Meta-analysis of the effects of sometribove zinc suspension on the production and health of lactating dairy cows

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Objective—To provide an updated evaluation of the efficacy and safety of sometribove zinc suspension (rbST-Zn), a form of recombinant bovine somatotropin, in lactating dairy cows.

Design—Meta-analysis.

Sample—26 studies published in peer-reviewed journals or reviewed by a regulatory agency.

Procedures—To be included, a study had to involve the use of the rbST-Zn formulation available to US producers in accordance with the label instructions for treatment initiation (57 to 70 days postpartum), dose (500 mg, q 14 d), and route (SC).

Results—For cows treated with rbST-Zn, mean milk, 3.5% fat-corrected milk, fat, and protein yields were increased by 4.00, 4.04, 0.144, and 0.137 kg/d (8.8, 8.89, 0.32, and 0.30 lb/d), respectively; however, the concentration of milk components did not change. Pregnancy proportion for the first 2 breeding cycles was increased by 5.4%, and pregnancy proportion for the duration of the trial was reduced by 5.5% for rbST-Zn–treated cows, compared with proportions for untreated cows. Mean body condition score (1 to 5 scale) was reduced by 0.06 points during the period of rbST-Zn use for treated cows. Administration of rbST-Zn had no effect on milk somatic cell count, the number of days to pregnancy, or inseminations per pregnancy; rates of fetal loss, twins, cystic ovaries, clinical lameness, lameness lesions, or traumatic lesions of the integumentary system; and odds of clinical mastitis or culling.

Conclusions and Clinical Relevance—Results indicated that rbST-Zn administration to dairy cows effectively increases milk production with no adverse effects on cow health and well-being. (*J Am Vet Med Assoc* 2014;245:550–564)

Recombinant bovine somatotropin is a production-enhancing technology that allows the dairy industry to produce milk more efficiently, which means that each liter of milk produced by cows treated with rbST requires fewer feed nutrients, results in less animal waste, and has a reduced carbon footprint, compared with each liter of milk produced by cows that are not treated with rbST.[1] Sometribove zinc formulation is the only form of rbST commercially available in the United States. After a thorough review of well-controlled studies, the FDA concluded that rbST-Zn could be used safely and effectively on US dairy farms, and commercial use of rbST-Zn by US dairy producers began in 1994. Although some researchers[2,3] suggested that commercial use of rbST would cause catastrophic health problems in dairy cows, the conclusions of investigators of numerous scientific reviews[4–9] of the effect of rbST-Zn on the efficiency, health, and welfare of dairy cows were similar to those of the FDA.

In contrast to the conclusions reached by the FDA and investigators of those scientific reviews,[4–9] an expert panel assembled by the CVMA concluded that health

Abbreviations

AI	Artificial insemination
BCS	Body condition score
CI	Confidence interval
CVMA	Canadian Veterinary Medical Association
ERP	Extended response period
FCM	Fat-corrected milk
logSCC	Logarithmic (base 10) transformation of somatic cell count
LRP	Limited response period
PP	Pregnancy proportion
rbST	Recombinant bovine somatotropin
rbST-Zn	Sometribove zinc formulation
SCC	Somatic cell count

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management practices on Canadian dairy farms were inadequate to address risks associated with rbST use.[10] Formed at the request of Health Canada, the mandate for the CVMA expert panel was to determine whether the use of rbST in accordance with its label directions would increase milk production without resulting in serious health problems that could not be adequately controlled by cattle management practices implemented at that time.[10] The CVMA expert panel's evaluation involved a series of meta-analyses of studies involving rbST administration to dairy cows. The results of those meta-analyses[10] indicated that administration of rbST to dairy cows increases milk production; however, it also had a negative impact on cow health and welfare, especially in the areas of udder health, lameness, body energy, and lifespan.

The CVMA expert panel meta-analysis[10] (CVMA meta-analysis) was subsequently published as 2 peer-reviewed articles,[11,12] and results of those articles[11,12] are often quoted when the animal health and welfare aspects of rbST are discussed. However, the FDA and other experts[13] have expressed concerns about the findings of the CVMA meta-analysis because it evaluated data from studies that used different formulations of rbST with varying doses and dosing frequencies and in which rbST administration was initiated at varying times during the lactation cycle.

Since the publication of the CVMA meta-analysis,[10–12] several large-scale studies[14–19] have been conducted to investigate the effects of rbST-Zn on commercial dairy farms, and rbST-Zn has been administered to > 35 million US dairy cows, with few reports of adverse health effects.[20] Results of those studies[14–19] and anecdotal experiences on commercial dairy operations provide no evidence to support the serious risks to cow health predicted by the CVMA meta-analysis.[10–12] Consequently, there was a perceived need for an updated evaluation of the safety and efficacy of rbST-Zn in lactating dairy cows, which led to the formation of another expert panel that consisted of a data manager and project coordinator, a professional statistician, and 6 domain (milk production and composition, udder health, reproduction, body condition, lameness, and culling) experts. The purpose of the study reported here was to describe the findings of that expert panel and provide dairy producers and veterinary practitioners with an updated review of the efficacy and safety of rbST-Zn. This evaluation was a meta-analysis of studies published in peer-reviewed scientific journals or reviewed by a regulatory agency in which rbST-Zn was administered to dairy cows in accordance with the FDA-approved label directions.

Materials and Methods

Quality and eligibility criteria for studies included in the meta-analysis—To be included in the meta-analysis, studies must have been published in a peer-reviewed scientific journal or reviewed by a regulatory agency, included a control group, and involved the administration of the rbST-Zn formulation[a] commercially available to US dairy producers in accordance with the FDA-approved label directions (500 mg, SC, q 14 d, beginning between 57 and 70 days postpartum). Studies that involved the administration of rbST-Zn in an extra-label manner or formulations of rbST not approved by the FDA were excluded from the meta-analysis.

Data sources—A literature search was conducted of studies indexed in PubMed, Agricola, Web of Science, and CAB Direct between 1975 and 2012 by use of the following search terms: bST, rbST, sometribove, sometribove zinc, Posilac, bovine somatotropin, and bovine growth hormone. All relevant abstracts were obtained electronically or scanned from the published articles maintained at The Ohio State University library or the USDA's National Agricultural Library. Abstracts of studies that did not involve the administration of rbST-Zn or did not report results pertinent to the meta-analysis (eg, dairy market analyses) were immediately discarded. The remaining abstracts were numbered, and the corresponding complete articles were obtained electronically or scanned from The Ohio State University library or the National Agricultural Library. The resulting list of studies was then compared with the list of 23 studies evaluated in the CVMA meta-analysis,[10] and the domain experts for the current meta-analysis added any other studies of which they were aware that met the inclusion criteria. The studies on the final list were reviewed by the domain experts to verify that they were conducted in compliance with the inclusion criteria. Twenty-six studies that involved a total of 13,784 cows met the inclusion criteria for the present meta-analysis (**Figure 1**), of which only 8 were included in the CVMA meta-analysis.[10]

Data collection—The CVMA meta-analysis[10] included studies used by Monsanto (the company that originally marketed rbST-Zn) in its submission to Health Canada for product approval. Wherever possible, those studies were located and their data extracted. If the original report for one of those studies could not be located or had not been published in a peer-reviewed scientific journal, it was discarded from the database (ie, none of the data used in the present meta-analysis were obtained from secondary references). From each study included in the present meta-analysis, the data manager extracted data for treatment means, SEs of the means, and other relevant statistics for all variables and entered it into an electronic database. Subsequently, each domain expert was provided with a reprint of each study relevant to his area of expertise, and the experts cross-checked and verified all entries in the database for their particular domain.

When the BCS domain data used in the CVMA meta-analysis[10] were evaluated, it was discovered that available data had been overlooked, and the only BCS information used was obtained from cows administered 750 mg of rbST-Zn biweekly in a dose-titration study,[21] data that were excluded from the present meta-analysis because those cows were administered 1.5 times the FDA-approved dose of rbST-Zn. It was also discovered that the CVMA meta-analysis[10] incorporated duplicate data in the milk production analysis; production data from the Franson et al[21] Monsanto report were also included in the Hartnell et al[22] study. In addition, the CVMA meta-analysis[10] miscoded limb skin abrasions as lameness.

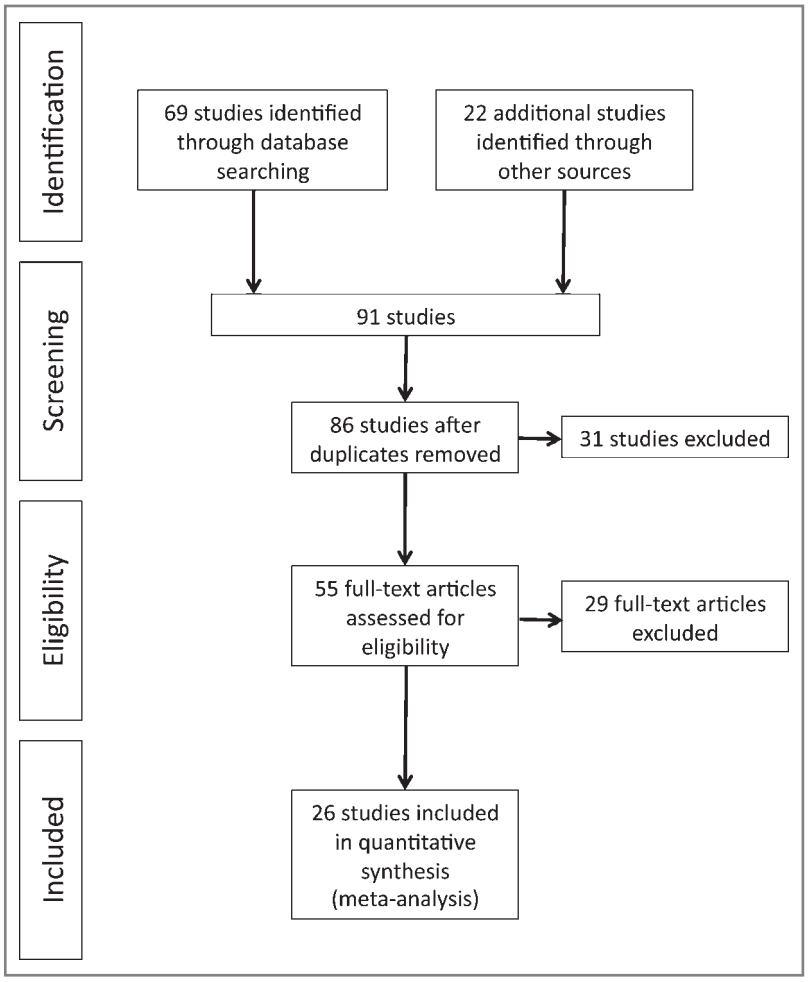

Figure 1—Flow diagram for studies considered in a meta-analysis of the effects of rbST-Zn administration on the production and health of lactating dairy cows.

Statistical methods—Data were analyzed by domain, and the respective outcomes of interest were compared between cows that were and were not (ie, controls) treated with rbST-Zn by meta-analysis methods. The 6 domains specified for the meta-analysis were milk production and composition, udder health, reproduction, body condition, lameness, and culling. The outcomes of interest for the milk production and composition domain were mean actual milk, fat, and protein yields; mean fat, protein, and lactose percentages; and mean 3.5% FCM yield. The outcomes of interest for the udder health domain were the clinical mastitis incidence rate/100 cow-days at risk and the mean logSCC. The outcomes of interest for the reproduction domain were the PP (ie, proportion of cows that conceived) during an LRP (ie, a period beginning at 7 to 9 weeks of lactation to evaluate the outcome from the first and second AIs) and ERP (ie, the full duration of the lactation or observation period of the study of origin), mean number of days from parturition to conception (days to pregnancy), mean number of inseminations per pregnancy, and the proportions of cows that had fetal loss, twins (or multiple births), and developed cystic ovaries. The outcome of interest for the body condition domain was BCS. The outcomes of interest for the lameness domain were the proportion of cows that developed clinical lameness; lesions that directly contribute to lameness such as, but not limited to, those associated with laminitis, subsolar abscess, or digital dermatitis (ie, lameness lesions); and lesions such as traumatically induced skin lesions that might not necessarily be the cause or result of lameness (ie, traumatic lesions). All proportions for the lameness domain were expressed as the number of affected cows/1,000 cow-days at risk. The outcome of interest for the culling domain was the culling density (number of cows culled/10,000 cow-days at risk).

Meta-analysis is a method used to combine information from several similar studies to obtain a generalized summary of the results.[23] Frequently, individual studies have a small number of animals enrolled in each treatment group, and although each study provides an estimate of the treatment effect, that effect may not differ significantly from 0 because of the small sample size. Moreover, individual studies that involve a similar topic or objective generally have study populations of varying sizes, and the estimates of the treatment effects are made on the basis of different levels of precision. In a meta-analysis, a weighted process is used to evaluate data from multiple studies to determine a combined estimate of the mean ± SE treatment effect.

A critical consideration and the basic assumption of a meta-analysis are that the studies included in the analysis were conducted in a similar manner (eg, the same treatment was used in all studies evaluated).[24] For example, studies that involved different doses of a specific treatment should not be combined in a meta-analysis. Furthermore, the studies included in a meta-analysis are assumed to represent the population of studies.[24] Although the same treatment might be used in all studies evaluated in a meta-analysis, the individual studies are generally conducted by different researchers in various environments with differing management practices; therefore, the estimated treatment effects typically vary from study to study. For the present meta-analysis, a random-effects model,[24] in which the evaluated studies were assumed to be a random sample from the population of such studies, was used to allow for a broad inference space.

The basic objective of a meta-analysis is to collect a set of studies that involve similar treatment protocols, extract data from each study for a combined analysis, and make inferences regarding treatment effects likely to be observed in a future study from a population of studies that used a treatment protocol similar to that of the studies evaluated.[24] Theoretically, data obtained from a single large study in which the same treatment protocol was implemented at a series of randomly se-

lected locations or study sites would provide the ideal database for a meta-analysis. In such a theoretical situation, the selected locations would represent a random sample from a population of locations to which treatment-effect inferences are to be made. Then, a mixed-effects model with treatment modeled as a fixed effect and study site modeled as a random effect could be used to describe the treatment response (eg, milk yield), and the interaction between study site and treatment could be used as the appropriate error term for the comparison of treatment responses among treatment groups.[25] Then, the SE estimate of the difference between 2 treatments (ie, difference between treated and untreated [control] groups) would include the study site by treatment interaction, which enables inferences to be made for the population of study sites. In reality, the studies included in a meta-analysis do not involve the use of the exact same treatment protocol but instead were conducted with similar protocols. For each study evaluated, the difference between the means of the rbST-Zn and untreated (ie, control) groups was calculated along with the SE for that difference. The variability of the treatment effects among the studies provided information about the magnitude of the study-by-treatment interaction, which can be incorporated with the SE for the treatment effect of each study to provide a measure of the study-by-treatment interaction, and the reciprocal of the resulting variances was used as the weights for the respective treatment effects for the studies evaluated in the meta-analysis. This is equivalent to the assumption that the studies in the meta-analysis represent a population of similar studies that have been or can be conducted by the use of similar protocols. This implies that the inferences from the meta-analysis can be extrapolated to the population of possible studies. The assumption that the sites (ie, studies) in a meta-analysis are a random sample of possible sites (ie, site or study is modeled as a random effect) enables broad inference to the possible treatment effects at a randomly selected site from the population of sites.[26,27] If site (ie, study) is modeled as a fixed effect during the meta-analysis, the results can only be inferred to the studies evaluated (ie, narrow inference).[26] Thus, the use of a random-effects model during a meta-analysis enables a broad inference about a given treatment effect.

The method of meta-analysis for a continuous response (eg, milk production) begins with estimates of a treatment effect from the i^{th} study denoted by $\hat{Y}_i$ with an estimated variance $\hat{V}ar(\hat{Y}_i)$, where there are n studies. If the weight of each study is denoted as $\hat{w}_i = 1/\hat{V}ar(\hat{Y}_i)$, with $i = 1, 2, \ldots, n$, then the weighted variance of the estimated treatment effects is computed as follows:

$$\hat{K} = \sum_{i=1}^{n} \hat{w}_i (\hat{Y}_i - \overline{\hat{Y}}_\bullet)^2$$

where

$$\overline{\hat{Y}}_\bullet = \frac{\sum_{i=1}^{n} \hat{w}_i \hat{Y}_i}{\sum_{i=1}^{n} \hat{w}_i}.$$

Next, compute

$$\hat{\Delta} = \sum_{i=1}^{n} \hat{w}_i - \left(\frac{\sum_{i=1}^{n} \hat{w}_i^2}{\sum_{i=1}^{n} \hat{w}_i} \right),$$

$$\hat{t} = Max\left[0, \frac{\hat{K} - (n-1)}{\hat{\Delta}} \right],$$

and

$$\hat{w}_i^* = 1/\left(\hat{V}ar(\hat{Y}_i) + \hat{t}\right),$$

$i = 1, 2, \ldots, n$. The meta-analysis estimate as determined by the random-effects model of the treatment effect is

$$\hat{Y} = \frac{\sum_{i=1}^{n} \hat{w}_i^* \hat{Y}_i}{\sum_{i=1}^{n} \hat{w}_i^*},$$

with estimated variance

$$\hat{V}ar(\hat{Y}) = \frac{1}{\sum_{i=1}^{n} \hat{w}_i^*}.$$

The estimate of the SE of $\hat{Y}$ is

$$SE_{\hat{Y}} = \sqrt{\hat{V}ar(\hat{Y})},$$

and the asymptotic 95% CI about the true effect is $\hat{Y} \pm 1.96SE_{\hat{Y}}$.

The method of meta-analysis for binomial data (eg, PP) uses the OR to compare the response for the treatment group with the response for the control group. The possible responses for a binomial variable can be expressed as follows:

	Response	
Population	**Responded**	**Did not respond**
Treatment group	n_{11}	n_{12}
Control group	n_{21}	n_{22}

where n_{11} = number of individuals in the treatment group that responded, n_{12} = number of individuals in the treatment group that did not respond, n_{21} = number of individuals in the control group that responded, and n_{22} = number of individuals in the control group that did not respond. Then, odds for the treatment group is

$$O_T = \frac{n_{11}}{n_{12}},$$

the odds for the control group is

$$O_C = \frac{n_{21}}{n_{22}},$$

and the estimated odds ratio for comparing the treatment group with the control group is

$$\hat{OR} = \frac{\left(\frac{n_{11}}{n_{12}}\right)}{\left(\frac{n_{21}}{n_{22}}\right)} = \frac{n_{11} \times n_{22}}{n_{12} \times n_{21}}.$$

When the meta-analysis involves studies with small sample sizes, the estimated OR can be adjusted for the small sample size by use of the following equation:

$$\hat{OR} = \frac{(n_{11} + 0.5)(n_{22} + 0.5)}{(n_{12} + 0.5)(n_{21} + 0.5)}.$$

The natural logarithm of the $\hat{OR}$ (ie, $\ln[\hat{OR}]$), which has an asymptotic variance,

$$\hat{Var}\left(\ln\left[\hat{OR}\right]\right) = \left[\frac{1}{n_{11} + 0.5} + \frac{1}{n_{12} + 0.5} + \frac{1}{n_{21} + 0.5} + \frac{1}{n_{22} + 0.5}\right],$$

is then used in the meta-analysis in a manner similar to that for the estimated treatment effect of a continuous variable, except that

$$\hat{Y}_i = \ln(\hat{OR}_i)$$

and

$$\hat{w}_i = 1 / \hat{Var}(\ln[\hat{OR}])$$

for $i = 1, 2, \ldots, n$. The 95% CI for $\ln(\hat{OR})$ is $\hat{Y} \pm 1.96SE_{\hat{Y}}$, and the 95% CI for the OR is $e^{\hat{Y} \pm 1.96SE_{\hat{Y}}}$.

Special computations—The SE of the mean response difference between rbST-Zn–treated cows and control cows for each study was used to compute the weight of that study in the meta-analysis. For some studies, the data provided included the estimated mean ± SE response difference between the rbST-Zn–treated cows and control cows. For other studies, the mean ± SE response was provided for both the rbST-Zn–treated cows and control cows, in which case the difference between the means was calculated and the estimated SE of the mean response difference was

$$SE_{diff} = \sqrt{\left(SE^2_{control} + SE^2_{rbST-Zn}\right)}.$$

For still other studies, the mean response was provided for both the rbST-Zn–treated cows and control cows along with the *P* value for a test of the equality of those means. In that case, given a significance level of *P*, the corresponding *t* value was $t_{1-(P/2)}$, the mean response difference was

$$\overline{Y}_{diff} = \overline{Y}_{rbST-Zn} - \overline{Y}_{control},$$

and the SE for the mean response difference was

$$SE_{diff} = \frac{\overline{Y}_{diff}}{t_{1-\frac{P}{2}}}.$$

For studies in which the SE for the mean response difference between the rbST-Zn–treated cows and control cows was not provided and the *P* value for the test of equality for the mean responses of the 2 treatment groups was provided as < 0.05 or < 0.01, the SE of the mean response difference was estimated as

$$\hat{SE}_{diff} = \sqrt{\left(SE^2_{control} + SE^2_{rbST-Zn}\right)},$$

provided that the SE of the mean response for each treatment group was provided or could be otherwise calculated.

For several studies, data regarding the mean milk production and composition (ie, mean percentages of milk fat and protein) for both the rbST-Zn–treated cows and control cows were available, but the mean ± SE actual milk fat and protein yields were not provided. In those instances, the variance of a product was used to approximate the SEs for the mean milk fat and protein yields. For example, the mean protein yield can be calculated as the product of milk yield and protein percentage, and the approximate variance of the protein yield can then be calculated as follows: variance of protein yield = (mean protein percentage^2 × SE milk yield^2) + (mean milk yield^2 × SE protein percentage^2). A similar method was used to calculate the mean fat yield along with its variance. Use of this approximation to calculate the variance for milk fat and protein yields resulted in the inclusion of 9 additional studies in the respective meta-analyses for fat and protein yields. When not provided, the 3.5% FCM yield was calculated from the mean milk and fat yields as follows: 3.5% FCM = (0.4324 × milk yield in kg) + (16.216 × protein yield in kg).

Udder health data were expressed as the incidence of clinical mastitis/100 cow-days at risk and were computed as follows: n_{11} = (number of rbST-Zn–treated cows) × (mastitis incidence rate for rbST-Zn–treated cows in the study) × (number of days/100), n_{12} = (number of rbST-Zn–treated cows) – n_{11}, n_{21} = (number of control cows) × (mastitis incidence rate for control cows in the study) × (number of days/100), and n_{22} = (number of control cows) – n_{21}. The $\hat{OR}$ for the clinical mastitis incidence in rbST–treated cows versus the clinical mastitis incidence in control cows was calculated, and the meta-analysis was then conducted with the method for a binomial outcome.

When possible, data regarding foot lesions were separated into 1 of 2 categories by the domain expert (JKS): lameness lesions (ie, lesions that directly cause lameness such as, but not limited to, those associated with laminitis, sole ulcers, and digital dermatitis) or traumatic lesions (ie, noninfectious lesions such as mechanically induced skin lesions that are rarely a direct cause or result of clinical lameness). The number of cows with each respective lameness outcome (clinically lame, lameness lesions, and traumatic lesions) was assumed to follow a Poisson distribution and was expressed as the number of cows with lesions/1,000 cow-days at risk. For a Poisson distribution, the variance is equal to the mean and the SD is equal to the square root of the mean. For each treatment group, the estimated SE for the lameness lesion score was calculated as the square root of the number of lesions/1,000 cow-days

at risk, and the meta-analysis was conducted with the method for a continuous outcome.

Culling density was expressed as the number of cows culled/10,000 cow-days at risk. The numbers of cow-days at risk were not the same for all studies, so the culling density was computed as follows: (number of cows culled/total number of cows) × (10,000/number of cow-days at risk). The number of cows culled (x) was considered to be part of the cow population at risk of being culled (n), and because cows from population n were or were not culled, the binomial distribution assumption was used to compute the variance. For example, the estimated proportion of cows culled can be denoted as $\hat{p} = x/n$ and the estimated variance of $\hat{p}$ represented as $\hat{V}ar(\hat{p}) = (\hat{p}[1 - \hat{p}])/n$. The estimated variance of the culling density/10,000 cow-days at risk was calculated as follows: $\hat{V}ar(\hat{p}_{10,000}) = (10,000 \times \hat{V}ar[\hat{p}])$/number of cows at risk. Culling density was then assessed by means of the meta-analysis methods for continuous data.

Results

Studies included in the meta-analysis—The studies that were considered for inclusion in the present meta-analysis were summarized (**Table 1**). The basis for exclusion of studies that were included in the CVMA meta-analysis[10] but not included in the present meta-analysis was also provided.

Table 1—List of references considered for a meta-analysis of the effects of rbST-Zn on the production and health of lactating dairy cows (present study), compared with the list of references used in a similar meta-analysis[10] conducted by the CVMA expert panel at the request of Health Canada in 1998.

Reference No.	Reference	CVMA expert panel meta-analysis		Present meta-analysis	
		Study No.	Used	Used	Basis for exclusion
28	Bell et al, 2008	—	No	Yes	—
29	Blevins et al, 2006	—	No	Yes	—
30	Cole et al, 1991	—	No	Yes	—
16	Collier et al, 2001	5,407	Yes	Yes	—
21	Franson et al, 1989	1	Yes	Yes	—
22	Hartnell et al, 1991	344	Yes	Yes	—
31	Huber et al, 1997	—	No	Yes	—
32	Jousan et al, 2007	—	No	Yes	—
18	Judge et al, 1997	20	Yes	Yes	—
19	Judge et al, 1999	—	No	Yes	—
33	Keister et al, 2002	—	No	Yes	—
34	Kirby et al, 1997	—	No	Yes	—
35	Luna-Dominguez et al, 2000	—	No	Yes	—
36	Moreira et al, 2000	—	No	Yes	—
37	Moreira et al, 2001	—	No	Yes	—
38	Pell et al, 1992	261	Yes	Yes	—
39	Phipps et al, 1990	—	No	Yes	—
40	Rijpkema et al, 1990	5,409	Yes	Yes	—
14	Ruegg et al, 1998	—	No	Yes	—
17	Santos et al, 2004	—	No	Yes	—
41	Starbuck et al, 2006	—	No	Yes	—
42	VanBaale et al, 2005	—	No	Yes	—
43	Vicini, 2003	—	No	Yes	—
44	Weller et al, 1990	644	Yes	Yes	—
45	Wells et al, 1995	1,552	Yes	Yes	—
46	White, 1990	—	No	Yes	—
47	Arambel et al, 1989	5,416	Yes	No	Days of initiation (57–180 d postpartum) off label
48	Barbano et al, 1992	2,215	Yes	No	IM injection
49	Bauman et al, 1987	7	Yes	No	IM injection
50	Cole et al, 1992	329	Yes	No	IM injection; doses of 600–3,000 mg; toxicology study
51	Eppard et al, 1991	1,076	Yes	No	IM injection
52	Erdman et al, 1989	5,418	Yes	No	Days of initiation (57–180 d postpartum) off label
53	Galton et al, 1989	5,417	Yes	No	Days of initiation (57–189 d postpartum) off label
54	Huber et al, 1990	5,422	Yes	No	IM injection
55	Jordan et al, 1991	425	Yes	No	Different product; daily injection initiated at 53–183 d postpartum.
56	Meserole et al, 1987	5,415	Yes	No	Days of initiation (57–189 d postpartum) off label
57	Meserole et al, 1992	2	Yes	No	2 Monsanto studies: No. 89-075, days of initiation (60–180 d postpartum) off label; No. 88-192, data and protocol could not be found
58	Metzger et al, 1993	5,425	Yes	No	Toxicology study looking at effects on F1 offspring
59	Olson et al, 1989	5,414	Yes	No	Days of initiation (57–189 d postpartum) off label and route of administration not specified
60	Thomas et al, 1991	416	Yes	No	Same data as that in CVMA study Nos. 5,415, 5,416, 5,417, 5,418, and days of initiation (57–189 d postpartum) off label
61	Vicini et al, 1988	5,421	Yes	No	IM injection; doses of 250–750 mg
62	Whitaker et al, 1988	730	Yes	No	IM injection

To be included in the present meta-analysis, a study had to be published in a peer-reviewed scientific journal or reviewed by a regulatory agency and involve the use of the rbST-Zn formulation available to US producers in accordance with the FDA-approved label instructions for treatment initiation (57 to 70 d postpartum), dose (500 mg, q 14 d), and route (SC).

— = Not applicable.

Outcome variables—For each outcome evaluated, the number of studies that provided data for the meta-analysis and the results of the test of heterogeneity were summarized (**Table 2**). The test for heterogeneity provided an indication of how similar the results for a particular variable were among the studies included in the analysis. An outcome variable with a significant ($P < 0.10$) result for the test for heterogeneity indicated that unidentified factors associated with the individual studies affected the magnitude of the difference between rbST-Zn–treated and untreated (control) cows. For all variables evaluated, the term response was used to indicate the difference between the rbST-Zn–treated cows and control cows. The mean response for each continuous outcome (**Table 3**) and the estimated OR for rbST-Zn–treated cows versus control cows for each binary outcome variable (**Table 4**) evaluated were summarized. In some instances, the estimated incidence rate for the control cows and the mean response or estimated OR were used to calculate the estimated incidence rate for rbST-Zn–treated cows to provide veterinary practitioners with the weighted mean for a particular variable across all studies. It is important to note that, in this analysis, only the estimated OR will remain constant across the studies evaluated; the back calculations of the estimated incidence rates for rbST-Zn–treated cows will vary depending on the setting or study protocol.

Milk production and composition—Information regarding milk yield was provided in 15 studies, and information regarding milk yield and percentages of fat and protein was provided in 13 studies, whereas information regarding lactose percentage was provided in only 11 studies. Of the 7 variables (milk, fat, and protein yields; percentages of fat, protein, and lactose; and 3.5% FCM yield) evaluated in the milk production and composition domain, all except lactose percentage had heterogeneous responses ($P < 0.10$) across the studies included in the meta-analysis (Table 2).

The mean ± SE milk (4.00 ± 0.404 kg/d [8.80 ± 0.889 lb/d]; $P < 0.001$), fat (0.144 ± 0.021 kg/d [0.317 ± 0.046 lb/d]; $P < 0.001$), protein (0.137 ± 0.018 kg/d [0.301 ± 0.040 lb/d]; $P < 0.001$), and 3.5% FCM (4.04 ± 0.410 kg/d [8.89 ± 0.902 lb/d]; $P < 0.001$) yields for cows administered rbST-Zn were significantly greater than those for control cows (Table 3). However, the mean percentages of fat ($P = 0.088$), protein ($P = 0.067$), and lactose ($P = 0.264$) in the milk produced (ie, milk composition) did not vary significantly between cows that were and were not treated with rbST-Zn.

Udder health—The clinical incidence rate for mastitis could be calculated for 14 studies, and the logSCC could be calculated for 9 studies. For both variables, the results were heterogenous across the studies included in the meta-analysis (Table 2), which indicated that the response for each variable varied and was dependent on factors that were not held constant across the studies evaluated.

The OR for clinical mastitis was estimated as 1.249 (95% CI, 0.942 to 1.655; Table 4) and indicated that clinical mastitis rates did not differ significantly ($P = 0.122$) between cows that were and were not treated with rbST-Zn.

Table 2—Results of tests of heterogeneity of the treatment response between cows that were and were not treated with rbST-Zn for each outcome variable evaluated in a meta-analysis of the effects of rbST-Zn administration on the production and health of lactating dairy cows.

Domain and variable	No. of studies	χ^2 Statistic for heterogeneity	*P* value
Milk production and composition			
Milk yield	15	26.76	0.021
Fat	13	28.97	0.004
Protein	13	19.17	0.085
Lactose	11	15.64	0.111
Fat yield	13	25.49	0.013
Protein yield	13	34.15	0.001
3.5% FCM	13	19.89	0.069
Udder health			
Mastitis incidence rate	14	23.62	0.035
LogSCC	9	23.37	< 0.001
Reproduction			
PP in LRP for all cows	9	8.53	0.383
PP in ERP			
All cows	6	7.77	0.170
Primiparous cows	4	1.83	0.609
Multiparous cows	4	4.04	0.257
Cystic ovaries	3	0.46	0.793
Fetal loss			
All cows	9	5.33	0.722
Primiparous cows	2	4.00	0.045
Multiparous cows	2	0.02	0.901
Twins (ie, multiple births)	2	0.07	0.792
Days to pregnancy			
All cows	5	8.13	0.087
Primiparous cows	2	1.02	0.313
Multiparous cows	2	0.09	0.763
Inseminations/pregnancy	4	3.51	0.319
Body condition			
BCS	15	20.90	0.104
Lameness			
Clinical lameness	7	< 0.01	> 0.999
Lameness lesions	3	< 0.01	> 0.999
Traumatic lesions	5	< 0.01	> 0.999
Culling			
Culling density	6	7.19	0.207

Data were separated into 6 domains (milk production and composition, udder health, reproduction, body condition, lameness, and culling) for analysis purposes. The ERP represents the full duration of the lactation or study. The LRP represents the period beginning at 7 to 9 weeks of lactation to evaluate the outcome from the first and second AIs.

Days to pregnancy = Number of days from parturition to pregnancy. Inseminations/pregnancy = Number of inseminations per pregnancy. *See* Table 1 for remainder of key.

The mean ± SE logSCC response was –0.034 ± 0.055 logSCC/mL (95% CI, –0.141 to 0.074 logSCC/mL; Table 3) and did not differ significantly ($P = 0.540$) between cows that were and were not treated with rbST-Zn.

Reproduction—The studies used for assessing pregnancy responses were divided into 1 of 2 groups on the basis of how long during lactation that reproductive data were collected for the cows. One group of studies (n = 9) provided reproductive data for cows for an LRP (ie, the period beginning at 7 to 9 weeks of lactation to evaluate the outcome from the first and second AIs), whereas the other group of studies (n = 6) provided reproductive data for cows during an ERP (ie, the entire duration of the lactation or the observation period of the study of origin). Of all the reproductive variables assessed, only the incidence rate of fetal loss in primiparous cows had evidence of significant heterogeneity across the studies evaluated (Table 2).

Table 3—Estimated mean response difference between rbST-Zn–treated and untreated (control) cows for each continuous outcome variable evaluated in a meta-analysis of the effects of rbST-Zn administration on the production and health of lactating dairy cows.

Domain and variable	Mean for control cows	Mean (SE) response difference	95% CI	*t* value	*P* value
Milk production and composition					
Milk yield (kg/d)	27.2	4.00 (0.404)	3.21 to 4.79	9.90	< 0.001
Fat (%)	3.64	–0.073 (0.043)	–0.156 to 0.011	–1.70	0.088
Protein (%)	3.15	0.025 (0.013)	–0.002 to 0.051	1.83	0.067
Lactose (%)	4.82	0.023 (0.021)	–0.017 to 0.063	1.12	0.264
Fat yield (kg/d)	1.08	0.144 (0.021)	0.104 to 0.185	6.95	< 0.001
Protein yield (kg/d)	0.86	0.137 (0.018)	0.101 to 0.173	7.49	< 0.001
3.5% FCM (kg/d)	29.2	4.04 (0.410)	3.24 to 4.84	9.86	< 0.001
Udder health					
LogSCC (/mL)	4.99*	–0.034 (0.055)	–0.141 to 0.074	–0.61	0.540
Reproduction					
Days to pregnancy (No.)					
All cows	104.2	–0.21 (4.18)	–8.39 to 7.98	–0.05	0.960
Primiparous cows	124.5	11.1 (7.39)	–3.45 to 25.6	1.49	0.135
Multiparous cows	137.0	2.80 (7.16)	–11.3 to 16.8	0.38	0.700
Inseminations per pregnancy	1.66	–0.25 (0.162)	–0.57 to 0.07	–1.55	0.121
Body condition					
BCS†	3.31	–0.064 (0.031)	–0.124 to –0.004	–2.09	0.037
Lameness					
Clinical lameness (No./1,000 cow-days at risk)	0.38	0.13 (1.14)	–2.18 to 2.21	0.13	0.991
Lameness lesions (No./1,000 cow-days at risk)	1.12	0.32 (29.2)	–55.4 to 56.0	0.11	0.991
Traumatic lesions (No./1,000 cow-days at risk)	0.11	0.093 (7.59)	–15.5 to 15.7	0.01	0.991
Culling					
Culling density (No./10,000 cow-days at risk)	4.64	0.603 (0.633)	–0.637 to 1.018	0.95	0.341

*A logSCC of 4.99 is equivalent to 97,734 somatic cells/mL. †Body condition score was expressed on a scale of 1 to 5, with 1 being severely emaciated and 5 being severely obese.
See Tables 1 and 2 for remainder of key.

Table 4—Estimated odds between rbST-Zn–treated and untreated (control) cows for each noncontinuous outcome variable evaluated in a meta-analysis of the effects of rbST-Zn administration on the production and health of lactating dairy cows.

Domain and variable	Rate for control cows	Estimated OR	95% CI	*P* value
Udder health				
Mastitis (No./100 cow-days at risk)	0.174	1.249	0.942–1.655	0.122
Reproduction				
PP				
LRP	0.291	1.281	1.072–1.530	0.007
ERP, all cows	0.761	0.753	0.568–0.997	0.048
LRP and ERP, primiparous cows	0.592	1.049	0.784–1.403	0.749
LRP and ERP, multiparous cows	0.666	0.641	0.467–0.880	0.006
Proportion of cows with fetal loss				
All cows	0.115	1.065	0.812–1.397	0.650
LRP and ERP, primiparous cows	0.107	0.616	0.159–2.384	0.483
LRP and ERP, multiparous cows	0.099	1.092	0.676–1.763	0.719
Proportion of cows with twins (ie, multiple births)	0.067	1.107	0.685–1.787	0.679
Proportion of cows with cystic ovaries	0.065	1.171	0.795–1.725	0.425

See Tables 1 and 2 for key.

Compared with the control cows, rbST-Zn–treated cows were significantly ($P = 0.007$) more likely to conceive during the LRP (OR, 1.281; 95% CI, 1.072 to 1.530; Table 4); thus, the estimated PP during the LRP for rbST-Zn–treated cows was 34.5%, which is 5.4% greater than that of the control cows (ie, 34.5% vs 29.1%). The PP during the LRP for the rbST-Zn–treated cows was greater than that for the control cows in 7 of the 9 studies evaluated and was significantly greater in 3 of those studies. Conversely, the rbST-Zn–treated cows were significantly ($P = 0.048$) less likely to conceive during the ERP than were the control cows (OR, 0.753; 95% CI, 0.568 to 0.997). The estimated PP during the ERP for rbST-Zn–treated cows was 70.6%, which is 5.5% less than that of the control cows (ie, 76.1% vs 70.6%). The PP during the ERP for rbST-Zn–treated cows was lower than that for the control cows in 4 of 6 studies evaluated and was significantly lower in 1

of those studies. The 2 studies[16,19] that had the greatest weights in the meta-analysis because of their large sample sizes had small and insignificant responses (–4.4% and 2.3%, respectively) in the PP during the ERP.

For 4 of 6 studies evaluated, the PP during the LRP and ERP could be evaluated separately for primiparous and multiparous cows. The PP during the LRP and ERP for primiparous cows did not differ significantly (P = 0.749) between cows that were and were not treated with rbST-Zn (OR, 1.049; 95% CI, 0.784 to 1.403; Table 4), but the PP during the LRP and ERP for multiparous cows was significantly (P = 0.006) lower for rbST-Zn–treated cows than that for control cows (OR, 0.641; 95% CI, 0.467 to 0.880). The estimated PP during the LRP and ERP for multiparous cows that were treated with rbST-Zn was 56.1%, whereas that for control cows was 66.6%, which represented a 10.5% decrease in the overall PP during the LRP and ERP for multiparous cows that were treated with rbST-Zn.

The incidence rate of fetal loss was calculated for 9 studies, and the incidence rates of fetal loss for primiparous and multiparous cows could be calculated for 2 of those studies.[16,17] Regardless of parity, the proportion of cows with fetal loss did not vary significantly between rbST-Zn–treated and control cows (Table 4). In 1 study,[17] the proportion of primiparous cows with fetal loss during an LRP of controlled breeding was significantly less for rbST-Zn–treated cows (4.8%) than that for control cows (15.8%). However, in the other study,[16] the proportion of primiparous cows with fetal loss during an ERP did not differ between cows that were and were not treated with rbST-Zn, and when the data from the 2 studies[16,17] were analyzed together, the proportion of primiparous cows with fetal loss did not differ significantly (P = 0.483) between rbST-Zn–treated and control cows (OR, 0.616; 95% CI, 0.159 to 2.384). The proportion of all cows with fetal loss in both studies[16,17] was 10.2%.

The incidence rate of twins could be calculated for only 2 studies. The proportion of cows that gave birth to twins did not vary significantly (P = 0.679) between cows that were and were not treated with rbST-Zn (OR, 1.107; 95% CI, 0.685 to 1.787; Table 4). The proportion of all cows that gave birth to twins in both studies was 6.7%.

The incidence rate of cystic ovaries was calculated for 3 studies. The proportion of cows that developed cystic ovaries did not differ significantly (P = 0.425) between cows that were and were not treated with rbST-Zn (OR, 1.171; 95% CI, 0.795 to 1.725; Table 4). The estimated mean incidence rate of cystic ovaries in rbST-Zn–treated cows was 7.5%, which was a nonsignificant increase of 1.0% from that for the control cows.

The number of days to pregnancy was calculated for 5 studies, and the number of days to pregnancy could be calculated separately for primiparous and multiparous cows for 2 of those studies. The mean response for days to pregnancy did not differ significantly between the rbST-Zn–treated and control cows across all parities or for primiparous or multiparous cows (Table 3). For the 5 studies evaluated in the meta-analysis, the number of days to pregnancy for rbST-Zn–treated cows was less than that for control cows in 3 studies and greater than that for control cows in 2 studies; however, in all 5 studies, the number of days to pregnancy did not differ significantly between rbST-Zn–treated and control cows.

The number of inseminations per pregnancy was calculated for 4 studies. The estimated mean number of inseminations per pregnancy did not differ significantly (P = 0.121) between cows that were and were not treated with rbST-Zn (mean difference ± SE, –0.25 ± 0.162 inseminations/pregnancy; 95% CI, –0.57 to 0.07 inseminations/pregnancy; Table 3).

Body condition—Body condition score data were available for 15 studies, and the test for heterogeneity of responses among the studies approached significance (P = 0.104; Table 2). The BCS data used in the meta-analysis consisted of the BCSs obtained during and after rbST-Zn administration. Cows treated with rbST-Zn had a significantly (P = 0.037) lower mean BCS than did the control cows (mean ± SE response, –0.064 ± 0.031 points; 95% CI, –0.124 to –0.004 points; Table 3).

Lameness—Data regarding the number of cows that were clinically lame, had lameness lesions, and had traumatic lesions were available for 7, 3, and 5 studies, respectively. The test for heterogeneity did not yield significant results for any of the 3 outcome variables (Table 2). The incidence rates for cows that were clinically lame, had lameness lesions, or had traumatic lesions did not vary significantly (P = 0.991) between cows that were and were not treated with rbST-Zn (Table 3).

Culling—The culling density could be calculated for 6 studies, and the results of the test for heterogeneity were not significant (Table 2). The culling density did not differ significantly (P = 0.341) between cows that were and were not treated with rbST-Zn (mean ± SE, 0.603 ± 0.633 cows culled/10,000 cow-days at risk; 95% CI, –0.637 to 1.018 cows culled/10,000 cow-days at risk; Table 3).

Discussion

Results of the present meta-analysis indicated that administration of the rbST-Zn formulation, which is commercially available to US producers, to lactating dairy cows in accordance with the FDA-approved label directions caused an increase in milk, fat, and protein yields with no significant or unmanageable adverse effects on milk composition (percentages of fat, protein, and lactose in milk), udder health, reproduction, body condition, lameness, or culling. These findings were consistent with those of various FDA evaluations,[63,64] scientific reviews,[4–9,65–67] and large-scale studies conducted on commercial dairy operations.[14–19,60] Findings of a meta-analysis[10] conducted by an expert panel identified by the CVMA at the request of Health Canada in the late 1990s (CVMA meta-analysis) suggested that, although rbST administration to lactating dairy cows caused an increase in milk yield, it had adverse effects on udder health, body condition, mobility, and longevity. The difference between the present meta-analysis and that performed by the CVMA may relate in part to the availability of additional studies that were conduct-

ed subsequent to the CVMA analysis. However, during the literature search for the present meta-analysis, several discrepancies were discovered among the studies evaluated in the CVMA meta-analysis,[10] including varying rbST formulations, doses, and administration routes and some data analyses errors (duplication, omissions, and miscoding) that could have also contributed to the conflicting findings between that meta-analysis[10] and the present one.

Results of the present meta-analysis indicated that mean daily milk and 3.5% FCM yields for rbST-Zn–treated cows increased 4.00 and 4.04 kg, respectively, compared with those for cows that were not treated with rbST-Zn (ie, control cows). This finding was consistent with those of other studies.[10,11,15] The investigators of the CVMA meta-analysis[10,11] reported that the mean daily 3.5% FCM yield was 4.4 to 4.7 kg greater for cows administered rbST versus control cows. Likewise, in a study[15] that involved > 80,000 dairy cows in 340 herds in the northeastern United States over an 8-year period, rbST-Zn administration resulted in an increase in the mean daily milk yield of 4 to 5 kg/cow. Results of other studies[65,66] also suggest that rbST administration increases milk production in cows of all breeds regardless of genetic merit and does not require that the cows be fed a special ration.

The composition of milk (percentages of fat, protein, and lactose in milk) produced by dairy cows varies naturally regardless of rbST-Zn administration and is affected by many factors including breed, genetic merit, stage of lactation, diet, environment, and season.[65,67,68] In the present meta-analysis, milk composition did not vary significantly between cows that were and were not treated with rbST-Zn. However, the mean daily yields of milk fat and protein of rbST-Zn–treated cows were increased 0.144 and 0.137 kg, respectively, from those of control cows. This increase in milk fat and protein yield is economically important because in many markets and countries, the price producers receive for milk is dependent on and positively associated with its fat and protein yields.

In the present meta-analysis, the risk of rbST-Zn–treated cows developing clinical mastitis did not differ significantly from that of control cows. The investigators of most of the studies evaluated in the present meta-analysis did not take mastitis-related variables into consideration when cows were assigned to either the rbST-Zn–treatment or control groups. In only 1 study[18] was the intramammary infection status of cows considered to ensure that the numbers of cows with and without intramammary infections assigned to the rbST-Zn–treatment and control groups were balanced. That study[18] was conducted in 4 well-managed, free-stall housed herds and involved 284 rbST-Zn–treated cows and 271 control cows. In that study,[18] no significant differences in the number of cows that developed clinical mastitis, number of days that milk was discarded because of mastitis, or number of cows culled because of mastitis were detected between cows that were and were not treated with rbST-Zn, despite the fact that the rbST-Zn–treated cows produced a mean of 2.9 kg/d (6.4 lb/d) more milk than did the control cows.

Across all studies, rbST-Zn–treated cows were significantly more likely to develop clinical mastitis than were control cows in only 4 of 14 studies evaluated. The results of the test for heterogeneity in the present meta-analysis suggested that the risk of clinical mastitis in cows among the studies evaluated was dependent on factors other than rbST-Zn administration. Factors associated with clinical mastitis in dairy cows include season, stage of lactation, and parity.[69] Unfortunately, the nature of the interactions among those factors could not be analyzed by means of meta-regression in the present analysis because of the limited number of studies evaluated, despite the large number of cows involved in those studies.

Investigators of multiple studies[70–73] have found a positive association between milk production and the incidence of clinical mastitis. In the present meta-analysis, the incidence rate of clinical mastitis did not differ significantly between cows that were and were not treated with rbST-Zn despite the fact that rbST-Zn–treated cows produced significantly more milk (mean, 4.0 kg/d) than did control cows. This finding supports the concept that the risk for development of clinical mastitis associated with increasing milk production can be compensated by improved management on modern commercial dairy operations.[18,69] Results of studies[74–76] conducted to investigate various factors associated with the risk of clinical mastitis on commercial dairy operations have led to a conclusion by the FDA Veterinary Medicine Advisory Committee[7] that, when examined on a per unit of milk basis, the increase in the incidence of clinical mastitis attributable to rbST-Zn administration (0.1 cases/cow/y) is approximately 4 to 9 times less than the increase in the incidence of clinical mastitis attributable to other factors such as season, parity, stage of lactation, and interherd variation.

The SCC in milk is an indicator of inflammation in the mammary gland, and the SCC will increase subsequent to both subclinical and clinical intramammary infections. During statistical analyses, a logarithmic transformation is routinely applied to milk SCC data to normalize its distribution, an important assumption that must be met for the performance of linear regression, and because milk production is negatively associated with logSCC.[77] Also, many government and milk procurement agencies throughout the world use the logSCC as a basis to determine regulatory actions and payment schemes. In the present meta-analysis, only logSCC data derived from randomized controlled trials were evaluated. Results from this meta-analysis indicated that the logSCC did not differ significantly between cows that were and were not treated with rbST-Zn, a finding that was consistent with that of an FDA report[78] regarding milk produced and sold during the period from 1995 through 2011. Additionally, during the period of that report,[78] the mean bulk-tank SCC decreased steadily and the percentage of milk tanker trucks with positive test results for antimicrobials decreased dramatically from those of previous years. Hence, the FDA concluded that the risk of increasing mastitis rates and SCCs associated with the use of rbST-Zn in lactating dairy cows appears to have been well managed by the US dairy industry.[78]

The present meta-analysis included the evaluation of reproductive data obtained from several studies that

were conducted after the CVMA meta-analysis[10] was performed. In the CVMA meta-analysis,[10] 38% more rbST-treated cows failed to conceive during an ERP, compared with the number of control cows that conceived during an ERP, a difference that was significant ($P < 0.01$). In the present meta-analysis, rbST-Zn–treated cows were 5.5% less likely to conceive than were control cows during an ERP. However, 5.4% more rbST-Zn–treated cows became pregnant during the LRP than did control cows. The decrease in the proportion of rbST-Zn–treated cows that became pregnant during an ERP, compared with that of control cows, is likely a consequence of suppressed estrous behavior in rbST-Zn–treated cows. Investigators of 1 study[17] found that the frequency of estrous detection in rbST-Zn–treated cows was significantly less than that in control cows, which meant that rbST-Zn–treated cows had fewer opportunities to be inseminated and conceive during an ERP than did control cows. Results of other studies[79–81] indicate that milk production is positively associated with the metabolism of the sex steroids estradiol and progesterone. Thus, as milk production increases (the primary and intended effect of rbST-Zn administration), the rates at which estradiol and progesterone are metabolized also increase, which in turn reduces estrous behavior in cows. Many commercial dairy operations routinely use various protocols during the early stages of lactation to control follicle development, corpus luteum regression, and time to ovulation so that AI can be scheduled to optimize the probability of conception. Those protocols ensure that all cows are inseminated within a prescribed number of days after parturition. Therefore, they are often only administered to cows for a predetermined time during the early stages of lactation, and for cows that fail to conceive during that period, management frequently resorts to estrous detection to identify cows for AI. The proportion of cows that failed to conceive in the CVMA meta-analysis[10,12] was significantly ($P = 0.04$) associated with the daily dose of rbST administered, a factor that did not have to be controlled for in the present meta-analysis because all rbST-Zn–treated cows were administered the same dose. The fact that the results of the present meta-analysis indicated that rbST-Zn–treated cows were significantly ($P = 0.007$) more likely to become pregnant during the LRP (ie, the period during which cows are generally enrolled in a timed AI protocol; OR, 1.281) than were control cows suggested that initiation of rbST-Zn administration did not impair, and might have a positive effect on, the reproductive performance of dairy cows during that period. This conclusion was further supported by the fact that rbST-Zn–treated cows had a lower, albeit insignificant, number of mean days to pregnancy and inseminations per pregnancy than did control cows in the present meta-analysis, which suggested that rbST-Zn–treated cows required fewer inseminations to become pregnant and thus became pregnant earlier during lactation than did control cows.

Investigators of a study[82] conducted to investigate the effects of rbST on ovarian function of dairy cows reported that rbST administration stimulated the pool of recruited follicles and reduced the period of follicle dominance. The CVMA expert panel[10,12] reported inconclusively that the incidence rate of twins in rbST-treated cows might be greater than that in control cows even though the results of their meta-analysis indicated that the incidence rate of twins did not differ significantly ($P = 0.26$) between cows that were and were not treated with rbST. The results of the present meta-analysis likewise indicated the incidence of twins did not differ significantly between cows that were and were not treated with rbST-Zn ($P = 0.679$).

In the present meta-analysis, the incidence rate of cystic ovaries did not differ significantly between rbST-Zn–treated cows and control cows. In the CVMA meta-analysis,[12] the incidence rate of cystic ovaries in rbST-treated cows was 1.7% greater than that in control cows, which was not significant, although the expert panel concluded that this finding was inconclusive evidence regarding the effect of rbST on the development of cystic ovaries. Given the results of the CVMA meta-analysis[12] and the present meta-analysis, it appears that rbST-Zn administration is not associated with ovulation failure and the development of cystic ovaries in dairy cows, a finding that was consistent with the results of another study[82] in which rbST-Zn treated cows had ovaries with healthy estrogen-active follicles.

In the CVMA meta-analysis[10,12] the only variable associated with body condition that was extracted from the studies evaluated was the BCS at the end of a treatment period that lasted ≥ 200 days. The mean BCS for rbST-treated cows following at least a 200-day treatment period was 0.2 points less than that for control cows.[10,12] It is important to note that the CVMA meta-analysis[10] included some studies with designs that did not adequately allow for changes in voluntary feed intake associated with an increase in milk yield; hence, the results of many of those studies suggest that rbST administration caused an increase in milk production and a decrease in BCS.

Although the BCSs for cows that were and were not treated with rbST-Zn were provided in many studies, the corresponding SEs for those BCSs were frequently not provided; consequently, that data could not be included in the present meta-analysis. Evaluation of the BCS data that were available indicated that the mean BCS for rbST-Zn–treated cows was < 0.1 point less than that for control cows, and even though this difference was significant, it would not be subjectively visible. When rbST administration to dairy cows was initially investigated, many researchers questioned whether rbST-treated cows would have to use extensive body reserves to support the increase in milk production and become excessively thin and emaciated. The results from the present meta-analysis suggested that this concern was unfounded. Results of other studies[9,65,83,84] suggest that the management of body condition does not differ between cows with similar levels of milk production that are and are not treated with rbST-Zn.

To better appreciate the clinically irrelevant, albeit significant, difference in BCS between rbST-Zn–treated cows and control cows identified in the present meta-analysis, the BCS response can be translated into body weight. Investigators of 1 study[85] reported that when the BCS of dairy cows is determined on a scale of 1 to 5, 1 point of BCS is equivalent to approximately 50 kg

(110 lb) of body weight. Other investigators[86] estimated that 1 point of BCS was equivalent to 35 to 44 kg (77 to 96.8 lb) of body weight in lactating cows, whereas still others[87] reported that 1 point of BCS was equivalent to 21.6 to 57 kg (47.5 to 125.4 lb) of body weight depending on many factors, including cow genotype and stage of lactation. If it is assumed that 1 point of BCS is equivalent to 50 kg of body weight, then the difference in mean body weight between the rbST-Zn–treated cows and control cows in this meta-analysis was 3.2 kg (7 lb), an amount less than the accuracy of most livestock scales and less than the mean change in body weight after a typical eating or drinking episode for a dairy cow. Additionally, the mean BCS for the rbST-Zn–treated cows in the present meta-analysis was within the industry-accepted range for individual high-producing cows in high-producing herds. In general, scientific reviews[65,67,68] and anecdotal reports from commercial dairy operations suggest that cows treated with rbST-Zn increase their voluntary feed intake to support the increase in milk production and thereby maintain adequate body reserves.

Lameness is defined as altered locomotion or mobility caused by a wide range of foot and leg disorders that result from disease, management, or environmental factors. In the present meta-analysis, only a small number of studies had sufficient reliable data for evaluation of lameness-related variables. Lameness data obtained from farm records are difficult to analyze and interpret because the nomenclature and abbreviations used within and among herds can be quite variable. The inconsistencies in the reporting of lameness data are likely the consequence of the fact that commonly used dairy record-keeping systems[b,c] did not offer a convenient or effective method to record lameness data until recently. Also, investigators of many studies who attempted to evaluate the effect of rbST-Zn on lameness frequently failed to distinguish between lesions of the integumentary system (ie, skin abrasions on the tibiotarsal or carpal regions) that are typically not the cause or result of lameness, except when cows are housed in poorly designed or bedded stalls,[88–92] and lesions directly associated with clinical lameness (eg, laminitis, sole ulcers, and digital dermatitis). In the CVMA meta-analysis,[10,12] lesions of the integumentary system were included as causes of lameness, and the results suggested that rbST-treated cows were 1.55 times as likely to develop lameness as were control cows (ie, the risk of developing lameness was 55% greater for rbST-treated cows than it was for control cows).

Of the 26 studies evaluated in the present meta-analysis, 7 contained data on the number of rbST-Zn–treated and control cows with clinical lameness, and lesions could be classified as those that directly cause lameness (eg, lameness lesions: laminitis, sole ulcers, and digital dermatitis) or those that are rarely a direct cause or result of clinical lameness (eg, traumatic lesions: mechanically induced skin lesions;) in only 3 and 5 studies, respectively. Two of the studies[16,45] evaluated had particularly rigorous protocols for assessing hoof lesions. In 1 study,[45] each of 94 rbST-Zn–treated cows from 8 herds were matched with 1 control cow on the basis of herd, parity, age, and stage of lactation. During a single herd visit, 2 investigators individually and simultaneously evaluated the gait of each rbST-Zn–treated cow and control cow on a scale of 0 to 3 (0 = no visible gait abnormality and no reluctance to walk [ie, normal gait]; 1 = mild gait abnormality or variation from normal gait at a walk; 2 = moderate and consistent gait asymmetry or symmetric gait abnormality and cow able to walk without continuous stimulation; 3 = severe gait abnormality with marked gait asymmetry or severe symmetric abnormality), and then they visually inspected and palpated the limbs of each cow.[45] Cows that were assigned a score of 2 or 3 by at least 1 of the 2 investigators were considered clinically lame.[45] Investigators categorized lesions by location, type, and severity; however, they did not lift the feet to examine for sole lesions.[45] In the other study[16] that involved 28 commercial dairy operations located in 4 regions of the United States and 1,128 cows (419 primiparous cows and 709 multiparous cows), health variables for rbST-Zn–treated and control cows were monitored for an entire lactation. On each operation, a farm employee recorded which cows were lame and the lesions observed in those cows.[16] The herd veterinarian would categorize all the lesions recorded by the farm employee, then examine the affected cows and record any additional lesions.[16] We used the data recorded by the herd veterinarians for the present meta-analysis because we believed it was the most robust and accurate.

Sole ulcers, white line disease, and traumatic lesions of the sole such as puncture by a nail or other sharp object and excessive wear that results in thinning of the sole surface are common causes of lameness in dairy cows.[93,94] Infectious skin lesions such as interdigital phlegmon (ie, foot rot) and digital dermatitis (ie, hairy heel warts) can also cause clinical lameness in dairy cows.[95] Approximately 6% to 10% of clinically lame dairy cows have disorders of the upper portion of the limbs (ie, proximal to the feet or hooves), which are typically caused by trauma from slips or falls, infectious disease (eg, septic arthritis), or congenital, heritable, or developmental disorders.[93,94] Laminitis or lesions associated with damage or weakening of the suspensory apparatus of the third phalanx are associated with metabolic anomalies such as rumen acidosis, abnormal or inappropriate activation of metalloproteinase enzymes, and peripartum hormonal changes.[95,96] Research[97,98] results suggest that cow comfort (ie, extent of adequate and comfortable space for lying and appropriate footing to avoid slipping and falling) during the peripartum period has a substantial effect on whether cows develop hoof lesions in the later stages of lactation. Dairy cows that are clinically lame also tend to have poor body condition, which was generally assumed to be a consequence of decreased feed intake. Although it is certainly plausible that lame cows forego eating to lie down or otherwise alleviate the discomfort caused by the lameness, investigators of 1 study[99] reported a significant positive association between body condition and the thickness of the digital cushion of dairy cows, whereby underconditioned cows had thin digital cushions, which predisposed them to the development of sole ulcers and white line disease. The results of the present meta-analysis indicated that the risk of devel-

oping clinical lameness, lameness lesions, or traumatic lesions (regardless of the cause) did not differ significantly between cows that were and were not treated with rbST-Zn, which indicated that rbST-Zn administration in accordance with label directions does not increase the risk of lameness for dairy cows.

Several of the studies used to evaluate culling density in the present meta-analysis were conducted after the CVMA meta-analysis[10] was performed. Results of the present meta-analysis indicated that the culling density between cows that were and were not treated with rbST-Zn did not differ significantly ($P = 0.34$). Of the 6 studies evaluated, the culling density for rbST-Zn–treated cows was numerically greater than that for control cows in 4 studies and less than that for control cows in 2 studies. The findings of the present meta-analysis regarding culling density corroborate those of a large longitudinal field study[15] that was conducted over 4 years on 340 commercial dairy herds in the northeastern United States in which rbST-Zn administration had no effect on stayability or herd-life.

Culling rate is often used incorrectly as an indicator of the quality of the production system and management. Because there is generally a cost associated with the replacement of a cow, it is assumed that there should be an economic advantage to decrease the culling rate. However, this assumption is incorrect because the replacement cow generally has a greater genetic ability than does the cow being replaced.[100] The optimal culling rate increases when there is a relative abundance of replacement cows and the cost of a replacement cow is similar to the slaughter value of the cow being replaced.

Results of the present meta-analysis and the CVMA meta-analysis[10–12] were in agreement that administration of rbST to dairy cows causes an increase in milk yield. However, contrary to the CVMA meta-analysis,[10–12] the results of the present meta-analysis found no evidence that the rbST-Zn formulation commercially available to US producers administered to lactating dairy cows in accordance with the FDA-approved label had any unmanageable adverse effects on milk composition, udder health, reproduction, body condition, lameness, or longevity. The general lack of evidence that rbST-Zn administration adversely affects the health and welfare of dairy cows in the present meta-analysis is consistent with the findings of the FDA and anecdotal reports regarding the use of rbST-Zn in > 35 million US dairy cows over 20 years. Collectively, these results provide definitive evidence that current management practices implemented by US dairy producers and veterinarians are adequate for the safe and effective commercial use of rbST-Zn.

a. Posilac, Elanco Animal Health, Indianapolis, Ind.
b. National Dairy Herd Information Association, Verona, Wis.
c. Dairy Comp 305, Valley Agricultural Software, Tulare, Calif.

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