An Updated Meta-Analysis of Bovine Somatotropin: Effects on Health and Welfare of Dairy Cows[1]

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Abstract

Recombinant bovine somatotropin is a technology that allows a liter of milk to be produced using fewer nutrients and a lower carbon footprint. Twenty years of commercial use of POSILAC® **(rbST)** in the US provides the backdrop for an updated revaluation of the effects on cow health and welfare. Our evaluation involved a meta-analysis of data from peer-reviewed publications or regulatory reports with the criteria being that rbST use was according to label specifications (St-Pierre et al., 2014). Twenty six studies were identified which had usable data (13,784 cows). Results indicated milk yield was increased by 8.8 lb/day, whereas milk fat, protein, and lactose contents were unaltered. Likewise, the use of rbST had little or no effect on variables associated with cow health and welfare. Overall, these results and 20 years of commercial experience demonstrate that management practices used by US dairy producers are adequate for the effective use of POSILAC to increase milk production with no adverse effects on cow health or well-being.

Introduction

Recombinant bovine somatotropin is a production–enhancing technology that allows the dairy industry to produce milk more efficiently. The commercial formulation is recombinant sometribove-zinc **(rbST)** which is marketed under the trade name POSILAC®. Cows treated with rbST produce a liter of milk with less feed resources and a reduced carbon footprint. As the first recombinant protein approved for use in production animals, rbST received unprecedented scrutiny. In the US, this included the traditional evaluation by FDA, as well as public hearings, science evaluations and legislative reviews (Bauman, 1992). After a thorough review of well-controlled studies, FDA concluded that rbST could be used safely and effectively by the US dairy industry. Use commenced in February 1994 and to date an estimated 35 million US dairy cows have received the commercial formulation of recombinant bovine somatotropin (St-Pierre et al., 2014).

Not all agreed with the above conclusions on the 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". CVMA formed a task force and addressed their mandate by using a meta-analysis of studies that used recombinant bovine somatotropin. The CVMA Report (Dohoo et al., 1998), subsequently published in the Canadian Journal of Veterinary Research (Dohoo et al., 2003a; 2003b), concluded that use of bST would

[1]Text and data derived from St-Pierre et al. (2014).

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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 (Dohoo et al., 2003a; 2003b).

Since the CVMA report, there have been several large scale rbST investigations relating to various aspects of cow health and welfare (e.g., Ruegg et al., 1998; Bauman et al., 1999; Judge et al., 1999; Collier et al., 2001; Santos et al., 2004). Results from these investigations and commercial experience on US dairy farms seem at odds with the conclusions reached by the CVMA (Dohoo et al., 2003a; 2003b). Thus, we undertook an updated evaluation of the impact of rbST on the efficacy, health and welfare of dairy cows.

Approach

To provide an updated evaluation of the efficiency and safety of rbST, we formed an expert panel made up of a data manager and project coordinator, a professional statistician, and 6 domain experts (St-Pierre et al., 2014). The evaluation involved a set of meta-analyses. Criteria to be included was that data were from peer-reviewed scientific publications or regulatory agency reports where rbST was used according to label. Data from studies involving off-label use of rbST or studies that used unapproved formulations or doses of rbST were excluded.

Potential data 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). Potential studies were identified and their abstracts obtained (Figure 1). All studies that were not conducted using the commercial formulation of rbST or that clearly did not report results pertinent to the analyses (e.g., dairy market analyses) were immediately discarded. The remaining studies were numbered and corresponding full publications were obtained. Twenty-six studies met the criteria and data from these formed our meta-database (Figure 1). Specific details of the methodology for the meta-analysis can be found in St-Pierre et al. (2014), and results of this analysis are presented in the following sections.

Results and Discussion

Milk Yield and Composition

Seven variables were analyzed to characterize milk and milk composition responses to rbST: 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 affected the magnitude of the response.

Results demonstrated that yield of milk and milk components were all increased by rbST treatment. Milk yield (8.8 lb/day) and 3.5% fat corrected milk (8.9 lb/day) were increased by about 15% over control cows (Table 1). However, milk composition for fat ($P = 0.09$), protein ($P = 0.07$), and lactose (P = 0.26) was not affected (Table 1). Thus, yield of these milk 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 0.317 and 0.301 lb/day, respectively. In agreement with the present meta-analysis, other summaries demonstrate that values for milk responses to rbST tend cluster about a range of 9 to 11 lb/day (Bauman, 1999). Likewise, other investigations have consistently observed that milk composition is not altered by rbST-treatment and factors which affect milk composition do so in an identical manner in rbST-treated cows (Bauman, 1992; National Research Council, 1994).

Udder Health

Milk SCC is an indicator of inflammation in the mammary gland, and the SCC of milk will increase in response to both subclinical and clinical mammary infections (Hogan and Smith, 2012). In our meta-analysis, tests for heterogeneity indicated significance for both milk log SCC (*P* < 0.001) and mastitis incidence rate (*P* < 0.04); 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 treatment (*P* = 0.54; Table 1). Likewise, the mastitis incidence rate was not different between the control and rbST-supplemented groups (*P* < 0.12; Table 2). These results are consistent with the systematic review of the effects of rbST on mastitis incidence and SCC conducted by JEFCA (2013). Their review of clinical and epidemiological studies found no effect of rbST on mastitis incidence. In the case of subclinical mastitis, they reported that the "vast majority of studies reported no effect of rbST treatment on SCC values, although a few studies reported small transient increases" (JEFCA, 2013).

Environmental and management factors are the major causes of mastitis, and they impact both SCC and mastitis incidence. 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 on mammary health are minimized or negated (Hogan and Smith, 2012).

Body Condition

Dairy cows need to maintain an 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* = 0.10). The BCS data used in the meta-analysis consisted of the BCS obtained during and after rbST treatment. Mean BCS was lower in cows treated with rbST as compared to control cows (*P* = 0.04), with the difference being –0.064 ± 0.031 points (mean ± SE; Table 1). Published studies indicate that 1 point of BCS represents about 110 lb BW (see St-Pierre et al., 2014), so the difference in BCS for the rbST-treated cows represents about 7 lb BW. While significant, this difference would not be visually detected and is about equivalent to the change in BW associated with a typical feeding or drinking episode for a dairy cow. Consistent with the meta-results, research has demonstrated that rbST-treated cows increase voluntary intake in an amount energetically comparable to the rbST-induced increases in milk yield (Chilliard, 1989).

Lameness

Lameness reflects altered locomotion or mobility caused by a range of foot and leg disorders that result from disease, management, or environment factors (Shearer et al., 2012). For our meta-analysis, data regarding the number of cows that were clinically lame are presented in Table 1. Where possible, data were separated into 2 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) (Shearer et al., 2012). The test for heterogeneity was not significant for any of the 3 outcome variables ($P = 0.999$). Likewise, incidence rates for cows that were clinically lame, had lameness lesions, or had traumatic lesions did not vary significantly between cows that were and were not treated with rbST ($P = 0.99$; Table 1).

Reproduction

A significant 5.4% improvement in pregnancy proportion was observed in the rbST supplemented cows for the first 2 breeding cycles after the voluntary wait period ($P < 0.01$; Table 2). When compared over the full length of the trial, the pregnancy proportion was reduced 5.5% for the group receiving rbST ($P < 0.05$; 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 2 breeding cycles, the period when cows are generally enrolled in a timed-AI protocol, suggests that rbST 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 on fetal loss, days open, services per conception, or twinning (Tables 1 and 2). Similarly, the incidence rate of cystic ovaries did not differ between controls and rbST-treated cows ($P = 0.43$; Table 2). The lack of effect on ovulation failure and cystic ovaries in dairy cows is consistent with the results in which rbST-treated cows ovaries with healthy estrogen-active follicles (De La Sota et al., 1993).

Culling

Results of our meta-analysis indicated that culling density did not differ between controls and cows treated with rbST ($P = 0.34$; Table 1). These findings corroborate those of a large longitudinal field study conducted over 4 years on 340 commercial dairy herds in the Northeasten US; results demonstrated that rbST use had no effect on stayability or herd-life (Bauman et al., 1999). 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 (St-Pierre et al., 2014).

Summary and Conclusions

Results of the meta-analysis carried out by St-Pierre et al. (2014) indicated that administration of the commercially available rbST formulation to lactating dairy cows according to FDA-approved label directions resulted in an increase in milk, fat, and protein yields with no unmanageable adverse effects on milk composition (percentages of fat, protein, and lactose), udder health, body condition, lameness, reproduction, or culling. These findings are contrary to the meta-analysis conducted by the CVMA (Dohoo et al., 2003a; 2003b). There are several reasons for conclusion differences as discussed by St-Pierre et al. (2014). Briefly, our meta-analysis was able to include studies conducted subsequent to the CVMA report (Dohoo et al., 1998), and several of these were large scale studies conducted on commercial dairy farms. Consistent with our objective, we included all studies which followed "label directions for use", 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 the CVMA database that would effect results (see discussion in St-Pierre et al., 2014).

Overall, our meta-analysis provided no evidence that use of rbST causes any unmanageable adverse effects on milk composition, udder health, reproduction, body condition, lameness, or longevity (St.-Pierre et al., 2014). These results are consistent with the various FDA evaluations (US FDA, 2014a; US FDA 2014b), numerous scientific reviews (e.g., Crooker and Otterby, 1991; Bauman, 1992; National Research Council, 1994), and large-scale studies conducted on commercial dairy operations (e.g., Ruegg et al.,1998; Bauman et al., 1999; Collier et al., 2001; Santos et al., 2004). Collectively, these results and 20 years of commercial experience involving rbST-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.

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

Variables	Number of Studies	Mean of Control Cows	Response Estimate	Standard Error of Estimate	*P* Value	95% Lower CL[5]	95% Upper CL
Milk production and composition							
Milk yield (lb/day)	15	59.8	8.8	0.9	<0.001	3.21	4.79
Fat (%)	13	3.64	-0.073	0.043	0.09	-0.156	0.011
Protein (%)	13	3.15	0.025	0.013	0.07	-0.001	0.051
Lactose (%)	11	4.82	0.023	0.021	0.26	-0.017	0.063
3.5% FCM (lb/day)	13	64.2	8.9	0.9	<0.001	3.24	4.84
Fat yield (lb/day)	13	2.38	0.317	0.046	<0.001	0.104	0.185
Protein yield (lb/day)	13	1.89	0.301	0.046	<0.001	0.101	0.173
Reproduction (all parities)							
Days open	5	104.2	-0.21	4.18	0.96	-8.39	7.98
Services per conception	4	1.66	-0.25	0.162	0.12	-0.57	0.07
Udder health							
Log_{10} somatic cell count	9	4.99[6]	-0.034	0.055	0.54	-0.141	0.074
Lameness and lesions[2]							
Clinical lameness	7	0.38	0.13	1.14	0.99	-2.18	2.21
Lameness lesions	3	1.12	0.32	29.2	0.99	-55.4	56.0
Traumatic lesions	5	0.11	0.093	7.59	0.99	-15.5	15.7
Body condition							
Body condition score[3]	15	3.31	-0.064	0.031	0.04	-0.124	-0.004
Culling							
Culling density[4]	6	4.64	0.603	0.633	0.34	-0.637	1.018

[1]From St. Pierre et al. (2014).
[2]Expressed as incidence rate per 1,000 cow-days at risk.
[3]Body condition score is expressed on a 1 to 5 scale, with 5 being severely over-conditioned.
[4]Culling density is expressed as incidence rate per 10,000 cow-days at risk.
[5]CL = confidence limit.
[6]Log10 somatic cell count of 4.99 = 97,734 somatic cells/mL milk.

Table 2. Estimates of responses to rbST expressed as odds ratios and associated statistics from the meta-analyses of non-continuous traits.[1]

Variables	Rate of Control Cows	Estimates of Odds Ratio	*P* Value	95% Lower CL[4]	95% Upper CL
Reproduction, all parities					
Pregnancy rate in LRP[2]	0.291	1.281	0.01	1.072	1.530
Pregnancy rate in ERP[3]	0.761	0.753	0.05	0.568	0.997
Fetal losses rate	0.115	1.065	0.65	0.812	1.397
Twinning rate	0.065	1.107	0.68	0.685	1.787
Cystic ovaries rate	0.065	1.171	0.43	0.795	1.725
Udder health					
Mastitis incidence rate	0.174	1.249	0.12	0.942	1.655

[1]From St. Pierre et al. (2014).
[2]Limited response period (first and second AI inseminations).
[3]Extended response period (full duration of the trial).
[4]CL = confidence limit.

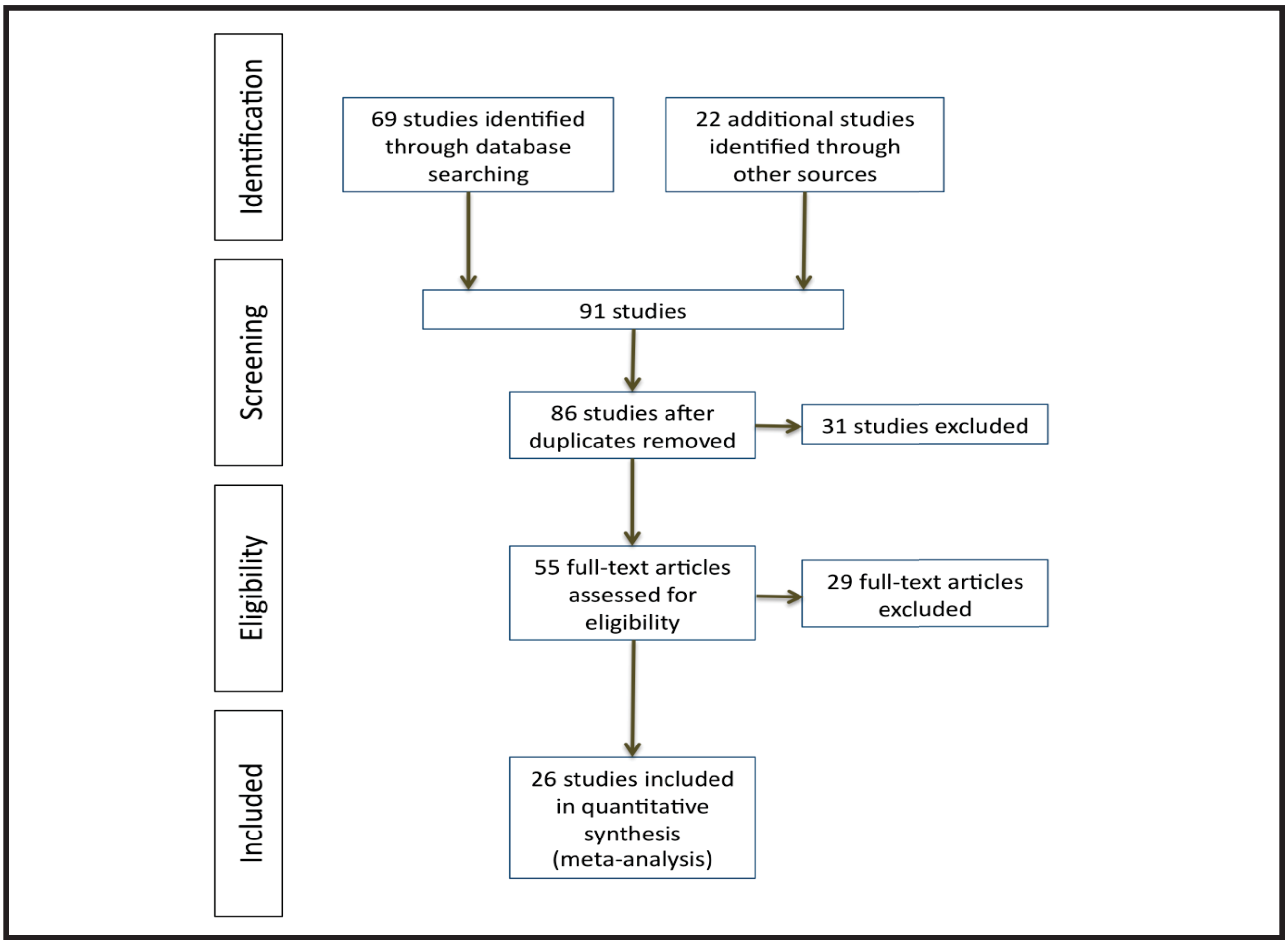

Figure 1. Flow diagram for studies considered in a meta-analysis of the effects of rbST administration on the production and health of lactating dairy cows (St-Pierre et al., 2014).