

AN UPDATE ON rbST - HUMAN SAFETY AND ANIMAL EFFICIENCY AND WELFARE

D. E. Bauman¹ and R. J. Collier²

¹Cornell University and ²The University of Arizona

INTRODUCTION

Recombinant bovine somatotropin (rbST), the first recombinant protein approved for use in production animals, has 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). It has been 20 years since the introduction of rbST (POSILAC ®) into the dairy industry of several countries, and to date in the US an estimated 35 million dairy cows have received Posilac supplements, the commercial formulation of rbST (personal communication, R. Cady, Elanco).

Recently, two studies were conducted to update the evaluation of the human safety and animal performance and welfare literature published since the approval of rbST, (Collier and Bauman, 2014; St Pierre et al. 2014). The following is a synopsis of those papers.

HUMAN SAFETY

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee administrated jointly by FAO of the United Nations and the World Health Organization. JECFA reviewed the human safety of rbST at their 40th conference in 1993 and the 50th conference in 1998 and concluded both times that "the lack of oral activity of rbSTs and insulin-like growth factor I (IGF-1) and the low levels and non-toxic nature of the residues of these compounds, even at exaggerated doses, results in an extremely large margin of safety for humans consuming dairy products from rbST-treated cows." Based on this the committee concluded that there was no need to establish an "acceptable daily intake" or "minimum residue levels", and that the use of rbST "does not represent a hazard to human health" (JECFA, 1993; JECFA, 1998). In early 2013 JECFA announced that they would be re-evaluating rbST at the 78th JECFA Conference and requested new data and information related to human health and the use of rbST. Listed topics of particular interest were: the possible increased use of antibiotics to treat mastitis in cows; possibility of increased levels of IGF1 in the milk of cows treated with rbST; potential effects of rbST on the expression of certain viruses in cattle; and possibility that exposure of human neonates and young children to milk from rbST-treated cows increases health risks, for example development of insulin-dependent diabetes mellitus.

Milk Antibiotic Residues

Antibiotics are used by the dairy industry to treat mastitis, and residues occur when the milk is saved before the antibiotics have fully cleared. Major factors affecting the incidence of mastitis are related to environmental conditions and management practices. There is also a small increase in mastitis incidence, expressed on a per cow basis, as milk production increases, and FDA concluded that the use of rbST was also associated with an increase in the relative risk of mastitis. The 50th JECFA Conference also evaluated the relationship between rbST use and the potential for milk antibiotic residues. They concluded “that the use of rbST will not result in a higher risk to human health due to the use of antibiotics to treat mastitis and that the increased potential for drug residues in milk could be managed by practices currently in use by the dairy industry and by following label directions for use” (JECFA, 1998). The following represents results from commercial use in the US and related scientific publications since the 50th JECFA.

The national data summary of milk antibiotic residue violations provides some insight on the potential impact of rbST use. The National Milk Drug Residue Data Base (NMDRD) is a voluntary industry reporting program but State Regulatory Agencies report all data received to the National Conference on Interstate Milk Shipments (NCIMS; (<http://www.ncims.org/>)). The system includes all milk, Grade “A” and non-Grade “A”, commonly known as manufacturing grade. Grade A milk represents approximately 95% of the US milk supply and is regulated through the NCIMS by the State Regulatory Agencies. Manufacturing grade milk is under the direction of the Regulatory Agencies in States where it is produced. In 1995 the industry testing program switched to a more sensitive test for antibiotics and there are continuing efforts to ensure uniform and accurate reporting of drugs and test methods among States.

The pattern of milk antibiotic residue violations for the US dairy industry from 1995 to 2012 is shown in Figure 1 (adapted from NMDRD, 2013). The percent of bulk milk tank trucks testing positive for antibiotic residues has steadily declined since 1996 and in 2012 was less than one-fifth of the level detected in 1995 (0.100% in 1995 versus 0.017% in 2012). Thus, there is no evidence of increased human risk for exposure to milk antibiotic residues related to the use of rbST in the U.S. dairy industry over the last 18 years.

Milk somatic cell count (SCC) is a measure of milk quality and a reflection of mammary health. SCC refers to the number of white blood cells, secretory cells, and squamous cells per milliliter of raw milk. Somatic cells from an infected quarter of the udder are present in milk at much higher numbers and these are predominately leukocytes or white blood cells including neutrophils (major form), macrophages and lymphocytes. Thus, SCC values provide insight related to milk quality and subclinical mastitis.

The USDA's Animal and Plant Health Inspection Service Centers for Epidemiology and Animal Health, in collaboration with USDA's Agricultural Marketing Service and the National Mastitis Council's Milk Quality Monitoring Committee, monitor the US milk quality using bulk-tank somatic cell count (BTSCC) data provided by 4 of the Nation's 10 Federal Milk Marketing Orders.

As reported by Collier and Bauman (2014), the US pattern for milk BTSCC declined steadily from 316,000 cells per mL of milk in 2001 to 224,000 cells/mL in 2010 and 206,000 cells/mL in 2011 (USDA, 2013). Thus, there is no evidence for an increase in the SCC for the US dairy herd over the interval of POSILAC use. Rather, the decline in SCC over the last decade indicates an improvement in milk quality and mammary health. van Schiak et al. (2002) demonstrated that "high SCC is a generic predictor of poor milk quality." Herds with 200,000 cells per ml of milk or less had the lowest incidence of antibiotic residues. Therefore, the inference from SCC data over the last 15 years is that the potential human threat from milk antibiotic residues has declined dramatically.

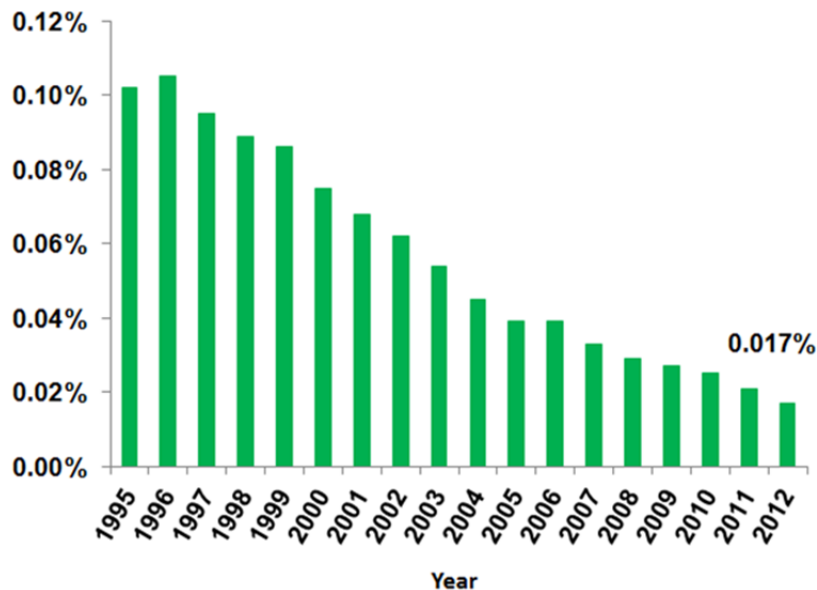


Figure 1. Percent of Bulk Milk Tankers Positive for Antibiotic Residues – 1995 to 2012

Insulin-like Growth Factors in Milk

The 50th Conference Report (JEFCA, 1998) concluded "that any increase of IGF-I in milk from rbST-treated cows is orders of magnitude lower than the physiological amounts produced in the gastrointestinal tract as well as in other parts of the body". The report further concluded that "the intake of IGF-I (from milk) will not increase either locally in the gut or systemically. Consequently, the potential for IGF-I to promote tumor growth will not increase when milk from rbST-treated cows is consumed, resulting in no appreciable risk for consumers" (JECFA, 1998).

Since the 1998 JECFA Report, the absorption of orally consumed IGF-I has been directly examined in humans, specifically premature neonates and young adults; results are convincing and provide no evidence that orally consumed IGF-I is absorbed in humans (Mero et al., 2002; Corpeleijn et al., 2008). IGF-I plays many important roles and almost every tissue in the body synthesizes IGF-I. While the IGF system is critical for normal growth and development, it can also play a key role in the survival and growth of malignant cells. Although outside the purview of this report, there has been a related interest in the possible role of milk consumption on the risk for various types of cancers. Milk is known to contain a number of components which have anticarcinogenic effects when tested in studies with animal biomedical models (e.g. Parodi, 2007). Likewise, epidemiology studies indicate that the consumption of milk and dairy products reduces the risk against many types of cancer including bladder, breast, and colon cancers (e.g. reviews by Kliem and Givens, 2011; Rice et al., 2013). An exception is prostate cancer where an overview of studies suggests a very modest positive association between milk consumption and the risk of prostate cancer; several mechanisms to explain this effect are being actively investigated (see review by Parodi, 2009). Overall, results since the 50th JECFA have provided additional evidence of the minimal effects of rbST on milk concentrations of IGF-I and further demonstrated a lack of absorption of orally consumed IGF-I in premature neonates and young adults.

Bovine Somatotropin and Viruses

The 1998 JECFA Conference concluded that there was no evidence that rbST affects the expression of BLV, a lentivirus, based on studies with a goat model that used caprine arthritis encephalitis virus. They also noted that BLV was destroyed by simulated pasteurization conditions when milk is heated to 60°C for 30 seconds and that there was no evidence of human susceptibility to ruminant retroviruses (JECFA, 1998). No new information on effect of rbST on expression of retroviruses in ruminants has been published since the 1998 Conference. However, several new research models have been developed to study retroviruses (see review by El Hajj et al., 2012) which may provide additional information in the future. The important role of somatotropin in the immune system has been clearly established (see review by Kelley et al., 2007). Additionally, research has demonstrated that human somatotropin increases immune system function in HIV infected people (e.g. Napolitano et al., 2008; Tesselaar and Miedema, 2008) and somatotropin administration to chickens increased resistance to Marek's virus (Liu et al., 2001). Overall, there is no evidence of increased expression of retroviruses in cattle treated with rbST or that retroviruses in cattle would pose a risk to human health.

Bovine Somatotropin and Diabetes Risk

Nutrients derived from the consumption of milk are important for normal growth and development in children, and in health maintenance and a reduction in risk for chronic diseases in adults. Past research on insulin-dependent diabetes mellitus has focused on diet and the concept that early introduction of complex foreign proteins might be a risk factor for β -cell autoimmunity thereby leading to Type 1 diabetes. Some reports

suggested early infant exposure to cow's milk protein was a predisposing factor that might increase the risk of Type 1 diabetes, whereas other observations found no causality. Nevertheless, the 1998 Conference concluded that the use of rbST would not impact the risk of Type1 diabetes because milk composition is unaltered (JECFA, 1998).

Milk protein was a major research focus in early work, but to date no specific dietary factor or food component has been shown to be an unequivocal risk factor for β -cell autoimmunity. Rather, recent research has suggested a much broader range of putative mechanisms in genetically susceptible individuals. Examples of purposed putative mechanisms include viral, microbial, diet-related, anthropometric and psychosocial factors (e.g. see reviews by Eringsmark et al., 2013; Pugliese, 2013). Overall, our review found no new data suggesting increased health risks in children or adults consuming milk and dairy products from rbST-supplemented cows. Milk composition is affected by many factors including genetics, stage of lactation, breed, diet, environment, and season, and these factors affect milk composition in an identical manner in rbST-supplemented cows (Bauman, 1992).

In addition to providing essential nutrients, there is increasing recognition that consumption of milk and dairy products is associated with improvement in health maintenance and the prevention of chronic diseases. Chronic diseases where a moderate health benefit is observed from the consumption of milk and dairy products include a reduced risk of Type 2 diabetes, improved bone health, lower blood pressure, and reduced risk of cardiovascular disease (e.g. see summaries in Elwood et al., 2008; Kliem and Givens, 2011; Rice et al., 2013). Given the composition of milk is not altered by the use of rbST, the beneficial effects of dairy products on health maintenance and reductions in risk of chronic diseases should not be affected.

ANIMAL EFFICIENCY AND WELFARE

In order to update the evaluation of the safety and efficiency of rbST-Zn an expert panel made up of a data manager and project coordinator, a professional statistician, and six domain experts was assembled (St. Pierre et al., 2014). The evaluation involved a set of meta-analyses using peer-reviewed research data from scientific publications or regulatory agency reports where rbST-Zn was used according to label. Data from studies involving off-label use of rbST-Zn or studies that used unapproved formulations of rbST were excluded. The data were collected for the meta-analysis in the following manner. An extensive literature search was conducted on PubMed (U.S. National Library of Medicine, U.S. National Institute of Health, Bethesda, MD), Agricola (National Agriculture Library, U.S. Department of Agriculture, Beltsville, MD), Web of Science (Thomson Reuters Science, New York, NY), and CAB Direct (CAB International, Wallingford, UK) using the following combination of search terms: bST, rbST, sometribove, sometribove zinc, Posilac, bovine somatotropin or bovine growth hormone. Potential studies were identified and abstracts were obtained. All studies that were not conducted using rbST-Zn 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 their corresponding full papers were obtained. Twenty-six studies met the criteria and data were drawn from them to form a meta-database. 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.

Milk Yield and Composition

Seven variables were analyzed to characterize the 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 affect the magnitude of the response.

Results indicated that yield of milk and milk components were all increased by rbST. Milk yield (+4.00 kg/d) and 3.5% fat corrected milk (+4.04 kg/d) were increased by about 15% over unsupplemented 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 (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 0.144 and 0.137 kg/d, respectively.

Udder Health

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 supplements ($P = 0.540$; Table 1). Likewise, the mastitis incidence rate was not different between the control and rbST-supplemented groups ($P < 0.122$; Table 2). Environmental and management factors are the major causes of mastitis. 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 (Hogan and Smith, 2012).

Body Condition

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 BCSs obtained during and after rbST administration. Cows treated with rbST had a significantly ($P = 0.037$) lower mean BCS than did the control cows with the difference being -0.064 ± 0.031 points (mean \pm SE; Table 1). Published studies indicate that 1 unit of BCS represents about 50 kg body weight, so the difference in BCS for the rbST treated cows represents about 3.2 kg. While significant, this difference would not be visually detected and is about equivalent

to the change in body weight associated with a typical feeding or drinking episode for a dairy cow.

Lameness

Data regarding the number of cows that were clinically lame are presented in Table 1. Where possible the data regarding foot lesions were 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) (Shearer et al., 2012). The test for heterogeneity was not significant for any of the 3 outcome variables ($P = 0.999$). 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-Zn ($P = 0.991$; Table 1).

Table 1. Estimates of responses to rbST and associated statistics from the meta-analyses of continuous traits¹.

Variables	Number of Studies	Mean of Control Cows	Response Estimate	Standard Error of Estimate	<i>P</i> Value	95% Lower CL ⁵	95% Upper CL
Milk Production and composition							
Milk yield (kg/d)	15	27.2	4.00	0.404	<0.001	3.21	4.79
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 (kg/d)	13	29.2	4.04	0.410	<0.001	3.24	4.84
Fat yield (kg/d)	13	1.08	0.144	0.021	<0.001	0.104	0.185
Protein yield (kg/d)	13	0.86	0.137	0.018	<0.001	0.101	0.173
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 ⁶	-0.034	0.055	0.540	-0.141	0.074
Lameness and lesions							
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 ³	15	3.31	-0.064	0.031	0.037	-0.124	-0.004
Culling							
Culling density ⁴	6	4.64	0.603	0.633	0.341	-0.637	1.018

¹From St. Pierre et al. (2014).

²Expressed as incidence rate per 1,000 cow-days at risk.

³Body condition score is expressed on a 1 to 5 scale, with 5 being severely over-conditioned.

⁴Culling density is expressed as incidence rate per 10,000 cow-days at risk.

⁵CL = confidence limit.

⁶Log₁₀ somatic cell count of 4399 = 97,734 somatic cells/mL.

Reproduction

A significant 5.4% improvement in pregnancy proportion was observed 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 ($P < 0.048$; Table 2), a reduction that was likely due to reduced estrous behavior. There was no effect of rbST on fetal loss, days open, services per conception, twinning, or cystic ovaries, Tables 1 and 2.

Table 2. Estimates of responses to rbST expressed as odds ratios and associated statistics from the meta-analyses of non-continuous traits¹.

Variables	Rate of Control Cows	Estimates of Odds Ratio	<i>P</i> Value	95% Lower CL ⁴	95% Upper CL
Reproduction, all parities					
Pregnancy rate in LRP ²	0.291	1.281	0.007	1.072	1.530
Pregnancy rate in ERP ³	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

¹From St. Pierre et al. 2014

²Limited response period (first and second AI inseminations).

³Extended response period (full duration of the trial).

⁴CL = confidence limit.

Summary of Meta-Analysis

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 in milk), udder health, reproduction, body condition, lameness, or culling. These findings are contrary to a meta-analysis commissioned by Health Canada (Dohoo et al., 2003), but are in line with conclusions of various FDA evaluations (US FDA, 2014a; US FDA 2014b), numerous scientific reviews (e.g. Crooker et al., 1991; Bauman, 1992), and large-scale studies conducted on commercial dairy operations (e.g. Ruegg et al. 1998; Bauman et al., 1999; Collier et al. 2001).

CONCLUSIONS

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 rbST in the US provides the backdrop for an updated review of the outcome of use on human safety and animal efficacy and welfare. A review of recent advancements in scientific knowledge confirms earlier conclusions and provides no evidence of possible human health issues related to the use of rbST by the dairy

industry. In the case of animal well-being, results indicated that rbST-Zn administration to dairy cows effectively increases milk production with no adverse effects on cow well-being. Overall, these results and 20 years' experience demonstrate that commercial use of rbST by dairy producers is safe, effective, and allows for the production of wholesome dairy products.

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