95% CI, 0.00 to 0.05). Estimated raw mean dry

matter intake of the peer reviewed studies during early lactation (< 70 DIM) and not-early lactation were 0.62 kg/d (95% CI, 0.21 to 1.02) and a decrease of 0.78 kg/d (95% CI, -1.36 to -0.21), respectively. These findings provide strong evidence that this commercially available yeast culture product provides a significant improvement in several important milk production outcomes as evaluated in production settings typical for commercial dairies in North America. Utilizing meta-analytic methods to study the complete breadth of information relating to a specific treatment by studying multiple overcomes of all eligible studies can reduce the uncertainty often seen in small individual studies designed without sufficient power to detect differences in treatments.

Introduction

Yeast products are commonly used around the world for inclusion in diets of production animals. It has been suggested that yeast products impact the rumen microbial population resulting in changes in ruminal VFA production resulting in increased milk production as well as an increase in milk fat **(FY)** and milk protein **(PY)** yield from lactating dairy cows (Erasmus, Botha, and Kistner 1992, Putnam et al. 1997). Increased DMI has been observed in some studies (Dann et al. 2000) and decreased DMI in other studies (Schingoethe et al. 2004) et al., 2004). Despite numerous peer reviewed and non-peer reviewed studies on the effects of feeding yeast products, the results of these studies in lactating dairy cows appear to be inconclusive. Some studies have identified significant effects on milk production (Harrison et al. 1988, Hippen et al. 2007, Lehloenya et al. 2008, Ramsing et al. 2009) others reported a trend in production Williams (Williams, Marsh, and Williams 1999, Dann et al. 2000, Wang, Eastridge, and Qiu 2001) or no significant differences (Robinson 1997, Schingoethe et al. 2004). Nutritionists, veterinarians, and dairymen need to know the efficacy of these yeast products on milk production measures in

order to make appropriate decisions about the use of these products in their management systems.

One possible source of variability in results is that many trials may have lacked sufficient sample size and consequently statistical power to demonstrate the differences in the production measures. Lack of statistical power can result in an increased risk of missing a true treatment effect and produce a false negative trial result that is a Type 2 statistical error (Freiman et al. 1978, Egger, Smith, and Altman 2001). Meta-analysis has been proposed as a method that can be used to obtain useful summary estimates of effect, especially when there are numerous small studies conducted in different study locations by different researchers using different study designs, which when considered individually may not provide conclusive evidence of effect (DerSimonian and Laird 1986, Lean et al. 2009).

Another possible source of variation in response to supplementation of yeast product may be the type of yeast products that are used. There are differences between active ingredients and putative modes of action of different products. There are two main categories of yeast products (AAFCO 2011). Yeast cultures that are produced through yeast fermentation contain fermentation by-products and are not dependent on the live yeast for their physiological effects. The fermentation products contain compounds that impact the growth of various types of rumen bacteria and protozoa (Wiedmeier, Arambel, and Walters 1987, Harrison et al. 1988, Callaway and Martin 1997). In contrast, active dry yeast products (AAFCO 2011) are products that by definition must have greater than 15 billion live yeast cells/g. The effect is assumed to be dependent on the yeast cell being alive in the rumen to have a production effect (Dawson, Newman, and Boling 1990, Newbold, Wallace, and McIntosh 1996)). A recent meta-analysis by Desnoyers et al. (2009) provides an example of how the lack of differentiation among these

products is common in the peer-reviewed literature. The aim of Desnoyers et al. (2009) meta-analysis was to estimate the effects of live yeast supplementation on intake, rumen fermentation, and milk production, however, the study mistakenly included 13 studies of yeast culture mislabeled as live yeast. Differences in both the manufacturing process of specific yeast products and the response of yeast products within different production system of herds may contribute to the variability of production responses.

The purpose of this study was to critically review all relevant research specific only to a single manufactured yeast culture product and to estimate the effect of a yeast culture product on milk yield (**MY**), FY, PY, ECM, and DMI of dairy cattle using meta-analytic methods. A secondary objective was to examine the differences in treatment effect and heterogeneity of various study designs (i.e. blinding and randomization) or other factors such as peer review that commonly lead to publication bias or heterogeneity of effect in other meta-analytic studies

Materials and Methods

All published and unpublished papers and reports that studied the effect of commercially available yeast culture products manufactured by Diamond V (Cedar Rapids, Iowa) that were conducted in lactating dairy cattle prior to 2011 were obtained from the manufacturer's records. A comprehensive search of English language published literature was also performed by utilizing 6 different search engines (Pubmed, scholar Google, Agricola, Sciencedirect, Scirus, and CAB) with the words yeast, cows, and lactation, to identify other research papers and reports that may not have been published.

Inclusion Criteria

All published and non-published studies in the English language were screened for inclusion in the meta-analysis using standardized criteria. To be included in the meta-analysis, studies must have evaluated at least one of the three yeast culture products (YC, XP, XPC) sold by a single company (Diamond V, Cedar Rapids, IA). The three products are equivalent products in manufacturing except for the concentration. The study must have included a concurrent negative control group, randomized treatment assignments (Lean and Rabiee 2011), must have been conducted in lactating dairy cows (not dry cows or *in-vitro* studies) and used a parallel group design (i.e. not crossover). Additionally, studies must have reported results of at least one of the production outcomes of interest [MY, ECM, % milk fat (**F%),** FY, % milk protein (**P%**), PY, 3.5% FCM, ECM or DMI], along with a measure of variance (SE or SD) or a *P* value for comparison of effects between treatment and control groups.

Data Extraction

Data were collated from the eligible studies reporting the effect of yeast culture on production outcomes. In addition to outcome measures regarding milk production, the following data were extracted from the trials for sub-group analysis if the information was present: location of the study (state, country), source of the paper (peer reviewed journal, conference abstract, or technical report), published in a peer reviewed journal (yes or no), if an explicit statement about the randomization of treatments was included (yes or no), analytical control for confounders (yes or no), if the treatment application was prior to calving date (yes, before calving vs. no), DIM at the start of the trial, stage of lactation for the study period (full lactation, <70 DIM, or ≥70 DIM), milking frequency (2X, 3X or unknown), calving season for the dairy (seasonal or all year around), diet (pasture or total mixed ration (**TMR**)), dietary vitamin supplementation (yes or no),

ionosphere supplements (yes or no), parity (primiparous only or a mix of multi and primiparous), breed (Holstein or other) BST administration (yes or no), type of yeast culture product (YC, XP or XPC), dosage of yeast culture (in grams), yeast culture delivery method (mixed or top-dressed), and how the treatment was delivered to the cow (individually or fed to a pen of cows).

Statistical Analysis

Meta-analysis was conducted using the methods described by Higgins and Green (2008a). Statistical analysis was conducted on the extracted production data using Comprehensive Meta-Analysis version 2.2.050 (Biostat, Englewood New Jersey 2009). Studies were weighted using the methods of inverse variance (DerSimonian and Laird 1986). If the selected studies have not reported measures of the variance of the interested outcomes, estimates of variability were extracted from the papers using the methods described by Rabiee et al. (2010). If the trial only reported a Z statistic or *P* value, the estimates for SE and SD were calculated using the difference in the mean and the number of cows for each trial (Higgins and Green 2008b). For studies that only reported significance relative to a given alpha cutpoint (i.e. $P \leq 0.05$), then this value was used to make a conservative estimate of SE and SD. For studies that only reported a non-significant effect, *P* values of 0.15, 0.3, and 0.5 were assigned and compared numerically to each other. The *P* value that produced the smallest (most conservative) estimate of the overall treatment effect was selected for the calculation of the SE (Sanchez et al. 2004). If F%, FY, P%, PY, 3.5% FCM (Dairy Records Management Systems, 2006), and ECM (Tyrrell and Reid 1965) were not reported, estimates of these parameters were calculated. The variance used for the calculated missing value was the variance for the corresponding outcome statistic from the same trial (F% from FY, FY from F%, PY from P%, P% from PY and 3.5% FCM and ECM from MY). Continuous data were analyzed both using the raw mean difference

(**RMD**) for both fixed effect and random effect models as described by Borenstein et al. (2010) for each study outcome and as a standardized mean difference (**SMD**) as described by Lean (2009). Differences in study designs or production system characteristics that were considered *a priori* to influence trial outcomes or where a high level of heterogeneity was observed were explored using stratification for comparison of these sub-groups. Sub-groups with less than 5 comparisons were not considered appropriate to report statistically as there were not enough comparisons to evaluate.

Multiple Comparison Outcomes

In studies with complex data structures such as those with multiple comparisons (i.e. one control group was compared to two different treatment groups or multiple outcomes were compared between groups at different stages of lactation), a synthetic treatment effect was calculated along with an adjustment of the variance to compensate for the correlated outcomes (Table 3.1). This was accomplished by first performing a fixed effects meta-analysis of the correlated outcomes in the study to obtain a synthetic point effect. The variance for the synthetic point effect was calculated using the variance inflation factor as described. This fixed effect point estimate was entered in the final meta-analysis as one study and the studies that were used to estimate the synthetic treatment effect were excluded. An example of how this was done is how Dan et al. (2000) was evaluated. In this study Dann et al., reported MY from d 1 to 21, 1 to 42 and 1 to 140. A correlation factor of 0.33 was estimated for these MY outcomes, as these reported MY outcomes are not independent of each other and yet each one has valuable information on how yeast culture impacts MY. The outcomes for MY difference were 1.4 kg/d, 1.6 kg/d and 0.6 kg/d respectively with an SD of 4.79, 4.70 and 4.36 for each. The synthetic mean difference in MY was calculated by combining these 3 outcomes by using a fixed meta-

Table 3.1. Descriptors of 61 research papers from 1988-2011 meeting specified selection[1] criteria and reporting the effect of Diamond-V yeast culture products on production outcomes in dairy cattle that were used in a meta-analysis of the effects of a single yeast culture product on milk production in dairy cows.

Study Name	Source[2]	Location[3]	Synthetic score[4]	Randomized[5]	Control confounde[6]	Start of treatment[7]	Stage of lactation[8]	Milking frequency[9]	Delivery methods[10]	Feeding method[11]	Comparisons[12]
Alshaikh et al., 2002	Journal	Saudi Arabia	No	Yes	Yes	After	Not Early	3X	Mixed	Group	1
Arambel and Kent, 1990	Journal	Utah	No	Yes	Yes	After	Not Early	2X	Top Dress	Indiv.	1
Bennett, 2004	Report	Australia.	No	No	Yes	After	Full	2X	Top Dress	Group	1
Bernard, 1992	Abstract	Tennessee	No	Yes	Yes	After	Early	2X	Mixed	Indiv	1
Braun, 1993	Report	Israel	No	Yes	Yes	After	Not Early	Unknown	Mixed	Group	1
Cooke et al., 2007	Journal	Georgia	No	Yes	Yes	After	Not Early	2X	Mixed	Indiv	3
Dann et al., 2000	Journal	Illinois3	Yes r=.33	Yes	Yes	Before	Early	2X	Top Dressed	Indiv	3
DV Mills and MW Feed Manf. Rrch Farm 1, 1989	Report	Midwest US	No	No	Yes	After	Not Early	Unknown	Top Dress	Indiv	1
DV Mills and MW Feed Manf. Rrch Farm 2, 1993	Report	Midwest US	No	Yes	Yes	After	Not Early	2X	Mixed	Group	1
DV_Mills and Union_Grove_Dairy, 1997	Report	North Carolina	Yes r=.33	No	No	After	Not Early	Unknown	Unknown	Group	3
DV_Mills and United_Molasses, 1994	Report	England	Yes r=.33	No	Yes	After	Early	Unknown	Mixed	Indiv	3
Dobos, 1998	Report	Australia	No	No	Yes	After	Early	2X	Mixed	Group	2
Erasmus et al., 2005	Journal	South Africa	No	No	Yes	Before	Early	2X	Mixed	Indiv	2
Fazenda, 1998	Report	Portugal	No	No	Yes	After	Not Early	3X	Mixed	Group	1

Study Name	Source[2]	Location[3]	Synthetic score[4]	Randomized[5]	Control confounde[6]	Start of treatment[7]	Stage of lactation[8]	Milking frequency[9]	Delivery methods[10]	Feeding method[11]	Comparisons[12]
Harris et al., 1992	Journal	Florida	No	Yes	No	After	Not Early	2X	Mixed	Indiv	1
Harris, 1988	Abstract	Florida	No	No	Yes	After	Both	3X	Mixed	Group	2
Harris, 1990	Abstract	Florida	No	No	Yes	After	Not Early	3X	Mixed	Group	1
Kim et al., 1994	Abstract	Utah	No	No	No	After	Not Early	Unknown	Top Dress	Indiv	1
Korniewicz, 2005	Journal	Poland	Yes r=.32	Yes	Yes	Before	Early	Unknown	Top Dress	Group	2
Lehloenya et al., 2008	Journal	Oklahoma	No	Yes	Yes	Before	Both	2X	Mixed	Group	6
Luhman, 1997	Abstract	Iowa	Yes r=.21	No	No	Before	Early	Unknown	Mixed	Group	2
Mangoni, 1998	Report	Argentina	No	Yes	Yes	After	Both	2X	Top Dress	Group	3
Nagy, 1996	Abstract	S. Carolina	No	No	No	After	Not Early	Unknown	Mixed	Group	2
Oraskovich and Linn, 1989	Report	Minnesota	No	No	No	After	Not Early	Unknown	Top Dress	Group	4
Ramsing et al., 2009	Journal	Oregon	Yes r=.5	Yes	Yes	Before	Early	2X	Top Dress	Indiv	2
Robinson, 1997	Journal	Canada	No	No	Yes	Before	Early	2X	Mixed	Indiv	1
Robinson and Garrett, 1999	Journal	Canada	No	No	Yes	Before	Early	2X	Mixed	Group	2
Sanchez et al., 1997	Abstract	Wash.	Yes r=.5	Yes	Yes	Before	Early	3X	Mixed	Group	2
Schingoethe et al., 2004	Journal	S Dakota	No	Yes	Yes	After	Not Early	3X	Mixed	Indiv	1

Study Name	Source[2]	Location[3]	Synthetic score[4]	Randomized[5]	Control confounde[6]	Start of treatment[7]	Stage of lactation[8]	Milking frequency[9]	Delivery methods[10]	Feeding method[11]	Comparisons[12]
Vogel, 2005	Abstract	Missouri	Yes r=.5	No	Yes	Before	Early	2X	Mixed	Indiv	2
Wang et al., 2001[13]	Journal	Ohio	Yes r=.27	No	Yes	Before	Both	2X	Mixed	Indiv	4
Ward and McCormick, 2001	Abstract	Louisiana	No	No	No	Before	Early	2X	Top Dress	Indiv	1
Williams et al., 1999	Report	UK	No	No	Yes	After	Not Early	2X	Top Dress	Group	1
Zhou, 2002	Report	China	No	No	No	After	Early	Unknown	Top Dress	Group	1
Zilin, 1996	Report	China	No	No	Yes	After	Not Early	3X	Mixed	Group	1
Zom, 2000	Report	Netherland	No	Yes	Yes	Before	Early	2X	Pellet	Indiv	3

[1] Inclusion criteria were: the study must have evaluated at least 1 type (concentration) of a commercial product sold by a single company (Diamond V, Cedar Rapids, IA), included a concurrent negative control group, randomized treatment assignments, conducted in lactating dairy cows, and used a parallel group design (i.e., not crossover). Additionally, the studies must have reported data regarding at least one of the production outcomes of interest [milk yield, % milk fat,**,** milk fat yield, % milk protein, milk protein yield, 3.5% fat corrected milk, energy corrected milk or DMI], along with a measure of variance (SE or SD) or a *P* value for comparison of effects between treatment and control groups.

[2] Journals represent studies from journals that are peer reviewed. Abstracts are non-peer reviewed published articles and reports are company or industry reports.

[3] Location of the studies.

[4] Studies for which the animals within the study were used in more than one comparison and were therefore not independent of each other. These comparisons were combined using a fixed effect meta-analysis. The combined variance was calculated using a variance inflation factor "r" (Borenstein et al., 2009a) to account for the correlation between the animals in the study. The synthetic point effect was then entered in the meta-analysis as a single study. Examples of complex data structures are 2 comparisons using the same control group or a reported treatment effect reported in the same animals at different DIM.

[5] Did the author explicitly declare randomization of treatments in the study.

[6] Did the author declare some type of control for confounding in the study design?.

[7] Did the treatment of yeast culture start before or after calving?.

[8] Studies that were primarily conducted in groups of cows less than 70 DIM are "Early" and ≥70 are "Not Early". Studies designated Full were comparisons that were from calving to the dry off period.

[9] Number of times the study cows were milked in 24 hours.

[10] The method of delivery of the treatments to the cow. Mixed is mixed in some portion of the feed such as a grain portion or TMR. Top- dressed was fed on top of the feed. Pellets had the treatments included in a pellet fed in the ration.

[11] Feeding Method is Indiv if the cows were randomized and fed at the cow level and the appropriate n was used in the statistical analysis. Group indicates the study appeared to randomize and feed the cows at the group level and use the individual cows in the statistical analysis.

[12] Number of comparisons within the study for which a treatment effect was reported.

[13] Wang et al. had 2 separately correlated data sets on 17% NDF and on 21%NDF all within one paper. An r of 0.27 was used for both combinations.

analysis technique which were weights using the inverse of their variance of the data for a mean milk difference of 1.16 kg/d and a variance of 18.23 which was entered into the meta-analysis as a single study (Borenstein et al. 2009a).

Assessment of Heterogeneity

Between study variability compared to within study variability which is called the heterogeneity of effect size was evaluated using both the chi-square (**Q**) test of heterogeneity and the I^2 statistic (Higgins et al. 2003). Negative values of I^2 were assigned a value of zero. An I^2 value of >35%, or a chi-square (Q) test with $P \leq 0.1$ was considered indicative of substantial heterogeneity. Q is a statistic that is sensitive to the ratio of the observed variation between studies to the within study variation. Under the null hypothesis where all studies share a common effect size, the Q statistic follows a central chi-squared distribution with degrees of freedom equal to k-1. A significant *P* value would lead one to reject the null hypothesis and conclude that the studies do not share a common effect size. Two groups can be evaluated if they share a common effect size by the same method. When two groups are being evaluated, we can calculate the Q as the effect sizes of the groups of studies now instead of two studies, and test the dispersion of the subgroup about a summary effect with degrees of freedom = 1 (Borenstein et al. 2009c).

The data were analyzed using both fixed effect and random effects models. The random effects model was determined more appropriate to report the treatment effects as this accounts for the impacts of study design, management and cow variation and other differences in study conduct on treatment effects (Borenstein et al. 2010).

Publication Bias

Publication bias was assessed using funnel plots (Light and Pillemer 1984). Trim and fill methods were used to assess the best estimate of the unbiased effect size (Duval and Tweedie 2000).

Results and Discussion

Reports Meeting Inclusion Criteria

A total of 61 research papers (published journal articles, published abstracts, reports, and technical reports) were provided by the manufacturer. The literature search did not find any other papers than those provided. Of the 61 studies, 36 separate studies (Table 3.1) met the criteria for inclusion into the meta-analysis. Papers were excluded if they only included positive treatment control groups (n = 17), used cross-over, Latin square or factorial design (n = 6), or failed to report a relevant treatment effect (n = 2) (Appendix Table A.1). Within the 36 separate studies, there were reported 69 separate comparisons. Correlations of studies (n=9) with multiple outcomes and multiple time points were estimated to make synthetic point effects to adjust for the change in variance for each of the outcomes (Table 3.1).

Heterogeneity Analysis

The analysis of milk yield showed a high level of heterogeneity (I^2 = 40.46%) along with a highly significant chi-square test of Q (P = 0.003; Table 3.2). Analysis for heterogeneity is important in meta-analysis because it tests the amount of variance within the group of studies compared to the within study variation. The chi-square test of Q is a test of the null hypothesis that all the studies share a common effect size. The I^2 statistic is the ratio of the between study variation or true heterogeneity to the total variance across the observed effect estimates. A high I^2 suggests the difference between individual study outcomes is greater (or more variable) than

Table 3.2. The estimated effect of yeast culture on milk yield in lactating dairy cows from all studies (sub-group analysis 1)[1] from a meta-analysis of yeast culture production effects from 1988 to 2011.

			RMD (95% CI)[2]		Heterogeneity				SMD (95% CI)[3]	
Milk Yield (kg/d)		**Trials comparisons (n)**	**Random effect**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Random effect**	***P* value**
All	All trials	57	1.03 (0.73 to 1.34)	0.001	73.90	44	0.003	40.46	0.35 (0.22 to 0.47)	0.001
Start treatment[4]	After	35	1.12 (0.73 to 1.50)	0.001	51.80	26	0.002	49.81	0.36 (0.18 to 0.55)	0.001
	Before	22	0.75 (0.36 to 1.14)	0.001	15.85	16	0.464	0.001	0.29 (0.16 to 0.42)	0.001
Stage of lactation[5]	Early	27	1.43 (0.89 to 1.96)	0.001	52.76	26	0.001	50.72	0.36 (0.22 to 0.50)	0.001
	Not Early	29	0.95 (0.67 to 1.23)	0.001	15.52	28	0.972	0.001	0.24 (0.12 to 0.35)	0.001
Delivery method[6]	Mixed	33	0.99 (0.69 to 1.30)	0.001	0.001	0	1.000	0.001	0.40 (0.22 to 0.57)	0.001
	Top-dress	19	1.30 (0.54 to 2.07)	0.001	24.40	14	0.041	42.63	0.31 (0.10 to 0.51)	0.004
Milking frequency[7]	2X	29	1.16 (0.66 to 1.66)	0.001	33.66	22	0.053	34.63	0.33 (0.21 to 0.46)	0.001
	3X	9	0.68 (0.29 to 1.07)	0.001	1.79	7	0.971	0.001	0.18 (0.07 to 0.29)	0.002
	Unknown[8]	18	1.36 (0.78 to 1.94)	0.001	18.59	12	0.099	35.46	0.43 (0.03 to 0.82)	0.036

[1] Studies are stratified by various factors controlled within the study design or reporting.

[2] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval

[3] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the standardized mean difference. The SMD can be viewed as a measure of overlap between 2 separate distributions.

[4] Treatment effect from all studies containing milk yield data included in the meta-analysis stratified by the start of treatment, before or after parturition.

[5] Treatment effect from all studies containing milk yield data included in the meta-analysis stratified by stage of lactation. Studies that were primarily conducted in groups of cows less than 70 DIM (early), and all other studies (not early).

[6] Treatment effect from all studies with milk yield data stratification by how the treatment was fed either top-dressed (fed separately on top of the feed) on the total mixed ration or mixed in the total mixed ration prior to being fed to the cows.

[7] Treatment effect from all studies with milk yield data stratified by how often the study cows were milked in 24 hours.

[8] Studies in which milking frequency for the study animals was not designated within the study.

expected. Excess variation may indicate more than one outcome is being measured and may not be appropriate to combine the studies for an average effect. The difference in treatment response may actually be due to differences due to other factors including breed responses such as Jersey *vs.* Holstein, type of ration fed, delivery method of the ration or stage of lactation. Alternatively but not exclusively, the heterogeneity could be due to differences in study designs such as the difference in how studies were randomized, how blinding was performed (if at all), how confounding was controlled for in the study design, and what to experimental unit did the study randomize the treatment? Stratification and meta-regression are two accepted methods that are used to evaluate the presence of heterogeneity and also to examine the impact of specific groups of studies on heterogeneity.

Milk fat yield had a high level of heterogeneity (I^2 = 36.69%, Q chi-square, P = 0.009) as did PY (I^2 = 35.12%, Q chi-square, P = 0.016). Dry matter intake studies had a moderate level of heterogeneity (I^2 = 18.33%, Q chi-square, P = 0.185).

Stratification was used to explore the potential sources of the high level of heterogeneity and whether there was a statistical difference between the subgroups. The following subgroups were explored and tested: i) if the study was reported in peer reviewed journals or not, ii) studies that declared their randomization or not, iii) studies that stated whether confounders were controlled or not, iv) the stage of lactation (less than 70 DIM (early) or later in lactation, (insufficient full lactation trials to analyze)), v) unit of feeding was at the individual cow level and the unit of allocation was at the cow level *vs.* having allocated the treatment at the group level but used the unit of measure at the cow level, vi) delivery method (top dressed versus mixed in the feed), and vii) milking frequency (2x, 3x, or unknown). A univariate regression analysis was performed on all subgroup covariates to test if any of these were with $P \leq 0.2$. No

subgroup covariate met this criterion, therefore, no multiple regression model was fitted to examine these data. Subgroup analysis was used to test if the use of estimated *P* values used to calculate SE had any significant effect on the outcomes. There was no statistical difference in MY for the calculated SE from estimated *P* values versus all other MY studies (*P*=0.854), or for MY peer reviewed studies (*P*=0.98). No difference was also observed in DMI (*P*=0.511), FY (*P*=0.210), or PY (*P*=0.703) as well.

The subgroup analysis of the studies showed that there was no evidence of significant heterogeneity in published peer reviewed journals (I^2 = 0.001%, Q chi-square, *P* = 0.904) (Table 3.2 and Table 3.3 and Table 3.4) compared to the data set that contained all studies. There was no evidence of significant heterogeneity in all the other subgroups used with peer reviewed studies (peer reviewed and randomized, peer reviewed by stage of lactation, peer reviewed 3.5% FCM, peer reviewed ECM, peer reviewed FY, peer reviewed PY, and peer reviewed DMI by stage of lactation).

In contrast, all other subgroup analysis retained a high level of heterogeneity in at least one of the strata. One possible explanation for the lack of evidence of significant heterogeneity when only peer reviewed studies are analyzed is because there may be increased rigor and control exercised in a randomized controlled trials targeted for publication against one conducted primarily to demonstrate an effect for informational purposes. Peer review should have the impact of requiring better control of experimental units, methods of randomization, errors in the data, and general oversight by the investigator. Some authors have advocated only reporting studies that are peer reviewed, relying on the peer review process as a proxy for paper quality (Weisz et al. 1995). Other authors disagree with this approach because non-peer reviewed papers, such as those from government, think tanks, consulting firms, or graduate theses, may

Table 3.3. The estimated effect of yeast culture on milk yield in lactating dairy cows from all studies (sub-group analysis 2) 1 from a meta-analysis of studies on the milk production from 1988 to 2011.

			RMD (95% CI)[2]		Heterogeneity				SMD (95% CI)[3]	
Milk yield (kg/d)		**Trials/ comparisons (n)**	**Random effect**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Random effect**	***P* value**
Peer reviewed[4]	No	36	1.01 (0.64 to 1.37)	0.001	65.36	28	0.001	57.16	0.36 (0.20 to 0.53)	0.001
	Yes	21	1.18 (0.55 to 1.81)	0.001	8.47	15	0.904	0.001	0.32 (0.14 to 0.50)	0.001
Randomized[5]	No	34	1.02 (0.61 to 1.43)	0.001	47.70	26	0.006	45.49	0.35 (0.16 to 0.55)	0.001
	Yes	23	1.04 (0.57 to 1.50)	0.001	24.19	17	0.115	29.70	0.33 (0.20 to 0.45)	0.001
Randomized and peer reviewed[6]	Yes	12	1.34 (0.51 to 2.18)	0.002	4.62	8	0.797	0.001	0.32 (0.10 to 0.55)	0.004
Control confounder[7]	No	11	1.18 (0.14 to 2.23)	0.027	15.74	10	0.107	36.45	0.28 (-0.02 to 0.57)	0.066
	Yes	45	0.98 (0.66 to 1.30)	0.001	57.27	33	0.005	42.38	0.37 (0.22 to 0.51)	0.001
Feeding method group[8]	Group	30	0.88 (0.59 to 1.17)	0.001	28.89	25	0.269	13.46	0.28 (0.18 to 0.38)	0.001
	Individual	27	1.16 (0.57 to 1.74)	0.001	33.75	18	0.014	46.67	0.41 (0.09 to 0.72)	0.011
Peer reviewed, stage of lactation[9]	Early	14	1.37 (0.63 to 2.11)	0.001	6.61	13	0.921	0.001	0.36 (0.17 to 0.56)	0.001
	Not Early	9	0.98 (0.01 to 1.95)	0.049	4.24	8	0.835	0.001	0.21 (-0.02 to 0.45)	0.075

[1] Studies are stratified by various factors controlled within the study design or reporting.

[2] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval.

[3] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the standardized mean difference. The SMD can be viewed as a measure of overlap between 2 separate distributions.

[4] Treatment effect from studies with milk yield data that were published in peer reviewed journals ("yes"), and the strata of trials from only abstracts and reports ("no").

[5] Treatment effect from studies that declared some form of randomization of treatments.

[6] Treatment effect from studies that were both from peer reviewed journals and declared some form of randomization of treatments.

[7] Treatment effect from studies that declared some form of control within the study for confounding.

[8] Treatment effect from trials with milk yield data stratified by how the cows were fed. The "group fed" appeared to have treatments fed to pens of cows but individual cow numbers were used in the calculation of n. The individual fed studies appeared to randomized treatments at the cow level and used an appropriate n in the statistical calculation.

[9] The treatment effect of comparisons with milk yield data from studies that were published in peer reviewed journals stratified by stage of lactation. Studies that were primarily conducted in groups of cows less than 70 DIM (early), and all other studies (not early).

Table 3.4. The estimated effect of the yeast culture on 3.5% FCM, ECM and milk components from peer reviewed studies. from a meta-analysis of studies on the milk production from 1988 to 2011.

		RMD (95% CI)[1]		Heterogeneity				SMD (95% CI)[2]	
	Trials comparisons (n)	Random effect	*P* value	Chi-square (Q)	df	*P* value	I^2 (%)	Random effect	*P* value
3.5 % FCM[3] (kg/d)	18	1.61 (0.92 to 2.29)	0.001	7.66	14	0.906	0.001	0.37 (0.19 to 0.56)	0.001
ECM[4] (kg/d)	18	1.65 (0.97 to 2.34)	0.001	9.53	14	0.795	0.001	0.38 (0.20 to 0.57)	0.001
Milk fat (%)[5]	19	0.04 (-0.07 to 0.14)	0.49	25.59	15	0.043	41.38	0.12 (-0.10 to 0.33)	0.297
Milk fat yield (kg/d)[6]	17	0.06 (0.01 to 0.10)	0.009	9.44	44	0.802	0.001	0.24 (0.06 to 0.43)	0.010
Milk protein (%)[7]	18	-0.03 (-0.07 to 0.02)	0.216	16.96	14	0.258	17.44	-0.05 (-0.27 to 0.17)	0.672
Milk protein yield (kg/d)[8]	16	0.03 (0.00 to 0.05)	0.026	8.40	13	0.817	0.001	0.24 (0.05 to 0.43)	0.014

[1] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval.

[2] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the standardized mean difference. The SMD can be viewed as a measure of overlap between 2 separate distributions.

[3] Peer reviewed studies with FCM data or sufficient data to calculate FCM are included in this data set. 3.5% FCM = (Milk lb × 0.432) + (Fat lb × 16.216) (Dairy Records Management Systems, 2006).

[4] Peer reviewed studies with ECM data or sufficient data to calculate ECM are included in this data set. ECM = 0.327 * milk lb + 12.97 × fat lb + 7.21×protein lb (Tyrrell and Reid, 1965).

[5] Only trials with milk fat % data or sufficient data to calculate milk fat % from studies published in peer reviewed journals are included in this data set.

[6] Only trials with milk fat yield data or sufficient data to calculate milk fat yield from studies published in peer reviewed journals are included in this data set.

[7] Only trials with milk protein % data or sufficient data to calculate milk protein % from studies published in peer reviewed journals are included in this data set.

[8] Only trials with milk protein yield data or sufficient data to calculate milk protein yield from studies published in peer reviewed journals are included in this data set.

not be published but could be studies of high quality (Borenstein et al. 2009b). A further contrasting view is that studies published in peer-reviewed journals represent a bias of publishing papers with a higher treatment effect. In this meta-analysis, there was no statistical difference in treatment outcome between studies that were peer reviewed versus the non-peer reviewed studies ($P > 0.20$). However, there was a substantial difference in the level of heterogeneity. A high level of heterogeneity suggests that combining the results of the dataset may not be appropriate, therefore only the treatment effects from the studies published in peer-reviewed journals were reported.

Production Outcomes

Adjustments were made in the estimates to account for multiple treatment comparisons to a single control group in a trial according to methods described by Borenstein (2009a). We note that there are limitations to this method as the estimates of correlations between groups and among groups can be flawed by the lack of essential data to calculate a correlation. However, it was considered that the method should be explored and used rather than ignore the clustering effects within study, which would give a less accurate estimate of variance.

Studies published in peer reviewed journals reported that treatment with yeast culture increased the MY 1.18 kg/d (95% CI, 0.55 to 1.81), while studies that were both peer reviewed and stated their randomization had a yeast culture treatment effect of 1.34 kg/d (95% CI, 0.51 to 2.18), (Table 3.3; Figure 3.1).

Yeast culture supplementation increased 3.5% FCM by 1.61 kg/d (95% CI, 0.92 to 2.29) and 1.65 kg/d (95% CI, 0.97 to 2.34) for ECM (Table 3.5). Milk fat yield and PY results showed significant treatment effect with 0.06 kg/d ($P = 0.009$) and 0.03 kg/d ($P = 0.026$);

Milk Yield Peer-Reviewed Studies

Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value	Control	Treated
Arambel and Kent, 1990	-0.316	0.450	-1.198	0.566	0.482	10	10
Wang et al., 2001 - Syn 17%NDF	-0.265	0.410	-1.069	0.538	0.518	12	12
Schingoethe et al., 2004	0.101	0.325	-0.535	0.738	0.755	19	19
Lehloenya et al., 2008 - Primi	0.114	0.646	-1.152	1.380	0.860	4	6
Harris et al., 1992	0.227	0.334	-0.428	0.883	0.497	18	18
Cooke et al., 2007	0.241	0.449	-0.639	1.121	0.591	10	10
Dann et al., 2000 -Syn	0.272	0.322	-0.359	0.903	0.398	19	20
Robinson - Garrett, 1999 - 2	0.279	0.394	-0.493	1.052	0.479	13	13
Erasmus et al., 2005 - 1	0.344	0.368	-0.377	1.065	0.350	15	15
Robinson, 1997	0.354	0.388	-0.407	1.115	0.362	13	14
Alshaikh et al., 2002	0.396	0.202	0.001	0.792	0.050	50	50
Erasmus et al., 2005 - 2	0.430	0.369	-0.294	1.154	0.244	15	15
Wang et al., 2001 - Syn 21%NDF	0.520	0.415	-0.294	1.333	0.210	12	12
Lehloenya et al., 2008 -Multi	0.572	0.618	-0.638	1.783	0.354	6	5
Robinson - Garrett, 1999 - 1	0.596	0.482	-0.348	1.540	0.216	9	9
Ramsing et al., 2009 - Syn	0.831	0.314	0.215	1.447	0.008	22	22
	0.321	0.091	0.143	0.499	0.000		

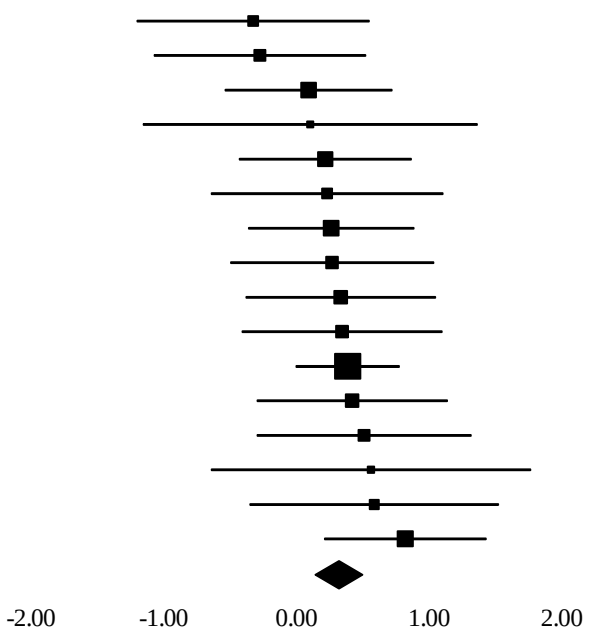


Figure 3.1. Forest plot of random effects SMD for milk yield. Only studies published in peer reviewed journals are represented. The black squares in the forest plot represent the weighting (by inverse variance) for the represented study. The horizontal bars represent the 95% CI for the study. The diamond figure center represents the standardized mean and the width of the diamond represents the 95% CI of the overall treatment effect. The outcome to the right of an imaginary vertical line through 0 represents an increase in milk fat yield.

Table 3.5, Appendix Figure A**.2** and Figure A**.3**) respectively. Although individual studies, showed non-significance results as demonstrated by the horizontal lines which represent the 95% CI within forest plots, the consistency of a positive treatment effect is evident for both summary statistics.

Dry matter intake was considered *a priori* to be heterogeneous between studies conducted in early lactation *vs*. late lactation. Sub-group analysis of DMI for studies in peer reviewed journals (Table 5) showed significant treatment effects when stratified by the stage of lactation. During the early lactation (< 70 DIM), DMI increased by 0.62 kg/d (95% CI, 0.21 to 1.02, $P = 0.003$) and during the late lactation studies, there was a significant decline in average DMI (0.78 kg/d; 95% CI -1.36 to -0.21; $P = 0.001$). The forest plot of DMI results (Figure 3.2) shows evidence of heterogeneity which could be due to the stage of lactation. The change in DMI in early lactation may be an opportunity for nutritionists and farm consultants to modify DMI of cows during the critical period of transition to increase intakes and possibly aid in transition health (Huzzey et al. 2007). Decreased DMI in later lactation along with increasing milk production will increase the efficiency of milk production.

Table 3.5. The estimated effect of yeast culture on DMI for peer reviewed studies from a meta-analysis of studies on the milk production from 1988 to 2011.

			RMD (95% CI) [1]		Heterogeneity				SMD (95% CI) [2]	
Dry matter intake (kg/d)		**Trials (n)**	**Random effect**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I2 (%)**	**Random effect**	***P* value**
Stage of Lactation[3]	Early	12	0.62 (0.21 to 1.02)	0.003	7.39	11	0.766	0.001	0.35 (0.15 to 0.55)	0.001
	Not early	7	-0.78 (-1.36 to -0.21)	0.008	5.11	6	0.530	0.001	-0.33 (-0.57 to -0.08)	0.009

[1] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval.

[2] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the standardized mean difference. The SMD can be viewed as a measure of overlap between 2 separate distributions.

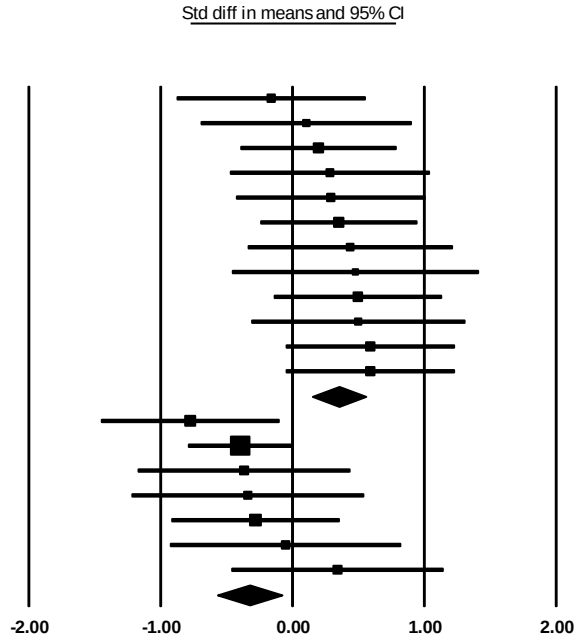
3 All trials that are from studies published in peer reviewed journals containing dry matter intake data included in the meta-analysis stratified by stage of lactation. Studies that were primarily conducted in groups of cows less than 70 DIM (early), and all other studies (not early).

One important bias in meta-analysis studies is the impact of publication bias. Although a meta-analysis will yield a mathematically accurate synthesis of the studies included in the analysis, if these studies are a biased sample of all relevant studies, the mean effect computed by the meta-analysis will reflect this bias (Borenstein et al. 2009b). The reasons for not having all relevant studies in the meta-analysis could be the tendency for negative trials and or small negative trials not to get published either by editorial bias or authors tending not be interested in publishing papers with negative results (Hopewell et al. 2009). Another reason for publication bias could be the tendency for reports produced for or by the "industry" to only be favorable thereby increasing the magnitude of publication bias towards the treatment effect of papers in the public domain (Rothstein, Sutton, and Borenstein 2005, Wellman and O'Connor 2007). In this study, the treatment effects were studied with and without the industry reports and abstracts. Although the industry reports added much more heterogeneity to the analysis, they did not increase the reported treatment effects. It is possible the small non-significant increase in treatment effect observed in the published studies could be editorial bias for publishing positive studies.

Dry Matter Intake, Peer Reviewed by Stage of Lactation

Group by Stage of lactation 2	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Early	Erasmus et al., 2005 - 1	-0.161	0.366	0.134	-0.878	0.556	-0.441	0.659
Early	Wang et al., 2001 - 1- 17% NDF	0.105	0.409	0.167	-0.696	0.906	0.257	0.797
Early	Ramsing et al., 2009 - 4X	0.197	0.302	0.091	-0.396	0.789	0.651	0.515
Early	Robinson, 1997	0.284	0.387	0.150	-0.475	1.042	0.733	0.464
Early	Erasmus et al., 2005 - 2	0.290	0.367	0.135	-0.429	1.010	0.791	0.429
Early	Ramsing et al., 2009 - 1X	0.351	0.304	0.092	-0.244	0.947	1.155	0.248
Early	Robinson - Garrett, 1999 - 2	0.438	0.397	0.158	-0.340	1.216	1.104	0.270
Early	Robinson - Garrett, 1999 - 1	0.477	0.478	0.229	-0.460	1.414	0.999	0.318
Early	Dann et al., 2000 - 3	0.496	0.325	0.106	-0.141	1.134	1.526	0.127
Early	Wang et al., 2001 - 1- 21% NDF	0.499	0.415	0.172	-0.314	1.311	1.203	0.229
Early	Dann et al., 2000 - 2	0.590	0.327	0.107	-0.051	1.232	1.803	0.071
Early	Dann et al., 2000 - 1	0.590	0.327	0.107	-0.051	1.232	1.803	0.071
Early		0.350	0.103	0.011	0.148	0.552	3.394	0.001
Not Early	Harris et al., 1992	-0.776	0.346	0.119	-1.453	-0.098	-2.245	0.025
Not Early	Alshaikh et al., 2002	-0.397	0.202	0.041	-0.793	-0.001	-1.964	0.049
Not Early	Wang et al., 2001 - 2- 17% NDF	-0.367	0.412	0.169	-1.174	0.439	-0.893	0.372
Not Early	Cooke et al., 2007	-0.339	0.450	0.203	-1.222	0.544	-0.753	0.452
Not Early	Schingoethe et al., 2004	-0.280	0.326	0.106	-0.919	0.359	-0.859	0.390
Not Early	Arambel and Kent, 1990	-0.053	0.447	0.200	-0.929	0.824	-0.118	0.906
Not Early	Wang et al., 2001 - 2- 21% NDF	0.341	0.411	0.169	-0.465	1.147	0.830	0.407
Not Early		-0.327	0.125	0.016	-0.572	-0.082	-2.617	0.009

Statistics for each study



Meta Analysis

Figure 3.2. Forest plot of random effects SMD for DMI. Only studies published in peer reviewed journals are represented. The studies are further stratified by studies that were conducted in early lactation, (<70 DIM) versus not early lactation (all others). The black squares in the forest plot represent the weighting (by inverse variance) for the represented study. The horizontal bars represent the 95% CI for the study. The diamond figure center represents the standardized mean and the width of the diamond represents the 95% CI of the overall treatment effect. The outcome to the right of an imaginary vertical line through 0 represents an increase in DMI and to the left of 0 is a decrease in DMI.

The funnel plot is an accepted method used to visually investigate if there is a relationship between study size and effect size. This method plots the treatment effect against the standard error. There should be a normal distribution around the true effect size that is funnel shaped as smaller studies are added to the graph. In addition, combining the funnel plot with the non-parametric trim and fill procedure allows one to estimate the impact that theoretically missing studies could have on the mean difference (Duval and Tweedie 2000) by removing studies that are not "balanced" on the opposite side of the funnel plot. A new treatment effect is calculated and then added back along with the hypothetical studies that would balance out the funnel to form a new estimate. The funnel plot of all MY outcomes is shown with the trim and fill in (Figure 3.3). The funnel plot appears to be imbalanced with possibly several smaller studies missing suggesting possible publication bias. The trim and fill method helps visualize these missing studies (represented by the black solid dots). Another explanation for asymmetry in the funnel plots could be due to the heterogeneity in the studies included in the analysis (Rothstein, Sutton, and Borenstein 2005). If the treatment effect for the studies represented a distribution of studies instead of one true point effect, it could be represented as a distinct grouping of studies on the funnel plot, which may indicate the presence of publication bias. The funnel plots of peer reviewed milk results (Figure 3.4) show a more symmetrical outcome with no imputed studies (black solid dots), which indicates a lack of evidence for publication bias.

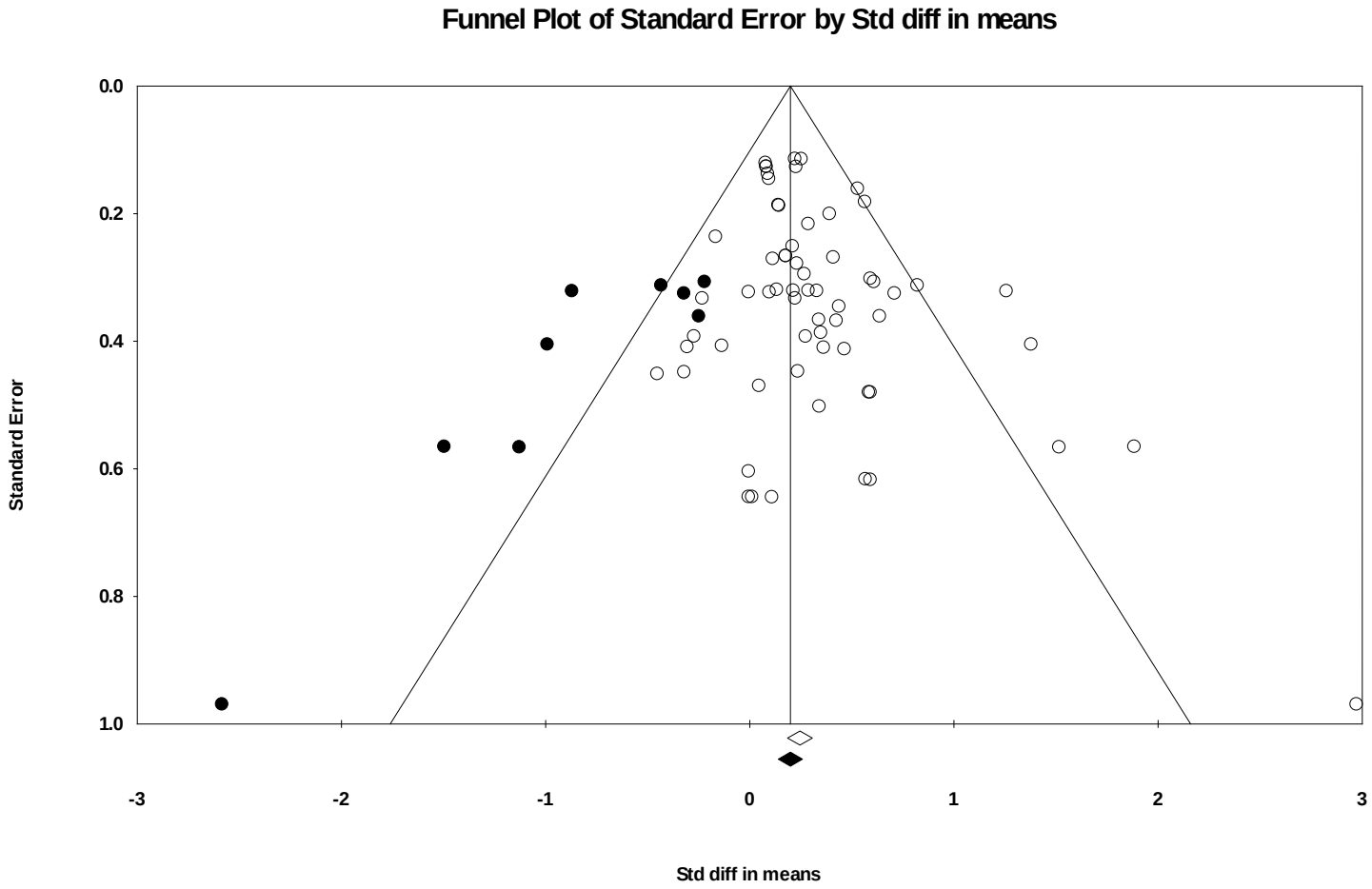


Figure 3.3. Funnel plot of the standardized mean difference (SMD) of studies (empty circles) from all studies with milk yield data, meeting the criteria to be included in the meta-analysis of the treatment effect of yeast culture on milk yield from from 1988 to 2011.. The solid dots are the potentially missing studies imputed from the trim and fill method (*Duval and Tweedie 2000*). The open diamond represents the mean plus confidence interval of the existing studies and the solid diamond represents the mean and confidence interval if the theoretically imputed studies were included in the meta-analysis. The funnel plot represents potentially a bias toward publishing favorable studies. The black diamond shows with missing studies added, the treatment effect is still within the 95% confidence interval of the current data set. The unbalanced funnel plot may also be indicative of heterogeneity of the treatment effects in the data set.

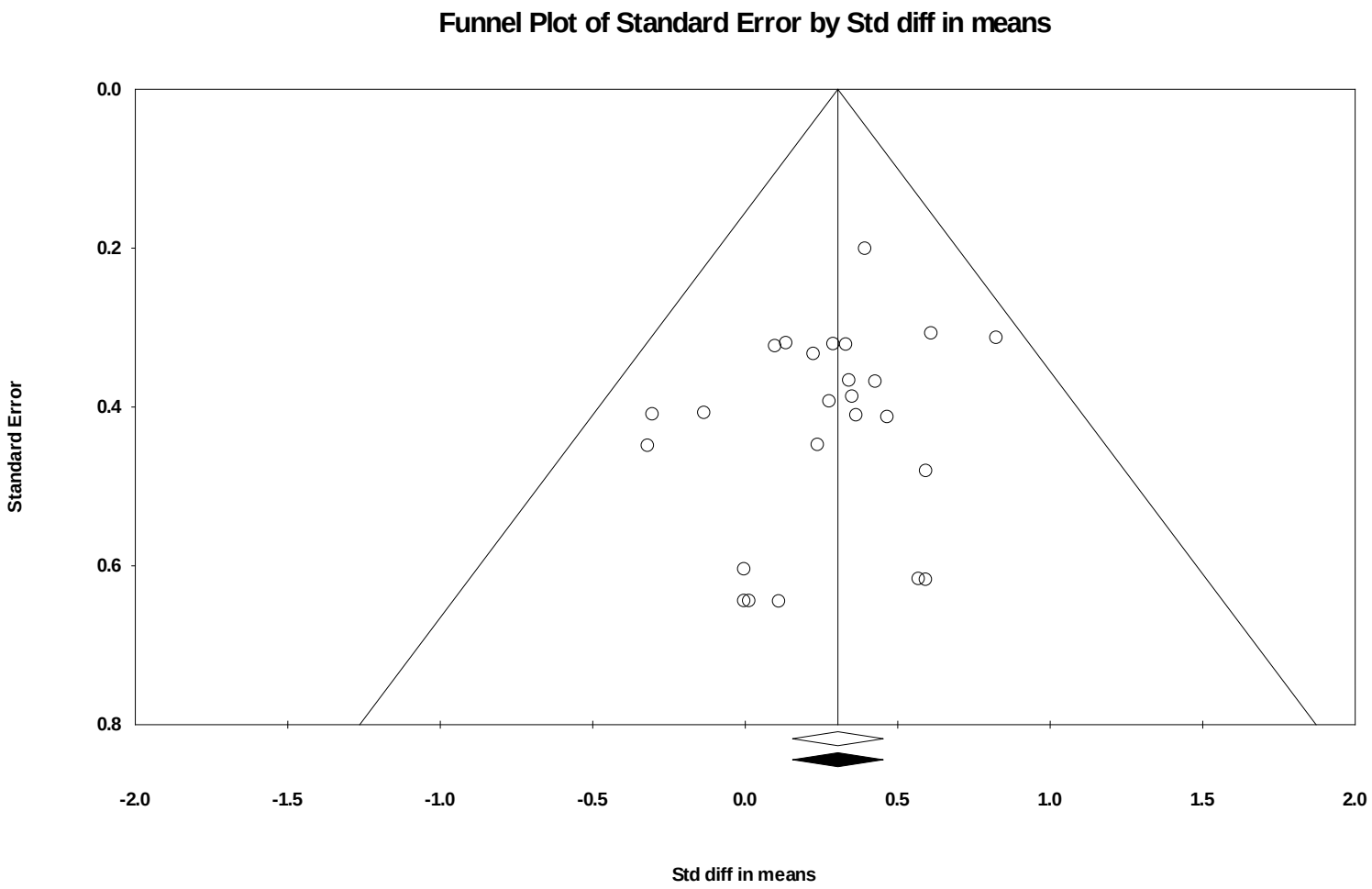


Figure 3.4. Funnel plot of the standardized mean difference (SMD) of treatment comparisons (empty circles) from studies published in journals only, representing the treatment effect of yeast culture on milk yield from a meta-analysis of studies on the milk production from 1988 to 2011. There are no potentially missing studies which would be represented by black dots using the trim and fill method of analysis (*Duval and Tweedie 2000*). The open diamond represents the mean plus confidence interval of the existing studies and the solid diamond represents the mean and confidence interval if the imputed studies were included. This funnel plot shows there is no evidence of bias from potentially missing studies.

Conclusion Chapter 3

This meta-analysis over a wide range of studies, designs and sub-group analysis, demonstrated feeding of this commercially available yeast culture to lactating dairy cows as evaluated in production settings typical for commercial dairies will increase production performance of lactating cows. The results indicate that MY is increased, as well as FY and PY, which resulted in higher ECM. With the increase in the sale of milk based on component pricing, this will provide additional options to nutritionists and dairymen in the development of feeding programs. Increased DMI (0.62 kg/d) during early lactation in lactating dairy cows supplemented with yeast culture will assist the dairy consultants and farm staff concerned with early lactation health, which often associated from declined in DMI of lactating cows. The decrease in DMI in late lactation represents an opportunity to gain efficiency in ration formulation in a high feed cost environment. Furthermore, utilizing meta-analytic methodology, specifically on one product, provides animal scientists with an effective tool to better understand treatment effects of interventions. This outcome may not have been achieved using smaller single studies or studies that combine dissimilar products into a single review that does not examine the heterogeneity attributable to differences in treatments. The assessment of heterogeneity is an important process in meta-analysis and allows us to better understand the effects of different study designs and management factors that may alter the inferences derived from the study.

CHAPTER 4

A META-ANALYSIS OF THE EFFECTS OF FEEDING OF COMMERCIALLY AVAILABLE ACTIVE DRY YEAST PRODUCTS OF *SACCHAROMYCES CEREVISIAE* ON MILK PRODUCTION OF LACTATING DAIRY COWS

Chapter 4 Executive Summary

The purpose of this study was to use meta-analytic methods on previously published randomized control trials (RCT) to estimate the effect of commercially available active dry yeast products on milk production and other production measures in lactating dairy cows. Four hundred ninety-seven published research articles were initially identified through an electronic literature search using 5 computerized search engines. Each paper was evaluated to determine if the trials contained the criteria required to be utilized in this study. Each trial utilized in the study had to be a randomized control trial, be published independently, be written in English, and be a lactating cow study. A trial was included if the product being evaluated was an active dry yeast product only (verses a control) and reported milk yield, milk fat, milk protein, fat corrected milk, energy corrected milk or dry matter intake. The trial descriptions had to have enough detail to evaluate the experimental methods and have information to evaluate the variance of the study. Trials were not included if they were cross over design studies. Twenty-two papers with 25 comparisons met the final criteria for inclusion in the meta-analysis. These studies evaluated active dry yeast products from 7 different companies and were conducted in 13 different countries. A random-effects meta-analysis showed there was high heterogeneity in the study outcome for milk yield making it an unreliable outcome to report. One sub-group analysis

identified an area of heterogeneity to be study location (in North America versus outside North America). Milk yield for the 7 studies conducted in North American was 0.49 kg/d versus 0.96 kg/d for 13 studies conducted outside North America. The mean difference in milk fat yield was 0.05 kg/d and there was a numerical difference in milk protein yield of 0.02 kg/d. No difference in dry matter intake was observed.

The use of funnel plots indicates possible publication bias in the published studies and could account for the large amount of heterogeneity observed in the outcomes of interest, particularly when study locations (North America, vs. outside North America) are plotted separately in the funnel plots.

Meta-analysis results show a production effect for active dry yeasts in lactating dairy cows, but the high level of heterogeneity indicate a high degree of variance that needs further exploration to provide confidence in trial results.

Key words: Active dry yeast, meta-analysis, lactating dairy cow

Introduction

Yeast products are common ingredients in animal feed around the world. In lactating dairy cattle, yeast products have been thought to improve production of milk yield **(MY),** milk fat yield **(FY),** and milk protein yield **(PY).** Yeast products have also been thought to improve energy corrected milk **(ECM),** which is a more representative biologically derived parameter that includes the components MY, FY, and PY and would be more representative of an economic parameter more closely aligned with value creation to the dairy producer. Although yeast products have been fed to dairy cows for more than 70 years, there is inconclusive evidence as to their effectiveness. One possible reason for ambiguity is the result of having 2 broad classes of yeast products with different putative modes of action that are often not differentiated in the

literature (AAFCO 2011) Yeast cultures, a product that is produced through yeast fermentation, contain fermentation end products and are not dependent on viability of the yeast for their physiological effects. These fermentation products contain compounds that affect the growth of various types of rumen bacteria and protozoa (Wiedmeier, Arambel, and Walters 1987, Harrison et al. 1988, Callaway and Martin 1997). These end products of *Saccharomyces cerevisiae* fermentation could be compared to other similar products in commercial use derived from bacteria or fungus, such as Penicillin from *Penicillium* fungi, Avermectins from *Streptomyces avermitilis*, and Monensin from *Streptomyces cinnamonensis*. In contrast, active dry yeast products (**ADY**) are products that by definition must contain greater than 15 billion live yeast cells/g (AAFCO, 2011). The effect of active dry yeast products is assumed to be dependent on the yeast cell being alive in the rumen (Dawson, Newman, and Boling 1990, Newbold, Wallace, and McIntosh 1996). The mode of action is an important consideration for the production effect of active dry yeast products. The viability of commercial product containing yeast have been shown to be highly variable in viability and to die rapidly in storage in temperatures as moderate as 40 degrees centigrade (Sullivan and Bradford 2011).

A recent meta-analysis of one commercial yeast culture (Poppy et al. 2012) utilized meta-analytic methodology to examine 36 separate random controlled trials (**RCT**) studies with 69 separate comparisons to examine the production outcomes in lactating dairy cattle. This meta-analysis of yeast culture showed 1.65 kg/d (95% CI = 0.97 to 2.34, $P = 0.001$) difference in ECM over control cows. Utilizing similar methodology to examine and review a complete comprehensive set of published information on active dry yeast would aid in providing for a more compete elucidation of yeast products on lactating dairy cattle. This evaluation would aid the animal scientist, nutritionist, and dairy manager in predicting production response to

commercial yeast products. Therefore, the primary purpose of this study was to critically review all relevant research of commercially available active dry yeast and to estimate the effect of active dry yeast on MY, FY, PY, ECM, and dry matter intake (**DMI)** of dairy cattle using meta-analytic methods. A secondary objective was to examine the differences in treatment effect and heterogeneity of various study characteristics that might alter the observed production response.

Materials and Methods

Literature Search

Electronic literature searches in PubMed (1950 to present), CAB (1973 to present), AGRICOLA (1970 to present), ScienceDirect (1995 to present), and Web of Science (1900 to present) were conducted. Terms that described the population, outcomes and treatments of interest were identified in the PubMed MESH database. Boolean terms were used to combine terms within a string (OR) and between strings (AND) and to exclude terms (NOT).

The search strings used was as follows: [ruminant* OR cow* OR cattle OR bovine] AND [lactati* OR postpartum OR milk OR dairy] AND [yeast OR "yeast culture" OR *Saccharomyces* OR *Saccharomyces cerevisiae*] AND ["dry matter intake" OR "energy corrected milk" OR "milk yield" OR "milk fat" OR "milk protein"] NOT [goat]. Retrieved citations were stored in reference management software (EndNoteWeb, version 3.5). Duplicate citations were removed by electronic and hand scanning of the database. When multiple instances of the same citation were identified, the most complete citation was retained.

Hand searching of the reference lists of relevant papers was conducted as the review progressed. Two reviewers (Poppy and Ruple-Czerniak) evaluated the reference list and identified potentially relevant citations. If the electronic search did not capture the citation, it was added to the reference management software.

Relevance Screening

A relevance screening was conducted to rapidly remove citations not relevant to the review, as the literature search process was highly sensitive, with low specificity. Eligible studies were primary research papers (peer reviewed journal articles) that reported the effects of feeding live or active dry yeast to lactating dairy cows. Two levels of relevance screening were used. For level 1 relevance screening, each abstract found in the database search was reviewed independently by two reviewers (Poppy and Ruple-Czerniak). Abstracts advanced to the second relevance screening if both reviewers agreed the abstract described primary research published in English pertaining to the effects of live or active dry yeast on milk production in dairy cows or if the abstract did not include enough information to determine eligibility. The second relevance screening was conducted by the same reviewers using the full published journal article whereupon the study was advanced to the final review utilizing the full manuscript for analysis of appropriate methodology for final inclusion (Figure 4.1).

Inclusion Criteria

Citations advanced to the final level of the review if the journal article met all the inclusion criteria for the final analysis. The final inclusion criteria were the study had to: be in English, be conducted using lactating dairy cattle, evaluate an active dry yeast product, include a concurrent negative control group, utilize randomized treatment assignments and use a parallel group design (i.e., no crossover studies). Additionally, studies must have reported results of at least one of the production outcomes of interest: MY, ECM, percent milk fat (**F%**), FY, percent milk protein (**P%**), PY, 3.5% fat corrected milk (**3.5% FCM**), or DMI, along with a measure of variance (standard error or standard deviation) or a *P* value for comparison of effects between treatment and control groups. The study had to provide enough information to establish if it met

the criteria for inclusion and be published as an independent study (peer reviewed journal article). Studies published by a commercial company as an internal report or advertisement were excluded.

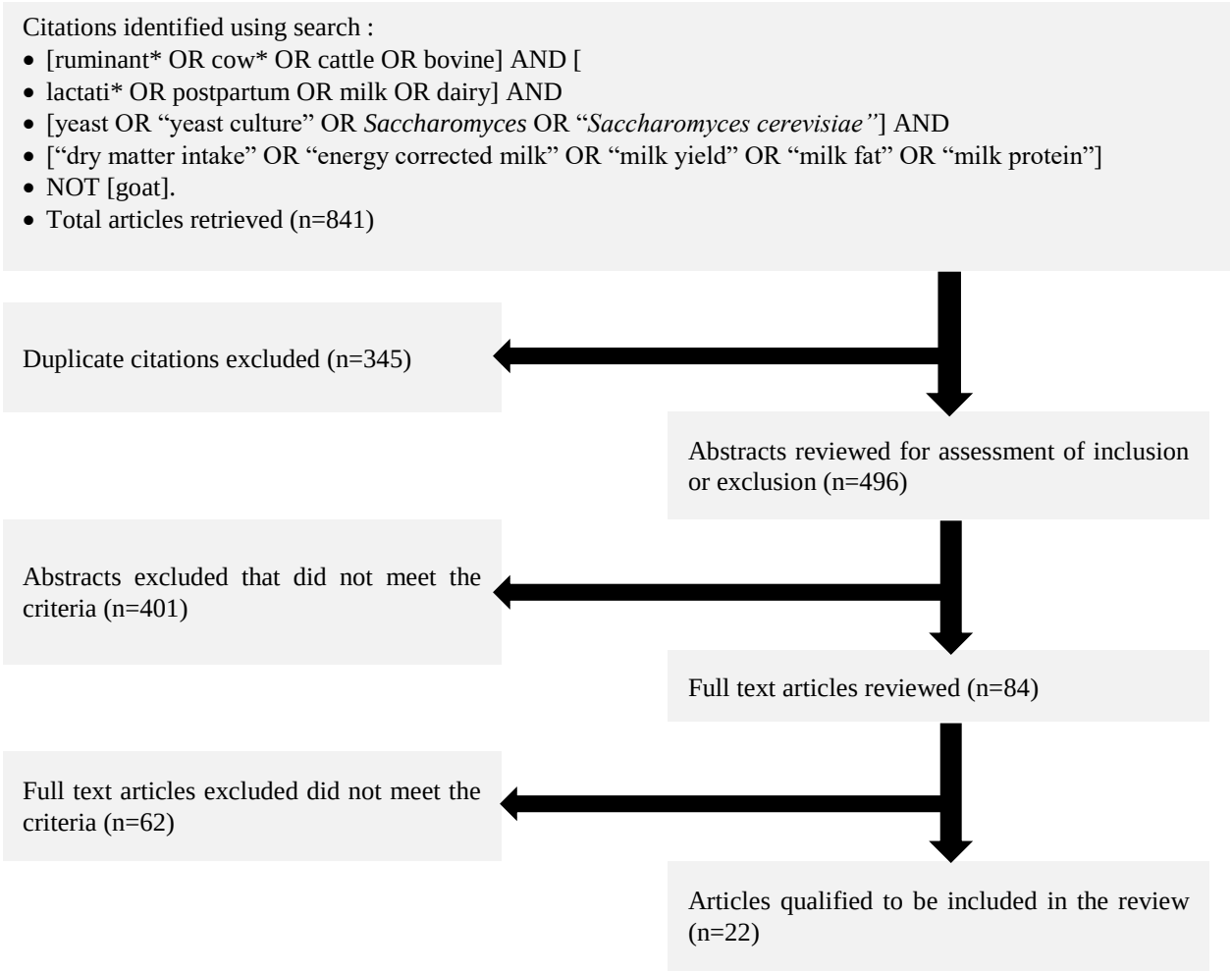


Figure 4.1. Flow diagram of search methodology and results from a review of articles targeting published studies on active dry yeast and its effect on milk production and DMI in dairy cows.

Statistical Analysis

Meta-analysis was conducted using the methods described by (Higgins and Green 2008a). Statistical analysis was conducted on the extracted production data using Comprehensive Meta-Analysis version 2.2.050 ((2008) Biostat, Englewood, New Jersey) and

(Stata/IC 2012); StataCorp V. 12.1 College Station, TX using the metan routine (Sterne 2009) Studies were weighted using the methods of inverse variance (DerSimonian and Laird 1986). If the selected studies did not report measures of variance of the interested outcomes, estimates of variability were extracted from the papers using the methods described by Rabiee et al. (Rabiee et al. 2010). If the trial only reported a Z statistic or *P* value, the estimates for SE and SD were calculated using the difference in the mean and the number of cows for each trial (Higgins and Green 2008a). For studies that only reported significance relative to a given alpha cut-point (i.e. $P \leq 0.05$), the value listed was used to make a conservative estimate of SE and SD. For studies that only reported a non-significant effect, *P* values of 0.15, 0.3, and 0.5 were assigned and compared numerically to each other. The *P* value that produced the smallest (most conservative) estimate of the overall treatment effect was selected for the calculation of the SE (Sanchez et al. 2004). If F%, FY, P%, PY, 3.5% FCM (Dairy Records Management Systems, 2006), and ECM (Tyrrell and Reid 1965) were not reported, estimates of these parameters were calculated. The variance used for the calculated missing value was the variance for the corresponding outcome statistic from the same trial (F% from FY, FY from F%, PY from P%, P% from PY and 3.5% FCM and ECM from MY). Continuous data were analyzed both using the raw mean difference (**RMD**) for both fixed effect and random effect models as described by Borenstein et al. (Borenstein et al. 2010) for each study outcome and as a standardized mean difference (**SMD**) as described by Lean et al. (Lean et al. 2009). Differences in study designs or production system characteristics that were considered *a priori* to influence trial outcomes or where a high level of heterogeneity was observed were explored using stratification for comparison of these sub-group comparisons. Sub-group analysis were conducted only when a minimum of 5 comparisons was available for inclusion in the analysis. Meta-regression of the variables was performed utilizing

STATA (2012; StataCorp V. 12.1 College Station, TX) with each subgroup first analyzed in a univariable analysis. Any variable subsequently found to be statistically related to the outcome with a wide threshold ($P \leq 0.20$) were entered into a multivariable meta-regression model. The variables included in the screening were if the study was conducted in North America (**NA**) (yes or no), total CFU of ADY fed as a continuous variables, stage of lactation (early < 70 DIM versus all studies), average DIM at start of trial as a continuous variable, number of times cows were milked per day, fed as a total mixed ration (TMR; yes or no), brand of ADY (brand X; yes or no), primiparous cows (yes or no), multiparous (yes or no), Holstein breed (yes or no), Friesian breed (yes or no), and if the ADY was top dressed on the feed (yes or no).

Assessment of Heterogeneity

Heterogeneity of effect size (between study variability compared to within study variability) was evaluated using both the chi-square test of Q for heterogeneity and the I^2 statistic (Higgins et al. 2003). Negative values of I^2 were assigned a value of zero. An I^2 value > 35% or a chi-square test of Q with $P \leq 0.20$ was considered indicative of substantial heterogeneity.

The Q statistic is a parameter that is sensitive to the ratio of the observed variation to the within study variation. Under the null hypothesis where all studies share a common effect size, the Q statistic follows a central chi-squared distribution with degrees of freedom equal to k-1. A significant *P* value would lead one to reject the null hypothesis and conclude that the studies do not share a common effect size and therefore should not be reported as a mean effect. Two groups can be evaluated if they share a common effect size by the same method. When two groups are being evaluated, Q is calculated as the effect size of the groups of studies instead of two studies. The dispersion of the subgroup about a summary effect can then be tested with degrees of freedom = 1 (Borenstein et al. 2009c).

The data were analyzed using both fixed effect and random effects models. The random effects model was determined more appropriate to report the treatment effects as this accounts for the impacts of study design, management and cow variation and other differences in study conduct on treatment effects (Borenstein et al. 2010).

Publication Bias

Publication bias was assessed using funnel plots (Light and Pillemer 1984). Trim and fill methods were used to assess the best estimate of the unbiased effect size (Duval and Tweedie 2000).

Results and Discussion

Reports Meeting Inclusion Criteria

Four hundred and ninety six papers were initially identified utilizing the search criteria and presented for relevance screening. The initial database search was designed as a highly sensitive, low specificity search so all relevant studies would be identified. After both relevance screenings were conducted only 22 studies with 25 comparisons remained for comparison. Papers were excluded from this study because the study was not written in English, had no negative controls, and evaluated yeast products along with another inclusion such as enzymes or minerals or protein sources. Many of the rejected papers were conducted in vitro, were yeast culture studies, or were conducted using species other than lactating dairy cows.

In the initial inclusion criteria, failure to appropriately use pen as an experimental unit in the statistical variance calculation when the treatment was fed at the pen level did not disqualify the study. The authors wished to analyze if using the inappropriate experimental unit biased the outcome of the study. Randomization at the treatment level is a critical criterion of study design in RCT. Even if the researcher felt that pen would have no confounding effect on the outcome of

the study, it is unknown confounders that RCT trials are designed to prevent. In addition to not knowing if pen produced confounding in the data, in a meta-analysis, the pseudo-replication resulting from inappropriately counting of cows as the experimental unit would artificially increase the precision of the study. Meta-analysis weights studies by the inverse variance, therefore, cow as the experimental unit would mathematically overweight the value of the study in the summarized report. Of the ADY papers identified in the systematic review, 5 of the studies (Garg et al. 2000, Alshaikh et al. 2002, Lethbridge, Margerison, and Parfitt 2007, Cakiroglu et al. 2010, Ondarza et al. 2010) calculated the variance at the cow level, but applied the treatment at the pen level. The appropriately designed studies had a mean MY difference of 0.81 kg/day (95% CI = 0.27 to 1.54). The 5 group fed studies had a MY difference of 1.20 kg/d (95% CI = 0.24 to 2.17). The difference between the group fed and individually fed studies (chi-square with 1 *df*) was not significant ($P = 0.16$). The studies utilizing the inappropriate variance were eliminated from the final analysis leaving 17 studies and 20 comparisons (Table 4.1).

Heterogeneity and Production Analysis

The analysis of MY showed substantial heterogeneity ($I^2 = 40.12\%$) as well as a highly significant chi-square test of Q ($P = 0.03$). Within a meta-analysis, the heterogeneity is an important evaluation because a high level of heterogeneity ($I^2 > 35\%$ or a Q test with $P \leq 0.10$) is an indication that the treatment effect is possibly reporting more than one distribution of outcomes within the analysis. The Q test is a test of the null hypothesis that the studies share a common effect size. Therefore, if heterogeneity is identified, a subgroup analysis can be used to try to identify characteristics of the studies that are contributing the heterogeneity. It may not be appropriate to report treatment effects with heterogeneity as they may misrepresent the true treatment effect (Kent 2010). In this study, the only sub-group that yielded low heterogeneity

Table 4.1. Estimated effect of active dry yeast on milk yield in lactating dairy cows. Random effects of the raw mean difference and stratified by subgroup from a meta-analysis of papers 1991 to 2010.

			RMD[1]			Heterogeneity				
Milk Yield (kg/d)		**Trials comparisons (n)**	**Random effect**	**(95% CI)**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Tau Squared**
All	All trials	25	0.94	(0.42 to 1.45)	0.001	46.55	24	0.004	48.4	0.65
	Group	5	1.21	(0.25 to 2.16)	0.013	12.83	4	0.012	68.83	0.65
Feeding Group[2]	Individual	20	0.813	(0.19 to 1.46)	0.010	31.78	19	0.033	40.12	0.69
	Difference between Group and Individual					1.93	1	0.164		
	No	13	0.96	(0.10 to 1.83)	0.029	30.39	12	0.003	59.5	1.24
North American Study[3,4]	Yes	7	0.49	(-0.45 to 1.43)	0.307	1.40	6	0.954	0.0	0.0
	Difference between Location of Study					0.41	1	0.524		
	Early	13	1.10	(0.26 to 1.94)	0.010	19.42	12	0.079	38.2	0.80
Stage of Lactation[3,5]	Not Early	7	0.40	(-0.48 to 1.27)	0.374	9.29	6	0.158	35.4	0.45
	Difference between Stage of Lactation					0.25	1	0.610		
	No	10	1.27	(0.72 to 1.80)	0.001	5.66	9	0.773	0.0	0.0
Commercial Brand X of ADY[3,6]	Yes	10	0.35	(-0.89 to 1.59)	0.577	19.03	9	0.025	52.7	1.72
	Difference between Brand of ADY					1.98	1	0.159		

[1] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval.

[2] Studies were grouped for analysis based on if matched the experimental unit to the variance in the statistical analysis. If treatments were fed to pen, data was analyzed to pen. If treatments were fed to individual cows, data was analyzed to cow. Studies that fed to pen and analyzed to cow were classified as group and removed from subsequent analysis because of the under estimation of variance.

[3] The analysis only contains data from herds which used the proper variance (studies classified as individual studies in the Feeding Group Yes subgroup).

[4] Analysis classifies subgroup for the study being conducted in North America (Yes or No).

[5] Treatment effect stratified by stage of lactation. Studies that were primarily conducted in groups of cows less than 70 DIM (early) and all other studies (not early).

[6] There was only one commercial brand of active dry yeast (ADY) with enough trials to analyze for meta-regression (Brand X: yes or no).

was the study was conducted NA (Canada or United States) versus not in NA. Studies conducted in NA (7 studies; MY = 0.49 kg/d, P = 0.307) had an I^2 = 0.0% and Q chi-squared P = 0.954. Studies conducted outside of NA (13 studies; MY = 0.96 kg/d, P = 0.029) had an I^2 = 59.5% and Q chi-squared P = 0.003 (Table 4.1). The SMD showed a similar result with the studies conducted in NA showing low heterogeneity (I^2 =0.0 %) and a MY of 0.04 (P = 0.606) and those conducted outside of NA high heterogeneity (I^2 =45.0 %) with a MY of 0.38 (P = 0.053) (Table 4.2). The forest plots for the RMD and the SMD stratified by study location visually show the difference in variation between the two subgroups (Figure 4.2 and Figure 4.3).

While the outcomes for 3.5 % FCM and ECM only had moderate heterogeneity (I^2 =19.29 % and 25.8 % respectively) (Table 4.3 and Table 4.4) the reported outcomes between the different subgroup stratifications were very different. The studies conducted in NA reported no significant change in 3.5 % FCM or ECM while the studies conducted outside of NA reported 1.20 kg/d (P = 0.001) and 1.19 kg/d (P=0.003) for 3.5 % FCM and ECM respectively (Table 4.3 and Table 4.4).

When MY, 3.5% FCM and ECM were stratified by Early (< 70 DIM) and Not Early (> 70 DIM) lactation, there was high heterogeneity in all groups (Table 4.1 to Table 4.4) so this stratification was not successful in identifying where the variation was originating.

Table 4.2. The estimated effect of active dry yeast on milk yield in lactating dairy cow from a meta-analysis performed on studies published from 1991 to 2010. Random effects of the standardized mean difference[1] and stratified by subgroup.

			SMD[2]			Heterogeneity				
Milk Yield (kg/d)		**Trials comparisons (n)**	**Random effect**	**(95% CI)**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Tau Squared**
All	All trials	25	0.29	(0.10 to 0.49)	0.003	48.70	23	0.002	50.50	0.09
Feeding Group[2]	Group	5	0.53	(0.01 to 1.06)	0.045	18.84	4	0.001	78.40	0.24
	Individual	25	0.21	(0.01 to 0.42)	0.042	29.40	18	0.084	32.10	0.06
	Difference between Group and Individual					0.53	1	0.465		
North American Study[3,4]	No	13	0.38	(-0.04 to 0.77)	0.053	22.69	12	0.039	45.0	0.20
	Yes	7	0.04	(-0.12 to 0.21)	0.606	2.14	6	0.890	0.0	0.0
	Difference between Location of Study					1.68	1	0.200		
Stage of Lactation[3,5]	Early	13	0.33	(-0.01 to 0.67)	0.05	16.9	12	0.155	28.8	0.10
	Not Early	7	0.12	(-0.12 to 0.36)	0.33	9.36	6	0.154	35.9	0.03
	Difference between Stage of Lactation					0.77	1	0.380		
Commercial Brand X of ADY[3,6]	No	10	0.21	(0.01 to 0.63)	0.018	17.39	9	0.043	48.3	0.08
	Yes	10	0.05	(-0.26 to 0.36)	0.751	10.20	9	0.334	11.8	0.029
	Difference between Brand of ADY					1.91	1	0.167		

[1] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the SMD. The SMD can be viewed as a measure of overlap between 2 separate distributions.

[2] Studies were grouped for analysis based on if matched the experimental unit to the variance in the statistical analysis. If treatments were fed to pen, data was analyzed to pen. If treatments were fed to individual cows, data was analyzed to cow. Studies that fed to pen and analyzed to cow were classified as group and removed from subsequent analysis because of the under estimation of variance.

[3] The analysis only contains data from herds which used the proper variance (studies classified as individual studies in the Feeding Group Yes subgroup).

[4] Analysis classifies subgroup for the study being conducted in North America (Yes or No).

[5] Treatment effect stratified by stage of lactation. Studies that were primarily conducted in groups of cows less than 70 DIM (early) and all other studies (not early).

[6] There was only one commercial brand of active dry yeast (ADY) with enough trials to analyze for meta-regression (Brand X: yes or no).

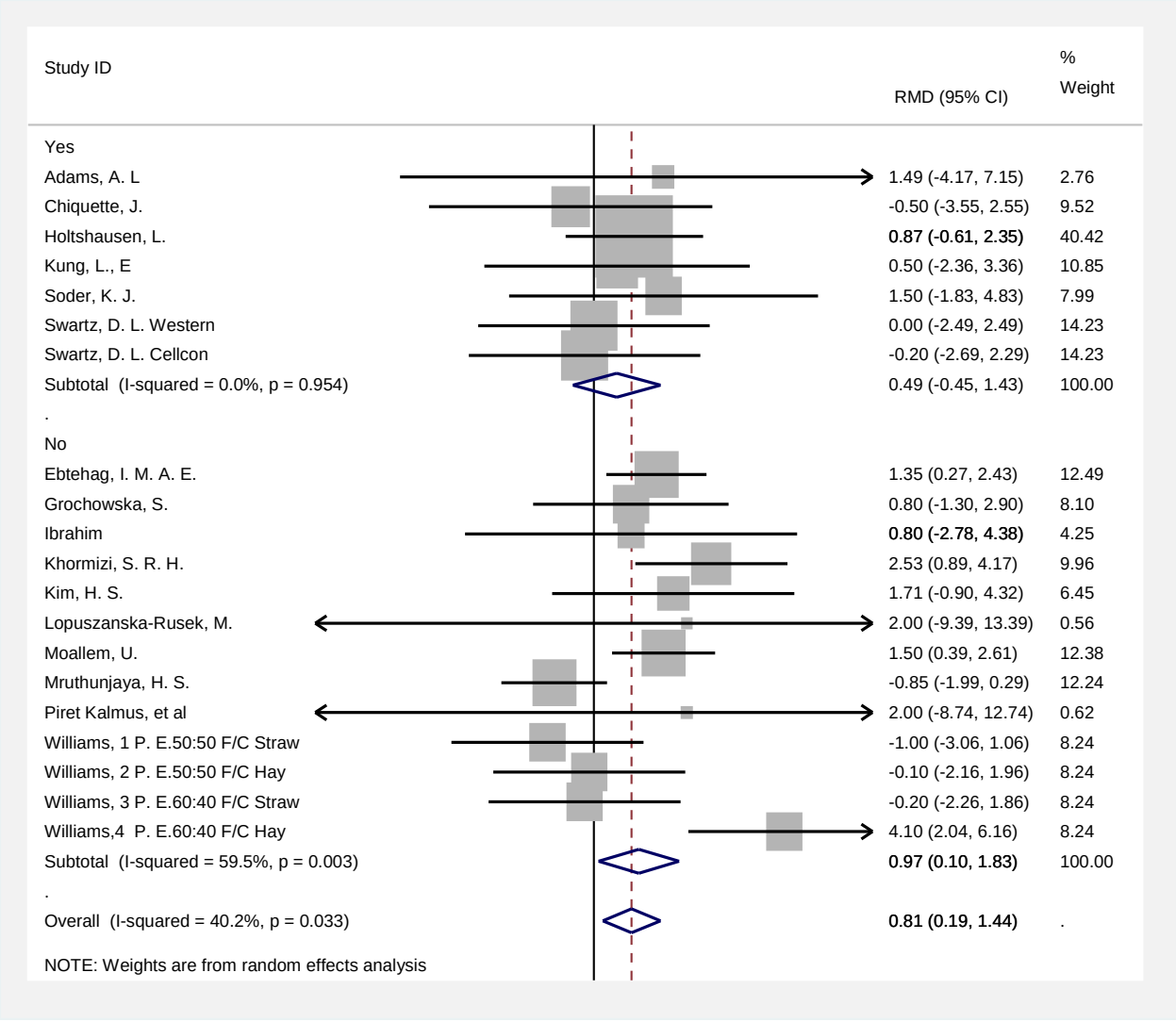


Figure 4.2. Forest plot of the Raw Mean Difference of milk yield grouped by study location (in or outside of North America). The size of the grey boxes is proportional to the weight of the study, the horizontal line represents the 95% CI of the individual study and the black dot represents the mean of the study. The triangles center is the mean of the study and the width represents the se of the study. The red dashed line represents the overall mean of the both subgroups in the meta-analysis of the effects or active dry yeast fed to dairy cows from studies between from a meta-analysis performed on studies published from 1991 to 2010.

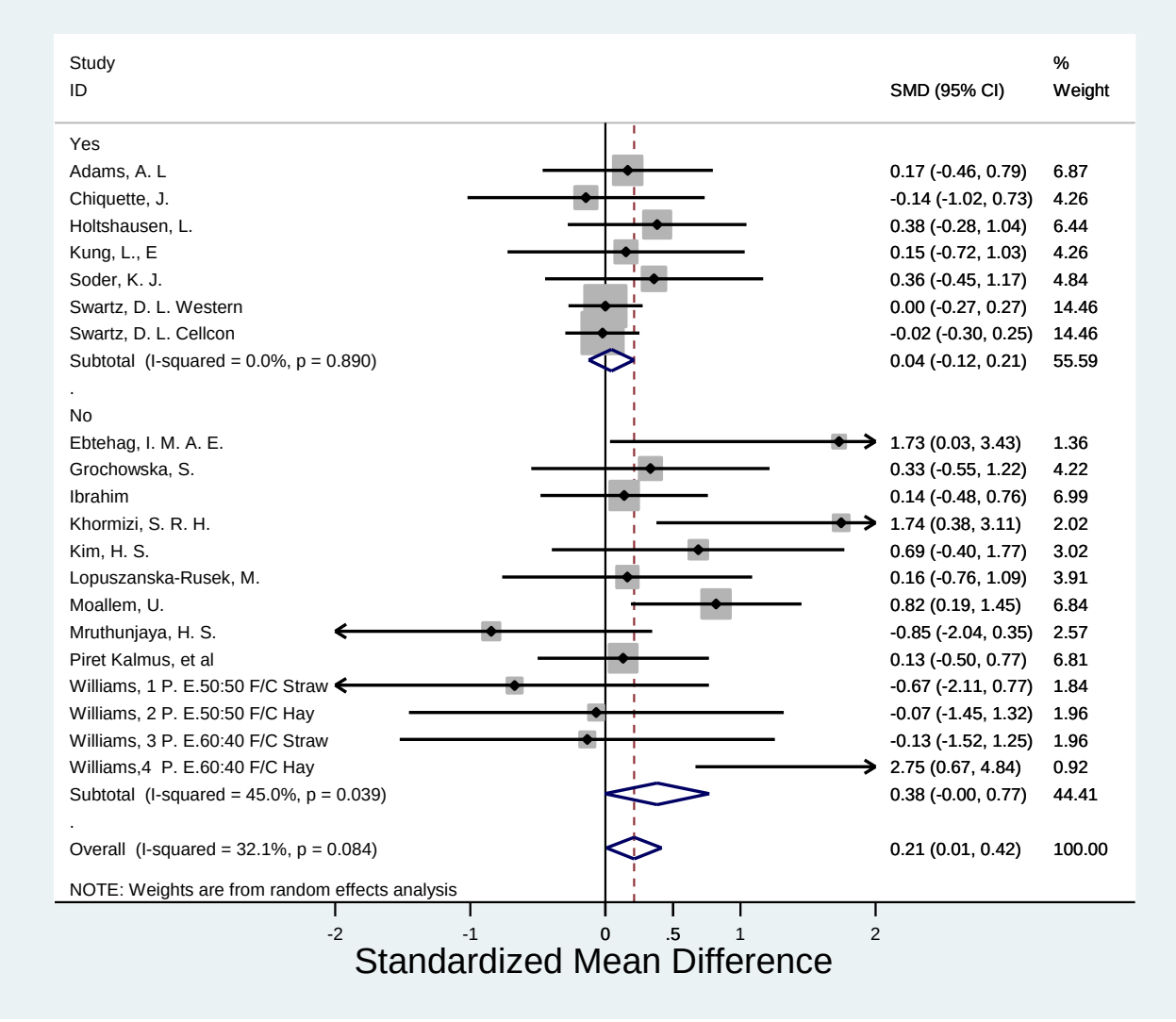


Figure 4.3. Forest plot of the Standardized Mean Difference of milk yield grouped by study location (in or outside of North America). The size of the grey boxes is proportional to the weight of the study, the horizontal line represents the 95% CI of the individual study and the black dot represents the mean of the study. The triangles center is the mean of the study and the width represents the se of the study. The red dashed line represents the overall mean of the both subgroups in the meta-analysis from a meta-analysis on active dry yeast on milk production and DMI performed on studies published from 1991 to 2010.

Table 4.3. The estimated effect of active dry yeast on FCM 3.5% and ECM Milk Fat Yield and Milk Protein Yield in lactating dairy cows using random effects of the raw mean difference and stratified by subgroup from a meta-analysis performed on studies published from 1991 to 2010.

			RMD[1]			Heterogeneity				
Production Effects (kg/d)		**Trials comparisons (n)**	**Random effect**	**(95% CI)**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Tau Squared**
FCM 3.5%[2, 7]	All trials	18	1.04	(0.47 to 1.61)	0.001	21.06	17	0.22	19.29	0.27
	Early	12	1.06	(0.32 to 1.80)	0.005	14.85	11	0.19	25.95	0.42
	Not Early	6	1.02	(0.03 to 2.02)	0.044	6.04	5	0.30	17.23	0.28
	Difference between Early and Not Early					0.02	1	0.90		
FCM 3.5%[2, 7]	NA No[3]	11	1.20	(0.51 to 1.89)	0.001	14.05	10	0.17	28.81	0.36
	NA Yes[3]	7	0.53	(-0.54 to 1.60)	0.334	5.57	6	0.47	0.0	0.0
	Difference between Location of Study					1.02	1	0.31		
Energy Corrected Milk[4, 7]	All	17	1.00	(0.40 to 1.59)	0.001	21.56	16	0.16	25.80	0.37
	Early	11	1.05	(0.21 to 1.89)	0.015	15.79	10	0.11	36.65	0.67
	Not Early	6	1.02	(0.16 to 1.88)	0.021	5.73	5	0.33	12.80	0.16
	Difference between Stage of Lactation					0.07	1	0.79		
Energy Corrected Milk[4, 7]	NA No[3]	10	1.19	(0.40 to 1.98)	0.003	15.29	9	0.08	41.15	0.60
	NA Yes[3]	7	0.54	(-0.40 to 1.48)	0.26	4.58	6	0.60	0.0	0.0
	Difference between study if conducted in North America					1.16	1	0.28		
Milk Fat Yield[5, 7]	All	18	0.05	(0.02 to 0.07)	0.001	12.32	17	0.78	0.00	0.00
	Early	12	0.05	(0.02 to 0.08)	0.001	8.13	11	0.70	0.00	0.00
	Not Early	6	0.04	(-0.01 to 0.08)	0.134	3.84	5	0.57	0.00	0.00
Milk Protein Yield[6, 7]	All	17	0.02	(-0.01 to 0.05)	0.174	3.54	16	1.00	0.00	0.0
	Early	11	0.02	(-0.04 to 0.08)	0.559	1.57	10	1.00	0.00	0.0
	Not Early	6	0.02	(-0.01 to 0.05)	0.219	1.97	5	0.854	0.00	0.0

[1] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval.

[2] All studies with FCM data or sufficient data to calculate FCM are included in this data set. 3.5% FCM = (Milk lb × 0.432) + (Fat lb × 16.216) (Dairy Records Management Systems, 2006).

[3] Analysis classifies subgroup for the study being conducted in North America (Yes or No).

[4] All studies with ECM data or sufficient data to calculate ECM are included in this data set. ECM = 0.327 * milk lb + 12.97 × fat lb + 7.21×protein lb (Tyrrell and Reid, 1965).

[5] Dataset is trials with milk fat yield data or sufficient data to calculate milk fat yield.

[6] Dataset is trials with milk protein yield data or sufficient data to calculate milk protein. The analysis only contains data from herds which used the proper variance (classified as individual studies in the Feeding Group Yes subgroup).

[7] The analysis only contains data from herds which used the proper variance (classified as individual studies in the Feeding Group Yes subgroup).

Table 4.4. The estimated effect of active dry yeast on FCM 3.5%, ECM, Milk Fat Yield, and Milk Protein Yield in lactating dairy cows using random effects of the standardized mean difference and stratified by subgroup from a meta-analysis performed on studies published from 1991 to 2010.

			SMD[1]			Heterogeneity				
Production Effects (kg/d)		**Trials comparisons (n)**	**Random effect**	**(95% CI)**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Tau Squared**
FCM 3.5%[2,7]	All trials	18	0.30	(0.06 to 0.53)	0.013	28.81	17	0.04	41.00	0.08
	Early	12	0.42	(0.10 to 0.75)	0.012	12.83	11	0.304	14.30	0.05
	Not Early	6	0.19	(-0.12 to 0.49)	0.237	12.22	5	0.032	59.10	.08
	Difference between Early and Not Early					1.19	1	0.26		
FCM 3.5%[2,7]	NA No[3]	11	0.56	(0.18 to 0.93)	0.004	13.86	10	0.18	27.90	0.11
	NA Yes[3]	7	0.03	(-0.14 to 0.20)	0.728	5.81	6	0.445	0.00	0.0
	Difference between Location of Study					5.62	1	0.018		
Energy Corrected Milk[4,7]	All	17	0.28	(0.04 to 0.52)	0.021	27.47	16	0.037	41.70	0.08
	Early	11	0.39	(0.27 to 0.76)	0.035	12.93	10	0.227	22.70	0.08
	Not Early	6	0.19	(-0.11 to 0.50)	0.220	11.92	5	0.036	58.00	0.07
	Difference between Stage of Lactation					0.72	1	0.395		
Energy Corrected Milk[4, 7]	NA No[3]	10	0.55	(0.12 to 0.97)	0.012	14.92	9	0.093	39.69	0.16
	NA Yes[3]	7	0.03	(-0.14 to 0.20)	0.71	5.38	6	0.500	0.00	0.0
	Difference between study if conducted in North America					4.50	1	0.115		
Milk Fat Yield[5, 7]	All	18	0.07	(-.07 to 0.23)	0.30	16.93	17	0.49	0.00	0.0
	Early	12	0.21	(-0.09 to 0.50)	0.170	10.30	11	0.50	0.00	0.0
	Not Early	6	0.05	(-0.14 to 0.24)	0.61	5.63	5	0.46	11.16	0.0
Milk Protein Yield[6, 7]	All	17	0.05	(-0.01 to 0.19)	0.525	4.86	16	1.00	0.00	0.0
	Early	11	0.09	(-0.21 to 0.39)	0.543	1.51	10	1.00	0.00	0.0
	Not Early	6	0.03	(-0.14 to 0.20)	0.699	3.24	5	0.66	0.00	0.0

[1] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the standardized mean difference. The SMD can be viewed as a measure of overlap between 2 separate distributions.

[2] All studies with FCM data or sufficient data to calculate FCM are included in this data set. 3.5% FCM = (Milk lb × 0.432) + (Fat lb × 16.216) (Dairy Records Management Systems, 2006).

[3] Analysis classifies subgroup for the study being conducted in North America (Yes or No).

[4] All studies with ECM data or sufficient data to calculate ECM are included in this data set. ECM = 0.327 * milk lb + 12.97 × fat lb + 7.21×protein lb (Tyrrell and Reid, 1965).

[5] The dataset is trials with milk fat yield data or sufficient data to calculate milk fat yield.

[6] The dataset is trials with milk protein yield data or sufficient data to calculate milk protein. The analysis only contains data from herds which used the proper variance (classified as individual studies in the Feeding Group Yes subgroup).

[7] Analysis only contains data from herds which used the proper variance (classified as individual studies in the Feeding Group Yes subgroup).

Milk fat yield and MP had low heterogeneity (I^2 = 0.00) for all studies, as well as, for the stratification of Early (< 70 DIM) and Not Early (> 70 DIM) lactation (I^2 = 0.00). The RMD for FY for cows supplemented with ADY was 0.05 kg/day (95% CI = 0.02 to 0.07, P = 0.001). The RMD for PY was 0.02 kg/d, although this value was not significant from 0 (95% CI = -0.01 to 0.05, P = 0.174, Table 4.3 and Table 4.4).

Dry matter intake had a high heterogeneity (I^2 = 59.66%, Q chi-squared P = 0.00) (Table 4.5). It was decided *a priori* to evaluate DMI by stage of lactation. There were 12 studies conducted for cows less than 70 DIM that included DMI. These studies had a RMD for cows supplemented with ADY of 0.42 kg/d (P = 0.25; 95% CI = -0.30 to 1.15, I^2 = 0.0%, Q chi-squared P = 0.90). There were insufficient studies containing DMI (n = 4) "not in early lactation" (> 70 DIM) to evaluate for heterogeneity or as a separate outcome.

Meta-regression

Univariable regression was performed on the variables; NA (yes or no) total CFU of ADY fed, stage of lactation, average DIM at start of trial, number of times cows were milked per day, fed as a TMR (yes or no), brand of ADY (brand X; yes or no), primiparous cows (yes or no), multiparous (yes or no), Holstein breed (yes or no), Friesian breed (yes or no), and if the ADY was top dressed on the feed (yes or no) Variables with a P value < 0.20 were to be included in the meta-regression model. Because only brand of ADY had a P < 0.20, multivariable regression to further examine the cause of heterogeneity was not performed.

Publication Bias

Publication bias as viewed in a meta-analysis is the tendency for certain reports intentionally or unintentionally to enter the public stream of information for evaluating proposed

Table 4.5. The estimated effect of active dry yeast on dry matter intake (DMI) from a meta-analysis performed on studies published from 1991 to 2010.

			RMD (95% CI)[1]		Heterogeneity				SMD (95% CI) [2]	
Dry matter intake (kg/d)		**Trials (n)**	**Random effect**	***P* value**	**Chi-square (Q)**	**df**	***P* value**	**I^2 (%)**	**Random effect**	***P* value**
Stage of Lactation[3,4]	All Studies	15	0.0 (-0.86 to 0.85)	0.994	37.18	15	0.001	59.66	-0.04 (-0.37 to 0.29)	**0.810**
	Early	12	0.42 (-0.31 to 1.15)	0.251	5.59	11	0.90	0.00	0.16 (-0.24 to 0.54)	0.42

[1] RMD is the raw mean difference of the treatment effect and its associated 95% confidence interval.

[2] SMD is the standardized mean difference of the treatment effect. This is estimated by dividing the mean difference for a study by the standard deviation for that study. A random effects model was then analyzed for the standardized mean difference. The SMD can be viewed as a measure of overlap between 2 separate distributions.

[3] Treatment effect stratified by stage of lactation. Studies that were primarily conducted in groups of cows less than 70 DIM (early) and all other studies (not early). There were not enough studies (4) to report a subgroup analysis for not early DMI.

[4] The analysis only contains data from herds which used the proper variance (classified as individual studies in the Feeding Group Yes subgroup).

interventions that may be of interest to the public. Although a meta-analysis will yield a mathematically accurate synthesis of the studies included in the analysis, if these studies are a biased sample of all relevant studies, the mean effect computed by the meta-analysis will reflect this bias (Borenstein et al. 2009c). In the agriculture industry, as opposed to other industries such a human pharmaceuticals, there are two classes of studies produced. There are the independent produced studies submitted for peer review, which, in theory, conform to a set standard of quality. There are also studies produced specifically to enhance the marketing of a product. Studies produced with the aim of marketing a product may not have the same rigor in standards of quality as studies produced for publication, which often has affiliations with third parties or Universities. Since there is no peer review process in place for marketing-driven studies, we cannot know if this is the case. However, if this is true, then one would worry about poor statistical design and non-control of confounding being present in non-published studies. If such flawed analysis were included in a meta-analysis, the true mean could be biased away from the null producing a type I error. In contrast in human pharmaceuticals, the danger is more likely to be that unpublished trials that may not be perceived as "beneficial" to the sponsoring company would not get submitted (file drawer bias) for publication (Rothstein, Sutton, and Borenstein 2005). In the latter case, the inclusion of all non-published papers would decrease the potential bias away from the null and move the effect toward the null. Due to the inability to validate the quality of unpublished reports or reports that are self-published without the benefit of peer review, these reports were not included in this meta-analysis.

No attempt was made by the authors to distinguish if the journal articles obtained in the literature search were truly peer-reviewed journals. There are many opportunities for papers, which do not meet the rigor of acceptable scientific methodology, to be published and enter the

journal databases (Bohannon 2013). All papers that were identified in the literature search that had sufficient detail of the experimental design were included in the meta-analysis. Abstracts would not meet this level of criteria as they do not contain materials and methods sections.

The numerical difference in RMD and SMD between MY for studies conducted in NA versus outside of NA, reflected in the high heterogeneity of MY (I^2 = 48.4, Table 4.3 and Table 4.4), might be due to different feeding and dairy management systems. It is reasonable to assume that the studies conducted under NA conditions and dairy management techniques were more similar in variance and outcome than studies conducted elsewhere. The non-NA studies were conducted in Egypt, India, Iran, Ireland, Israel, Korea, Poland, Estonia, and Scotland. Whether it can be assumed these dairy management systems would constitute a uniform subgroup is not possible to determine with these studies. In the studies conducted in North America, it is possible the dairy management systems are less compatible with the maintenance of viable live yeast than in feeding systems in other areas of the world. How the product is fed and the time lag from manufacturing to ingestion could be different in the different subgroups. Only three studies (Kung et al. 1997, Al Ibrahim et al. 2010, Shwartz et al. 2009) measured the colony forming units (cfu) of *Saccharomyces cerevisiae* fed in their studies. Shwartz et al., adjusted their feeding rate for the viable cfu counts in the commercial product to feed the recommended rate (Table 4.6). Al Ibrahim, et al., 2010 fed the recommended amount of product which would have been 1.00×10^{10} cfu but only ended up feeding 6×10^{8} cfu/kg fed and Kung et al., only reported the actual cfu fed (10 g of 3.5×10^{9} cfu of yeast/g of supplement). All other studies fed the recommended dose from the manufacturer with no test of viability. Publication bias may also be a factor if manufacturers of live yeast products have more influence over what papers are published in areas outside of North America, resulting in heterogeneity of the

Table 4.6. Studies on active dry yeast products meeting selection[1] criteria representing years 1991 to 2010 and used in the meta-analysis.

Study Name	Location[2]	CFU Fed[3]	Stage of Lactation[4]	Avg. DIM at trial start[5]	Length of trial[6]	Milking Frequency[7]	Brand[8]	Parity[9]	Breed[10]	Delivery method[11]	Feeding method[12]
Adams et al,1995	US	5.00E+10	Not Early	Early and Mid	84	3X	Yea-Sacc 1026	Both	Holstein	Top-Dress	Individual
Alshaikh et al., 2002	Saudi Arabia	3.90E+05	Not Early	118-134	70	3X	Yea-Sacc 1026	Multi	Holstein	Mixed	Group
Cakirogiu et al., 2010	Turkey	1.00E+09	Early	45	21	2X	Yea-Sacc 1026	Multi	Jersey	Drench	Group
Chiquette et al., 1995	Canada	5.00E+10	Early	42	35	2X	Yea-Sacc 1026	Multi	Holstein	Mixed	Individual
Ebtehag et al., 2011	Egypt	1.00E+10	Early	0	75	2	Epix	Multi	Crossbred	Mixed	Individual
Garg et al., 2000	India	5.00E+10	Not Early	80	91	2	Yea-Sacc 1026	Multi	Holstein Friesian	Mixed	Group
Grochowska et al., 2009	Poland	7.00E+10	Early	-21	70 dim	UK	Biosaf SC 47	Multi	Unknown	Unknown	Individual
Holtshausen, et al., 2010	Canada	5.00E+9	Not Early	51-159	42	2	Levucell SC 1077	Both	Holstein	Mixed	Individual
Al Ibrahim, et al., 2010	Ireland	3.00E+11	Early	-14	70 dim	2	Yea-Sacc 1026	Both	Holstein Friesian	Mixed	Individual
Khormizi, et al., 2010	Iran	1.00E+11	Early	35-43	75	3	Biosaf SC 47	Both	Holstein	Top-Dress	Individual
Kalmus, et al., 2009	Estonia	5.00E+10	Early	-14	98 dim	2	Yea-Sacc 1026	Unknown	Eastonian Holstein	Top-Dress	Individual

Study Name	Location[2]	CFU Fed[3]	Stage of Lactation[4]	Avg. DIM at trial start[5]	Length of trial[6]	Milking Frequency[7]	Brand[8]	Parity[9]	Breed[10]	Delivery method[11]	Feeding method[12]
Kim, et al., 2006	Korea	1.5E+11	Early	-21	41 dim	UK	Yea-Sacc 1026	Multi	Holstein	Mixed	Individual
Kung, et al., 1997	US	1.75E+11	Not Early	130-189	63	2	Biomate	Multi	Holstein	Top-Dress	Individual
Lethbridge, et al.,2007	New Zealand	1.00E+10	Early	0	114	2	Unknown	Primi	Unknown	Mixed	Group
Lopuszanska-Rusek, et al., 2011	Poland	5.00E+10	Early	-21	70 dim	2	Yea-Sacc 1026	Multi	Polish Holstein	Mixed	Individual
Moallem, et al.,	Israel	6.00E+10	Not Early	60-168	90	3	Biosaf SC 47	Both	Israeli Holstein	Top-Dress	Individual
Mruthunjaya, et al., 2003	India	5.00E+10	Not Early	67-116	49	UK	Yeas-Sacc 1026	Multi	Crossbred	Mixed	Individual
Ondarza et al., 2010	US	5.00E+10	Not Early	21	84	3	ABVista Yeast	Multi	Holstein	Mixed	Group
Soder et al., 1999	US	7.50E+10	Early	-28	91 dim	UK	Biomate	Both	Holstein	Top-Dress	Individual
Swartz et al., 2009	US	5.03E+10	Not Early	120	98	UK	Western	Unknown	Holstein	Top-Dress	Individual
Swartz et al., 2009	US	5.10E+10	Not Early	120	98	Uk	Cellcon	Unknown	Holstein	Top-Dress	Individual
Williams et al., 1991[13]	Scotland	5.00E+10	Early	36	36	2	Yea-Sacc 1026	Multi	Fresian	Top-Dress	Individual

[1] Inclusion criteria were: the study had to be in English, was performed on lactating dairy cattle, evaluated an active dry yeast product, the study included a concurrent negative control group, utilized randomized treatment assignments and used a parallel group design, (i.e., not crossover). Additionally, studies must have reported results of at least one of the production outcomes of interest (milk yield, % milk fat,**,** milk fat yield, % milk protein, milk protein yield, 3.5% fat corrected milk, energy corrected milk, or DMI), along with a measure of variance (standard error or standard deviation) or a *p* value for comparison of effects between treatment and control groups. The study had to provide enough information in it to establish if it met the criteria for inclusion and be published as an independent study, not as a commercial company internal report.

[2] Country the research was conducted in.

[3] Colony Forming Units of Active Dry Yeast fed to the treated animals in the study if reported. When the CFU fed was not reported this value was calculated from the concentration of the product X in grams of product fed.

[4] Studies that were primarily conducted in groups of cows less than 70 DIM are "Early" and ≥70 DIM are "Not Early".

[5] Average days in milk when cows began receiving Active Dry Yeast. If the range of days in milk was reported, it is reported here.

[6] Length of trial or DIM when trial was concluded.

[7] Number of times the cows were milked in 24 hours. UK is unknown. The paper did not report milking frequency.

[8] Commercial brand of Active Dry Yeast fed in the trial if reported.

[9] Parity of cows used in the trial. Both includes primiparous and multiparous,

[10] Breed of cow as reported in the trial.

[11] Active Dry Yeast treatment was fed either top-dressed on the feed or mixed into the TMR (total mixed ration).

[12] Treatments were fed either to the group (pen) of animals or individual animals. All the studies calculated the variance at the individual cow level, giving an over estimate of the precision to group fed studies. Subsequently, all group fed studies were removed from calculations.

[13] There were 4 separate comparisons by Williams in this paper. They were treated (ADY) versus control (no ADY) comparisons on feed to concentrate feed at 50/50 using hay in one comparison and straw in a second. The hay and straw were again evaluated using a 60/40 ratio. All 4 outcomes were analyzed as separate trials.

outcomes. The use of funnel plots to visually assess if publication bias is present was utilized (Sterne, Becker, and Egger 2005). Funnel plots are plotted for the SMD against the SE of the studies. The larger studies with the smaller SE are higher on the graph (Figure 4.4). The funnel plot shows asymmetry with several small studies missing showing a bias to higher outcome studies that are positive. To further assess bias, the funnel plot was plotted with the red dots representing studies conducted outside NA the black dots representing studies conducted in NA (Figure 4.4). There appears to be much more possible evidence of publication bias as seen by the increased asymmetry of the red dot representing studies conducted outside of NA. The symmetry of the studies conducted in NA indicates possibly less publication bias. The larger example demonstrated by the funnel plot is that heterogeneity within a funnel plot can show little bias but the outcomes do not represent a consistent understanding of the true point effect (Ioannidis 2005).

Heterogeneity of Milk Yield and Mechanism of Action

There has been much discussion about how ADY would increase milk production or have a biological impact on a lactating cow's performance. This meta-analysis shows a high degree of heterogeneity in the study outcomes as discussed above. Another explanation other than strictly publication bias for the high level of heterogeneity may lie in the mechanism of action of ADY in the rumen. The function of ADY may depend on the viability of the yeast cells and therefore their physiological function in the rumen for example to scavenge oxygen from the rumen environment which seems to be the leading theory presently. Past studies on autoclaved yeast cells have shown that dead yeast cells have no effect on ruminal VFA, (Dawson, Newman, and Boling 1990). The difficulty in keeping the yeast alive from manufacture to ingestion by the cow could account for much of the variability in the outcomes seen in the meta-analysis. Further

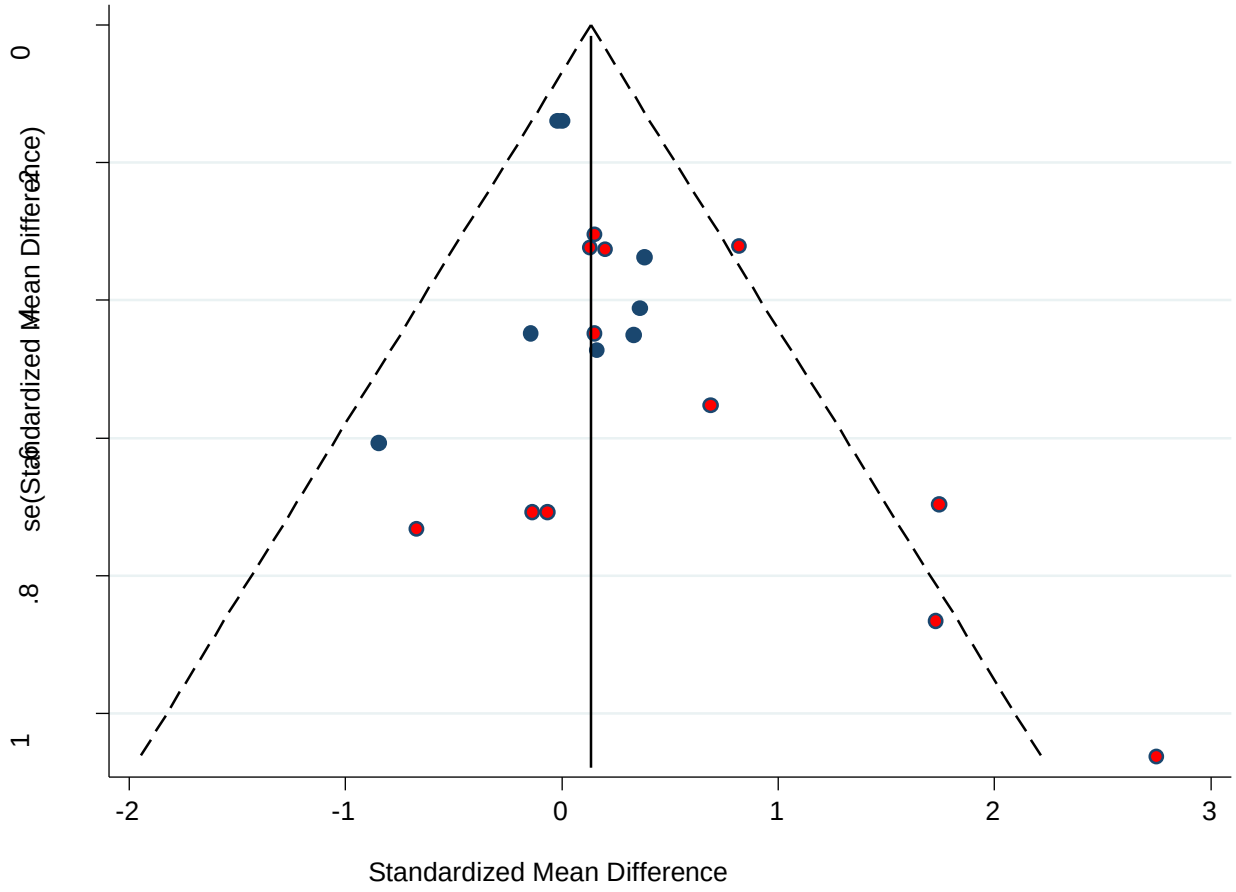


Figure 4.4. Funnel plot of milk yield with pseudo 95% confidence limits. The Standardized Mean Difference is plotted against the standard error of the point effect. The central line shows the overall point effect. The red dots represent the SMD of studies conducted outside of North America and the black dots represent studies conducted in North America. Overall the symmetry shows a slight bias to the right. When observed by location of study, the studies conducted outside of North America appear asymmetrical. The SMD comes from a meta-analysis on active dry yeast on milk production and DMI performed on studies published from 1991 to 2010.

questions of the mode of action of the live yeast once they arrive in the rumen are still present. Newbold et al. (Newbold, Wallace, and McIntosh 1996) tested the oxygen scavenging theory utilizing an in vitro model that injected oxygen into a simulated rumen environment. Although results showed that three out of five (or 60%) *Saccharomyces cerevisiae* strains tested stimulated oxygen uptake from rumen fluid and dissolved oxygen reached baseline levels within 90 seconds of yeast supplementation, this was conducted with a 200 mg yeast in 150 mL buffered rumen

fluid equivalent to 126 g yeast for a cow with 95 L rumen liquid volume (more than 100 times higher dose of yeast than fed commercially), and the oxygen levels were much higher than seen in the rumen of a normal cow (Ellis, Williams, and Lloyd 1989). Furthermore, the VFA concentrations were far outside the normal levels in the rumen, (40mM vs. 117 mM) which would have a large impact on the yeast ability to uptake oxygen (Lee et al. 2003)(Lee et al. 2003). This leaves the mechanism for ADY to increase milk production and its role in the heterogeneity of effect open to further research.

Conclusion Chapter 4

Commercially available products of active dry yeast supplementation failed to show a significant increase in milk production in studies conducted in North America (0.49 kg/d, P = 0.307) or in ECM (0.54 kg/d, P = 0.260). In all studies including studies conducted both in and outside of NA, MY increased by 0.81 kg/d, (P = 0.010) and ECM increased 1.0 kg/d (P = 0.001) but with high heterogeneity (I^2 = 40.10%, I^2 = 25.80% respectively). Publication bias analysis indicates that there may be several missing papers from the literature of studies conducted outside of NA that would have lower point effects. Active dry yeast supplementation failed to show a significant increase in DMI in early lactation (0.42 kg/d, P = 0.25). The high heterogeneity seen in studies may be due to publication bias, or lack of yeast viability in different dairy feeding and management systems. The mode of action for ADY on milk production in dairy cows has not been fully elucidated to understand if yeast viability is crucial to the production effect ADY may have on the lactating dairy cow. This meta-analysis was done on studies (with the exception of Swartz et al.) that did not adjust for possible changes in cfu counts in the product. Caution should be used in interpreting the validity of this study for actual ADY effect versus the production effect of commercially available products.

CHAPTER 5

PROBABILISTIC MODELING TO SUPPORT DECISIONS REGARDING THE USE OF ACTIVE DRY YEAST AND YEAST CULTURE

Chapter 5 Executive Summary

The purpose of a veterinary consultant may be to help a business owner to decide between multiple mutually exclusive interventions. As agricultural systems become more complex and overlapping, intuition becomes less appropriate and the need for mathematical models depicting the possible system before and after the intervention are needed. One such model is the use of deterministic and stochastic partial budgets. The interventions for addition of yeast culture into a dairy cow diet is examined in a meta-analysis (Poppy et al. 2012) that should represent an accurate summary of the random controlled yeast culture studies at the time of its publication. Likewise, a meta-analysis of feeding active dry yeast (Poppy et al. 2017) gives us the parameters for that intervention.

Using a deterministic partial budget, utilizing the mean changes for milk yield (MY), fat yield (FY), protein yield (PY), and dry matter intake (DMI), the difference of income over feed cost (IOFC) for an intervention of feeding yeast culture to dairy cows in early lactation (<70 DIM) is $0.399 /cow/d, and for mid-to-late lactation dairy cows is $0.584 /cow/d. Likewise, using the meta-analysis for an intervention of feeding active dry yeast (Poppy et al. 2017) using a deterministic partial budget is $0.413 /cow/d for early lactation and $0.548 for mid-to-late lactation cows. The use of the deterministic partial budgets show very little differentiation from these two mutually exclusive interventions, but the information in the meta-analysis is not fully utilized due to the lack of incorporation of the variance measures of uncertainty found in these

studies. Using the standard error and between and within variance to yield the uncertainty measures found in the mean and the random effects using stochastic analysis (ModelRisk 5.1.1 Vose Software BVBA, Belgium, 2015) helps determine the possible risk measures. The stochastic analysis for the partial budget of yeast culture estimates that based on the meta-analysis (Poppy et al. 2012) the risk of the producer being below breakeven for the intervention in early lactation is 0.269% and the probability the returns to the dairy of being between $0 and $0.80 /cow/d is 99.46%. Likewise, the risk of being below breakeven in mid-to-late lactation is 0.309%. On the other hand, using the values from the active dry yeast meta-analysis (Poppy et al.,2017) the probability of being below breakeven for the intervention is 38.86% for early lactation and about 59.78% of being somewhere between $0.00 and $4.00. Likewise, in mid-to-late lactation, for ADY, the stochastic partial budget estimates 39.20% probability of being below breakeven and a 55.62% probability of being between $0.00 and $4.00. If one defines risk as being unsure of the true outcome, then the interventions based on the published studies in the ADY meta-analysis gives little information for dairy operation to utilize in making and informed decisions and would constitute a risky decision for the producer.

Introduction

A veterinary consultant to an animal enterprise may have as their most important contribution that of helping the management team correctly assess the uncertainty surrounding the business decision to be made. Having the correct assessment of the conditional probabilities associated with both the biological process as well as the economic uncertainty and correctly applying these probabilities to assess the economic outcome and the uncertainty surrounding that outcome is the key task in advising the managerial decision maker. Decreasing the risk of the decision is the process of more accurately predicting the outcome with certainty. Often

obtaining accurate information regarding the expected change due to a proposed intervention and the uncertainty surrounding that intervention is difficult to obtain. While making decisions in the face of uncertainty is a manager's job (Drucker 1973), reducing the extent of that uncertainty is the key to making fewer decision errors. Robert Schlaifer states (1959b):

> *"When all the facts bearing on a business decision are accurately known-when the decision is made "under certainty"-careless thinking is the only reason why the decision should turn out, after the fact, to have been wrong. But when the relevant facts are not all known - when the decision is made "under uncertainty, it's impossible to make sure that every decision will turn out to have been right in this same sense. Under uncertainty, the businessman is forced, in effect, to gamble. Under such circumstances, a right decision consists in the choice of the best possible bet, whether it is won or lost after the fact".*

Correctly assessing the uncertainty or assigning the correct conditional probabilities is the heart of the business decision and has to be one of the first steps in reducing risk. The use of models or prior research can only inferentially be assigned to a specific business case, and being able to assess the strength of that inference for both the mean and variance is difficult. The internal and external validity of the available studies as well as how disagreements in available studies can be combined and then applied to the question being asked is a key component in decreasing uncertainty for the decision outcome. Veterinarians, as practitioners of evidenced based medicine processes, finding studies, correctly interpreting the relevancy of the studies to the current problem and making correct inferences from the studies to the relevant problem is an area we have the background education to achieve. One recent tool to help access the broad scope of relevant studies is the use of meta-analysis combined with systematic reviews. Although veterinarians may have a broad background in interpreting studies as single point outcomes, as agricultural enterprises become more complex, incorporating the multiple impacts of a single intervention within the complex agricultural system, and assessing both the biological

outcomes as well as financial implications of the interventions becomes more difficult as much as it becomes an imperative if one hopes to correctly characterize possible solutions.

One tool available to the veterinary practitioner to help model the impact of an intervention in an agricultural system is the partial budget. The partial budget is a comparison of the current economical state of the production or disease state compared to the predicted economic state after the proposed intervention. Partial budgets are often part of more complex models as seen in the Markov chain models (Dijkhuizen, Renkema, and Stelwagen 1984) or models using Monte-Carlo simulation (Galvao et al. 2013, Overton 2006). The simplest partial budget, is one that utilizes deterministic values for dairy production and uses a reported biological output with no uncertainty from a dairy study coupled with the economic value for that output minus the cost of implementing that specific intervention. More advanced deterministic partial budgets could incorporate multiple effects of a single intervention or multiple effects from multiple simultaneous interventions still incorporating a single point effect with no uncertainty. The deterministic partial budget gives a mean change which while simple to calculate, fails to account for the variability or uncertainty associated with the change in the mean value. Because the complex partial budget change is made up of several parameter estimates each with a different variance or confidence interval, neither the biological or economic risk for the decision maker can be easily estimated mentally without further analysis. The use of stochastic analysis using Monte Carlo simulation can be used to estimate the risk for this partial budget. Monte Carlo simulation is a method for making artificial trials or experiments to assess the probabilities on the basis of the relative frequencies that each artificial event occurs (Schlaifer 1959a). The use of stochastic analysis and the incorporation of the

uncertainty could give a more accurate picture of the proposed intervention, not recognized through the use of deterministic partial budgeting alone.

Therefore, the purpose of this paper is to develop of partial budget for two different, but similar proposed interventions in a commercial dairy herd and compare the risk of the proposed interventions using both deterministic and stochastic partial budgets.

Materials and Methods

A partial budget (Dijkhuizen et al., 1995) was constructed to model the net change in income from an intervention of a feed additive of yeast culture (SCFP) or an intervention of a feed additive of active dry yeast (ADY). The input data for the yeast culture was obtained from a meta-analysis of the use of yeast culture analysis (Poppy et al. 2012), and the input data for active dry yeast was from a similar meta-analysis (Poppy et al. 2017). The parameter values for the mean change, SE and Total Variance (TV) for kg of milk (MY), kg of milk fat (FY), kg of protein (PY) and dry matter intake (DMI) for both early lactation, (DIM < 70) or mid-to-late lactation were obtained from each meta-analysis. The values for the economics of each parameter in the partial budget include the values from the published federal milk order 33 for November 2016 (USDA 2016) converted to the value /100 kg of milk, fat, protein and other solids. The base amount of milk was 39 kg/d for the early lactation cows and 32 kg/d in the mid-to-late lactation cows. FY was calculated by 3.5% x MY to obtain FY for the early lactation cows and 3.7% x MY for the mid-to-late lactation cows. PY was calculated as 3.1% x MY to obtain PY for the early lactation cows and 3.2% x MY for the mid-to-late lactation cows. Other solids were calculated as 5.7% x MY for both early and mid-to-late lactation cows. The base DMI for early lactation cows was 23.5 kg/d and 23 kg/d for mid-to-late lactation cows. Dry matter cost was $0.22 /kg for early lactation cows and $0.198 /kg/d for mid-to-late lactation

cows. Both yeast culture and active dry yeast cost are $0.05 /cow/d. The cost of feeding the cow each day is (DMI cost/cow/d) calculated by multiplying the DMI and the Cost of DMI. The income generated each day per cow (Income/Cow/d) was obtained by multiplying the sum of Class 1 ($4.409), Hauling (-$2.205), Promotion (-$0.331) and Quality ($1.653) $3.527 /100 x MY, plus FY x $4.518, plus PY x $5.065, plus kg of other solids x $0.298. The income per 100 kg of milk produced (Income/100 kg) is the Income/cow/d divided by MY x 100). The income over feed cost (IOFC) was calculated by subtracting the DMI cost/cow/d from Income/Cow/d. Yeast culture or ADY change was calculated by subtracting the IOFC pre-intervention from the post intervention partial budget.

The Monte Carlo stochastic analysis allows one to replicate the experiment of calculating the partial budget many iterations, each time using an input for the mean change in the mean parameter based on the relative frequency distribution we assigned to each of the variance parameters. For this trial, we assign a normal distribution for the total variation for each of the parameters calculated in the partial budget from the meta-analysis to model the uncertainty using ModelRisk 5.1.1 (Vose Software BVBA, Belgium, 2015). The Monte Carlo simulation generated 10,000 iterations of the partial budget and plotted these outcomes in a frequency histogram. The parameters that were modeled with uncertainty from values in the two meta-analysis were MY, FY, PY and DMI. The parameter values for the deterministic and stochastic partial budget modes were found in Poppy et al. (2012) for the YC analysis and Poppy et al. (2017) for the ADY analysis (Table 5.1). The values in the YC analysis were for peer reviewed papers only, while the ADY analysis were sub group values for all ADY papers, not North American only. The method for obtaining the stochastic value for each parameter (MY, FY, PY and DMI) was to assign a VoseNormal distribution and use of the SE parameter provided from

the meta-analysis to model the uncertainty surrounding the mean change. This distribution was then used to model each output parameter in the partial budget. The variance values in the mixed model meta-analysis are the uncertainty between studies which is called Tau squared, T^2, as well as the uncertainty within studies what we would normally think of as variance (V) or the square of variance, the standard deviation. The total variance (TV) for the mixed model is the weighted average of all the variances ($1/V+ T^2$), for each study and the standard error (SE) of the mean is the square root of the TV (Borenstein et al., 2010). Because the SE incorporates both the between group and the within group variance and the uncertainty around the mean we can multiply the SE by the Vose distribution which is the equation parameter to replicate the equation each time using a SE and Mean outcome chosen from the chosen distribution in the Vose software program ModelRisk. This develops an output graph which is a histogram of all the outcomes. For example, for MY we use VoseNormal(MY mean change, MY SE) with the MY SE representing the total variance for milk yield. This parameter was used to multiply by the base MY early lactation to arrive at the post intervention MY for early lactation. The partial budget then calculated each value for MY, FY, PY, and DMI and arrived at a combined histogram, of the variance of the outcome.

Table 5.1 Parameter values for the Yeast Culture (YC)[1] and Active Dry Yeast (ADY[2]) deterministic and stochastic partial budgets. The variance equals total variance both between and within group.

	YC1					
	Early			Mid/Late		
	Mean	**SE**	**Variance**	**Mean**	**SE**	**Variance**
MY	1.370	0.3757	0.141	0.980	0.4968	0.247
FY	0.057	0.028	0.001	0.051	0.030	0.001
PY	0.025	0.012	0.000	0.039	0.028	0.001
DMI	0.615	0.2077	0.043	-0.782	0.2938	0.086

	ADY[2]					
	Early			Mid/Late		
	Mean	**SE**	**Variance**	**Mean**	**SE**	**Variance**
MY	1.172	0.0404	0.163	0.439	0.5300	0.281
FY	0.052	0.016	0.000	0.026	0.019	0.000
PY	0.039	0.312	0.097	0.029	0.417	0.174
DMI	0.423	0.3700	0.137	-1.570	0.5770	0.333

[1] Parameter values from Poppy et al. (2012) for peer reviewed papers only.

[2] Parameter values from Poppy et al. (2017) for all studies, not restricted to NA only.

The cost of obtaining a Type 1 error, the estimated amount of money the producer would could lose if he implemented an intervention when the true outcome was less than breakeven, was obtained by multiplying the value associated with each histogram below break-even bin value times its probability or relative frequency and adding them up (the area under the curve less than $0). The cost of the Type 2 error, the estimated money the producer would lose if the true outcome was the product worked but the producer failed to implement the intervention, is the same procedure for the histogram bins above break-even.

Results and Discussion

The values from the meta-analysis for yeast culture and active dry yeast were calculated (Table 5.1). The deterministic partial budget utilizing the values for yeast culture (Table 5.2) calculates a change in mean income in early lactation of $0.399/cow/d for the addition of yeast culture to early lactation for an investment of $0.05/cow/d. Likewise using an average mid-to-late lactation cow for the partial budget yields an advantage for the intervention in mid-to-late lactation cows of $0.584 /d. The deterministic partial budget revels an important aspect of incorporating the economic value into understanding the full impact of the biological change. In

this partial budget, while early lactation cows show an increase in DMI from the intervention, the mid-to-late lactation cows had a decrease in mean DMI of 0.782 kg / day which improved the value of the intervention by $0.15/cow/day. Modeling only the value of the milk change would have missed this important aspect of the economic value of the intervention.

Table 5.2. Partial Budget for adding yeast culture to early and late lactation dairy cows from meta-analysis (Poppy et al. 2012).

	Early Lactation[1]			Mid/Late Lactation[2]		
	Control	**Meta-analysis**	**Yeast Culture**	**Control**	**Meta-analysis**	**Yeast Culture**
Milk Yield, kg	39.000	1.370	40.370	32.000	0.980	32.980
Fat %	0.035		0.035	0.037		0.037
kg of fat	1.365	0.057	1.422	1.184	0.051	1.235
Protein %	0.031		0.031	0.032		0.032
kg of Protein	1.209	0.025	1.234	1.008	0.039	1.047
OS %	0.057		0.057	0.057		0.057
kg of Other Solids	2.223		2.301	1.824		1.880
DMI, kg	23.500	0.615	23.543	23.000	-0.782	22.218
Cost dry matter /kg	0.220		$0.22	0.198		$0.20
DMI cost/cow/d	5.170		$5.18	4.554		$4.40
Yeast cost/cow/d			$0.05			$0.05
Income/Cow/d	$14.33		$14.79	$12.13		$12.61
Income/100 kg	$36.74		$36.629	$37.90		$38.223
IOFC Advantage[3]	$9.16		$9.557	$7.57		$8.157
Yeast Culture change			$0.399			$0.584
Value of components in 100* Kg[4]						
Fat	$4.518	Class I	$4.409			
Protein	$5.065	Hauling	$(2.205)			
Other Solids	$0.298	Promo	$(0.331)			
Total[5]	$3.527	Quality	$1.653			

[1] Results from the meta-analysis for yeast culture for cows less than 70 DIM.

[2] Results from the meta-analysis for yeast culture of cows not less than 70 DIM.

[3] IOFC is Income over feed cost or the revenue from the milk minus the feed cost estimate/cow/d.

[4] From the Federal Order 33 milk pricing for November 2016. The values paid converted to kg from CWT milk. http://www.fmmaclev.com/Releases/ClassPrice/classpr.pdf.

[5] Sum of Class I differential plus and estimated hauling charge, promotion charge and quality bonus.

The deterministic partial budget for the addition of ADY (Table 5.3) estimates a change in income for the early lactation intervention of $0.413 per cow per day and $0.548 for mid-to-late lactation cows. Again, as in the yeast culture example a large part of the economic change in the estimated value comes from the decrease in DMI for the mid-to-late lactation cows.

Table 5.3. Partial budget of Active Dry Yeast fed to dairy cattle using the parameter estimates from a meta-analysis Poppy et al. 2017).

	Early Lactation[1]			**Mid/Late Lactation[2]**		
	Control	**Meta-analysis**	**Active Dry Yeast**	**Control**	**Meta-analysis**	**Active Dry Yeast**
Milk Yield, kg	39.000	1.172	40.172	32.000	0.439	32.439
Fat %	0.035		0.035	0.037		0.037
kg of fat	1.365	0.052	1.417	1.184	0.026	1.210
Protein %	0.031		0.031	0.032		0.032
kg of Protein	1.209	0.039	1.248	1.008	0.029	1.037
OS %	0.057		0.057	0.057		0.057
kg of Other Solids	2.223		2.290	1.824		1.849
DMI, kg	23.500	0.423	23.640	23.000	-1.570	21.430
Cost dry matter /kg	0.220		$0.22	0.198		$0.20
DMI cost/cow/d	5.170		$5.20	4.554		$4.26
Yeast cost/cow/d			$0.05			$0.05
Income/Cow/d	$14.33		$14.82	$12.13		$12.41
Income/100 kg	$36.74		$36.897	$37.90		$38.269
IOFC [3]	$9.16		$9.571	$7.57		$8.121

	Early Lactation[1]			Mid/Late Lactation[2]		
	Control	**Meta-analysis**	**Active Dry Yeast**	**Control**	**Meta-analysis**	**Active Dry Yeast**
ADY change			$0.413			$0.548
Value of components in 100* Kg[4]						
Fat	$4.518	Class I	$4.409			
Protein	$5.065	Hauling	$(2.205)			
Other Solids	$0.298	Promotion	$(0.331)			
Total[5]	$3.527	Quality	$1.653			

[1] Results from the meta-analysis for Active Dry Yeast for cows less than 71 DIM.

[2] Results from the meta-analysis for Active Dry Yeast of cows not less than 70 DIM.

[3] IOFC is Income over feed cost or the revenue from the milk minus the feed cost estimate/cow/d.

[4] From the Federal Order 33 milk pricing for November 2016. The values paid converted to kg from CWT milk. http://www.fmmaclev.com/Releases/ClassPrice/classpr.pdf.

[5] Sum of Class I differential plus and estimated hauling charge, promotion charge and quality bonus.

For an aid in determining a possible intervention both the YC and ADY appear from the deterministic partial budget to be of possible value to the dairy, but is not good at distinguishing between the interventions if only one can be implemented assuming they are mutually exclusive, i.e. you would not get an additive response if both interventions were implemented. Also, neither partial budget helps us know the risk nor how sure are we of achieving the reported amount. More importantly, the producer often wants to know, if I implement this intervention, what is the probability I will be below breakeven? One could also ask what is the cost of making the wrong decision when incorporating all the information? It is readily evident that in the deterministic partial budget valuable information from the meta-analysis is not used, the values of uncertainty for each parameter. Stochastic analysis allows the use of the uncertainty in each parameter to be added to the model. The uncertainty around the mean change reported in the

study is used in each iteration. The shape of the distribution assigned to the parameter determines the relative frequency of the value within the bounds determined by the variance parameter. Although for this analysis we used normal distributions, other distributions were possible depending on one's interpretation of the data and the actual fitting of the raw data.

The stochastic partial budget for yeast culture utilizes the uncertainty of the various parameter estimates used in the partial budget. For MY in early lactation we see there is an estimated mean change of 1.37 kg, with a SE of 0.3757 kg (Table 5.1). This represents the uncertainty we have around the estimated mean change. In addition to the total variance surrounding MY, we also have from the partial budget the economic value for the mean change in FY (0.057), PY (0.025) and DMI (0.615) along with the SE for each parameter multiplied together to see the true uncertainty surrounding the event of adding yeast culture to early lactation cows. Utilizing the values from the meta-analysis, a partial budget was built for both yeast culture and active dry yeast (Figures 5.2 and 5.3). The stochastic partial budget for yeast culture shows a mean response of approximately $0.39 as seen in the deterministic partial budget, but now utilizing the variance from the meta-analysis we can see there is a very small 0.270% chance the outcome based on the biology as well as the economics for the partial budget the producer may actually have an income of $0.00 or less (Figure 5.1). The probability of having an income between $0.00 and $0.80 is 99.46%. There is a 0.27% probability the income resulting from the intervention is greater than $0.80. Similarly, the results of the Monte Carlo simulation for the mid-to-late lactation parameters from the yeast culture meta-analysis (MY = 0.980, SE = 0.497), (BF = 0.051, SE = 0.030), (PY = 0.039, SE = 0.028), (DMI = -0.782, SE = 0.294), predicts a mean of approximately $0.59 with a 97.62% probability of being between $0.00 and $1.00 (Figure 5.2). The probability of being below breakeven is again very low at 0.31%. Overlaying the graphs, one can see that while

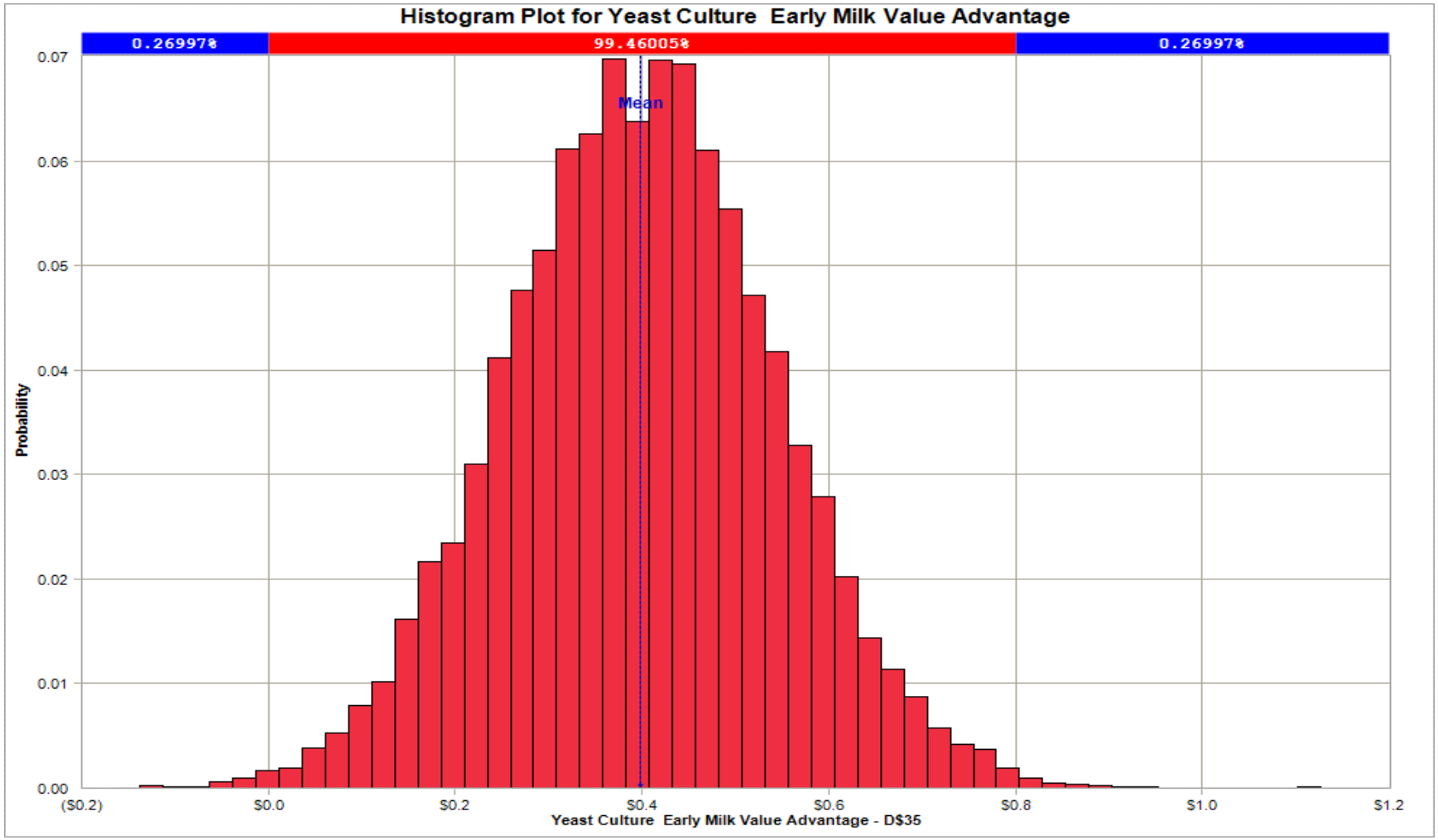


Figure 5.1. Histogram of the risk for the partial budget of the change in income due to adding yeast culture to early lactation cows (<71 DIM). There is very low probability of 0.269 the income for the intervention of yeast culture will be below $0 based on the variance from the meta-analysis (Poppy et al. 2012) There is a 99.4% chance the income will fall between $0.0 and $0.80/cow/d.

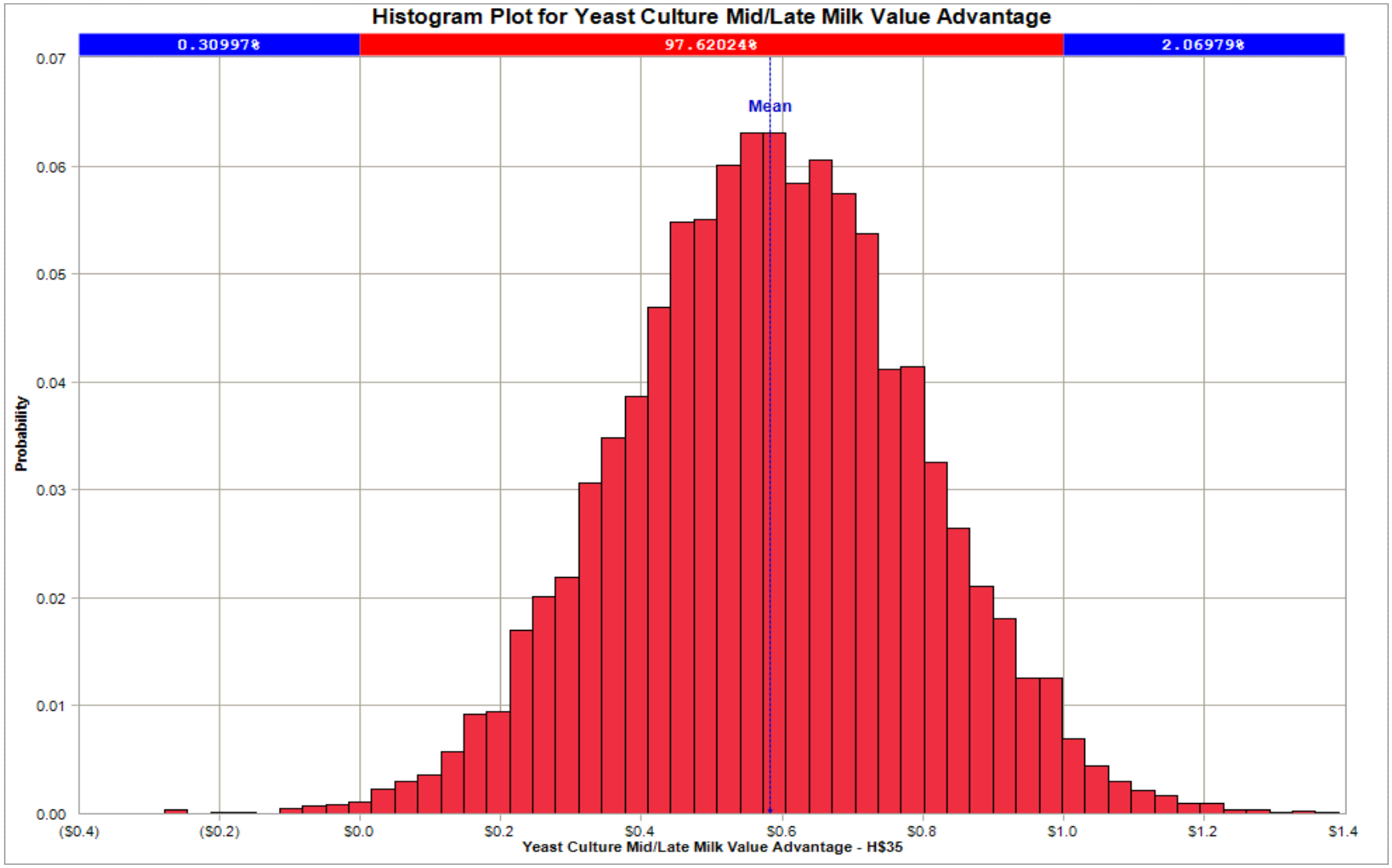


Figure 5.2. Histogram of the risk for the partial budget of the change in income due to adding yeast culture to mid-to-late lactation cows (>70 DIM). There is near 0.309% probability based on the variance from the meta-analysis (Poppy et al. 2012) the net income will fall below $0. There is a 97.6% chance the income will fall between $0.0 and $1.00/cow/d.

the mid-to-late lactation graph lies to the right or has a higher mean income, it is also more risky because it has a wider distribution or more uncertainty around the possible outcome (Figure 5.3). Overton in a study (2005) looking at implementing AI synchronization, calculated the cost for Type 1 and Type 2 in a dairy herd. Using this same methodology one can see (Figure 5.1 or 5.2) that multiplying the bins of the histogram times their probability or relative frequency and summing them (the area under the curve less than $0) would provide an estimate of the cost of a Type 1 error. The producer would make a Type 1 error if he gambled and added yeast culture to the herd in expectation of a profit when he would actually lose money. In this case, the cost of the Type 1 error would be less than $0.001 /cow/d which is very low. The cost for a Type 2 error can be calculated as well by summing the relative frequencies for bins greater than $0.00. A Type 2 error would occur when a producer does not use a possible intervention when it would make him or her money. In this stochastic analysis, the estimated cost for the Type 2 error is approximately $0.377/cow/d. The Type 2 error cost for mid-to-late lactation cows on yeast culture was 0.564/cow/d. It is important to note these are the estimated probabilities surrounding the decision. Once the producer actually implements the intervention there is no uncertainty in the outcome.

Building the risk graph using Monte Carlo simulation for the Active Dry Yeast meta-analysis demonstrates the problem with evaluating tables with parameter estimates without calculating the impact of the variance for the same parameters. Similar to the deterministic partial budget for yeast culture, the partial budget for ADY shows a gain in net income for adding ADY to the early lactation animals of $0.41/cow/d. Likewise, the mid-to-late lactation partial budget shows $0.55 per cow per day. Building a risk graph taking into account the uncertainty surrounding these parameters (for early lactation cows (MY = 1.172, SE = 0.040),

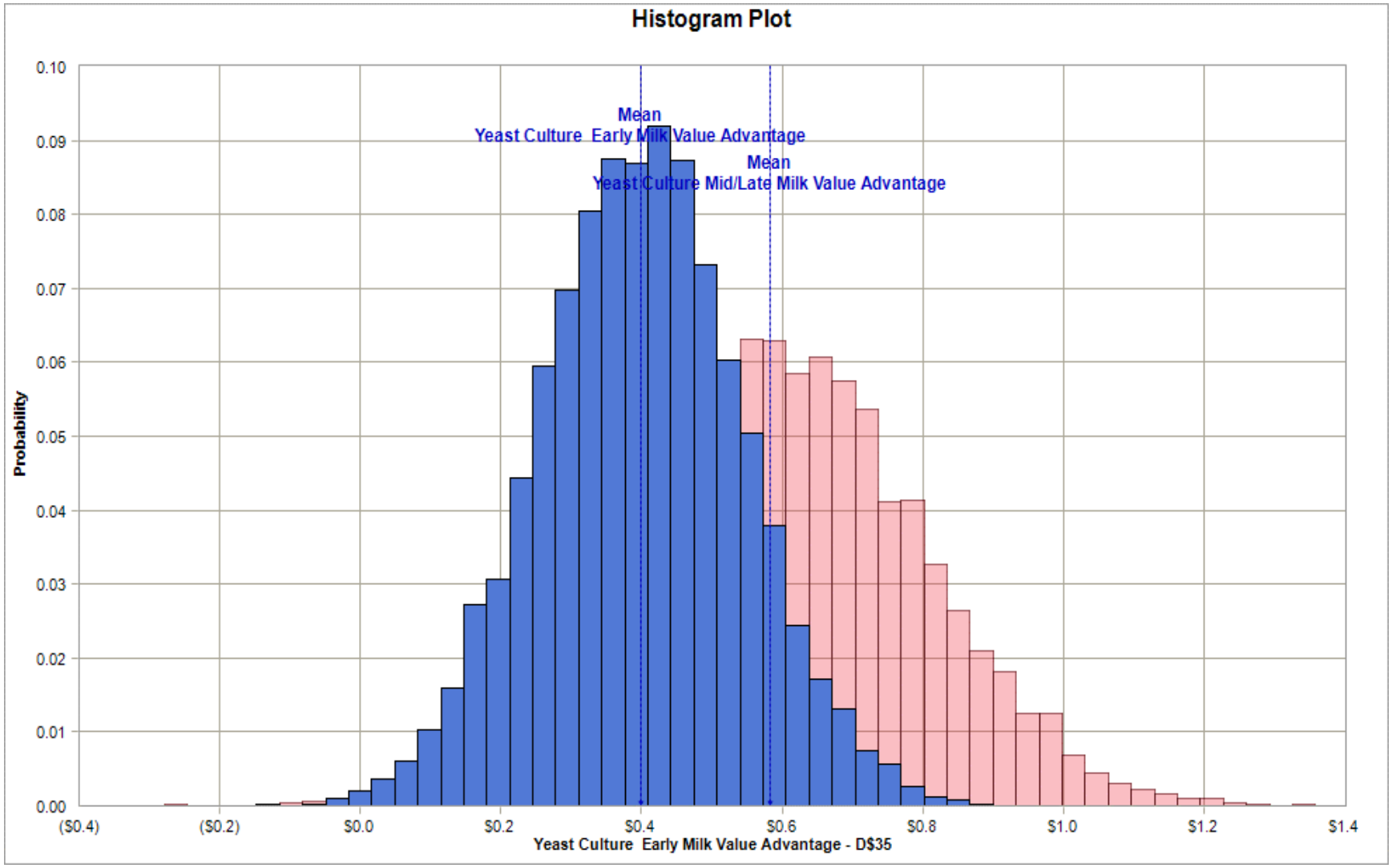


Figure 5.3. Histogram of the risk for the partial budget of the change in income due to adding yeast culture to both early lactation and mid-to-late lactation cows. The mean of the mid-to-late lactation graph while higher than the early lactation graph has more risk as the variance is wider. The producer can choose how much risk versus income to choose. Parameter estimates are from Poppy et al. 2012.

(FY = 0.052, SE = 0.016), (PY = 0.039, SE = 0.312), (DMI = 0.423, SE = 0.370) and for mid-late lactation cows (MY = 0.439, SE = 0.530), (FY = 0.026, SE = 0.019), (PY = 0.029, SE = 0.417), (DMI = -1.570, SE = 0.577) from the meta-analysis for Active Dry Yeast (Table 5.1). This stochastic analysis shows less predictive value for making a business decision (Figure 5.4 and Figure 5.5). The stochastic analysis shows the probability of the actual net income being below $0 as 38.86% for the early lactation active dry yeast intervention. The intervention has a 59.78% probability of being between $0 and $4.00/cow/d. Likewise, the mid-to-late lactation cows estimates a 39.20% probability of being less than breakeven and a 55.62% probability of being between $0.00 and $4.00/cow/d. Summing the bin values times their probability for the early lactation cows in the ADY partial budget we had an estimated the cost of making a Type 1 error, the error using the product when you should not is $0.505/cow/d, and the cost of a Type 2 error (not using the product when you could have made a profit) of $0.828 /cow/d. Likewise, the Type 1 error for mid-to-late lactation ADY interventions was $0.630/cow/d and the Type 2 error was $1.099/cow/d. The magnitude of both errors is large compared to a $0.05 investment demonstrates a great deal of uncertainty in the outcome of the intervention (Figure 5.6). If as Schlaifer said (1959b) the decision made under certainty is the desired business proposition, then these would represent the opposite for the decision-making process.

Conclusion Chapter 5

From the addition of adding Monte Carlo simulation to the analysis of the decision, it is seen that accurately predicting the variance by using meta-analytic studies and the addition of stochastic analysis to partial budgets is a method veterinary consultants can use to improve their advice to managerial decision makers on dairy farms and other animal agriculture enterprises. Partial budgets can be a valuable aid to the dairy decision maker for understanding the

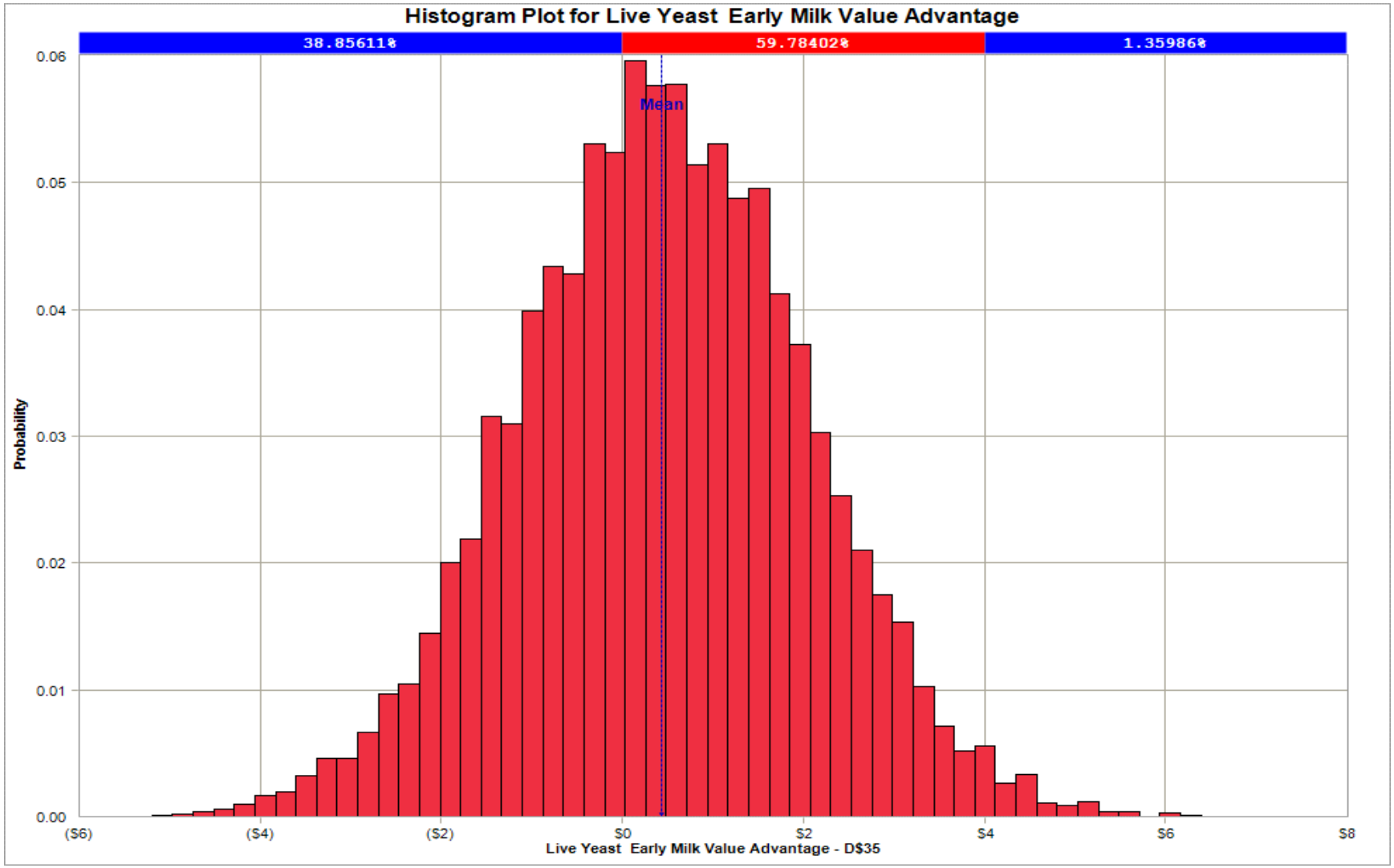


Figure 5.4. Histogram of the risk for the partial budget of the change in income due to adding Active Dry Yeast to early lactation (<70 DIM). The graph shows a 38.8% probability the producers income will fall below $0 for a net loss, and a 59.7% probability the income will be between $0 and $4.00. Parameter estimates are from Poppy et al. 2017.

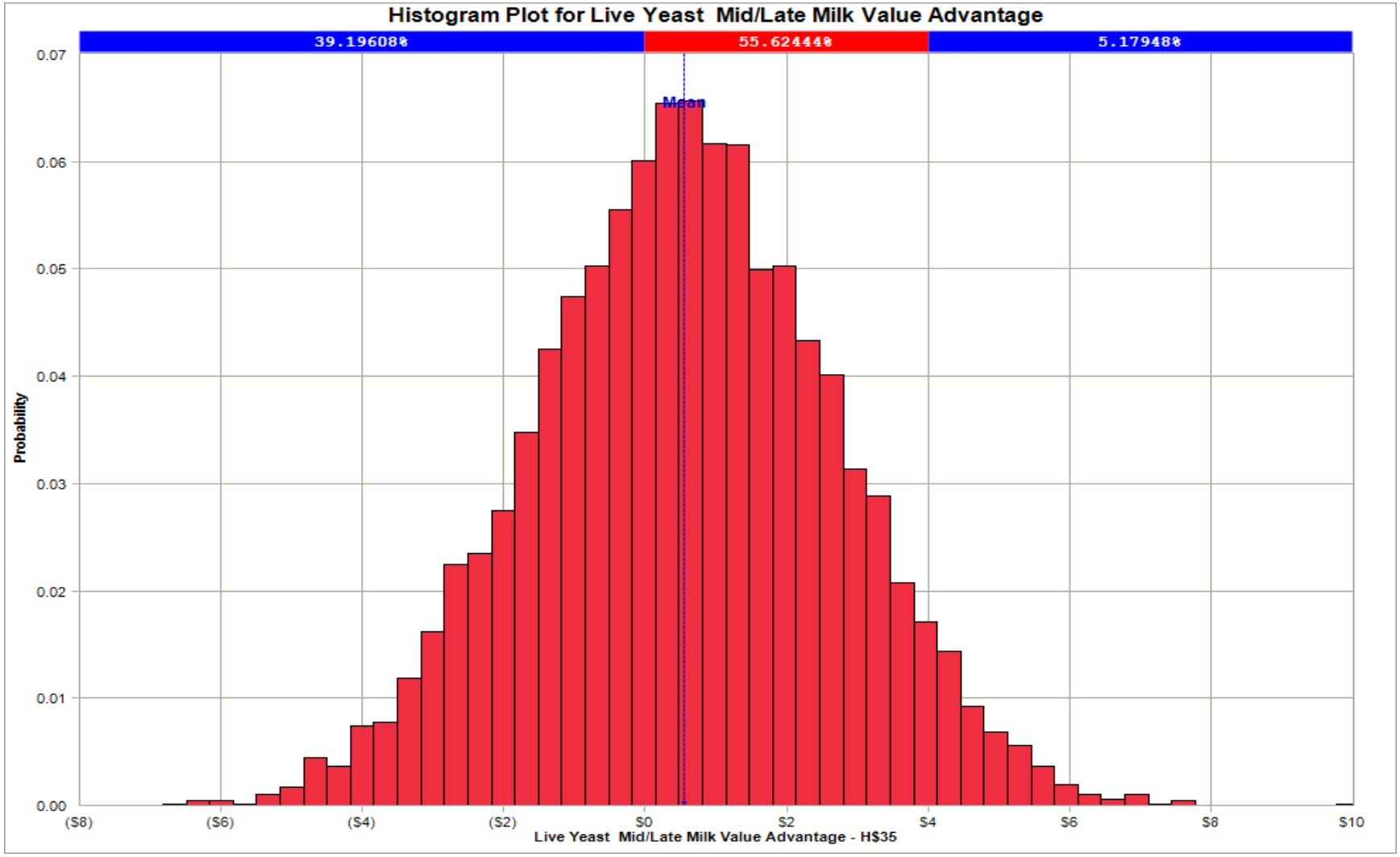


Figure 5.5. Histogram of the risk for the partial budget of the change in income due to adding Active Dry Yeast to mid-to-late lactation (>69 DIM). The graph shows a 39.2% probability the producer will fall below $0 for a net loss and a 55.6% probability of falling between $0 and $4.00 c/d. Parameter estimates are from. Poppy et al. 2017.

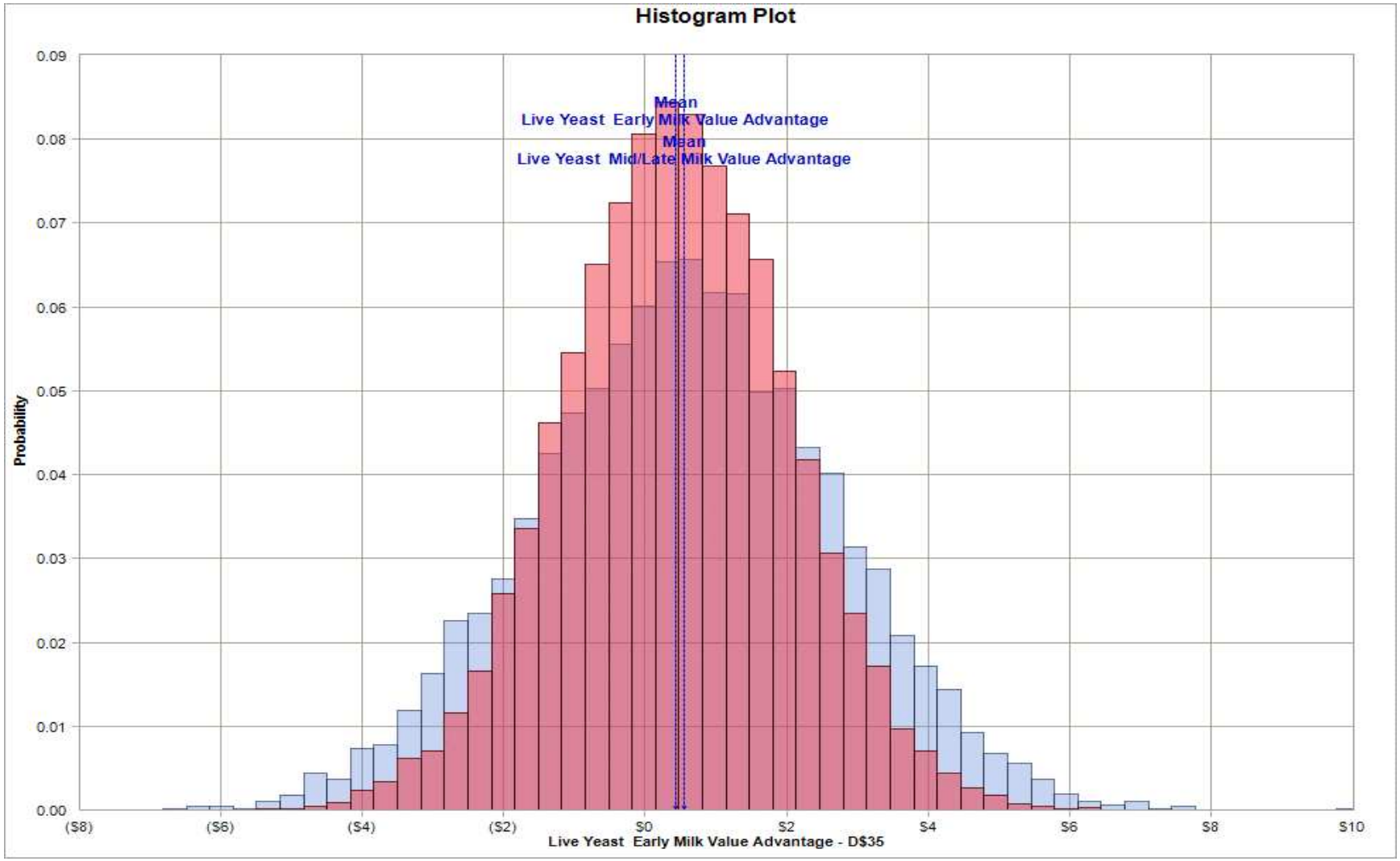


Figure 5.6. Histogram of the risk for the partial budget of the change in income due to adding Active Dry Yeast graph for both early lactation and mid-to-late lactation cows stochastic analysis. The means of the two-different analysis overlay each other with the Early lactation in red being slightly narrower. Both graphs show excessive variance of the underlying partial budget. Parameter estimates are from Poppy et al. 201.

complexity of the biological changes and provide a method for attaching the predicted economic values to the biological changes in a systematic method. Pre and post intervention outcomes help one to see if the cost of adding the intervention has a predicted net increase or decrease in income for the producer. Where partial budgets, which are normally done as a deterministic model, lack the understanding of the extent of the uncertainty and its impact on the parameter values in the partial budget that are highlighted in stochastic analysis of the partial budget. In the case of the possible ADY intervention, if the goal is to help the producer make a decision that has low uncertainty, the true outcomes could not be achieved with the use of deterministic partial budgets alone. Using the variance parameters from a meta-analysis as the gold standard for combining multiple often conflicting random control trials can aid in better understanding the impact of the uncertainty on the risk of the final decision by using stochastic analysis instead of a deterministic approach to partial budgets. Further interpretation of the uncertainty in the information and incorporating both biological as well as economic data into the decision models will improve the value of the advice and prove an important function of evidence based medicine and ultimately better advice to agricultural producers.

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APPENDIX A

Table A.1. Studies not included in the meta-analysis Poppy et al. 2012 for yeast culture due to failure to meet the inclusion criteria.

Non Eligible Studies	Reason for Exclusion
Diamond_V_Mills and Calif._Dairy, 2007	No negative control switchback
Diamond_V_Mills and Comm._Dairy, 2003	No negative control switchback
Diamond_V_Mills and Florida_Dairy, 2003	No negative control switchback
Diamond_V_Mills and Idaho_Dairy, 2004	No negative control switchback
Diamond_V_Mills and Ind._Dairy_1, 2006	No negative control switchback
Diamond_V_Mills and Ind._Dairy_2, 2006	No negative control switchback
Diamond_V_Mills and Ind._Dairy_3, 2006	No negative control switchback
Diamond_V_Mills and Mich._Dairy_1, 2006	No negative control switchback
Diamond_V_Mills and Mich._Dairy_2, 2005	No negative control switchback
Diamond_V_Mills and MW_Dairy_1, 2006	No negative control switchback
Diamond_V_Mills and MW_Dairy_2, 2006	No negative control switchback
Diamond_V_Mills and NE_Feed_Man., 1983	No treatment effect reported
Diamond_V_Mills and NW_Dairy, 2005	No negative control
Diamond_V_Mills and Ohio_Dairy, 2009	No negative control switchback
Diamond_V_Mills and Wisc._Dairy_1, 2005	No negative control switchback
Diamond_V_Mills and Wisc._Dairy_2, 2006	No negative control switchback
Erdman and Sharma, 1989	Cross over
Hippen et al., 2010	2x2 Factorial
Longuski et al., 2009	Cross Over
Miller, 1994	No treatment effects
Rumenco and Diamond_V_Mills, 1993	Cross-Over
Sanchez et al., 2005	No negative control switchback
Shaver and Garrett, 1997	No negative control
White et al., 2008	Cross-over
Wiedmeier et al., 1987	Latin Square

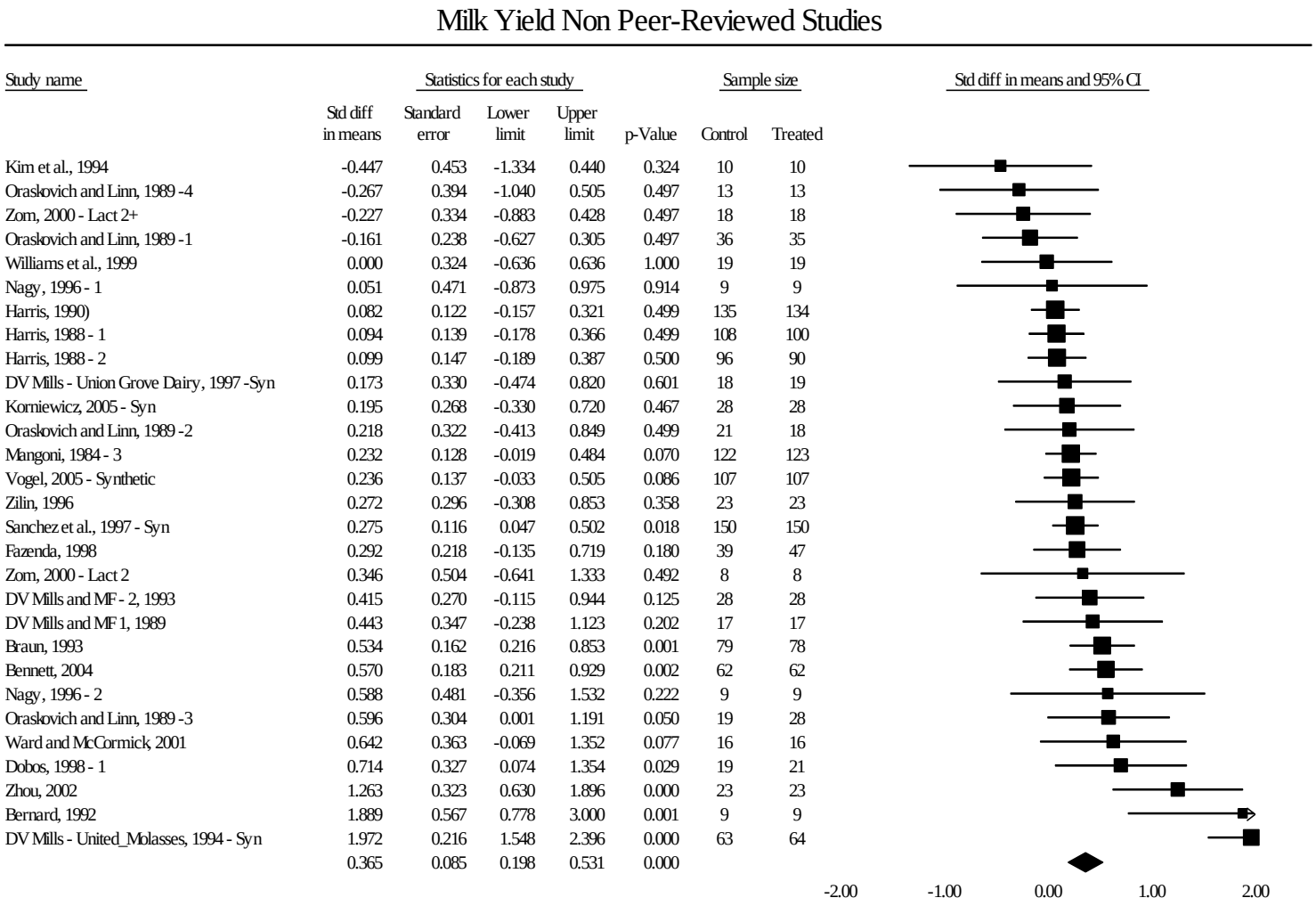

Figure A.1. Forest plot of random effects SMD for milk yield. Only studies not published in peer reviewed journals are represented. The black squares in the forest plot represent the weighting (by inverse variance) for the represented study. The horizontal bars represent the 95% CI for the study. The diamond figure center represents the standardized mean and the width of the diamond represents the 95% CI of the overall treatment effect. The outcome to the right of an imaginary vertical line through 0 represents an increase in milk fat yield. (Poppy et al 2012).

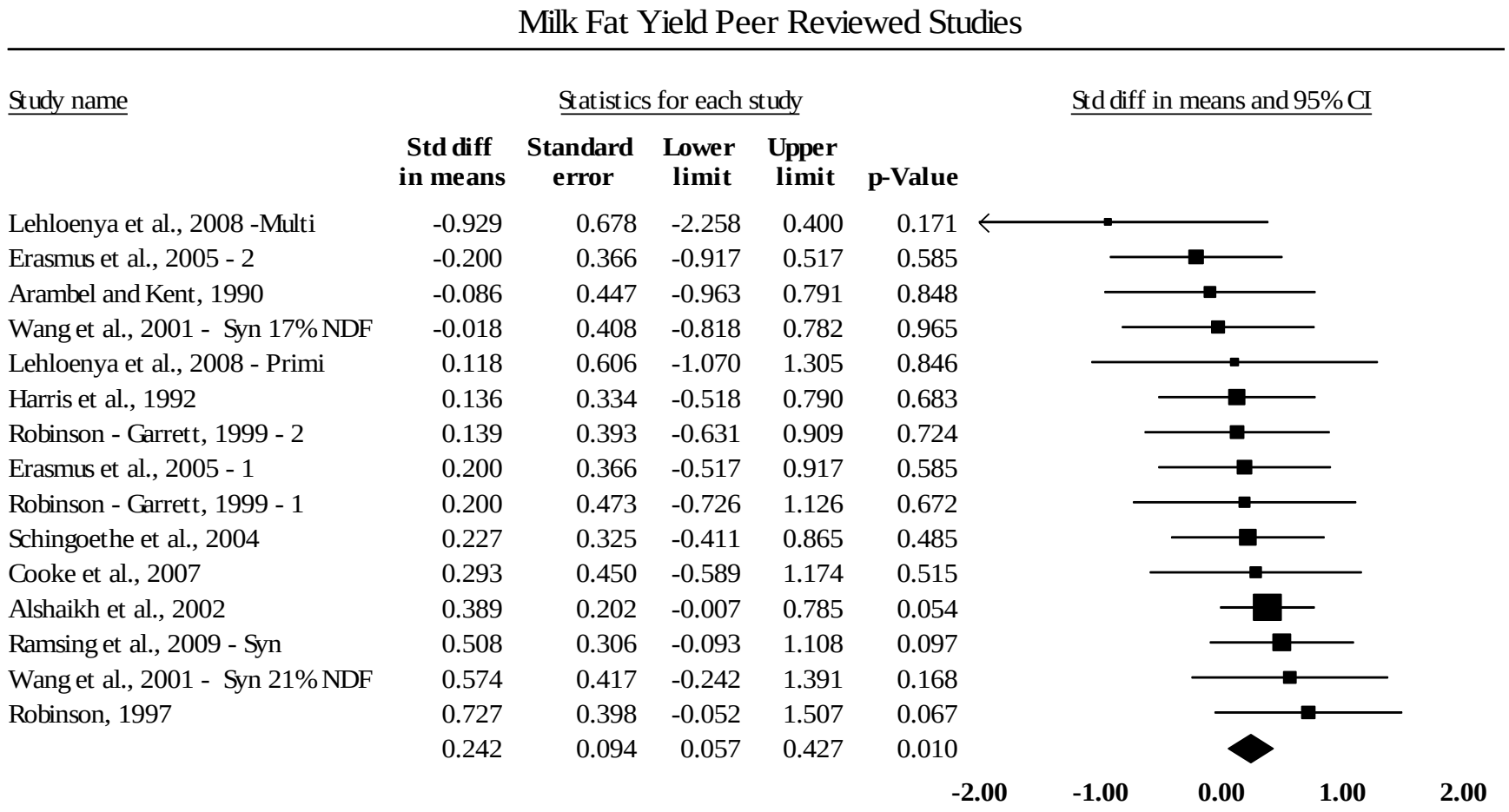

Figure A.2. Forest plot of random effects SMD for milk fat yield. Only studies published in peer reviewed journals are represented. The black squares in the forest plot represent the weighting (by inverse variance) for the represented study. The horizontal bars represent the 95% CI for the study. The diamond figure center represents the standardized mean and the width of the diamond represents the 95% CI of the overall treatment effect. The outcome to the right of an imaginary vertical line through 0 represents an increase in milk fat yield (Poppy et al 2012)..

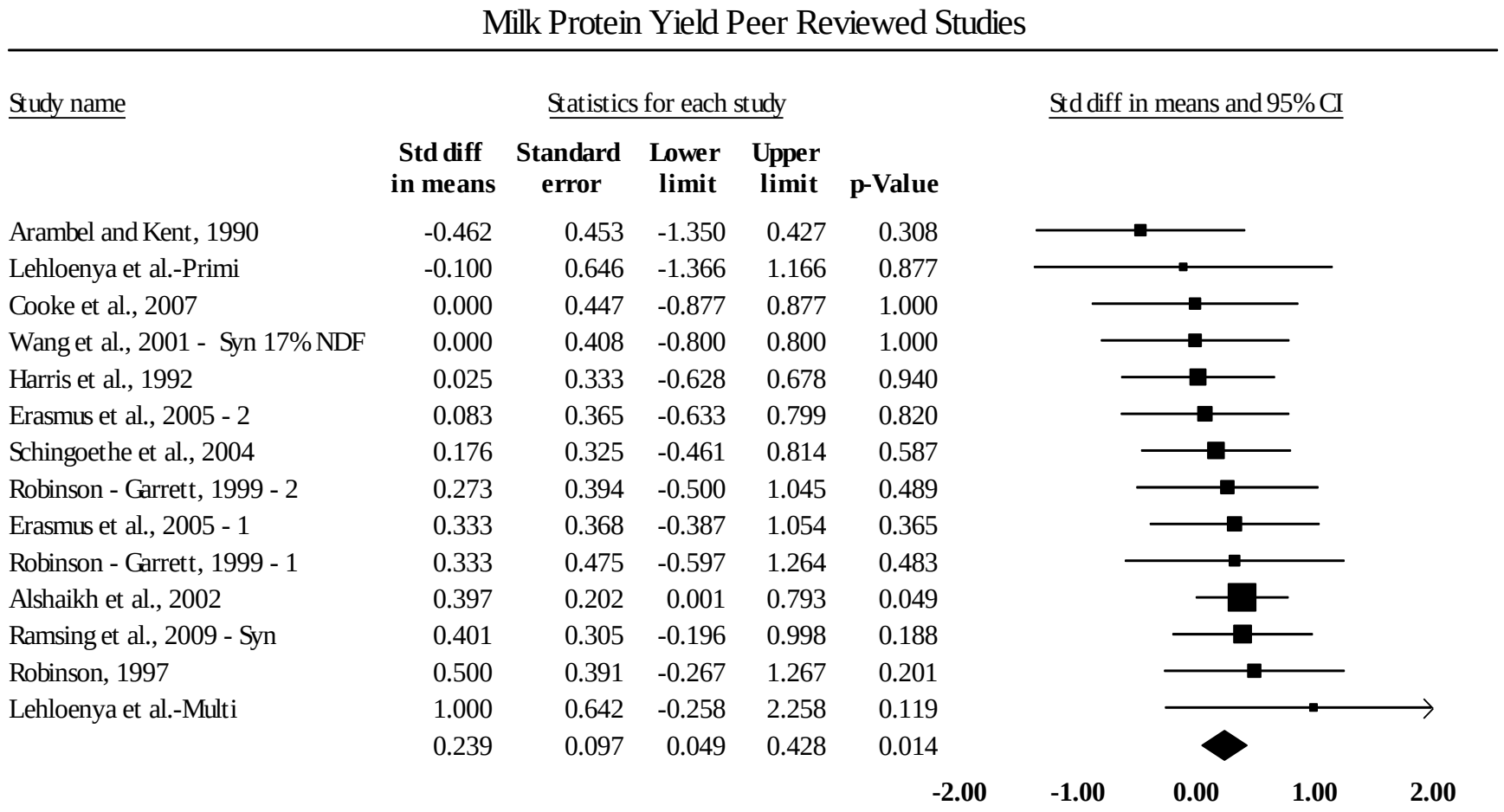

Figure A.3. Forest plot of random effects SMD for milk protein yield. Only studies published in peer reviewed journals are represented.The black squares in the forest plot represent the weighting (by inverse variance) for the represented study. The horizontal bars represent the 95% CI for the study. The diamond figure center represents the standardized mean and the width of the diamond represents the 95% CI of the overall treatment effect. The outcome to the right of an imaginary vertical line through 0 represents an increase in milk fat yield (Poppy et al 2012).

APPENDIX B

Dairy Longitudinal Survey Page 1

Hello, my name is *(enter your name so we know who did the surve* y) I work for Diamond V, and we are working withColorado State University on a dairy study to look at risk factors for severe diarrhea in dairy herds across the US.

Did you receive the letter from Colorado State about the survey.

Yes ☐ No ☐

Your dairy was selected from a randomized sample of dairys to provide data for the analysis. The interview will take about 15 minutes to complete is voluntary and your answers will be kept confidential.

Will you participate in the survey and answer questions about your dairy and provide a backup of the records needed to analyzed for the diarrhea events?

Yes ☐ No ☐

Is this a good time for the discussion

Yes ☐ [continue with survey]

No ☐ When would be a better time to call back. [Record name and time for return call]

I am going to ask you a series of questions about your dairy. Please respond as well as you are able

First we need to collect information to make sure we match the dairy with the cow records

Dairy Name _____

Phone Number _____

Address _____

City _____

State _____

Zip _____

GPS _____

Owner	Phone number
Herdsman	Phone number
Veterinarian	Phone number
Nutritionist	Phone number

This Information for Risk Factors from the operational characteristics of the farm

Dairy Size

Total Cows	
Milking Cows	

Breed of Cows

Holstein	% of herd
Jersey	% of herd
Other	% of herd

Facilities Type check one

Dry Lot		
Freestall		
Tie Stall		
Cross Ventilated		
Tunnel Ventilated		
Saudi Style		
Utah Style		
Other		Describe

Milking Parlor Type check one

Rotary		
Parallel		
Herringbone		
Tie Barn		
Stanchion		
Other		Describe

Type of Dairy Records Check one

DC305		
DHI Plus		
PC Dart		
other		Describe

(If not one of these 3 end survey, and explain it is in the criteria for the survey and thank them for their time)

Feeding Method

TMR		
Grazing		
Other		Describe
Times Fed per day		
Times pushed up per day		

What do they use to push up, describe

Primary Forage fed on dry matter basis

Alfalfa		Aprox lbs / day (As Fed	
Corn Silage			
Alfalfa Haylage			
Small Grain			

Secondary Forage Fed

Alfalfa		Aprox lbs / day (As Fed	
Corn Silage			
Alfalfa Haylage			
Small Grain			

Tertiary Forage Fed

Alfalfa		Aprox lbs / day (As Fed	
Corn Silage			
Alfalfa Haylage			
Small Grain			

Herd has been vaccinated in the last year with?

IBR	
BVD	
SRP	
J5	
Bovivac S	
Autogenous Salmonella bactrin	
Endovac Bovi	
Other ecoli vaccine	

How do you define Severe Diarrhea in your herd (as opposed to normal diarrhea)

Do you treat Severe Diarrhea different than Normal diarrhea,

Yes ☐ No ☐

Describe the treatment protocol

Do you record Severe Diarrhea event in your computer records

Yes ☐ No ☐

If you do not record would you be willing to record Diarrhea events.

Yes ☐ No ☐

How do you record Severe Diarrhea in your records

How would you record a cow with diarrhea and not running a fever and not down in Milk? How would your record a cow with diarrhea and running a 104 degree fever,
How would you record a cow with bloody watery diarrhea with a 99 degree temperature and not giving much milk, and very depressed.

We are interested in any feed additives you have fed for the previous 6 months. Please indicate if you feed any of the following products and when you started feeding them and to which groups in the herd
(Please repeat until you have 6 months of information

Diamond V Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date
YC XP XPC

Bovamine Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Priority One Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Omnigen Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Celmanx Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Amax Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Aspergillus oryzae - Amaferm
Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Live Yeast Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date
What brand of Live Yeast

Other Direct Fed Microbial?
Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date
What brand

What is the reason you fed the feed additive

We are interested in any feed additives you have fed for the previous 6 months. Please indicate if you feed any of the following products and when you started feeding them and to which groups in the herd **page 2 of additives**
(Please repeat until you have 6 months of information

Diamond V Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date
YC XP XPC

Bovamine Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Priority One Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Omnigen Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Celmanx Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Amax Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date

Aspergillus oryzae - Amaferm
Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date
☐

Live Yeast Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No Start date
What brand of Live Yeast

Other Direct Fed Microbial? example MOS or other bacteria
Yes ☐ % of herd or groups, (ie fresh cows only) ☐
No ☐ Start date
What brand

What is the reason you fed the feed additive

Do you feed Rumensin

Yes ☐ % of herd or groups, (ie fresh cows only) ☐

No ☐ Start date

Collect a Back up file from their computers
What is the back up file named

Is it ok to contact your nutritionist to verify or find out any nutritional information you were unable to confirm

Yes ☐

No ☐

(Fill in blank areas if needed from nutritionist.)

Thank you for your help on this project. We will be returning in 6 months to pick up another back up and see if anything has changed in your feeding program or dairy operation since this interview

Do you have a phone number I can call to make an appointment? ☐

Thanks

Figure B.1. Survey instrument used for study of the association of various on farm risk factors and direct fed microbial products on the incident rate of diarrhea in dairy cattle in the US in 2013 and 2014.