

Recombinant bovine somatotropin: overview and results from a recent meta-analysis of effects on health and welfare of dairy cows

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Abstract

Historically, the dairy industry has made remarkable gains in productivity and a gallon of milk can be produced today with less feed resource inputs and a markedly reduced carbon footprint. Recombinant bovine somatotropin is a production-enhancing technology and 20 years commercial use of POSILAC® (rbST-Zn) provided the backdrop for an updated meta-analysis of effects on cow health and welfare. Our meta-analysis used data from peer reviewed publications or regulatory reports in which the commercial formulation of rbST-Zn was used was according to label specifications.²⁹ Twenty six studies were identified which had usable data (13,784 cows). Results indicated milk yield was increased by about 9 lb/d whereas milk fat, protein, and lactose content were unaltered. For health and welfare variables, treatment with rbST-Zn had little or no effect on udder health, reproduction, lameness, body condition or culling. Overall, these results and 20 years of US commercial experience demonstrate that management practices used by US dairy producers are adequate for the effective use of rbST-Zn to increase milk yield and productivity with no unmanageable adverse effects on cow health or welfare.

Key words: dairy, health, lactation, productivity, rbST, somatotropin, welfare.

Résumé

Historiquement, l'industrie laitière a fait des gains remarquables dans la productivité et un gallon de lait peut être produite aujourd'hui avec moins d'intrants provenant des ressources d'alimentation et d'une empreinte carbone réduite de façon marquée. La somatotropine bovine recombi-

nante est une technologie d'amélioration de la production et 20 ans de l'utilisation commerciale de POSILAC® (STBR-Zn) ont fourni le contexte pour une mise à jour de méta-analyse des effets sur la santé de la vache et du bien-être social. Notre méta-analyse a utilisé des données provenant de publications révisées par des pairs ou des rapports réglementaires dans lesquels la formulation commerciale de la Stbr-Zn a été utilisé conformément aux instructions figurant sur l'étiquette.²⁹ Vingt-six études ont été identifiées qui avaient des données utilisables (13,784 vaches). Les résultats indiquent le rendement en lait a augmenté d'environ 9 lb/D. considérant que les matières grasses du lait, de protéines et de lactose contenu n'étaient pas altérés. Pour Santé et Bien-être social variables, le traitement par la Stbr-Zn avaient peu ou pas d'effet sur la santé du pis, la reproduction, la boiterie, la condition physique ou l'abattage. Dans l'ensemble, ces résultats et 20 années d'expérience commerciale aux États-Unis démontrent que les pratiques de gestion utilisés par les producteurs laitiers américains sont adéquats pour l'utilisation efficace de la Stbr-Zn à augmenter le rendement laitier et la productivité sans ingérable des effets nocifs sur la santé de la vache ou du bien-être social.

Introduction

Increases in productivity have been the engine of growth for U.S. agriculture. For the dairy cow, productivity can be defined as "milk output per unit of resource input", and it represents a key component of sustainability. The dairy industry has made remarkable gains in productivity; over the last 70 years milk yield per cow has more than quadrupled and associated with this the carbon footprint in production of a gallon of milk has been reduced by more than two-thirds.⁶ As milk production increases, total nutrient requirement also

increases but productive efficiency is improved because the fixed cost (maintenance) is diluted out over more units of milk production. Dilution of maintenance is usually thought of in terms of feed resources, but benefits also apply more broadly to all cow-related fixed costs of producing milk including renewable and non-renewable resources as well as the costs for facilities and labor.

The impressive gains in productivity reflect a better understanding of the biology of the dairy cow. Thus, the dairy industry has utilized AI and genetic selection to increase the production potential of dairy cows and at the same time implemented management practices and technologies which provide an opportunity for cows to achieve their high milk potential. One production-enhancing technology that allows the dairy industry to produce milk more efficiently is recombinant bovine somatotropin.

Recombinant Bovine Somatotropin

The bovine somatotropin (bST) story began in the 1930's when it was first demonstrated that injection of a crude pituitary extract caused a transient increase in milk production in low producing cows.¹ Over the next 50 years, these results were verified and bST was identified as the galactopoietic factor in pituitary extracts. In the late 1970's and early 80's, studies utilized highly purified bST and demonstrated the bioenergetics of the gains in efficiency and the effectiveness of bST in high producing cows.² Additional information about the historical aspects of bST and details as to its mechanism of action are available elsewhere.^{3,15}

The 1980's also ushered in a new era in science with the introduction of biotechnology and the use of recombinant DNA techniques. The potential application in the dairy industry was obvious and recombinant bovine somatotropin (rbST) was among the first proteins produced through the use of "biotechnology". As the first recombinant protein with potential use in production animals, several companies were involved in developing methods to produce rbST and production studies involved a number of different formulations carried out mainly at land-grant universities. Evaluation was extensive and rbST received an unprecedented scrutiny. In the US this included the traditional evaluation by FDA as well as public hearings, science evaluations and legislative reviews.^{2,3} After a thorough review of well-controlled studies, FDA concluded that rbST could be used safely and effectively by the US dairy industry. The commercial formulation of rbST approved by FDA is recombinant sometribove-zinc (rbST-Zn), a formulation given every two weeks. Commercially marketed under the trade name POSILAC®, sales of rbST-Zn began on February 1984. To date an estimated 35 million US dairy cows have received the commercial formulation of rbST-Zn²⁹ and results have confirmed that cows treated with rbST produce a litter of milk with less feed resources and a reduced carbon footprint.⁷

Updated Meta-Analysis of rbST-Zn effects on Animal Health and Welfare

Not everyone agreed with the FDA conclusions on use of rbST. Health Canada requested that the Canadian Veterinary Medical Association (CVMA) evaluate if "rbST used in accordance with label directions will increase milk production without resulting in serious health problems which cannot be adequately controlled by current management practices".¹² CVMA formed a task force and addressed this mandate by conducting a meta-analysis of results from rbST studies. The CVMA Report,¹² subsequently published in the Canadian Journal of Veterinary Research, concluded that use of rbST would increase yields of milk and milk components, but would also adversely impact cow health and welfare, especially udder health, lameness, body condition, reproduction and lifespan.^{13,14} Other less rigorous evaluations also predicted catastrophic health and welfare problems for rbST treated cows.^{5,24}

Since the CVMA Report,¹² there have been several large scale rbST investigations relating to various aspects of cow health and welfare, e.g.^{4,9,22,26,27} Results from these investigations and over 20 years of commercial experience on US dairy farms appear at odds with the conclusions reached by the CVMA.^{13,14} Thus, an updated evaluation of the impact of rbST on the efficacy and the health and welfare of dairy cows would be of value.

Objective and Approach

To provide an updated evaluation of the efficiency and safety of rbST we formed an expert panel. It consisted of a data manager and project coordinator, a professional statistician, and six domain experts and results of were recently published.²⁹ Briefly, our evaluation involved a set of meta-analyses using data that had been published in peer-reviewed scientific journals or regulatory agency reports. Our criterion was that the commercially approved rbST-Zn formulation was used according to label; data from studies involving off-label use of rbST-Zn or studies that used unapproved formulations or doses of rbST were excluded.

Studies for the analysis were identified by an extensive literature search using PubMed (US National Library of Medicine, US National Institute of Health, Bethesda, MD), Agricola (National Agriculture Library, US Department of Agriculture, Beltsville, MD), Web of Science (Thomson Reuters Science, New York, NY), and CAB Direct (CAB International, Wallingford, UK). We identified a total of 26 studies that met the criteria and data from these formed our meta-analysis database. The sequence followed in identifying studies that met the criteria and specific details of the methodology for the meta-analysis are given in St-Pierre et al.²⁹

Results and Discussion

Seven variables were analyzed to characterize the milk and milk composition responses to rbST-Zn milk yield, percent milk fat, percent milk true protein, percent lactose, 3.5% fat-corrected milk yield, fat yield and protein yield. Except for the percentage of lactose in milk, responses across studies were heterogeneous ($P < 0.10$), indicating that unidentified factors associated with individual studies affect the magnitude of the response. Meta-analysis results indicated that yield of milk and milk components were all increased by rbST-Zn (Table 1). Treatment with rbST-Zn increased milk yield (+8.8 lb/d) and 3.5% fat corrected milk (+8.9 lb/d) by about 15% over control cows (Table 1). However, milk composition for fat ($P = 0.088$), protein ($P = 0.067$), and lactose ($P = 0.264$) were not affected by rbST-Zn (Table 1). Thus, yield of these components increased in parallel to milk production with daily yields of fat ($P < 0.001$) and protein ($P < 0.001$) being increased by an average of 13.3% and 15.9%, respectively.

Milk yield results from our meta-analysis are in agreement with other summaries that indicate rbST-Zn treatment results in an increase in milk which is typically 8 to 12

lb/d.^{3,7,25} Likewise, reviews have consistently observed that the yield of milk components increases to the same extent as milk yield and as a consequence rbST-Zn treatment has no effect on milk composition.^{2,21,25}

Milk somatic cell count (SCC) is an indicator of inflammation in the mammary gland, and milk SCC will increase in response to both sub-clinical and clinical mastitis.²⁰ Therefore, our evaluation of udder health included SCC as well as the incidence of clinical mastitis. Tests for heterogeneity indicated significance for both milk log SCC ($P < 0.001$) and mastitis incidence rate ($P < 0.035$); thus, unidentified factors associated with individual studies affect the observed values. In the case of SCC, the control group averaged nearly 100,000 SCC/mL, and there was no effect of rbST-Zn supplementation ($P = 0.540$; Table 1). Likewise, mastitis incidence rate was not different between the control and rbST-supplemented groups ($P < 0.122$; Table 2). Across all studies, rbST-Zn treated cows were significantly more likely to develop clinical mastitis in only 4 of the 14 studies evaluated. Only one study²³ conducted cultures and used intramammary infection status to ensure a balance in treatment group assignment. That study involved 4 herds (total cows = 555) and results indicated

Table 1. Estimates of responses to rbST and associated statistics from the meta-analyses of continuous traits.^a

Variables	Number of studies	Mean of control cows	Response estimate	Standard error of estimate	P value	95% Lower CL ^e	95% Upper CL
Milk production & composition							
Milk yield (lb/d)	15	60.0	8.82	0.891	<0.001	7.08	10.56
Fat (%)	13	3.64	-0.073	0.043	0.088	-0.156	0.011
Protein (%)	13	3.15	0.025	0.013	0.067	-0.001	0.051
Lactose (%)	11	4.82	0.023	0.021	0.264	-0.017	0.063
3.5% FCM (lb/d)	13	64.4	8.91	0.904	<0.001	7.143	10.67
Fat yield (lb/d)	13	2.38	0.317	0.046	<0.001	0.229	0.408
Protein yield (lb/d)	13	1.90	0.302	0.397	<0.001	0.227	0.381
Reproduction (all parities)							
Days open	5	104.2	-0.21	4.18	0.960	-8.39	7.98
Services per conception	4	1.66	-0.25	0.162	0.121	-0.57	0.07
Udder health							
Log ₁₀ somatic cell count	9	4.99 ^f	-0.034	0.055	0.540	-0.141	0.074
Lameness and lesions ^b							
Clinical lameness	7	0.38	0.13	1.14	0.991	-2.18	2.21
Lameness lesions	3	1.12	0.32	29.2	0.991	-55.4	56.0
Traumatic lesions	5	0.11	0.093	7.59	0.991	-15.5	15.7
Body condition							
Body condition score ^c	15	3.31	-0.064	0.031	0.037	-0.124	-0.004
Culling							
Culling density ^d	6	4.64	0.603	0.633	0.341	-0.637	1.018

^aFrom St. Pierre et al.²⁹

^bExpressed as incidence rate per 1,000 cow-days at risk.

^cBody condition score is expressed on a 1 to 5 scale, with 5 being severely over-conditioned.

^dCulling density is expressed as incidence rate per 10,000 cow-days at risk.

^eCL = confidence limit.

^fLog₁₀ somatic cell count of 4.99 = 97,734 somatic cells/mL milk.

there were no significant differences in number of cows that developed clinical mastitis or number of days that milk was discarded because of mastitis.²³

Udder health results from our meta-analysis were consistent with the recent systematic review of the effects of rbST-Zn on mastitis incidence and SCC conducted by JEFCA.²¹ Their review of clinical and epidemiological studies found no effect of rbST-Zn on mastitis incidence. In the case of sub-clinical mastitis, they reported that the “vast majority of studies reported no effect of rbST-Zn treatment on SCC values, although a few studies reported small transient increases”.²³ Our results were also consistent with the conclusions of the public hearing conducted by the FDA Veterinary Medicine Advisory Committee.¹⁸ Environmental and management factors are major causes of mastitis and they impact both SCC and mastitis incidence.²⁰ In addition, genetic studies have demonstrated a small positive relationship between mastitis risk and milk production. However, high producing herds are better managed so that effects of increased milk production are minimized or negated.²⁰

Dairy cows need to maintain adequate body condition over the lactation cycle. Thus, it was of interest whether rbST-treated cows would become thin and emaciated due to the use of body reserves to support the increased milk production. Data for body condition score (BCS) were available for 15 studies, and the test for heterogeneity of responses among studies approached significance ($P = 0.104$). The BCS data used in the meta-analysis consisted of the BCS obtained during and after rbST-Zn treatment. Mean BCS was significantly lower in cows treated with rbST-Zn as compared to control cows ($P = 0.037$) with the difference being -0.064 ± 0.031 points (mean \pm SE; Table 1). As reviewed in St-Pierre et al.,²⁹ published studies indicate that 1 point of BCS represents about 110 lb (50 kg) body weight. Thus, the difference in BCS for the rbST-treated cows observed in our meta-analysis represents about 7 lb (3.2 kg) body weight. While significant,

this difference would not be visually apparent and is about equivalent to the change in body weight associated with a typical feeding or drinking episode for a dairy cow. Thus, our meta-analysis indicates that treatment with rbST-Zn has little or no effect on body condition in spite of the increase in milk yield. The explanation for this comes from the review by Chillard⁸ who demonstrated that across studies cows treated with rbST-Zn increased voluntary intake in an amount energetically comparable to the rbST-induced increases in milk yield.

Lameness is the most visible animal welfare issue for the US dairy industry. The altered locomotion or mobility that occurs with clinical lameness represents a range of foot and leg disorders that can result from disease, management, or environmental factors.²⁸ Results of our meta-analysis for clinical lameness demonstrated that treatment with rbST-Zn had no effect ($P = 0.999$; Table 1). Wherever possible, data for foot lesions were also separated into two categories - lameness lesions and traumatic lesions. Lameness lesions are lesions that directly cause clinical lameness (e.g. laminitis, sole ulcers or digital dermatitis) whereas traumatic lesions are lesions that rarely cause or result in lameness (e.g. mechanically induced skin lesions).²⁸ We observed that incidence rates for either lameness lesions or traumatic lesions did not differ between control cows and cows that received rbST-Zn ($P = 0.991$; Table 1).

Reproductive variables were of special interest in our evaluation. Results from the meta-analysis indicated a significant 5.4% improvement in pregnancy proportion in the rbST-supplemented cows for the first two breeding cycles after the voluntary wait period ($P < 0.007$; Table 2). When compared over the full length of the trial, the pregnancy proportion was reduced 5.5% for the group receiving rbST-Zn ($P < 0.048$; Table 2), a reduction that was likely due to reduced estrous behavior. The fact that rbST-treated cows were more likely to become pregnant during the first two

Table 2. Estimates of responses to rbST expressed as odds ratios and associated statistics from the meta-analyses of non-continuous traits.^a

Variables	Rate of Control Cows	Estimates of Odds Ratio	<i>P</i> Value	95% Lower CL ^d	95% Upper CL
Reproduction, all parities					
Pregnancy rate in LRP ^b	0.291	1.281	0.007	1.072	1.530
Pregnancy rate in ERP ^c	0.761	0.753	0.048	0.568	0.997
Fetal losses rate	0.115	1.065	0.650	0.812	1.397
Twinning rate	0.065	1.107	0.679	0.685	1.787
Cystic ovaries rate	0.065	1.171	0.425	0.795	1.725
Udder health					
Mastitis incidence rate	0.174	1.249	0.122	0.942	1.655

^aFrom St. Pierre et al.²⁹

^bLimited response period (first and second AI inseminations).

^cExtended response period (full duration of the trial).

^dCL = confidence limit.

breeding cycles, the period when cows are generally enrolled in a timed-AI protocol, suggests that rbST-Zn did not impair, and might even have a positive effect on the reproductive performance of dairy cows during this period.

There was no effect of rbST-Zn on days to pregnancy, inseminations per conception, fetal losses, or twinning incidence (Tables 1 and 2). Similarly, the incidence rate of cystic ovaries did not differ between controls and rbST-treated cows ($P = 0.425$; Table 2). The lack of effect on ovulation failure and cystic ovaries in dairy cows is consistent with the results from De La Sota et al.¹¹ in which rbST-treated cows had ovaries with healthy estrogen-active follicles.

Culling was also examined and meta-analysis results indicated that culling density did not differ between controls and cows treated with rbST-Zn ($P = 0.341$). These findings corroborate those of a large longitudinal field study conducted over 4 years on 340 commercial dairy herds in the Northeastern US; those results demonstrated that rbST-Zn use had no effect on stayability or herd-life.⁴ Culling rate is often incorrectly assumed to reflect the quality of the production and management system. The optimal culling rate increases when there is a relative abundance of replacements and the cost of a replacement cow is similar to the slaughter value of the cow being replaced.²⁹

Meta-analysis Summary

Overall, results of our updated meta-analysis indicated that administration of the commercially available rbST formulation to lactating dairy cows according to FDA-approved label directions resulted in an increase in yields of milk and milk components with no unmanageable adverse effects on milk SCC, incidence of mastitis, reproduction, body condition, lameness, or culling.²⁹ These findings are contrary to the earlier meta-analysis conducted by the CVMA.^{13,14} The bases for conclusion differences have been extensively discussed.²⁹ In particular our updated meta-analysis included studies conducted subsequent to the CVMA Report (1998), and several of these were large scale studies conducted on commercial dairy farms. Further, we included only studies that used the commercial formulation of rbST-Zn according to “label directions”, whereas the CVMA Report combined rbST studies that varied in formulation, dose, administration route, and period of use. In addition, we identified several errors in CVMA’s data base that would affect results.²⁹ Suffice to say conclusions from our updated meta-analysis were consistent with FDA evaluations, the minimal reports of adverse drug experiences,¹⁷ numerous scientific reviews,^{3,10,16,19,21,25} and large-scale studies conducted on commercial dairy operations.^{4,9,22,23,26,27}

Conclusions

The dairy industries advances in management practices and the application of new technologies has resulted in im-

pressive gains in productivity. Recombinant bovine somatotropin is a production-enhancing technology that allows cows to produce a gallon of milk using fewer nutrients and a lower carbon footprint. Our meta-analysis indicated that administration of the commercially available rbST-Zn formulation according to FDA-approved label directions increased yields of milk and milk components with no unmanageable adverse effects cow health or welfare. Collectively these results and 20 years of commercial experience involving rbST-Zn treatment of over 35 million US dairy cows provide definitive evidence that management practices used by US dairy producers are adequate for the safe and effective use of rbST-Zn.

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