# ARCHIVED - Report of the Canadian Veterinary Medical Association Expert Panel on rbST

November 1998

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* Published material not available in HTML format; for information contact Hank Schriel at (613) 957-3051.

# Executive Summary

At Health Canada's request, the Canadian Veterinary Medical Association (CVMA) established an Expert Panel to review the issues of the efficacy and safety of recombinant bovine somatotropin (rbST). The Panel was formed in March, 1998 and had expertise in epidemiology (Dr. Ian Dohoo - Chair), dairy health management (Dr. Luc DesCôteaux, Dr. Ken Leslie and Dr. Wayne Shewfelt), dairy nutrition (Dr. Alan Fredeen), livestock management and animal welfare (Dr. Allan Preston) and clinical pharmacology/large animal internal medicine (Dr. Patricia Dowling). The Panel operated completely independently from Health Canada and the CVMA.

The Panel reviewed material provided by Health Canada from Monsanto's submission to have rbST (sometribove) approved for use in Canada and carried out an extensive review of the published literature on the subject. While studies based on Monsanto's product and other companies' products were all considered, emphasis was placed on the former. The review process focused on studies which measured clinically relevant outcomes. The effects of rbST were assessed in the following main areas: milk yield, milk composition, nutritional implications, body condition, udder health, reproduction, lameness, other health concerns, culling and animal welfare. Within each area, key measures of effect (eg. 3.5% fat-corrected-milk for milk yield) were identified and all data from the literature review were extracted. These data were summarized in one or more meta-analyses to generate overall estimates of effect. Other related, but less commonly reported, measures of effect were also considered in a more subjective manner. If a detrimental effect was observed, the Panel discussed whether or not current dairy health management practices were adequate to control or eliminate the effect. Finally, the Panel

discussed whether or not additional information was required in order to adequately assess the effects of rbST.

The Panel concluded that rbST does increase milk yield (3.5% FCM) by an average of 11.3% in primiparous cows and 15.6% in multiparous cows. There was considerable variation in the response between studies but all but one study reported a positive effect. There was evidence of a very small increase in the butterfat content (% fat) in the milk and in the protein content (% protein) in multiparous cows but the magnitude of the effects was too small to be of any consequence.

Treatment with rbST reduced the body condition of cows and although treated cows consistently increased their dry matter intake during the treatment period and on into the subsequent lactation, this did not appear adequate to offset the increased energy output associated with the higher yield. Consequently, treated cows started their next lactation in lower body condition than untreated cows.

Use of rbST increased the risk of clinical mastitis by approximately 25%. It appeared that there was also a slight increase in the prevalence of subclinical intramammary infections at the end of the treatment period. The Panel felt that while current dairy health management techniques could reduce this increased risk, they are not adequate to eliminate it. When the expected number of extra cases of mastitis was computed on a "per litre of milk shipped"basis, the increase was approximately 10%. Given this relatively small increase and the current programs for ensuring that antibiotic residues are not present in milk sold for human consumption, the Panel felt that the risk of increased antibiotic residues in dairy products was very small.

There were a number of effects on reproductive performance that were associated with the use of rbST. These included a substantial increase in the risk of non-pregnancy and a slight increase in days open in cows that do conceive. There was also inconclusive evidence of increased risks of cystic ovaries and twinning (multiple births). These adverse effects could be controlled by delaying use of the drug until cows were confirmed pregnant. There was some limited evidence of an increased risk of retained placenta and abortion/fetal loss in treated cows but there were insufficient data to draw a firm conclusion about these potential effects.

Treated cows experienced approximately a 50% increase in the risk of clinical lameness. Many of the lameness cases involved fore and hind limb joints. The Panel felt that current health management practices were not able to eliminate this increased risk.

Use of rbST reduced the risk of ketosis and some other metabolic diseases in the postpartum period in the lactation following one in which rbST had been used. This was probably due to a combination of the reduced body condition of cows at calving at the start of the next lactation and the higher levels of dry matter intake in the subsequent postpartum period.

Treated cows were at higher risk of being culled. This was particularly true in multiparous cows. Most of the data on culling did not include removal for reproductive reasons so the increased risk of non-pregnancy would exacerbate this problem in commercial dairy herds.

The Panel felt that there were a number of legitimate animal welfare concerns associated with the use of rbST. These included an increased risk of clinical mastitis and lameness, and a reduction in the lifespan of treated cows. Without better data on the frequency and severity of injection site reactions, the Panel could not determine if these represented a significant animal welfare concern.

In general, the Panel felt that there were sufficient data available to make a reasonably informed assessment of the effects of rbST. There were four specific conditions (risk of cystic ovaries, twinning, retained placenta, and abortion/fetal loss) for which there appeared to be an effect associated with the use of the drug, but for which there was insufficient evidence to draw firm conclusions. There was also insufficient information to determine how frequently injection site reactions occur. If the product is approved for sale, more information will be required about the nature of the increased risk of mastitis and lameness in order to manage those problems as effectively as possible.

# 1. Mandate

The mandate of the CVMA Expert Panel on rbST, as provided by Health Canada, was to:

- Review the scientific data used by the Bureau of Veterinary Drugs to determine that Nutrilac (rbST) when used in accordance with its label directions will increase milk production without resulting in serious health problems which cannot be adequately controlled by current cattle management practices.
- Make observations and recommendations regarding the adequacy of the scientific data submitted by the manufacturer of Nutrilac (rbST) or existing elsewhere to make sound scientific assessments regarding the product efficacy and animal health risks associated with the use of Nutrilac (rbST) in Canadian dairy cattle.

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January 1999

## CVMA Expert Panel on rbST

We submit the following report to Health Canada to assist them in their evaluation of Monsanto's submission requesting the licencing of Nutrilac (rbST).

- Dr. Luc DesCôteaux
- Dr. Ian Dohoo (Chair)
- Dr. Patricia Dowling

- Dr. Alan Fredeen
- Dr. Ken Leslie
- Dr. Allan Preston
- Dr. Wayne Shewfelt

# 2. Committee Process

## 2.1 Selection of Panel

The Canadian Veterinary Medical Association (CVMA) accepted a request from Health Canada to establish an expert panel to review the Animal Safety and Efficacy of rbST. The CVMA's sole responsibility was to recruit appropriate expertise for the panel. A panel chair with expertise in epidemiology, Dr. Ian Dohoo, was selected in February 1998. During March of 1998 panel members with expertise in dairy health management (Dr. Ken Leslie, Dr. Luc DesCôteaux, Dr. Wayne Shewfelt), dairy nutrition (Dr. Alan Fredeen), livestock management and animal welfare (Dr. Allan Preston), and clinical pharmacology (Dr. Patricia Dowling) were recruited for the Panel. A brief description of the background of each Panel member is included in Appendix 1.

The CVMA council reviewed the Chair's recommendations for panel membership and approved the composition of the Panel in late March, 1998. All Panel members served without any remuneration.

## 2.2 Conflict of Interest Screening

The CVMA distributed to all Panel members copies of the Health Canada policy on conflict of interest along with the conflict of interest declaration form. The CVMA compiled the complete package of conflict of interest declaration forms and forwarded them to Health Canada who was responsible for reviewing the declarations and determining that no Panel members had conflicts of interest. The issue of conflicts of interest was also reviewed with all Panel members at the first meeting of the Panel on May 1, 1998.

## 2.3 Operation of Panel

Once established, the Panel operated independently from CVMA and from Health Canada. The obligation of the Panel was to prepare a report for Health Canada with a target date of October 31. Operational support for the Panel was provided by Health Canada in terms of setting up meetings and covering Panel members expenses. In addition, a technical assistant (veterinary summer student-Ms. Nicole Schaeffer) was hired by Health Canada to assist with some of the information management tasks for the Panel.

### 2.3.1 Panel Meetings

The first meeting of the Panel was held on May 1 in Ottawa. Dr.'s Dohoo, DesCôteaux, Leslie, Preston, and Shewfelt were present in person and Dr. Dowling and Dr. Fredeen participated for part of the meeting by conference call. The major items of discussion and decisions arising from that meeting were as follows.

- Panel members were reminded of the need to completely divulge any real or perceived conflicts of interest.
- The Panel reviewed and accepted the mandate as presented with the note that animal welfare was to be considered within the heading of animal safety.
- The Panel agreed that a press kit should be prepared for distribution to interested media but that further questions or requests for information should be forwarded to the Panel chair.
- The Panel spent considerable time developing a complete list of issues to be considered in a review of the literature and this complete list is presented in section 3.8 of this report. The Panel agreed that they would consider all information provided by Health Canada from the Monsanto submission as well as information obtained from a search of the peer reviewed scientific literature.
- The panel agreed that conclusions would be based primarily on information derived from studies involving the Monsanto product (Nutrilac). However, studies conducted using other rbST preparations would also be considered.
- A number of administrative and procedural matters were discussed.

The Panel held a conference call on May 21 with all members except Dr.'s Dowling and Shewfelt participating. The major issues and decisions from that meeting were as follows.

- The Panel discussed a number of requests for information which it had received. The Panel agreed to identify working groups of two, three, or four people within the Panel to address each of the major subject areas (efficacy, udder health, reproduction, feet and legs, general health, culling, drug interactions, nutritional implications, body condition score, and animal welfare).
- Considerable discussion of the literature review process was held.

The Panel held an in-person meeting on July 9 with all members except Dr. Fredeen present. Specific points covered in the meeting were as follows.

- Considerable time was spent reviewing the list of references retrieved from the published literature or identified in Monsanto's submission data (provided by Health Canada).

- There was considerable discussion about the mechanism for summarizing information from the multiple studies and the process for extracting relevant data.
- The structure of the report was discussed and the Panel agreed on a draft structure for the report.
- A reduced list of key outcome measures in each of the major categories was agreed to. This list of key outcome measures is presented in section 3.7 of this report.

In early September, the various working groups within the Panel held a series of conference calls to discuss the preliminary finding in each of the major subject areas. This process was also used to identified deficiencies in the data retrieval process and identify areas in which additional preparatory work needed to be done.

The Panel held an in-person meeting in Montreal on October 5th with all members except Dr. Dowling present. At that meeting all of the results from the literature review data extraction and data summarization process were reviewed and the major conclusions of the Panel were determined.

Subsequent to that meeting, multiple draft versions of the report were circulated amongst Panel members for comment and revision.

The Panel held a final conference call meeting on November 16th . At that meeting the final wording of all sections of the report was agreed to.

## 2.4 Materials provided by Health Canada

Over the time period in which the Panel carried out its work, Health Canada provided information from several sources. In general this information included:

- reports of studies carried out by Monsanto (submitted to Health Canada as part of Monsanto's submission)
- reports from Monsanto summarizing various aspects f the effects of rbST
- additional documentation from the published literature (and other relevant sources) that was pertinent to the submission
- summaries of Health Canada's evaluation of various aspects of the submission

The material provided was extensive and it filled over 15 large binders.

The Panel made a decision that it would focus its efforts on reviewing results from original studies rather than concentrating on summary reports produced by either Monsanto or Health Canada scientists. Consequently, we focussed on reports of original studies derived from both the submission and the published literature.

# 3. Review Process

## 3.1 Considerations in Defining the Process

A number of factors needed to be considered in determining what review process the Panel would follow.

- It was recognized that the Panel had a very broad mandate that dealt with both efficacy and animal health issues. In the animal health area there were many possible effects which needed to be considered and amongst these was the potential impact of the use of the drug on animal welfare. Consequently the Panel needed to consider many possible outcome measures in their review process.

- It was recognized that there was considerable evidence as to the effects of rbST that would be available from both the Monsanto submission to Health Canada, and in the peer reviewed published literature. The latter would include studies based on the Monsanto product (sometribove) and other rbST formulations from other manufactures. It was felt that, although it was necessary to focus on data obtained from studies involving sometribove, the results of other studies should be considered as well.

- While studies that were reported in the submission or the published literature would each have a primary outcome (usually related to efficacy), most studies would have additional data on other outcomes (e.g. health effects). However these results would not necessarily be reported in a standardized manner across studies.

Consequently the Panel recognized that there would be a need to have a process that would enable us to combine information from multiple studies. This need to combine information across studies is described in more detail in section 3.2. Three possible approaches to combing information were considered and these are described in sections 3.3 - 3.5.

## 3.2 The Need to Combine Data

While many studies of rbST have been carried out, most of the studies had small or moderate sample sizes (less than 100 cows). While a study of this size may be adequate to evaluate some of the major production effects of rbST, it would have insufficient power to detect either beneficial or harmful health effects associated with the use of the drug.

The power of a study is defined as the probability of finding a statistically significant effect if, in fact, a true effect of a defined magnitude is present. Studies with insufficient power may not detect important effects associated with the use of a drug. The power of a study depends upon:

- The magnitude of the difference between the treated and control cows in the effect of interest.
- The sample size of the study (i.e. number of cows)
- The variability (expressed as standard deviation or variance) in the response among cows in each study group (i.e. treated and control groups).

For example, the sample required to be reasonably sure (power = 80%) of detecting a significant effect of the drug on milk production under the following assumptions:

- true (but unknown) effect of drug = 4 kg increase in milk production
- between cow standard deviation = 4 kg

would be 16 cows in each of the treated and control groups.([1])

However, the same study would require over 700 cows in each group if the objective was to identify a 25% increase in risk of clinical mastitis ( e.g. from 28% of cows affected to 35%). In general, much larger sample sizes are required to detect drug effects on parameters measured on a dichotomous scale (e.g. presence/absence of clinical mastitis) than outcomes measured on a continues scale (e.g. milk production).

The consequence of insufficient power in individual studies may be that five studies each report no significant effect on an outcome of interest. However, this may be primarily due to the lack of power in each individual study, rather than the lack of a true effect. Consequently, some method of combining data from multiple studies is required to detect these potentially important effects.

In general there are three approaches to combining data from multiple studies:

- a qualitative assessment of each study and subjective pooling of the results
- directly pooling the data from multiple studies into one single
- meta-analysis of results from multiple studies.

Each of the above options has advantages and disadvantages and each will be discussed below.

## 3.3 Qualitative Assessment and Subjective "Pooling"

This approach is most appropriate if there are a very limited number of studies and considerable detail about each of those studies is available. This is probably the common approach when dealing with submissions from pharmaceutical manufacture's, in which only a limited number of studies, carried out to support the submission, are being considered. However, those studies are reported in great detail. There are several disadvantages to this approach. First, if a large number of studies have been carried out, the evaluation of the detail of those studies becomes an overwhelming task. Secondly, there is a tendency when subjectively combining data from multiple studies to assign roughly equal weights to each of the studies. As will be see later in this report, it is clear that some studies should be assigned more weight than other studies.

In general, this approach was not considered viable given the large number of studies that have been carried out, the large number of outcomes or dependent variables that the Panel needed to consider and the relatively limited time frame in which to complete the task.

## 3.4 Pooling Data

Directly pooling data from multiple studies and repeating an analysis based on a larger number of cows is one effective way of increasing the power of a group of studies to detect effects. Monsanto has carried out and reported a number of these pooled analyses. The drawback to this approach is that these analyses can only be carried out by the manufacturer because only they would have the raw data required from multiple studies. (It is generally not appropriate to simply compute an average of the summary statistics presented in a study report.) Consequently only outcomes the manufacture chose to evaluate would be considered. This approach also does not allow for inclusion of any data from studies carried out by any other manufacturers. Finally, this approach does not provide any assessment of the diversity of results across studies. Knowing whether an observed effect is relatively constant across studies may be an important consideration in the review process.

## 3.5 Meta-analysis

Meta-analysis has been defined as "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" ([2]). It is a formal statistical process which starts with reported results from multiple studies and produces three main outputs.

- An overall estimate of the effect (e.g. effect of rbST on risk of clinical mastitis).
- An estimate of the heterogeneity (i.e. variability) of results among studies.
- A visual presentation of the results to enable the reviewer to easily assess the evidence.

There are a number of issues that need to be considered when carrying out a meta-analysis. These include:

- the statistical methods used to combine the results.
- the comparability of the studies included in the analysis and the generalizability of the results.
- the heterogeneity of results across studies.
- the quality of studies included in the review.
- the possibility of publication bias.

Each of these issues will be considered below. A more thorough review of meta-analysis techniques is included in Appendix 2. ([3])

### 3.5.1 Statistical Methods in Meta-analysis

There are a variety of statistical procedures that can be used in a meta-analysis. However, the most important consideration is whether the procedure assumes a fixed effect or random effects. An analysis based on a fixed effect assumes that the effect of the drug being evaluated is the same in all studies. A random effects analysis does not make that assumption although it still computes an overall estimate of the effect. Meta-analyses in this review estimated effects using both fixed and random effects analyses. Graphic presentation of results was based on the fixed effects analysis unless otherwise specified. All analyses were carried out using the statistical program Stata (Stata Corp., College Station, Tx). Details of the statistical methods used in the calculations are presented in the Appendix 3. Guidelines for interpreting the output from the meta-analyses are described in section 3.5.6.

### 3.5.2 Comparability of Studies and Generalizability of Results

In general it is easiest and safest to combine results from studies that have the same design, the same treatment protocol and which measured the outcomes of interest in a consistent manner. All of the rbST studies included in meta-analyses employed the same general study design (randomized clinical trial) but the studies where based on various manufacturers' products and various dosage and administration regimes. There was also considerable variability in how outcomes were measured across studies. Consequently, some of the differences between studies are attributable to these variations in design. However, if multiple studies carried out in various settings and using a variety of treatment protocols tend to show the same result the generalizability of these results is enhanced. This increases the reviewer's confidence that similar effects would be observed in other settings. It is also important to consider whether the results of individual studies and the meta-analysis make sense biologically.

### 3.5.3 Heterogeneity of Results

A meta-analysis should include a formal test of the heterogeneity (variability) of results across studies. If statistically significant heterogeneity is present the reviewer must then question whether it is legitimate to combine the results from the various studies. Reasons for the potential variability should be evaluated and, at very least, overall effects based on a random effects analysis should be considered.

### 3.5.4 Study Quality

Obviously, the results from a meta-analysis depend on the quality of the studies which have been included in it. In general, there are three key quality issues to be considered in randomized clinical trials:

- randomization of study subjects to treatment groups
- how withdrawals from the study are handled

- use of blind techniques such as placebo treatments (most important for subjective outcomes)

All studies included in meta-analyses in this report had random assignment of cows to treatment groups. There was some variability in how withdrawals from studies were handled. However, most studies were relatively short-term in nature and few animals were removed form the study. The use of a placebo in the control cows was common, but it was not universal across studies. There is some debate about the value of placebo treatments in rbST studies given that the product tends to produce a fairly obvious increase in production that negates the blinding effect of the placebo.

While it is possible to include subjective assessments of study quality in a meta - analysis, this was not done in this review.

### 3.5.5 Publication Bias

Since the review process included data from the published literature as well as data from the Monsanto submission there is a possibility of publication bias affecting these results. This bias arises from a tendency to publish only significant results in the published literature. The most serious concern in this regard arises from the evaluation of secondary outcomes in many studies. For example, a study designed primarily to evaluate the efficacy of rbST may only have reported health effects (harmful or beneficial) that were statistically significant, or which at least had a substantial difference between the treatment and control groups. The consequence of this is that overall estimates obtained from a meta-analysis may be biased away from the null, that is toward finding a significant effect.

### 3.5.6 Guidelines for Interpreting Meta-analysis Output Interpreting the Output

The following guidelines can be used in the interpretation of the meta-analysis results included in this report.

### Fixed Effect Estimation

This overall estimate is based on the assumption that the effect of rbST was the same in across all studies. For example, the overall effect of rbST on 3.5% FCM was estimated to be 4.465 kg/day, the confidence interval for the estimate was 4.153 to 4.777 and the P value was reported as 0.000.

### Random Effects Estimation

This overall estimate is based on the assumption that the effect of rbST may vary over studies (groups of cows). For 3.5% FCM the estimate was 4.434 kg/day.

### Test of Heterogeneity

This test evaluates the assumption that the effect of rbST was the same in all studies. If it is significant (i.e. $p < 0.05$) then there is evidence that the effect of rbST does vary across studies. For 3.5% FCM (All Companies) the test was highly statistically significant ($p = 0.000$)

## List of Studies and Weights

This list provides the "weights" assigned to each study in the fixed and random effects meta-analyses and the individual parameter estimates from each study. These parameter estimates will be the same as the ones listed on the complete database printout in Appendix 9.

## Study Labels

Each study (group of cows) was identified by a label which provides a bit of information about the study. For example the first study in the 3.5% FCM is labeled:

1 Mm 1
1 = reference number
M = Monsanto
m = parity of cows in the study (group of cows)
p = primiparous
m = multiparous
a = all cows together
1 = study year (only > 1 if multi-lactation study)

## Graphs

The components of each graph are as follows:

**Horizontal Lines** - one line for each study (group of cows) and the length of the line represents the 95% confidence interval for the parameter estimate for the study. Studies with long lines (i.e. wide confidence intervals) have a very imprecise estimate of the parameter.

**Shaded Boxes** - the centre of the box marks the point estimate of the parameter from that study. The area of the box is proportional to the weight assigned to the study in the meta analysis. Studies with large boxes have had a strong influence on the overall estimate.

**Dashed Vertical Line** - this marks the overall estimate of effect (based on the fixed effect estimation unless otherwise specified)

**<>** - at the bottom of the dashed line shows the confidence interval for the overall effect estimations

**Solid Vertical Line** - this marks the value where rbST is having no effect (i.e. a mean difference of "0" or a relative risk of "1")

## 3.6 Literature Review

In order to ensure that all relevant literature was considered in the review process, a computer based bibliographic search was carried out. It included the following databases: Medline Express (1991 to May 1998), Agricola (1984 to March 1998), and CABWeb Databases including Index Veterinarius and Veterinary Bulletin (up to May 1998).

The following search strategy was employed:

The searches always included "(rbST or somatotropin or somatotrophin or growth hormone) and (bovine or cow or cows or cattle or dairy)". For each topic area the following words were used along with the above using "and" as a connector. (Note an * indicates that all words starting with the identified letters would be found. For example, "cull*" would locate cull, culls, culled, culling, etc.)

- Efficacy - "(efficacy or response or milk or production or yield)"
- Udder Health - "(udder or mastitis or mammary)"
- Reproduction - "(reproduc* or pregnancy or calving or abortion or conception or gestation or birth or calf health)"
- Feet and Legs - "(feet or foot or leg or legs or hoof or hooves or joint or joints or lame* or knee or knees or laminitis)"
- General Health was broken into two categories
    - Digestive Disorders - "(digest* or disorder or disorders or diarrhea or bloat or indigest* or off feed or ketosis or acetonemia)"
    - Other - "(immun* or metabol* or disorder or disorders or reaction or reactions or inject* or medica* or treatment or treatments or ill* or general health or lesion or lesions)"
- Culling - "(cull*)"
- Drug Interactions - "(drug* or interaction or interactions or prostaglandin or prostaglandins or side effect or effects or reaction or reactions)"
- Nutrition - "(nutrition* or feed* or rotation or rotations or nutrient*)"
- Body Condition - "(BCS or body condition score or weight or condition)"
- Animal Welfare - "(welfare or concerns or well being or behavior)"

All references which were identified were retrieved and put into a reference management program. During the "capture" of each of the topic areas, a keyword was assigned (to each reference). Duplicate record searches were preformed and keywords were reassigned as required when duplicates were detected.

A total of 1777 references were identified, using the above literature search strategies. All studies reported in the Monsanto submission were added to the reference list. References were then deleted if any of the following criteria applied to the reference:

- non-bovine species (e.g. relating to dairy goats)

- beef cattle papers
- use in calves
- use in growing heifers
- pre-parturition use
- use in tropical environments
- mechanism of action (as opposed to effects)
- effects on human health
- most commentaries, news articles, books
- most conference proceedings before 1995
- most articles in non-research journals
- most Agricultural Experimental Station Bulletin publications
- most foreign language papers

Following deletion of the papers meeting the criteria above 242 "relevant" articles remained (Appendix 4). Each Panel member reviewed the list and identified studies which they felt were "key" to the review. A total of 83 reports were ultimately identified as "key" and these are listed separately in Appendix 5. They included 59 reports in the published literature and 24 studies reported only in the Monsanto submission provided by Health Canada. "Key" references that were not part of the Monsanto submission were obtained from University libraries. A table outlining all of the material submitted to the Panel by Health Canada is included in Appendix 6.

## 3.7 Data Extraction

The 83 key studies identified above were divided among Panel members for review and data extraction. The review and data extraction process involved two steps. First, basic information about the study (e.g. location, number of cows/herds, dose of rbST, etc.) was recorded on a cover sheet for each study. At the bottom of each cover sheet observations, comments and general conclusions about the study were recorded as the reviewer felt was appropriate. The complete set of these cover sheets is included in Appendix 7. For the data extraction portion of the review process, the following key parameters were identified by the Panel.

**Key Outcomes Measured**

| Topic | Measure | Acronym | Units | Type of outcome |
|---|---|---|---|---|
| Efficacy | 3.5 % FCM | FCM | kg/d | md |

| | | | | |
|---|---|---|---|---|
| | % protein | ptn | % | md |
| | % lactose | lact | % | md |
| | %fat | fat | % | md |
| Udder Health | clinical mastitis (cm) incidence rate ratio | cm irr | NA | irr |
| | cm- incidence rate difference | cm ird | NA | ird |
| | cm-risk ratio | cm rr | NA | rr, or |
| | prevalence-quarter intra-mammary infection | prev ¼ IMI | % | md |
| | prev-SCC-log | SCC log | log scale | md |
| | prev-SCC-lin | SCC lin | score | md |
| | discard milk days | m disc ds | days | md |
| Reproduction | days open | do | days | md |
| | overall non-pregnancy rate | non preg | NA | rr, or |
| | services per conception | spc | # | md |
| | gestation length | gest | days | md |

| | | | | |
|---|---|---|---|---|
| | abortion-risk ratio | abort | NA | rr, or |
| | cystic ovaries | co | NA | rr |
| | twinning | twins | NA | rr |
| Feet and Legs | lameness-risk | lame risk | NA | rr, or |
| | lameness-sick days | lame sick ds | days | md |
| General Health | sick-days general | sick ds gen | days | md |
| | sick days-digestive | sick ds dig | days | md |
| | discarded milk days | dh disc ds | days | md |
| Body Condition Score (@ end of tx period) | BCS<200 | BCS<200 | units (1-5) | md |
| | BCS>200 | BCS>200 | units (1-5) | md |
| Culling | culling-risk | cull risk | NA | rr, or |
| | death-risk | dth risk | NA | rr, or |

| | | | | |
|---|---|---|---|---|
| Nutrition | dry matter intake | dmi | kg/d | md |
| | net energy intake | nei | mcal/d | md |
| | gross feed efficiency | gfe | kgFCM/ mcal | md |

If a study reported quantitative data for any of these key parameters the following information was recorded (if available).

- the parameter of interest.
- the standard error or confidence interval of the parameter.
- the P value from the test of significance of the treatment effect
- whether or not the parameter estimate had been adjusted for level of milk production.

In many cases measures of health effects were not specifically presented in the study report or paper. However, it was often possible to obtain the information needed to compute some of the key parameters. For example, a paper may not have reported the relative risk of clinical mastitis but it may have reported the number of cows affected, and the number at risk of mastitis in each of the treatment groups. From these data, the relative risk of mastitis and its confidence interval were computed. Data extraction guidelines used by the Panel are presented in Appendix 8.

A few important points about the data extraction process are as follows:

- Many of the studies were dose titration trials designed to determine the dose-efficacy relationship. For these multi-dose studies, data from the dose of rbST which was closest to the proposed Monsanto label daily dose (500 mg/14d = 35.7mg/d) were used.

- Data which had already been pooled across doses in multiple dose studies were not used.

- Most papers provided mean values and standard errors for variables measured on a continues scale (e.g. 3.5% FCM).

- Computation of relative risks (rr) and their confidence intervals were generally done from data extracted from tables in the reports.

- If data were reported separately by parity (usually primiparous vs. multiparous), they were recorded as such.

- If data were reported separately by study year (such as Year 1, Year 2, etc. in multi-lactations studies) they were recorded as such.

- The early period (e.g. first 60 days) of a lactation which followed a lactation in which rbST had been used was defined as the "Carry-over Period".
- If neither the standard error or the confidence interval was reported for a parameter, the results could not be used in the meta-analyses.

Data were entered into a data base which was stored initially as a Quattro Pro (Corel Corp. Ottawa) spreadsheet file and subsequently converted into a Stata statistics file. Each entry (record) in the data base represents one outcome of interest in one group of cows in a study. For example, one entry might represent the effect of rbST on the somatic cell count (log transformed) in primiparous cows in one study. Since not all studies reported outcomes using key parameters identified by the Panel, other outcomes were also recorded in the database but not used in the meta-analyses.

One difficulty encountered in extracting the data was the fact that the same data may have appeared in several reports and publications. For example Monsanto carried out a multi - location study in New York, Arizona, Utah and Michigan. Results from multiparous cows in this study were presented in detail in a report titled "Long term evaluation of zinc methionyl bovine somatotropin treatment in a prolonged release system for lactating multiparous cows at four U.S. clinical trial sites" ([4]). Results from both primiparous cows and multiparous cows were reported under the heading "Multi-location intramuscular single dose study (Single dose IM)" ([5]) in the Freedom of Information report. However, in the latter report some results were presented for that study alone while others were pooled with results from other IM injection studies. These same results may also have appeared in subject specific review reports prepared by Monsanto.

Similarly, results may have been presented in both Monsanto reports and the published literature. For, example results from a multi-lactation chronic animal toxicity study appeared in one Monsanto report ([6]) and two published papers ([7],[8]), all with different titles and senior authors.

All reasonable efforts were made to ensure that the data were only included in the database once. If data were found in both the Monsanto submission and the published literature, the reference in the database is to the published study.

A total of 541 outcomes from 94 groups of cows in 53 studies were included in the database. The following table lists the main characteristics for each of the studies in the database. The column heading are as follows:

- Ref - reference number in the database
- Company - (M = Monsanto, U = Upjohn, E = Eli Lily, C = Cyanamid)
- Role - the role of the company in the study (PI = principal investigator, CI = co - investigator, F = funded, P = provided product only, N = none)
- Author - last name of senior author
- Year - year of publication
- Loc - location of study

- Herds - number of herds in study
- Cows - number of cows in study
- Breed - breed of cows in study (H = Holstein, J = Jersey, BF = British fresion, Mix = mixed breed
- Dur - duration of treatment in days (studies which started approximately 60 days after calving and went to the end of lactation are all listed as having a 255 day duration)
- Dose inject - dosage injected at each treatment
- Dose/day - average daily dose (for example: 500mg/14d = 35.7 mg/d)
- dose dose
- ref company role author yr loc herds cows breed dur injct /day
- 1 M pi Franson 1989 NY,AZ,FL,UT 4 255 H 255 500 35.7
- 2 M pi Meserole 1992 AZ 1 138 J 126 500 35.7
- 5 M pi White 1990 MO 1 64 H 255 500 35.7
- 7 M pi Bauman . NY AZ,UT,MO 4 364 H 255 500 35.7
- 20 M p Judge 1997 MI 4 555 H 255 500 35.7
- 34 M ci Huber 1997 AZ 1 78 H 234 500 35.7
- 124 U f Esteban 1994 CA 1 156 H 255 51.6 51.6
- 126 U ci Speicher 1994 MI 1 118 H 230 14 14.0
- 127 U f Esteban 1994 CA 1 156 H 255 51.6 51.6
- 136 E ? McClary 1994 6 States 6 352 H 255 960 34.3
- 157 U f Esteban 1994 CA 1 156 H 255 51.6 51.6
- 168 C ci Hansen 1994 MN 6 352 H 255 16.5 16.5
- 249 E ci Oldenbroek 1993 Hol 1 177 Mix 168 960 34.3
- 261 M ci Pell 1992 VT 1 46 J 255 500 35.7
- 279 C ci Jenny 1992 SC 1 24 J 255 310 22.1
- 281 C ? Zhao 1992 ON 1 74 H 255 350 25.0
- 291 U ci Stanisiewski 1992 MI 1 210 H 116 14 14.0
- 329 M pi Cole 1992 MO 1 82 H 255 600 42.9
- 344 M ci Hartnell 1991 AZ,FL,UT 4 254 H 252 500 35.7
- 403 C n Morbeck 1991 NC 1 32 H 255 16.5 16.5
- 406 C f Lissemore 1991 ON 1 37 H 266 41.2 41.2
- 416 M ci Thomas 1991 6 states 15 890 ? 84 500 35.7
- 425 M ci Jordan 1991 CO 1 104 H 84 25 25.0
- 539 M n Kirby 1997 MO 1 30 Mix 42 500 35.7
- 605 C ci McBride 1990 ON 1 43 H 266 20.6 20.6
- 627 C f Burton 1990 ON 1 38 H 266 41.2 41.2
- 644 M ci Weller 1990 UK 1 90 BF 255 500 35.7
- 645 M ci Phipps 1990 UK 1 60 BF 255 500 35.7
- 730 M ? Whitaker 1988 UK 1 38 Mix 255 500 35.7
- 802 Peel 1985 Aust. 1 10 Mix 154 39 39.0
- 1076 M pi Eppard 1990 MO 1 82 H 255 600 42.9
- 1218 C pi Burton 1990 ON 1 43 H 266 20.6 20.6
- 1289 C ci Waterman 1993 KT 1 22 H 196 40 40.0

- 1552 M ci Wells 1995 MI,NY,PN 8 188 ? 255 500 35.7
- 2104 U ci Lean 1994 CA 1 34 H 255 51.6 51.6
- dose dose
- ref company role author yr loc herds cows breed dur injct /day
- 2215 M ci Barbano 1992 NY 1 80 H 255 500 35.7
- 5135 C ci Hemken 1991 KT 1 30 H 273 20.6 20.6
- 5298 E p Leonard 1990 QU 1 60 H 252 960 34.3
- 5403 C ci Chalupa 1996 KT,MN,PN,OH 4 136 Mix 266 41.2 41.2
- 5407 M pi Collier 1996 10 states 28 1213 Mix 255 500 35.7
- 5409 M ci Rijpkema 1990 Hol 1 64 H 255 500 35.7
- 5410 M ? Gavert 1989 Ger 1 60 H 255 500 35.7
- 5411 M ? Schockmel 1988 Fr 1 58 H 255 500 35.7
- 5413 M ? Adriaens 1991 UK 1 90 BF 255 500 35.7
- 5414 M ? Olson 1989 CO 2 152 ? 84 500 35.7
- 5415 M ci Meserole 1990 MI,NY 7 462 H 84 500 35.7
- 5416 M ci Arambel 1989 UT 3 154 H 84 500 35.7
- 5417 M ? Galton 1989 NY 4 231 H 84 500 35.7
- 5418 M ? Erdman 1989 MD,PN 2 76 ? 84 500 35.7
- 5419 M pi Ruegg 1998 IN,MI,OH 32 5468 H 255 500 35.7
- 5421 M pi Vicini 1988 MO 1 84 H 255 500 35.7
- 5422 M ? Huber 1990 NY,AZ,UT,MO 4 272 H 255 500 35.7
- 5425 M pi Eppard 1993 MO 1 50 H 255 500 35.7

A complete list of the extracted data is included in Appendix 9.

## 3.8 Complete List of Issues

Although the review process focused on the key parameters identified in section 3.7, the Panel identified the following complete list of issues to be considered in reviewing the submission documents and published papers. Consequently, all of these possible effects were considered when reviewing studies, but they were not necessarily included in the database.

**Efficacy:**

- dose response studies (is the recommended dose appropriate?)
- immediacy of response
- persistence of response
- through injection interval
- with repeated treatment (shape of lactation curve)
- milk composition (fat, protein, and lactose)
- age effects on response
- breed effects on response
- validity of analyses

**Udder Health:**

- incidence of clinical mastitis
- treatment days (discarded milk)
- sub-clinical mastitis
- somatic cell count (SCC)
- culling for mastitis
- death or loss due to mastitis (quarter loss)
- bacteriology

**Reproduction:**

- days open
- pregnancy rate (total percent pregnant at the end of study)
- twinning (multiple births)
- abortion/fetal loss
- calving difficulties of subsequent pregnancies
- conception rate by service
- cystic ovaries
- culling for fertility
- gestation length
- retained placenta

**Feet and Legs:**

- swollen joints (producer observed)
- foot disease
- lameness with specific diagnosis, if available
- treatment days for lameness
- culling for lameness

**General Health:**

- digestive disorders
- days off feed
- indigestion
- bloat
- diarrhea
- impact on immune function
- metabolic disorders
- injection site reactions
- increased frequency of use of medication/treatment days

**Culling:**

- rates
- reasons

**Drug Interactions:**

- is there any literature?
- are interactions likely?
- prostaglandin was raised as a specific concern

**Nutritional Implications:**

- is the recommendation to meet or exceed nutritional requirements?
- efficiency of feed utilization/conversion
- are there any implications for treating thin cows?
- if nutritional requirements are not met, what happens?
- no response vs loss in body condition score

**Body Condition Score:**

- do treated cows have lower BCS than non-treated cows?
- change in BCS over time
- use in thin cows

**Animal Welfare:**

- incorporate into other components
- potentially separate in report if warranted

## 3.9 General Structure for Presenting Outcome Evaluations

Each of the following 10 sections of this report (i.e. #4 - #13) present the results of the evaluation of the effect of rbST in one general area. For example section 4 deals with "Efficacy" and within that section, 4 specific outcome parameters are considered (3.5% fat-corrected-milk, % fat, % lactose, % protein).

For each outcome parameter assessed the results of 2 or more meta-analyses are presented along with a section of "Comments and Conclusions". In this section, additional information not included in the meta-analyses is presented along with the conclusions of the Panel as to the effects of rbST.

If the Panel concluded that rbST has detrimental effects in a given area, then the Panel's assessment of the adequacy of current dairy health management techniques to control or

eliminate the detrimental effect(s) is presented. This may be related to a specific outcome parameter (e.g. section 7.1.6 - clinical mastitis) or to a general area (e.g. section 8.9 - reproduction).

There are also a number of specific sub sections dealing with individual issues which the Panel considered important (e.g. section 7.1.4 - Expected Increase in Cases of Clinical Mastitis).

# 4. Efficacy

Under this heading the panel considered the effect of rbST on level of milk production (milk yield) and milk composition (percent fat, percent lactose, and percent protein).

## 4.1 Milk Yield

Most North American studies reported milk production in terms of 3.5% fat-corrected-milk (3.5% FCM) while European studies tend to report 4% FCM. Meta-analyses were only carried out for studies reporting 3.5% FCM.

### 4.1.1 Meta-analysis

This section presents five separate meta-analyses.

- Effect of rbST on 3.5% FCM based on studies using all companies' products.
- Effect of rbST on 3.5% FCM based on studies using Monsanto's product.
- Effect of rbST on 3.5% FCM in primiparous Holsteins based on studies using all companies' products.
    - Effect of rbST on 3.5% FCM in multiparous Holsteins based on studies using all companies' product.
    - Effects of rbST on 3.5% FCM in the "carry-over period" based on studies using all companies' products (Note the "carry-over period" was the early lactation period in a lactation subsequent to one in which rbST had been used).

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-2) rtrunc(12) xlabel (-2, 0, 2, 4, 6, 8, 10, 12) b2("**3.5% FCM - All Companies**")

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 4.465 | 4.153 | 4.777 | 28.078 | 0.000 | 28 |
| Random | 4.434 | 3.851 | 5.016 | 14.911 | 0.000 | |

Test for heterogeneity: Q= 79.866 on 27 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 1.424

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1.01 | 0.41 | 3.60 | 1.65 | 5.55 |
| 1 Mp1 | 1.60 | 0.49 | 3.60 | 2.05 | 5.15 |
| 2 Ma1 | 1.64 | 0.49 | 4.50 | 2.97 | 6.03 |
| 34 Ma9 | 1.02 | 0.42 | 3.20 | 1.26 | 5.14 |
| 126 Um1 | 0.89 | 0.39 | 4.30 | 2.22 | 6.38 |
| 126 Up1 | 1.99 | 0.52 | 5.00 | 3.61 | 6.39 |
| 168 Cm1 | 2.35 | 0.54 | 5.30 | 4.02 | 6.58 |

| | | | | | |
|---|---|---|---|---|---|
| 168 Cm2 | 0.85 | 0.38 | 3.50 | 1.37 | 5.63 |
| 168 Cp1 | 2.27 | 0.54 | 2.20 | 0.90 | 3.50 |
| 168 Cp2 | 0.41 | 0.26 | 0.30 | -2.75 | 3.35 |
| 261 Ma1 | 0.85 | 0.38 | 5.30 | 3.17 | 7.43 |
| 279 Ca1 | 0.83 | 0.38 | 5.90 | 3.75 | 8.05 |
| 281 Ca1 | 0.61 | 0.33 | 1.76 | -0.75 | 4.27 |
| 344 Mm1 | 1.39 | 0.47 | 4.60 | 2.94 | 6.26 |
| 344 Mp1 | 1.64 | 0.49 | 3.50 | 1.97 | 5.03 |
| 425 Ma1 | 2.05 | 0.52 | 6.30 | 4.93 | 7.67 |
| 1076 Ma1 | 0.58 | 0.32 | 7.20 | 4.62 | 9.78 |
| 1076 Ma2 | 0.26 | 0.19 | 10.60 | 6.77 | 14.43 |
| 2215 Ma1 | 2.85 | 0.56 | 2.52 | 1.36 | 3.68 |
| 5298 Ea2 | 0.13 | 0.11 | 5.40 | -0.14 | 10.94 |
| 5298 Em1 | 0.03 | 0.03 | 6.60 | -5.28 | 18.48 |

| | | | | | |
|---|---|---|---|---|---|
| 5298 Ep1 | 0.11 | 0.10 | -0.70 | -6.52 | 5.12 |
| 5403 Ca1 | 1.39 | 0.47 | 5.40 | 3.74 | 7.06 |
| 5415 Ma1 | 2.42 | 0.54 | 5.80 | 4.54 | 7.06 |
| 5416 Ma1 | 6.16 | 0.63 | 5.10 | 4.31 | 5.89 |
| 5417 Ma1 | 0.94 | 0.40 | 6.01 | 3.99 | 8.03 |
| 5418 Ma1 | 1.02 | 0.42 | 4.30 | 2.36 | 6.24 |
| 5422 Mm1 | 2.27 | 0.54 | 3.90 | 2.60 | 5.20 |

3.5% FCM - All Companies

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-2) rtrunc(12) xlabel (-2, 0, 2, 4, 6, 8, 10, 12) b2("**3.5% FCM - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 4.623 | 4.250 | 4.995 | 24.328 | 0.000 | 16 |
| Random | 4.716 | 4.016 | 5.416 | 13.212 | 0.000 | |

Test for heterogeneity: Q= 46.719 on 15 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 1.272

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1.01 | 0.44 | 3.60 | 1.65 | 5.55 |
| 1 Mp1 | 1.60 | 0.53 | 3.60 | 2.05 | 5.15 |
| 2 Ma1 | 1.64 | 0.53 | 4.50 | 2.97 | 6.03 |
| 34 Ma9 | 1.02 | 0.44 | 3.20 | 1.26 | 5.14 |
| 261 Ma1 | 0.85 | 0.41 | 5.30 | 3.17 | 7.43 |
| 344 Mm1 | 1.39 | 0.50 | 4.60 | 2.94 | 6.26 |
| 344 Mp1 | 1.64 | 0.53 | 3.50 | 1.97 | 5.03 |
| 425 Ma1 | 2.05 | 0.57 | 6.30 | 4.93 | 7.67 |
| 1076 Ma1 | 0.58 | 0.33 | 7.20 | 4.62 | 9.78 |
| 1076 Ma2 | 0.26 | 0.20 | 10.60 | 6.77 | 14.43 |

| | | | | | |
|---|---|---|---|---|---|
| 2215 Ma1 | 2.85 | 0.62 | 2.52 | 1.36 | 3.68 |
| 5415 Ma1 | 2.42 | 0.59 | 5.80 | 4.54 | 7.06 |
| 5416 Ma1 | 6.16 | 0.70 | 5.10 | 4.31 | 5.89 |
| 5417 Ma1 | 0.94 | 0.43 | 6.01 | 3.99 | 8.03 |
| 5418 Ma1 | 1.02 | 0.44 | 4.30 | 2.36 | 6.24 |
| 5422 Mm1 | 2.27 | 0.58 | 3.90 | 2.60 | 5.20 |

3.5% FCM-Monsanto

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-2) rtrunc(12) xlabel (-2, 0, 2, 4, 6, 8, 10, 12) b2("**3.5% FCM-primiparous cows**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 3.300 | 2.608 | 3.992 | 9.347 | 0.000 | 6 |
| Random | 3.027 | 1.741 | 4.313 | 4.615 | 0.000 | |

Test for heterogeneity: Q= 14.235 on 5 degrees of freedom (p= 0.014)
Moment-based estimate of between studies variance = 1.487

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mp1 | 1.60 | 0.47 | 3.60 | 2.05 | 5.15 |
| 126 Up1 | 1.99 | 0.50 | 5.00 | 3.61 | 6.39 |
| 168 Cp1 | 2.27 | 0.52 | 2.20 | 0.90 | 3.50 |
| 168 Cp2 | 0.41 | 0.26 | 0.30 | -2.75 | 3.35 |
| 344 Mp1 | 1.64 | 0.48 | 3.50 | 1.97 | 5.03 |
| 5298 Ep1 | 0.11 | 0.10 | -0.70 | -6.52 | 5.12 |

3.5% FCM-primiparous cows

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-2) rtrunc(12) xlabel (-2, 0, 2, 4, 6, 8, 10, 12) b2("**3.5% FCM - multiparous cows**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 4.361 | 3.700 | 5.022 | 12.923 | 0.000 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Random | 4.361 | 3.700 | 5.022 | 12.923 | 0.000 | |

Test for heterogeneity: Q= 3.981 on 6 degrees of freedom (p= 0.679)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1.01 | 1.01 | 3.60 | 1.65 | 5.55 |
| 126 Um1 | 0.89 | 0.89 | 4.30 | 2.22 | 6.38 |
| 168 Cm1 | 2.35 | 2.35 | 5.30 | 4.02 | 6.58 |
| 168 Cm2 | 0.85 | 0.85 | 3.50 | 1.37 | 5.63 |
| 344 Mm1 | 1.39 | 1.39 | 4.60 | 2.94 | 6.26 |
| 5298 Em1 | 0.03 | 0.03 | 6.60 | -5.28 | 18.48 |
| 5422 Mm1 | 2.27 | 2.27 | 3.90 | 2.60 | 5.20 |

3.5% FCM - multiparous cows

. meta val se , pr gr(f) id(stdy_lbl) cl xline(0) ltrunc(-4) rtrunc(6) xlabel (-4, -2, 0, 2, 4, 6) b2("**3.5% FCM - Carry-over Period**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.656 | -0.878 | 2.190 | 0.838 | 0.402 | 3 |
| Random | 0.656 | -0.878 | 2.190 | 0.838 | 0.402 | |

Test for heterogeneity: Q= 0.990 on 2 degrees of freedom (p= 0.610)
Moment-based estimate of between studies variance = 0.000

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 34 Ma. | 0.14 | 0.14 | -1.40 | -6.67 | 3.87 |
| 1076 Ma1 | 0.31 | 0.31 | 1.80 | -1.74 | 5.34 |
| 5422 Mm1 | 1.19 | 1.19 | 0.60 | -1.20 | 2.40 |

3.5% FCM - Carry-over Period

### 4.1.2 Comments and Conclusions

The overall effects of rbST was to produce an increase in fat-corrected milk of approximately 4.4 to 4.7 kg per day. However, it was noted that there was considerable variability amongst studies so separate analyses for primiparous and multiparous Holstein cows were carried out. This substantially reduced the variability among studies and suggested that, on average, primiparous Holsteins produced an extra 3.0 kg per day while multiparous Holsteins produced an extra 4.3 kg per day when treated with rbST. The average production levels in primiparous and multiparous cows in the control groups of these studies were 26.6 and 27.9 kg per day so the average percentage increase in milk production was 11.3% for primiparous cows and 15.6% for multiparous cows.

The meta-analysis of production during the "carry-over" period suggested that there was no effect of rbST on production in the early lactation period in a lactation subsequent to one in which rbST had been used.

A second measure of overall efficacy recorded in the database was 4% FCM derived from studies carried out in the United Kingdom ([9]), France ([10]) and Germany ([11]). The first two studies reported increased yields similar to those observed in North American studies. However, the German study reported reduced yields in each of the three study years although none of the individual year reductions were statistically significant. However, it does indicate that the yield increase is not observed under all management circumstances.

The final measure of overall efficacy recorded in the database was "raw milk production" (i.e. unadjusted for fat content). These results were similar to those observed for 3.5% FCM.

It was noted that most of the studies had been carried out in institutional herds (university or pharmaceutical company). However, regardless of the location of these herds, they had received high level nutritional management. It was unfortunate that much of the production data which should have been available from the Post Approval Monitoring Program (PAMP) study ([12]) were either not collected or not reported. These data would have provided a better indication of how the product worked in a range of commercial enterprises.

The Panel did not feel that any additional data were required to establish the efficacy of drug in terms of increasing milk production. However, they did note that studies carried out in a wider range of commercial enterprises would provide a better estimate of the range of responses that could be expected by Canadian dairy producers.

## 4.2 Percent Fat (Butterfat)

### 4.2.1 Meta-analysis

This section presents the results from two meta-analyses:

- Effect of rbST on percent fat based on studies using all companies' products.
- Effect of rbST on percent fat based on studies using Monsanto's product.

. meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-.4) rtrunc(.4) xlabel(-.4, -.2, 0, .2, .4) b2("**% Fat - All Companies**") t2("random effects")

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.062 | 0.035 | 0.088 | 4.563 | 0.000 | 27 |
| Random | 0.060 | 0.033 | 0.088 | 4.284 | 0.000 | |

Test for heterogeneity: Q= 26.607 on 26 degrees of freedom (p= 0.430)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 198.37 | 193.51 | -0.07 | -0.21 | 0.07 |
| 1 Mp1 | 73.05 | 72.38 | -0.08 | -0.31 | 0.15 |
| 2 Ma1 | 96.12 | 94.96 | 0.17 | -0.03 | 0.37 |
| 126 Um1 | 79.72 | 78.92 | 0.02 | -0.20 | 0.24 |
| 126 Up1 | 48.90 | 48.60 | -0.06 | -0.34 | 0.22 |
| 168 Cm1 | 268.74 | 259.89 | 0.14 | 0.02 | 0.26 |
| 168 Cm2 | 106.28 | 104.87 | 0.01 | -0.18 | 0.20 |

| | | | | | |
|---|---|---|---|---|---|
| 168 Cp1 | 106.28 | 104.87 | -0.01 | -0.20 | 0.18 |
| 168 Cp2 | 67.19 | 66.62 | -0.06 | -0.30 | 0.18 |
| 261 Ma1 | 37.64 | 37.46 | -0.13 | -0.45 | 0.19 |
| 279 Ca1 | 21.84 | 21.78 | 0.08 | -0.34 | 0.50 |
| 281 Ca1 | 35.43 | 35.27 | -0.09 | -0.42 | 0.24 |
| 344 Mm1 | 198.37 | 193.51 | -0.07 | -0.21 | 0.07 |
| 344 Mp1 | 79.72 | 78.92 | -0.08 | -0.30 | 0.14 |
| 425 Ma1 | 198.37 | 193.51 | 0.10 | -0.04 | 0.24 |
| 645 Ma1 | 148.72 | 145.97 | 0.03 | -0.13 | 0.19 |
| 645 Ma2 | 148.72 | 145.97 | 0.02 | -0.14 | 0.18 |
| 2215 Ma1 | 132.12 | 129.94 | 0.09 | -0.08 | 0.26 |
| 5298 Ea2 | 5.19 | 5.19 | -0.05 | -0.91 | 0.81 |
| 5298 Em1 | 3.48 | 3.48 | 0.00 | -1.05 | 1.05 |
| 5298 Ep1 | 79.72 | 78.92 | 0.23 | 0.01 | 0.45 |

| | | | | | |
|---|---|---|---|---|---|
| 5403 Ca1 | 61.04 | 60.57 | 0.15 | -0.10 | 0.40 |
| 5415 Ma1 | 1479.29 | 1245.68 | 0.08 | 0.03 | 0.13 |
| 5416 Ma1 | 318.88 | 306.49 | 0.14 | 0.03 | 0.25 |
| 5417 Ma1 | 1040.58 | 919.31 | 0.09 | 0.03 | 0.15 |
| 5418 Ma1 | 132.12 | 129.94 | 0.12 | -0.05 | 0.29 |
| 5422 Mm1 | 318.88 | 306.49 | -0.01 | -0.12 | 0.10 |

%Fat - All Companies

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.4) rtrunc(.4) xlabel (-.4, -.2, 0, .2, .4) b2("**% Fat - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.061 | 0.032 | 0.090 | 4.127 | 0.000 | 15 |
| Random | 0.051 | 0.013 | 0.089 | 2.632 | 0.008 | |

Test for heterogeneity: Q= 18.633 on 14 degrees of freedom (p= 0.179)
Moment-based estimate of between studies variance = 0.001

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 198.37 | 159.72 | -0.07 | -0.21 | 0.07 |
| 1 Mp1 | 73.05 | 67.07 | -0.08 | -0.31 | 0.15 |
| 2 Ma1 | 96.12 | 86.03 | 0.17 | -0.03 | 0.37 |
| 261 Ma1 | 37.64 | 35.99 | -0.13 | -0.45 | 0.19 |
| 344 Mm1 | 198.37 | 159.72 | -0.07 | -0.21 | 0.07 |
| 344 Mp1 | 79.72 | 72.65 | -0.08 | -0.30 | 0.14 |
| 425 Ma1 | 198.37 | 159.72 | 0.10 | -0.04 | 0.24 |
| 645 Ma1 | 148.72 | 125.88 | 0.03 | -0.13 | 0.19 |
| 645 Ma2 | 148.72 | 125.88 | 0.02 | -0.14 | 0.18 |
| 2215 Ma1 | 132.12 | 113.78 | 0.09 | -0.08 | 0.26 |
| 5415 Ma1 | 1479.29 | 527.47 | 0.08 | 0.03 | 0.13 |
| 5416 Ma1 | 318.88 | 229.58 | 0.14 | 0.03 | 0.25 |
| 5417 Ma1 | 1040.58 | 458.53 | 0.09 | 0.03 | 0.15 |

| | | | | | |
|---|---|---|---|---|---|
| 5418 Ma1 | 132.12 | 113.78 | 0.12 | -0.05 | 0.29 |
| 5422 Mm1 | 318.88 | 229.58 | -0.01 | -0.12 | 0.10 |

%Fat - Monsanto

### 4.2.2 Comments and Conclusions

There was evidence of a very small but statistically significant increase in the level of butterfat in the milk from treated cows. However, most of the evidence for this increase came from 2 short term (12 week) studies carried out in New York ([13]) and Michigan/New York ([14]). In addition, in relative terms an increase of 0.06 percentage points in the butterfat level would represent only a 1.5 to 2.0% increase. The Panel felt that this effect, even if consistently obtained, would not be of any substantial consequence to the dairy industry.

The Panel did not feel any additional information was required to evaluate this effect.

## 4.3 Percent Lactose

### 4.3.1 Meta-analysis

This section presents the results from two meta-analyses:

- Effect of rbST on percent lactose based on studies using all companies' products.
- Effect of rbST on percent lactose based on studies using Monsanto's product.

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.4) rtrunc(.4) xlabel(-.4, -.2, 0, .2, .4) b2("**% Lactose - All Companies"**)

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.015 | -0.001 | 0.032 | 1.789 | 0.074 | 15 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Random | 0.015 | -0.001 | 0.032 | 1.789 | 0.074 | |

Test for heterogeneity: Q= 7.923 on 14 degrees of freedom (p= 0.893)
Moment-based estimate of between studies variance = 0.000

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 472.59 | 472.59 | 0.01 | -0.08 | 0.10 |
| 1 Mp1 | 1479.29 | 1479.29 | 0.03 | -0.02 | 0.08 |
| 2 Ma1 | 1040.58 | 1040.58 | 0.00 | -0.06 | 0.06 |
| 261 Ma1 | 472.59 | 472.59 | 0.02 | -0.07 | 0.11 |
| 281 Ca1 | 106.28 | 106.28 | 0.02 | -0.17 | 0.21 |
| 344 Mm1 | 594.88 | 594.88 | 0.01 | -0.07 | 0.09 |
| 344 Mp1 | 1040.58 | 1040.58 | 0.06 | 0.00 | 0.12 |
| 425 Ma1 | 4444.44 | 4444.44 | 0.00 | -0.03 | 0.03 |
| 645 Ma1 | 472.59 | 472.59 | 0.03 | -0.06 | 0.12 |
| 645 Ma2 | 229.57 | 229.57 | -0.10 | -0.23 | 0.03 |

| | | | | | |
|---|---|---|---|---|---|
| 2215 Ma1 | 1040.58 | 1040.58 | 0.04 | -0.02 | 0.10 |
| 5298 Ea2 | 48.90 | 48.90 | 0.06 | -0.22 | 0.34 |
| 5298 Em1 | 15.38 | 15.38 | -0.04 | -0.54 | 0.46 |
| 5298 Ep1 | 48.90 | 48.90 | -0.05 | -0.33 | 0.23 |
| 5422 Mm1 | 2500.00 | 2500.00 | 0.02 | -0.02 | 0.06 |

%Lactose - All Companies

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.4) rtrunc(.4) xlabel(-.4, -.2, 0, .2, .4) b2("**% Lactose - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.015 | -0.001 | 0.032 | 1.787 | 0.074 | 11 |
| Random | 0.015 | -0.001 | 0.032 | 1.787 | 0.074 | |

Test for heterogeneity: Q= 7.567 on 10 degrees of freedom (p= 0.671)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 472.59 | 472.59 | 0.01 | -0.08 | 0.10 |
| 1 Mp1 | 1479.29 | 1479.29 | 0.03 | -0.02 | 0.08 |
| 2 Ma1 | 1040.58 | 1040.58 | 0.00 | -0.06 | 0.06 |
| 261 Ma1 | 472.59 | 472.59 | 0.02 | -0.07 | 0.11 |
| 344 Mm1 | 594.88 | 594.88 | 0.01 | -0.07 | 0.09 |
| 344 Mp1 | 1040.58 | 1040.58 | 0.06 | 0.00 | 0.12 |
| 425 Ma1 | 4444.44 | 4444.44 | 0.00 | -0.03 | 0.03 |
| 645 Ma1 | 472.59 | 472.59 | 0.03 | -0.06 | 0.12 |
| 645 Ma2 | 229.57 | 229.57 | -0.10 | -0.23 | 0.03 |
| 2215 Ma1 | 1040.58 | 1040.58 | 0.04 | -0.02 | 0.10 |
| 5422 Mm1 | 2500.00 | 2500.00 | 0.02 | -0.02 | 0.06 |

%Lactose - Monsanto

### 4.3.2 Comments and Conclusions

Although there appeared to be a very small effect on the lactose concentration in milk, this effect was not statistically significant. Even if the apparent effect was real, the Panel felt it was too small to be of any practical consequence.

The Panel did not feel any additional information was required to evaluate this effect.

## 4.4 Percent Protein

### 4.4.1 Meta-analysis

Four meta-analyses were carried out to evaluate the effects of rbST on percent protein.

- Effect of rbST on percent protein based on studies using all companies' products.
- Effect of rbST on percent protein based on studies using Monsanto's product.
- Effect of rbST on percent protein in primiparous cows (Holstein) based on studies using all companies' products.
- Effect of rbST on percent protein in multiparous cows (Holstein) based on studies using all companies' product.

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.2) rtrunc(.2) xlabel(-.2, -.1, 0, .1, .2) b2("**% Protein - All Companies**")

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | -0.022 | -0.033 | -0.012 | -4.085 | 0.000 | 27 |
| Random | 0.013 | -0.014 | 0.039 | 0.933 | 0.351 | |

Test for heterogeneity: Q= 110.129 on 26 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 0.003

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1040.58 | 255.00 | 0.02 | -0.04 | 0.08 |
| 1 Mp1 | 771.61 | 234.93 | -0.01 | -0.08 | 0.06 |
| 2 Ma1 | 1040.58 | 255.00 | -0.01 | -0.07 | 0.05 |
| 126 Um1 | 594.88 | 215.44 | 0.04 | -0.04 | 0.12 |
| 126 Up1 | 594.88 | 215.44 | -0.06 | -0.14 | 0.02 |
| 168 Cm1 | 1040.58 | 255.00 | 0.04 | -0.02 | 0.10 |
| 168 Cm2 | 318.88 | 164.02 | 0.06 | -0.05 | 0.17 |
| 168 Cp1 | 771.61 | 234.93 | 0.05 | -0.02 | 0.12 |
| 168 Cp2 | 384.47 | 179.80 | 0.15 | 0.05 | 0.25 |
| 261 Ma1 | 268.74 | 149.66 | -0.02 | -0.14 | 0.10 |
| 279 Ca1 | 79.72 | 64.50 | 0.00 | -0.22 | 0.22 |
| 281 Ca1 | 132.12 | 94.97 | 0.05 | -0.12 | 0.22 |

| | | | | | |
|---|---|---|---|---|---|
| 344 Mm1 | 1040.58 | 255.00 | 0.02 | -0.04 | 0.08 |
| 344 Mp1 | 594.88 | 215.44 | -0.01 | -0.09 | 0.07 |
| 425 Ma1 | 1040.58 | 255.00 | 0.10 | 0.04 | 0.16 |
| 645 Ma1 | 594.88 | 215.44 | 0.10 | 0.02 | 0.18 |
| 645 Ma2 | 594.88 | 215.44 | 0.07 | -0.01 | 0.15 |
| 2215 Ma1 | 1040.58 | 255.00 | 0.08 | 0.02 | 0.14 |
| 5298 Ea2 | 106.28 | 80.84 | -0.08 | -0.27 | 0.11 |
| 5298 Em1 | 19.93 | 18.82 | 0.00 | -0.44 | 0.44 |
| 5298 Ep1 | 61.04 | 51.69 | -0.01 | -0.26 | 0.24 |
| 5403 Ca1 | 594.88 | 215.44 | -0.01 | -0.09 | 0.07 |
| 5415 Ma1 | 0000.00 | 326.73 | -0.06 | -0.08 | -0.04 |
| 5416 Ma1 | 4444.44 | 313.91 | -0.05 | -0.08 | -0.02 |
| 5417 Ma1 | 4444.44 | 313.91 | -0.08 | -0.11 | -0.05 |
| 5418 Ma1 | 594.88 | 215.44 | -0.08 | -0.16 | 0.00 |

| | | | | | |
|---|---|---|---|---|---|
| 5422 Mm1 | 771.61 | 234.93 | 0.06 | -0.01 | 0.13 |

% Protein - All Companies

. meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-.2) rtrunc(.2) xlabel (-.2, -.1, 0, .1, .2) b2("**% Protein - Monsanto**") t2("random effects")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | -0.031 | -0.043 | -0.019 | -5.223 | 0.000 | 15 |
| Random | 0.005 | -0.027 | 0.037 | 0.314 | 0.754 | |

Test for heterogeneity: Q= 81.966 on 14 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 0.003

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1040.58 | 255.90 | 0.02 | -0.04 | 0.08 |
| 1 Mp1 | 771.61 | 235.70 | -0.01 | -0.08 | 0.06 |
| 2 Ma1 | 1040.58 | 255.90 | -0.01 | -0.07 | 0.05 |

| | | | | | |
|---|---|---|---|---|---|
| 261 Ma1 | 268.74 | 149.98 | -0.02 | -0.14 | 0.10 |
| 344 Mm1 | 1040.58 | 255.90 | 0.02 | -0.04 | 0.08 |
| 344 Mp1 | 594.88 | 216.09 | -0.01 | -0.09 | 0.07 |
| 425 Ma1 | 1040.58 | 255.90 | 0.10 | 0.04 | 0.16 |
| 645 Ma1 | 594.88 | 216.09 | 0.10 | 0.02 | 0.18 |
| 645 Ma2 | 594.88 | 216.09 | 0.07 | -0.01 | 0.15 |
| 2215 Ma1 | 1040.58 | 255.90 | 0.08 | 0.02 | 0.14 |
| 5415 Ma1 | 0000.00 | 328.22 | -0.06 | -0.08 | -0.04 |
| 5416 Ma1 | 4444.44 | 315.28 | -0.05 | -0.08 | -0.02 |
| 5417 Ma1 | 4444.44 | 315.28 | -0.08 | -0.11 | -0.05 |
| 5418 Ma1 | 594.88 | 216.09 | -0.08 | -0.16 | 0.00 |
| 5422 Mm1 | 771.61 | 235.70 | 0.06 | -0.01 | 0.13 |

% Protein - Monsanto

. meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-.2) rtrunc(.2) xlabel (-.2, -.1, 0, .1, .2) b2("**% Protein - Primiparous**") t2("random effects")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.015 | -0.020 | 0.049 | 0.821 | 0.412 | 6 |
| Random | 0.018 | -0.039 | 0.076 | 0.623 | 0.533 | |

Test for heterogeneity: Q= 12.190 on 5 degrees of freedom (p= 0.032)
Moment-based estimate of between studies variance = 0.003

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mp1 | 771.61 | 241.90 | -0.01 | -0.08 | 0.06 |
| 126 Up1 | 594.88 | 221.29 | -0.06 | -0.14 | 0.02 |
| 168 Cp1 | 771.61 | 241.90 | 0.05 | -0.02 | 0.12 |
| 168 Cp2 | 384.47 | 183.86 | 0.15 | 0.05 | 0.25 |
| 344 Mp1 | 594.88 | 221.29 | -0.01 | -0.09 | 0.07 |
| 5298 Ep1 | 61.04 | 52.02 | -0.01 | -0.26 | 0.24 |

% Protein - Primiparous

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.2) rtrunc(.2) xlabel(-.2, -.1, 0, .1, .2) b2("**% Protein - Multiparous**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.036 | 0.008 | 0.064 | 2.482 | 0.013 | 7 |
| Random | 0.036 | 0.008 | 0.064 | 2.482 | 0.013 | |

Test for heterogeneity: Q= 1.213 on 6 degrees of freedom (p= 0.976)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1040.58 | 1040.58 | 0.02 | -0.04 | 0.08 |
| 126 Um1 | 594.88 | 594.88 | 0.04 | -0.04 | 0.12 |
| 168 Cm1 | 1040.58 | 1040.58 | 0.04 | -0.02 | 0.10 |
| 168 Cm2 | 318.88 | 318.88 | 0.06 | -0.05 | 0.17 |
| 344 Mm1 | 1040.58 | 1040.58 | 0.02 | -0.04 | 0.08 |

| | | | | | |
|---|---|---|---|---|---|
| 5298 Em1 | 19.93 | 19.93 | 0.00 | -0.44 | 0.44 |
| 5422 Mm1 | 771.61 | 771.61 | 0.06 | -0.01 | 0.13 |

% Protein - Primiparous

### 4.4.2 Comments and Conclusions

When looking at all of the studies together, there was no consistent evidence of an overall effect on the protein composition of milk produced by treated cows. While there were three specific studies ([13-15]) which reported statistically significant reductions, there were many other studies which reported increases.

The Panel was concerned that the protein composition may differ between primiparous and multiparous cows and consequently separate meta-analyses for these groups were carried out. These results suggested that there was no effect of rbST on protein % in primiparous cows but a small positive effect in multiparous cows of 0.036 percentage points (approximately a 1% increase). The Panel felt that this effect was too small to be of any practical consequence to the dairy industry.

The Panel did not feel any additional information was required to evaluate this effect.

# 5. Nutritional Implications

The Panel evaluated several nutritional factors including dry matter intake, gross feed efficiency and a net energy intake. Of these, only dry matter intake was evaluated in detail and summarized for two reasons. First, the methods of reporting the other parameters were quite variable across studies. Second, measure of efficiency of feed utilization relate primarily to the economic consequences of using, or not using, the drug. The mandate for the Panel did not include an evaluation of the economic consequences.

## 5.1 Dry Matter Intake (DMI)

### 5.1.1 Meta-analysis

Two meta-analyses were carried out to evaluate the effects of rbST on dry matter intake.

- Effect of rbST on DMI based on studies using all companies' products.
- Effect of rbST on DMI based on studies using Monsanto's product.

. meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-1) rtrunc(4) xlabel (-1,0,1,2,3,4) b2("**Dry Matter Intake** - **All Companies**") t2("random effects")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.464 | 1.249 | 1.679 | 13.317 | 0.000 | 22 |
| Random | 1.518 | 1.136 | 1.901 | 7.775 | 0.000 | |

Test for heterogeneity: Q= 56.224 on 21 degrees of freedom (p= 0.000) Moment-based estimate of between studies variance = 0.474

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 3.48 | 1.31 | 1.50 | 0.45 | 2.55 |
| 1 Mp1 | 3.77 | 1.35 | 1.80 | 0.79 | 2.81 |
| 261 Ma1 | 2.04 | 1.04 | 2.40 | 1.03 | 3.77 |
| 279 Ca1 | 5.59 | 1.53 | 1.20 | 0.37 | 2.03 |
| 281 Ca1 | 1.88 | 0.99 | 0.35 | -1.08 | 1.78 |

| | | | | | |
|---|---|---|---|---|---|
| 344 Mm1 | 3.12 | 1.26 | 1.50 | 0.39 | 2.61 |
| 344 Mp1 | 3.12 | 1.26 | 1.90 | 0.79 | 3.01 |
| 645 Ma1 | 4.45 | 1.43 | 1.60 | 0.67 | 2.53 |
| 645 Ma2 | 2.14 | 1.06 | 1.30 | -0.04 | 2.64 |
| 1076 Ma1 | 3.48 | 1.31 | 2.70 | 1.65 | 3.75 |
| 1076 Ma2 | 0.79 | 0.57 | 3.40 | 1.20 | 5.60 |
| 5135 Ca1 | 1.39 | 0.84 | 1.60 | -0.06 | 3.26 |
| 5135 Ca2 | 1.39 | 0.84 | 2.40 | 0.74 | 4.06 |
| 5403 Ca1 | 3.12 | 1.26 | 1.70 | 0.59 | 2.81 |
| 5410 Ma1 | 4.75 | 1.46 | -0.90 | -1.80 | 0.00 |
| 5410 Ma2 | 2.76 | 1.20 | 0.20 | -0.98 | 1.38 |
| 5410 Ma3 | 1.46 | 0.86 | 0.60 | -1.02 | 2.22 |
| 5413 Ma3 | 3.00 | 1.24 | 1.50 | 0.37 | 2.63 |
| 5413 Ma4 | 5.59 | 1.53 | 1.70 | 0.87 | 2.53 |

| | | | | | |
|---|---|---|---|---|---|
| 5421 Mm1 | 1.54 | 0.89 | 1.50 | -0.08 | 3.08 |
| 5421 Mp1 | 2.05 | 1.04 | 3.50 | 2.13 | 4.87 |
| 5422 Mm1 | 21.84 | 1.93 | 1.50 | 1.08 | 1.92 |

Random Effects: Dry Matter Intake - All Companies

.meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-1) rtrunc(4) xlabel (-1,0,1,2,3,4) b2("**Dry Matter Intake - Monsanto**") t2("random effects")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.483 | 1.248 | 1.719 | 12.353 | 0.000 | 17 |
| Random | 1.556 | 1.092 | 2.020 | 6.574 | 0.000 | |

Test for heterogeneity: Q= 52.059 on 16 degrees of freedom (p= 0.000) Moment-based estimate of between studies variance = 0.600

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 3.48 | 1.13 | 1.50 | 0.45 | 2.55 |

| | | | | | |
|---|---|---|---|---|---|
| 1 Mp1 | 3.77 | 1.16 | 1.80 | 0.79 | 2.81 |
| 261 Ma1 | 2.04 | 0.92 | 2.40 | 1.03 | 3.77 |
| 344 Mm1 | 3.12 | 1.09 | 1.50 | 0.39 | 2.61 |
| 344 Mp1 | 3.12 | 1.09 | 1.90 | 0.79 | 3.01 |
| 645 Ma1 | 4.45 | 1.21 | 1.60 | 0.67 | 2.53 |
| 645 Ma2 | 2.14 | 0.94 | 1.30 | -0.04 | 2.64 |
| 1076 Ma1 | 3.48 | 1.13 | 2.70 | 1.65 | 3.75 |
| 1076 Ma2 | 0.79 | 0.54 | 3.40 | 1.20 | 5.60 |
| 5410 Ma1 | 4.75 | 1.23 | -0.90 | -1.80 | 0.00 |
| 5410 Ma2 | 2.76 | 1.04 | 0.20 | -0.98 | 1.38 |
| 5410 Ma3 | 1.46 | 0.78 | 0.60 | -1.02 | 2.22 |
| 5413 Ma3 | 3.00 | 1.07 | 1.50 | 0.37 | 2.63 |
| 5413 Ma4 | 5.59 | 1.28 | 1.70 | 0.87 | 2.53 |
| 5421 Mm1 | 1.54 | 0.80 | 1.50 | -0.08 | 3.08 |

| | | | | | |
|---|---|---|---|---|---|
| 5421 Mp1 | 2.05 | 0.92 | 3.50 | 2.13 | 4.87 |
| 5422 Mm1 | 21.84 | 1.55 | 1.50 | 1.08 | 1.92 |

Random Effects: Dry Matter Intake - Monsanto

### 5.1.2 Comments and Conclusions

There was considerable variability among studies with respect to the observed effect of rbST on dry matter intake in dairy cows. However, overall, the dry matter intake of treated cows was increased, on average, by approximately 1.5 kg per day. It was noted that this increase in dry matter intake would not likely be sufficient to meet the increased energy output associated with increased milk production during the treatment period. However, there was evidence that the increased dry matter intake carried over to the early lactation period in the subsequent lactation. Two studies ([16,17]) both reported dry matter intakes during the "carry-over period" and both found significantly increased dry matter intake during this period.

As indicated above, a number of studies reported "gross feed efficiency" and "net energy intake". These studies generally show an increase in the efficiency of nutrient utilization by treated cows. However, the definitions of these parameters (and method of calculation) varied across studies so it was not possible to use meta-analyses to summarize them. The Panel did not feel any additional information was required to evaluate the effects of rbST on the dry matter intake of cows.

# 6. Body Condition

There are multiple ways to measure the effects of rbST on body condition. The data base includes values for each of the following parameters.

- BCS through tx period - this represents the average difference between body condition scores (measured on a scale of 1 to 5) when assessed at regular intervals throughout the treatment period.
    - BCS > 200 - this represents the difference between treated and control cows in final body condition score (measured on a scale of 1 to 5) for studies in which the treatment period was over 200 days.
    - BCS < 200 - this represents the difference between treated and control cows in their final body condition score following a treatment period of less than 200 days.
- Body Weight - the difference in body weight between treated and control cows at the end of the treatment period.

- Change in BCS - the relative difference between treated and control cows in the change in body condition score over the treatment period.
- Daily weight change - the difference between treated and control cows in their daily average weight gain over the treatment period.

Although all these parameter were included in the database, BCS > 200 was most commonly extracted from studies reviewed and was the subject of a series of meta- analyses.

## 6.1 BCS > 200

### 6.1.1 Meta-Analysis

Three meta-analyses were carried out to evaluate the effects of rbST on body condition.

- Effect of rbST on body condition score based on studies using all companies' product.
- Effect of rbST on body condition score based on studies using Monsanto's product.
- Effect of rbST on body condition score in the "carry-over" period.

Although body condition score data (BCS > 200) were reported in many studies, many studies did not report standard errors of the estimates and consequently these results could not be included in the meta-analyses.

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.5) rtrunc(.3) xlabel (-.5, -.3, -.1, 0, .1, .3) b2("**BCS > 200 days - All Companies**")

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | -0.188 | -0.258 | -0.117 | -5.219 | 0.000 | 4 |
| Random | -0.218 | -0.344 | -0.092 | -3.392 | 0.001 | |

Test for heterogeneity: Q= 8.718 on 3 degrees of freedom (p= 0.033) Moment-based estimate of between studies variance = 0.011

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 118.15 | 52.51 | -0.25 | -0.43 | -0.07 |
| 1 Mp1 | 229.57 | 66.95 | -0.17 | -0.30 | -0.04 |
| 168 Cm1 | 106.28 | 50.03 | -0.42 | -0.61 | -0.23 |
| 168 Cp1 | 318.88 | 72.90 | -0.10 | -0.21 | 0.01 |

BCS > 200 days - All Companies

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-.5) rtrunc(.3) xlabel(-.5, -.3, -.1, 0, .1, .3) b2 ("**BCS > 200 days - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | -0.197 | -0.302 | -0.092 | -3.677 | 0.000 | 2 |
| Random | -0.197 | -0.302 | -0.092 | -3.677 | 0.000 | |

Test for heterogeneity: Q= 0.499 on 1 degrees of freedom (p= 0.480) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 118.15 | 118.15 | -0.25 | -0.43 | -0.07 |
| 1 Mp1 | 229.57 | 229.57 | -0.17 | -0.30 | -0.04 |

BCS > 200 days - Monsanto

. meta val se , pr gr(f) id(stdy_lbl) cl xline(0) ltrunc(-.5) rtrunc(.3) xlabel( -.5, -.3, -.1, 0, .1, .3) b2("**BCS > 200 days - Carry-over Period**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | -0.194 | -0.319 | -0.069 | -3.043 | 0.000 | 3 |
| Random | -0.194 | -0.319 | -0.069 | -3.043 | 0.000 | |

Test for heterogeneity: Q= 0.082 on 2 degrees of freedom (p= 0.960) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 5421 Mm1 | 52.51 | 52.51 | -0.20 | -0.47 | 0.07 |
| 5421 Mp1 | 25.25 | 25.25 | -0.14 | -0.53 | 0.25 |
| 5422 Mm1 | 168.66 | 168.66 | -0.20 | -0.35 | -0.05 |

BCS > 200 - Carry-over Period

### 6.1.2 Comments and Conclusions

The overall estimate of the effect of rbST on body condition score was a reduction of approximately 0.2 units (on a scale of 1 to 5) at the end of the treatment period. However, only 2 studies ([18,19]) had reported adequate data (i.e. point estimates and standard errors) to allow them to be included in the meta-analysis. Other studies which reported point estimates of body condition scores at the end of the treatment period (i.e. BCS > 200) reported an average reduction of 0.15 units (based on a simple arithmetic average).

There was evidence that this reduction in body condition carried over into the early lactation period of the subsequent lactation period. Although this was recorded from relatively few studies, the meta - analysis of 3 studies which did report this parameter found a significant reduction in body condition of approximately 0.2 units in the early lactation period.

## 6.2 Other Estimates of Body Condition

Two studies ([10,20]) involving 4 groups of cows reported body conditions scores throughout the treatment period. On average they reported scores approximately 0.4 units lower in treated cows than in control cows. Statistical significance was only assessed in the former study and in that study the reductions were significant.

Of the 5 studies which reported body condition scores at the end of a treatment period which had been less than 200 days in length, 4 of them reported a reduction in body condition.

Body weights at the end of a treatment period were recorded from 5 groups of cows with lower body weights in treated cows being reported in 3 groups. However, body weight is influenced by the amount of feed in the digestive tract so it may not be as reliable an estimate of body condition.

Change in body condition score values were reported from 4 groups of cows on 2 studies with control cows gaining less body condition than treated cows in all groups. Two studies reported change in body weight as daily weight changes and once again, treated cows gained less weight than control cows.

## 6.3 Comments and Conclusions - Body Condition

The effect of rbST on body condition was reported in many different ways across many studies. Overall though, it was evident that treatment with rbST results in lower body condition at the end of the treatment period. It was also evident that this reduction in body condition persists into the early period of the subsequent lactation.

The Panel concluded that treatment with rbST did reduce body condition scores in cows in the research studies evaluated.

The Panel did not feel any additional information was required to evaluate the effect of rbST in the research herds. The Panel noted that it was unfortunate that body condition scores had not been recorded in the PAMP study as this would have provided a better estimate of the effect of rbST on body condition in a variety of commercial herds.

## 6.4 Ability to Control/Eliminate Detrimental Effects

The Panel noted that most of the studies were carried out in institutional research herds and were subjected to very good nutritional management. Despite the increase in dry matter intake associated with treatment and the high level of nutritional management, treated cows entered the subsequent lactation in a lower state of body condition than control cows.

Programs for balancing dairy cow rations are constantly being improved. However, achieving the ideal of a completely balanced ration requires excellence in many areas (eg. forage production, ration balancing, feeding management etc.) and that excellence is rarely achieved in all of these areas together. Consequently, the Panel concluded that using the nutritional management programs that are common on the majority of commercial dairy herds, it would be a challenge to maintain body condition in cows treated with rbST.

# 7. Udder Health

The effects of rbST on udder health were divided into the effects on the frequency of clinical mastitis and the effects on subclinical mastitis (prevalence of intramammary infections).

## 7.1 Clinical Mastitis Rate and Risk

The panel examined evidence of the effect of rbST on two measures of clinical mastitis frequency.

- The incidence rate of clinical mastitis was computed by dividing the total number of clinical mastitis cases by the number of cow days at risk. In many studies, the total number of clinical mastitis cases was presented for each study group (treated and control) but the total number of cows days at risk was not presented. For these studies, the number of cow

days at risk was estimated based on the duration of treatment and the assumption that lactation lengths in the two groups were equal. The incidence rate ratio (irr) is the ratio of the incidence rate in the treated group divided by the incidence rate in the control group.

- Clinical mastitis risk was computed by dividing the number of cows that were affected by one or more case of mastitis during the treatment period by the number of cows at risk. As with incidence rate data, the relative risk of clinical mastitis was often not presented, per se, but the number of cows affected in each group could be determined from the tables in the report. From these data the relative risk and its confidence interval were calculated.

### 7.1.1 Meta-analysis

Four meta-analyses were carried out to evaluate the effect of rbST on clinical mastitis frequency.

- Effects of rbST on clinical mastitis incidence rate (i.e. incidence rate ratio) based on studies using all companies' products.
    - Effects of rbST on clinical mastitis incidence rate (i.e. incidence rate ratio) based on studies using Monsanto's product.
    - Effects of rbST on clinical mastitis incidence risk (i.e. relative risk) based on studies using all companies' products.
    - Effects of rbST on clinical mastitis incidence risk (i.e. relative risk) based on studies using Monsanto's product.

. meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline( 1) ltrunc (.33) rtrunc (8) xlabel (.33, .5, .75, 1, 1.5, 2, 3,8 ) b2 ("**Clinical Mastitis Rate - All Companies**")

**Meta-analysis (exponential form)**

#### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.242 | 1.100 | 1.403 | 3.498 | 0.000 | 18 |
| Random | 1.242 | 1.100 | 1.403 | 3.498 | 0.000 | |

Test for heterogeneity: Q= 13.876 on 17 degrees of freedom (p= 0.676) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 14.47 | 14.47 | 1.19 | 0.71 | 1.99 |
| 1 Mp1 | 5.04 | 5.04 | 0.73 | 0.30 | 1.75 |
| 136 Em1 | 24.83 | 24.83 | 0.75 | 0.51 | 1.11 |
| 136 Ep1 | 15.76 | 15.76 | 1.54 | 0.94 | 2.52 |
| 168 Cm1 | 8.77 | 8.77 | 1.81 | 0.93 | 3.51 |
| 168 Cm2 | 3.03 | 3.03 | 1.53 | 0.50 | 4.71 |
| 168 Cp1 | 2.01 | 2.01 | 2.25 | 0.56 | 8.96 |
| 168 Cp2 | 1.57 | 1.57 | 0.88 | 0.18 | 4.21 |
| 644 Ma1 | 0.94 | 0.94 | 1.00 | 0.13 | 7.58 |
| 644 Ma2 | 0.46 | 0.46 | 8.00 | 0.44 | 145.51 |
| 5298 Ea2 | 2.60 | 2.60 | 1.33 | 0.39 | 4.48 |

| | | | | | |
|---|---|---|---|---|---|
| 5407 Mm1 | 80.67 | 80.67 | 1.32 | 1.06 | 1.64 |
| 5407 Mp1 | 29.47 | 29.47 | 1.22 | 0.85 | 1.75 |
| 5409 Ma1 | 3.61 | 3.61 | 1.38 | 0.49 | 3.87 |
| 5409 Ma2 | 1.23 | 1.23 | 0.60 | 0.10 | 3.51 |
| 5409 Ma3 | 1.67 | 1.67 | 0.93 | 0.20 | 4.24 |
| 5415 Ma1 | 10.45 | 10.45 | 1.45 | 0.79 | 2.66 |
| 5422 Mm1 | 53.73 | 53.73 | 1.29 | 0.99 | 1.69 |

Clinical Mastitis Rate - All Companies

. meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline (1) ltrunc (.33) rtrunc (8) xlabel (.33, .5, .75, 1, 1.5, 2, 3,8 ) b2 ("**Clinical Mastitis Rate-Monsanto**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.269 | 1.106 | 1.457 | 3.387 | 0.001 | 11 |
| Random | 1.269 | 1.106 | 1.457 | 3.387 | 0.001 | |

Test for heterogeneity: Q= 4.450 on 10 degrees of freedom (p= 0.925) Moment-based estimate of between studies variance = 0.000

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 14.47 | 14.47 | 1.19 | 0.71 | 1.99 |
| 1 Mp1 | 5.04 | 5.04 | 0.73 | 0.30 | 1.75 |
| 644 Ma1 | 0.94 | 0.94 | 1.00 | 0.13 | 7.58 |
| 644 Ma2 | 0.46 | 0.46 | 8.00 | 0.44 | 145.51 |
| 5407 Mm1 | 80.67 | 80.67 | 1.32 | 1.06 | 1.64 |
| 5407 Mp1 | 29.47 | 29.47 | 1.22 | 0.85 | 1.75 |
| 5409 Ma1 | 3.61 | 3.61 | 1.38 | 0.49 | 3.87 |
| 5409 Ma2 | 1.23 | 1.23 | 0.60 | 0.10 | 3.51 |
| 5409 Ma3 | 1.67 | 1.67 | 0.93 | 0.20 | 4.24 |
| 5415 Ma1 | 10.45 | 10.45 | 1.45 | 0.79 | 2.66 |
| 5422 Mm1 | 53.73 | 53.73 | 1.29 | 0.99 | 1.69 |

Clinical Mastitis Rate - Monsanto

meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline(1) ltrunc (.33) rtrunc (6) xlabel (.33, .5, .75, 1, 1.5, 2, 3,6 ) b2 ("**Clinical Mastitis Risk -All Companies**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.271 | 1.131 | 1.429 | 4.016 | 0.000 | 29 |
| Random | 1.271 | 1.131 | 1.429 | 4.016 | 0.000 | |

Test for heterogeneity: Q= 16.443 on 28 degrees of freedom (p= 0.959) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 3.28 | 3.28 | 0.91 | 0.31 | 2.69 |
| 1 Mp1 | 4.28 | 4.28 | 0.83 | 0.32 | 2.14 |
| 20 Ma1 | 18.90 | 18.90 | 1.08 | 0.69 | 1.70 |
| 136 Em1 | 19.47 | 19.47 | 0.90 | 0.58 | 1.40 |
| 136 Ep1 | 9.18 | 9.18 | 1.30 | 0.68 | 2.48 |

| | | | | | |
|---|---|---|---|---|---|
| 168 Cm1 | 8.45 | 8.45 | 1.45 | 0.74 | 2.85 |
| 168 Cm2 | 4.23 | 4.23 | 1.35 | 0.52 | 3.50 |
| 168 Cp1 | 3.05 | 3.05 | 1.75 | 0.57 | 5.38 |
| 168 Cp2 | 2.06 | 2.06 | 0.83 | 0.21 | 3.26 |
| 261 Ma1 | 3.93 | 3.93 | 2.50 | 0.93 | 6.72 |
| 279 Ca1 | 1.32 | 1.32 | 1.00 | 0.18 | 5.51 |
| 281 Ca1 | 11.68 | 11.68 | 0.96 | 0.54 | 1.70 |
| 329 Ma1 | 3.27 | 3.27 | 0.95 | 0.32 | 2.81 |
| 329 Ma2 | 2.60 | 2.60 | 1.31 | 0.39 | 4.42 |
| 416 Ma1 | 18.13 | 18.13 | 1.45 | 0.92 | 2.30 |
| 425 Ma1 | 4.83 | 4.83 | 1.02 | 0.42 | 2.49 |
| 627 Ca1 | 8.29 | 8.29 | 1.40 | 0.71 | 2.77 |
| 730 Ma1 | 2.55 | 2.55 | 1.80 | 0.53 | 6.14 |
| 5403 Ca1 | 6.18 | 6.18 | 1.91 | 0.87 | 4.20 |

| | | | | | |
|---|---|---|---|---|---|
| 5407 Mp1 | 24.37 | 24.37 | 1.19 | 0.80 | 1.77 |
| 5409 Ma1 | 3.60 | 3.60 | 1.40 | 0.50 | 3.93 |
| 5409 Ma2 | 1.30 | 1.30 | 0.67 | 0.12 | 3.73 |
| 5409 Ma3 | 2.51 | 2.51 | 1.11 | 0.32 | 3.83 |
| 5414 Ma1 | 0.85 | 0.85 | 4.87 | 0.58 | 40.80 |
| 5418 Ma1 | 4.37 | 4.37 | 2.60 | 1.02 | 6.64 |
| 5421 Mm1 | 0.90 | 0.90 | 4.00 | 0.51 | 31.42 |
| 5422 Mm1 | 36.16 | 36.16 | 1.37 | 0.99 | 1.90 |

Clinical Mastitis Risk - All Companies

. meta val cilow cihigh , ci eform pr gr(f) id (std_lbl) cl xline(1) ltrunc (.33) rtrunc(6) xlabel (.33, .5, .75, 1, 1.5, 2, 3,6 ) b2 ("**Clinical Mastitis Risk - Monsanto**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.291 | 1.123 | 1.483 | 3.600 | 0.000 | 18 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Random | 1.291 | 1.123 | 1.483 | 3.600 | 0.000 | |

Test for heterogeneity: Q= 10.422 on 17 degrees of freedom (p= 0.885) Moment-based estimate of between studies variance = 0.000

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 3.28 | 3.28 | 0.91 | 0.31 | 2.69 |
| 1 Mp1 | 4.28 | 4.28 | 0.83 | 0.32 | 2.14 |
| 20 Ma1 | 18.90 | 18.90 | 1.08 | 0.69 | 1.70 |
| 261 Ma1 | 3.93 | 3.93 | 2.50 | 0.93 | 6.72 |
| 329 Ma1 | 3.27 | 3.27 | 0.95 | 0.32 | 2.81 |
| 329 Ma2 | 2.60 | 2.60 | 1.31 | 0.39 | 4.42 |
| 416 Ma1 | 18.13 | 18.13 | 1.45 | 0.92 | 2.30 |
| 425 Ma1 | 4.83 | 4.83 | 1.02 | 0.42 | 2.49 |
| 730 Ma1 | 2.55 | 2.55 | 1.80 | 0.53 | 6.14 |
| 5407 Mm1 | 63.36 | 63.36 | 1.26 | 0.98 | 1.61 |

| | | | | | |
|---|---|---|---|---|---|
| 5407 Mp1 | 24.37 | 24.37 | 1.19 | 0.80 | 1.77 |
| 5409 Ma1 | 3.60 | 3.60 | 1.40 | 0.50 | 3.93 |
| 5409 Ma2 | 1.30 | 1.30 | 0.67 | 0.12 | 3.73 |
| 5409 Ma3 | 2.51 | 2.51 | 1.11 | 0.32 | 3.83 |
| 5414 Ma1 | 0.85 | 0.85 | 4.87 | 0.58 | 40.80 |
| 5418 Ma1 | 4.37 | 4.37 | 2.60 | 1.02 | 6.64 |
| 5421 Mm1 | 0.90 | 0.90 | 4.00 | 0.51 | 31.42 |
| 5422 Mm1 | 36.16 | 36.16 | 1.37 | 0.99 | 1.90 |

Clinical Mastitis Risk - Monsanto

### 7.1.2 Comments and Conclusions

The incidence rate ratios and the relative risk estimates from the four meta-analyses ranged from 1.24 to 1.29. This would correspond to a 24 to 29 % increase in the frequency of clinical mastitis. Most of the evidence about the effect of rbST on clinical mastitis frequency came from the PAMP study ([12]) and Monsanto's multi-location study ([4]) (i.e. these studies were assigned the greatest weight in the meta-analyses).

One recent study was designed specifically to evaluate the effect of rbST on clinical mastitis ([21]). That study reported an overall incidence rate ratio (irr) of 1.22 which would agree quite closely with the results of the meta-analyses. In that study, 1 farm had a statistically significant increased frequency of clinical mastitis while 3 other farms had non-significant increases or decreases. Since the standard error of the incidence rate ratio could not be determined from the report, these results were not included in the meta-analyses.

Overall, the panel concluded that current evidence suggests that rbST increases the frequency of clinical mastitis by approximately 25% during the treatment period.

### 7.1.3 Are the Effects Direct or Indirect ?

There has been some discussion in the literature as to whether the increased frequency of clinical mastitis associated with rbST is due simply to the indirect effects of increasing milk production or if there is a direct increased risk associated with use of the product. It has been argued that this point is academic in that, even if the effect is indirect (i.e. mediated through increased milk production), it still represents an effect of administration of the drug ([22]). However, very few studies attempted to address this question directly by carrying out separate analyses that control or do not control for level of milk production using multi-variable models.

It is generally accepted that there is genetic antagonism between milk production and risk of mastitis. As cows are selected for higher milk producing ability the risk of mastitis increases. In a review of the genetics of disease resistance, Shook reported estimates of the genetic correlation between milk yield and clinical mastitis that ranged from -0.35 to +0.76 ([23]). Two simulation studies evaluating the potential impact of genetic selection for milk production assumed an average genetic correlation of 0.3.

However, although milk production levels of cows are continually increasing over time the overall incidence of clinical mastitis does not appear to be increasing as rapidly. The lactation incidence risk reported for cows in Southern Ontario was 16.8 % in the early 1980's ([24]) and approximately 15 years later in the mid 1990's it was 19.8 % ([25]). Over the same period milk production has risen approximately 40% per cow. Although it was inevitable that there were some differences in definitions and recording procedures between the two studies the lack of a substantial difference may indicate either that the expected increase in the frequency of clinical mastitis associated with genetic progress in milk production is not really large or that improvements in management practices have kept pace with the increased risk through genetic selection.

### 7.1.4 Expected Increase In Cases of Clinical Mastitis

However, it is important to note that an increased risk of 25% does not equate to an overall increase of 25% in the number of cases of clinical mastitis in the dairy industry for two reasons. First, the increase in risk is only observed during the treatment period which should commence at 56-70 days after calving according to the proposed label direction. Secondly, Canada has a supply management milk marketing system which endeavours to match milk supply with demand. If a producer reduced the number of cows milked to offset the increased production associated with the use of the product then the total number of cases would also be reduced. In order to obtain an estimate of the expected number of additional cases of mastitis some computations based on the distribution of mastitis and the distribution of milk production over a lactation were carried out. The details of the calculations and the assumptions used are included in Appendix 10.

Results of the calculations suggest that rbST would produce an increase of approximately 19.4% in the total number of cases of mastitis per cow. If the producer reduced the herd size to keep

total milk production constant (given that production per cow has increased) there will be approximately a 10.4% increase in the total number of cases of mastitis expected.

### 7.1.5 Antibiotic Residues

Based on the assumption of an approximate 10% increase in the risk of clinical mastitis cases per liter of milk produced, the Panel considered the potential for increased levels of antibiotic residues entering the food chain. There is now a great awareness amongst dairy producers of the problem of antibiotic residues in milk. In addition, there is rigid program for regular monitoring of all milk shipments to dairy processors (involving every tanker load of milk being tested for antibiotic residues). Consequently, the Panel felt that the probability of increased antibiotic residues in dairy products was very small.

### 7.1.6 Ability to Control/Eliminate Detrimental Effects

An assessment of whether or not udder health management practices available today are adequate to control or eliminate the increase risk of clinical mastitis is, at best, a subjective assessment. There are certainly new procedures available which may reduce levels of clinical mastitis in a herd and these include improved cow comfort and environmental management systems, the use of core antigen vaccines, pre-milk teat preparation, and improved monitoring programs for clinical mastitis. However, it was the view of the Panel that while these would reduce the risk of increased clinical mastitis, they would not eliminate it. It is also important to note that the availability of management practices to control clinical mastitis does not equate to the adoption of these practices. Whether or not advanced mastitis control practices would be adopted in herds using rbST is not known.

### 7.1.7 Additional Information Required

The Panel did not feel that additional information was required to determine whether or not rbST has an effect on the frequency of clinical mastitis.

However, there was little information in the literature about the nature of the cases of clinical mastitis observed. In particular, the distribution of etiologic agents was not determined in many studies. This information is important in evaluating whether newer udder health management programs will adequately control the problem. For example, one of the relatively new techniques, vaccination with a core antigen vaccine, is specifically for use against coliform infections. The Panel felt that additional information about the nature of the increased frequency of clinical mastitis would be required to do the best possible job of managing the problems in herds in which rbST was used.

## 7.2 Subclinical Mastitis

The prevalence of subclinical mastitis in treated and non - treated cows was assessed by looking at two general parameters. First, somatic cell counts, which are a measure of inflamation in the udder and are an indirect indicator of subclinical infections were examined. Second the prevalence of intramammary pathogens as determined from cultures of milk samples were considered.

Somatic cell count data were reported in various studies using any of the following scales: untransformed data, $\log_2$ transformed data, $\log_{10}$ transformed data, or natural log ($\log_e$) transformed data . Previous research has shown that somatic cell count data should be log transformed for appropriate analysis. Consequently, papers which reported somatic cell counts as raw counts (untransformed data) were not included in the analyses.

Most studies evaluated the effects of rbST on SCC throughout the treatment period through the regular collection of milk samples for analysis. While it is appropriate to evaluate the effect of rbST on milk production throughout the treatment period because the response to the drug is very rapid, it can be argued that any effect of rbST on the somatic cell count would be delayed in onset. This would likely arise from cows requiring a period of time on rbST before the prevalence of intramammary infections would rise and, in turn, result in an increased somatic cell count. Consequently, estimates of the effects of rbST on subclinical mastitis as measured by SCC may be biased towards the null (i.e. no effect) by the inclusion of data from the beginning of the treatment period.

While several studies reported culture results from samples collected throughout the treatment period, only data from the last sample collection in which most of the cows were still milking were used in the meta-analyses. Consequently, the relative risk for the occurrence of a pathogen was based on only one sampling period per cow. This avoided the statistical problem of dealing with repeated measures since this problem could not be readily handled without the raw individual cow data being available for analysis.

### 7.2.1 Meta-analysis

Six meta-analyses were carried out to evaluate the effect of rbST on the prevalence of subclinical mastitis.

- Effects of rbST on linear score SCC based on studies using all companies' products.
- Effects of rbST on linear score SCC based on studies using Monsanto's product.
- Effects of rbST on $\log_{10}$ SCC based on studies using all companies' products.
- Effects of rbST on $\log_{10}$ SCC based on studies using Monsanto's product.
- Effects of rbST on prevalence of intramammary pathogens from bacteriological cultures of milk samples based on studies using all companies' products.
- Effects of rbST on prevalence of intramammary pathogens from bacteriological cultures of milk samples based on studies using Monsanto's product.

. meta val se , pr gr(f) id (std_lbl) cl xline(0) ltrunc(-.6) rtrunc (.4) xlabel (-.6, -.4, -.2, 0, .2, .4) b2 ("**SCC Linear Score - All Companies**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.083 | -0.002 | 0.168 | 1.915 | 0.055 | 5 |
| Random | 0.076 | -0.026 | 0.179 | 1.456 | 0.145 | |

Test for heterogeneity: Q= 5.102 on 4 degrees of freedom (p= 0.277) Moment-based estimate of between studies variance = 0.003

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 5135 Ca1 | 198.37 | 124.65 | 0.08 | -0.06 | 0.22 |
| 5135 Ca2 | 198.37 | 124.65 | 0.13 | -0.01 | 0.27 |
| 5407 Mm1 | 29.54 | 27.15 | -0.30 | -0.66 | 0.06 |
| 5407 Mp1 | 24.03 | 22.42 | 0.20 | -0.20 | 0.60 |
| 5417 Ma1 | 82.64 | 66.31 | 0.08 | -0.14 | 0.30 |

SCC Linear Score - All Companies

. meta val se , pr gr(f) id (std_lbl) cl xline(0) ltrunc(-.6) rtrunc(.4) xlabel (-.6, -.4, -.2, 0, .2, .4) b2 ("**SCC Linear Score - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.019 | -0.149 | 0.187 | 0.219 | 0.827 | 3 |
| Random | 0.000 | -0.262 | 0.263 | 0.003 | 0.998 | |

Test for heterogeneity: Q= 4.100 on 2 degrees of freedom (p= 0.129) Moment-based estimate of between studies variance = 0.028

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 5407 Mm1 | 29.54 | 16.21 | -0.30 | -0.66 | 0.06 |
| 5407 Mp1 | 24.03 | 14.40 | 0.20 | -0.20 | 0.60 |
| 5417 Ma1 | 82.64 | 25.03 | 0.08 | -0.14 | 0.30 |

SCC Linear Score - Monsanto

. meta val se, prgr (f) id (std_lbl) cl xline (0) ltrunc(-1) rtrunc (1) xlabel (-1, -.75, -.5, -.25, 0, .25, .5, .75,1) b2 ("**SCC Log 10 - All Companies**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.023 | -0.016 | 0.063 | 1.151 | 0.250 | 11 |
| Random | 0.023 | -0.016 | 0.063 | 1.151 | 0.250 | |

Test for heterogeneity: Q= 9.807 on 10 degrees of freedom (p= 0.458) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 168.66 | 168.66 | 0.07 | -0.08 | 0.22 |
| 1 Mp1 | 198.37 | 198.37 | 0.05 | -0.09 | 0.19 |
| 2 Ma1 | 17.36 | 17.36 | 0.51 | 0.04 | 0.98 |
| 34 Ma9 | 318.88 | 318.88 | -0.04 | -0.15 | 0.07 |
| 261 Ma1 | 0.56 | 0.56 | 0.00 | -2.63 | 2.63 |
| 281 Ca1 | 7.63 | 7.63 | 0.21 | -0.50 | 0.92 |

| | | | | | |
|---|---|---|---|---|---|
| 344 Mm1 | 168.66 | 168.66 | 0.07 | -0.08 | 0.22 |
| 344 Mp1 | 198.37 | 198.37 | 0.05 | -0.09 | 0.19 |
| 2215 Ma1 | 35.43 | 35.43 | 0.20 | -0.13 | 0.53 |
| 5415 Ma1 | 1275.51 | 1275.51 | 0.00 | -0.05 | 0.05 |
| 5422 Mm1 | 42.72 | 42.72 | 0.20 | -0.10 | 0.50 |

SCC Log $_{10}$ - All Companies

. meta val se, pr gr (f) id (std_lbl) cl xline (0) ltrunc (-1) rtrunc (1) xlabel (-1,-.75,-.5,-.25, 0, .25, .5, .75,1) b2 ("**SCC Log 10 - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.023 | -0.017 | 0.063 | 1.121 | 0.262 | 10 |
| Random | 0.027 | -0.017 | 0.071 | 1.208 | 0.227 | |

Test for heterogeneity: Q= 9.541 on 9 degrees of freedom (p= 0.389) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 168.66 | 159.85 | 0.07 | -0.08 | 0.22 |
| 1 Mp1 | 198.37 | 186.29 | 0.05 | -0.09 | 0.19 |
| 2 Ma1 | 17.36 | 17.26 | 0.51 | 0.04 | 0.98 |
| 34 Ma9 | 318.88 | 288.78 | -0.04 | -0.15 | 0.07 |
| 261 Ma1 | 0.56 | 0.56 | 0.00 | -2.63 | 2.63 |
| 344 Mm1 | 168.66 | 159.85 | 0.07 | -0.08 | 0.22 |
| 344 Mp1 | 198.37 | 186.29 | 0.05 | -0.09 | 0.19 |
| 2215 Ma1 | 35.43 | 35.03 | 0.20 | -0.13 | 0.53 |
| 5415 Ma1 | 1275.51 | 900.17 | 0.00 | -0.05 | 0.05 |
| 5422 Mm1 | 42.72 | 42.13 | 0.20 | -0.10 | 0.50 |

SCC Log $_{10}$ - Monsanto

. meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline (1) ltrunc (.33) rtrunc (6) xlabel (.33, .5, .75, 1, 1.5, 2, 3,6 ) b2 ("**Subclinical Mastitis Pre valence - All Companies**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.065 | 0.839 | 1.353 | 0.518 | 0.604 | 7 |
| Random | 1.065 | 0.839 | 1.353 | 0.518 | 0.604 | |

Test for heterogeneity: Q= 5.588 on 6 degrees of freedom (p= 0.471) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 5.64 | 5.64 | 1.50 | 0.66 | 3.42 |
| 1 Mp1 | 6.30 | 6.30 | 1.50 | 0.69 | 3.28 |
| 5 Mm1 | 2.86 | 2.86 | 1.33 | 0.42 | 4.24 |
| 5 Mp1 | 1.84 | 1.84 | 3.69 | 0.87 | 15.67 |
| 136 Em1 | 21.16 | 21.16 | 0.89 | 0.58 | 1.36 |
| 136 Ep1 | 15.28 | 15.28 | 1.03 | 0.62 | 1.70 |

| | | | | | |
|---|---|---|---|---|---|
| 406 Ca1 | 14.04 | 14.04 | 0.88 | 0.52 | 1.48 |

Subclinical Mastitis Pre valence - All Companies

. meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline(1) ltrunc (.33) rtrunc(6) xlabel (.33, .5, .75, 1, 1.5, 2, 3,6 ) b2 ("**Subclinical Mastitis Pre valence - Monsanto**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.623 | 1.004 | 2.624 | 1.975 | 0.048 | 4 |
| Random | 1.623 | 1.004 | 2.624 | 1.975 | 0.048 | |

Test for heterogeneity: Q= 1.427 on 3 degrees of freedom (p= 0.699) Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 5.64 | 5.64 | 1.50 | 0.66 | 3.42 |
| 1 Mp1 | 6.30 | 6.30 | 1.50 | 0.69 | 3.28 |
| 5 Mm1 | 2.86 | 2.86 | 1.33 | 0.42 | 4.24 |

| | | | | | |
|---|---|---|---|---|---|
| 5 Mp1 | 1.84 | 1.84 | 3.69 | 0.87 | 15.67 |

(Meta-analysis based in sampling periods 5 and 7 in studies #1 and #5 respectively)

Subclinical Mastitis Pre valence - Monsanto

### 7.2.2 Comments and Conclusions

In general the meta-analyses of somatic cell count data did not show much evidence of an effect of rbST. The fixed effect analysis of the SCC-linear score using data from all companies' products achieved marginal statistical significance (P = 0.055) but the result of this meta-analysis was substantially driven by a single small two lactation study involving 30 cows ([26]). The PAMP linear score data ([12]) was based only on linear scores determined between treatment days 110 and 200.

The $\log_{10}$ SCC results were heavily influenced by a single, short term (12 week) study ([14]) in which no effect on SCC was observed but which apparently had very precise estimates of the average SCC. If this study was omitted from the meta-analysis, the overall effect increased to 0.049 (P=0.095).

Overall, the Panel concluded that although their was an apparent trend toward slightly increased SCC during the treatment period, no firm conclusion that such an effect was present could be drawn. Even if the effect were present, it was relatively small. An increase of 0.05 units in the $\log_{10}$ SCC over the baseline in the control cows would only correspond to an increase from 38,900 cells/ml to 43,600 cells/ml.

When the prevalence data were examined it was evident that the point estimates of the relative risk for the prevalence of subclinical mastitis varied quite widely, especially when results from all companies' studies were included. Consequently, the Panel focused on studies based on Monsanto's products even though results were only available from 4 groups of cows in 2 studies. The results were also based on all organisms combined since there were too few isolates of individual organisms to support meaningful analyses. In all 4 groups, the point estimate of the relative risk was greater than 1 and the pooled estimate was 1.62 (P=0.048) suggesting a 62% increase in the prevalence of intramammary infections. However, the confidence interval for this estimate was very wide (1.004, 2.624).

The only other direct measure of intramammary infections recorded in the database was an estimate of the new infection rate determined in each year of a 2 year study ([26]) using Cyanamid's product. That study reported relative risks of new infections greater than 1 in each of the two years although neither was statistically significant. The Panel concluded that there was an increase in the prevalence of subclinical mastitis. However, it should be noted that although the point estimate of the relative risk was 1.62 (equivalent to a 62% increase in the prevalence of intramammary pathogens) this estimate had a very wide 95% confidence interval of 1.004 to 2.62.

When the evidence from the analyses of somatic cell counts and milk sample cultures were taken together, the data available did not allow the Panel to draw strong conclusions about the potential effects of rbST on subclinical mastitis. In general, subclinical mastitis is difficult to quantify and it is even more difficult to get a good evaluation of the etiological agents involved. Most of the trials conducted were directed at evaluating the effect of the drug on milk production. These studies were not designed to delve into the potential problem of subclinical mastitis in any depth. There appeared to be a discrepancy between the somatic cell count data and the prevalence data with the former suggesting little effect and the latter identifying a increased prevalence of subclinical mastitis. Much of this difference could be attributed to the fact that the cell count data were accumulated over the whole treatment period while the prevalence of infection data were selected from the end of the treatment period. Overall, the Panel concluded that there probably was an increased prevalence of subclinical intramammary infections in rbST treated cows, but that it was difficult to quantify the magnitude of the increase.

### 7.2.3 Ability to Control/Eliminate Detrimental Effects

In general, increased levels of subclinical mastitis may be more amenable to control than an increased frequency of clinical mastitis. Dry cow antibiotic therapy at the end of lactation could be expected to eliminate many of these subclinical infections. However, the use of dry cow therapy is variable across herds. The Panel did recognize a concern if there was an increased prevalence of Staph. aureus infections. These are often difficult to eliminate and represent a considerable biosecurity risk for spread of infection to other cows. However, in general the Panel felt that the effect on rbST on subclinical mastitis was manageable.

### 7.2.4 Additional Information Required

In general, there was relatively little information about the effects of rbST on subclinical mastitis. More information about the nature of udder health problems, and in particular the etiologic agents involved would be required to better assess the effects of rbST and to deal effectively with any problems that arose from use of the product.

# 8. Reproduction

The panel evaluated a number of measures of reproductive health and performance. Parameters that either affect or reflect the breeding performance will be presented first. These include:

- incidence of cystic ovaries,
- number of services required per conception,
- average duration from calving to conception (days open),
- incidence of twinning (multiple births) and,
- overall risk of a cow not becoming pregnant.

Subsequently three parameters that reflect the state of the cow during her gestation period and at the subsequent calving were evaluated and these included:

- the risk of abortion/fetal loss,
- effect of rbST on gestation length, and
- incidence of retained placenta.

## 8.1 Incidence of Cystic Ovaries

Most studies reported the incidence of cystic ovaries in terms of the risk of this condition (i.e.the number of cows affected divided by the number of cows at risk).

### 8.1.1 Meta-analysis

Two meta-analyses were carried out.

- Effects of rbST on the risk of cystic ovaries based on studies using all companies' products.
- Effects of rbST on the risk of cystic ovaries based on studies using Monsanto's product.

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1)ltrunc(.33) rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Cystic Ovaries Risk - All Companies**")

**Meta-analysis (exponential form)**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.224 | 0.953 | 1.572 | 1.583 | 0.113 | 8 |
| Random | 1.269 | 0.946 | 1.703 | 1.590 | 0.112 | |

Test for heterogeneity: Q= 8.330 on 7 degrees of freedom (p= 0.304)
Moment-based estimate of between studies variance = 0.028

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 3.64 | 3.30 | 1.09 | 0.39 | 3.04 |
| 1 Mp1 | 2.66 | 2.47 | 1.20 | 0.36 | 3.99 |
| 7 Mm1 | 13.76 | 9.89 | 1.80 | 1.06 | 3.05 |
| 7 Mp1 | 2.50 | 2.33 | 2.56 | 0.74 | 8.85 |
| 291 Ua1 | 1.29 | 1.24 | 1.68 | 0.30 | 9.44 |
| 1218 Ca1 | 1.91 | 1.81 | 3.46 | 0.84 | 14.27 |
| 5407 Mm1 | 22.03 | 13.56 | 0.88 | 0.58 | 1.33 |
| 5407 Mp1 | 13.63 | 9.83 | 1.08 | 0.64 | 1.84 |

Cystic Ovaries Risk - All Companies

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1)ltrunc(.33) rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Cystic Ovaries Risk - Monsanto**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Fixed | 1.174 | 0.908 | 1.518 | 1.227 | 0.220 | 6 |
| Random | 1.201 | 0.891 | 1.619 | 1.204 | 0.228 | |

Test for heterogeneity: Q= 6.036 on 5 degrees of freedom (p= 0.303)
Moment-based estimate of between studies variance = 0.024

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 3.64 | 3.35 | 1.09 | 0.39 | 3.04 |
| 1 Mp1 | 2.66 | 2.50 | 1.20 | 0.36 | 3.99 |
| 7 Mm1 | 13.76 | 10.33 | 1.80 | 1.06 | 3.05 |
| 7 Mp1 | 2.50 | 2.36 | 2.56 | 0.74 | 8.85 |
| 5407 Mm1 | 22.03 | 14.39 | 0.88 | 0.58 | 1.33 |
| 5407 Mp1 | 13.63 | 10.26 | 1.08 | 0.64 | 1.84 |

Cystic Ovaries Risk - Monsanto

### 8.1.2 Comments and Conclusions

With the exception of the multiparous cows in the PAMP study ([12]), all studies reported an increased risk of cystic ovaries associated with rbST treatment, although only one of the individual relative risk estimates was statistically significant. This one significant result was derived from a study in which rbST had been administered intramuscularly ([5]). Overall, it

appeared that treatment increased the risk by approximately 20% although this apparent increase was not statistically significance (P = 0.11).

Two of the papers reviewed, evaluated the mechanism by which rbST may affect ovarian performance and it was found to have an affect on the development and size of ovarian follicles ([27,28]). This would be consistent with a possible increase in the frequency of cystic ovaries.

The Panel concluded that although there appeared to be an increased risk of cystic ovaries in treated cows, most of the evidence for this effect came from a study in which rbST was administered intramuscularly. The Panel concluded that there were insufficient data to draw a firm conclusion about the effect of rbST on cystic ovaries.

## 8.2 Services per Conception (SPC)

Services per conception reflects the number of times that cows which ultimately conceived had to be bred in order to conceive. The parameter does not take into account cows which were bred but which did not conceive.

### 8.2.1 Meta-analysis

Two meta-analyses were carried out to evaluate the effects of rbST on the number of services per conception.

- Effects of rbST on the number of services per conception based on studies using all companies' products.
- Effects of rbST on the number of services per conception based on studies using Monsanto's product.

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-3) rtrunc(3) xlabel(-3, -2, -1, 0, 1, 2, 3) b2("**Services Per Conception - All Companies**")

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.001 | -0.218 | 0.220 | 0.009 | 0.993 | 12 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Random | -0.002 | -0.258 | 0.254 | -0.014 | 0.989 | |

Test for heterogeneity: Q= 13.371 on 11 degrees of freedom (p= 0.270)
Moment-based estimate of between studies variance = 0.035

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 4.96 | 4.23 | -0.80 | -1.68 | 0.08 |
| 1 Mp1 | 5.72 | 4.78 | -0.70 | -1.52 | 0.12 |
| 168 Cm1 | 12.66 | 8.80 | 0.28 | -0.27 | 0.83 |
| 168 Cp1 | 12.66 | 8.80 | 0.10 | -0.45 | 0.65 |
| 168 Cm2 | 5.59 | 4.68 | 0.04 | -0.79 | 0.87 |
| 168 Cp2 | 3.12 | 2.82 | 0.88 | -0.23 | 1.99 |
| 261 Ma1 | 5.59 | 4.68 | 0.30 | -0.53 | 1.13 |
| 644 Ma1 | 0.27 | 0.27 | 0.46 | -3.32 | 4.24 |
| 644 Ma2 | 0.45 | 0.44 | 0.26 | -2.67 | 3.19 |
| 5298 Ea2 | 5.67 | 4.74 | 0.45 | -0.37 | 1.27 |

| | | | | | |
|---|---|---|---|---|---|
| 5418 Ma1 | 2.35 | 2.17 | -0.90 | -2.18 | 0.38 |
| 5422 Mm1 | 20.85 | 12.10 | -0.10 | -0.53 | 0.33 |

Services Per Conception - All Companies

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-3) rtrunc(3) xlabel(-3, -2, -1, 0, 1, 2, 3) b2("**Services Per Conception - Monsanto**")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | -0.255 | -0.564 | 0.054 | -1.618 | 0.106 | 7 |
| Random | -0.258 | -0.572 | 0.056 | -1.613 | 0.107 | |

Test for heterogeneity: Q= 6.061 on 6 degrees of freedom (p= 0.416)
Moment-based estimate of between studies variance = 0.002

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 4.96 | 4.91 | -0.80 | -1.68 | 0.08 |
| 1 Mp1 | 5.72 | 5.65 | -0.70 | -1.52 | 0.12 |

| | | | | | |
|---|---|---|---|---|---|
| 261 Ma1 | 5.59 | 5.52 | 0.30 | -0.53 | 1.13 |
| 644 Ma1 | 0.27 | 0.27 | 0.46 | -3.32 | 4.24 |
| 644 Ma2 | 0.45 | 0.45 | 0.26 | -2.67 | 3.19 |
| 5418 Ma1 | 2.35 | 2.33 | -0.90 | -2.18 | 0.38 |
| 5422 Mm1 | 20.85 | 19.92 | -0.10 | -0.53 | 0.33 |

Services Per Conception - Monsanto

### 8.2.2 Comments and Conclusions

The Panel concluded that there was no effect of rbST on the number of services per conception required in cows which did conceive.

## 8.3 Days Open (DO)

Days open is the number of days from calving until a cow is rebred and conceives. It can only be computed for cows which have a confirmed pregnancy.

### 8.3.1 Meta - Analysis

Two meta-analyses were carried out to evaluate the effects of rbST on the number of days open.

- Effects of rbST on the number of days open based on studies using all companies' products.
- Effects of rbST on the number of days open based on studies using Monsanto's product.

. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-50) rtrunc(100) xlabel(-50, -25, 0, 25, 50, 75, 100) b2("**Days Open - All Companies**")

**Meta-analysis**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 5.120 | 1.230 | 9.010 | 2.579 | 0.010 | 18 |
| Random | 7.151 | 1.115 | 13.188 | 2.322 | 0.020 | |

Test for heterogeneity: Q= 23.212 on 17 degrees of freedom (p= 0.142)
Moment-based estimate of between studies variance = 34.096

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 0.00 | 0.00 | -7.00 | -36.35 | 22.35 |
| 1 Mp1 | 0.00 | 0.00 | -24.00 | -63.78 | 15.78 |
| 7 Mm1 | 0.03 | 0.02 | 2.00 | -8.71 | 12.71 |
| 7 Mp1 | 0.02 | 0.01 | 16.00 | 2.14 | 29.86 |
| 124 Um1 | 0.00 | 0.00 | 76.00 | 19.46 | 132.54 |
| 124 Up1 | 0.00 | 0.00 | 18.00 | -43.04 | 79.04 |
| 124 Ua2 | 0.00 | 0.00 | 56.00 | -2.77 | 114.77 |

| | | | | | |
|---|---|---|---|---|---|
| 168 Cm1 | 0.01 | 0.01 | 17.50 | -3.29 | 38.29 |
| 168 Cp1 | 0.01 | 0.00 | -5.40 | -32.84 | 22.04 |
| 168 Cm2 | 0.13 | 0.02 | 2.20 | -3.34 | 7.74 |
| 168 Cp2 | 0.00 | 0.00 | 29.80 | -11.50 | 71.10 |
| 403 Cp1 | 0.00 | 0.00 | 66.00 | -55.96 | 187.96 |
| 644 Ma1 | 0.00 | 0.00 | 21.00 | -99.49 | 141.49 |
| 644 Ma2 | 0.00 | 0.00 | 7.00 | -96.56 | 110.56 |
| 5298 Ea2 | 0.00 | 0.00 | 18.00 | -23.58 | 59.58 |
| 5407 Mm1 | 0.03 | 0.01 | 7.00 | -5.32 | 19.32 |
| 5407 Mp1 | 0.01 | 0.01 | 16.00 | -2.16 | 34.16 |
| 5418 Ma1 | 0.01 | 0.01 | -8.00 | -29.07 | 13.07 |

Days Open - All Companies

```
. meta val se , pr gr(f) id(std_lbl) cl xline(0) ltrunc(-50) rtrunc(100)
xlabel(-50, -25, 0, 25, 50, 75, 100) b2("Days Open - Monsanto")
```

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 5.627 | -0.376 | 11.629 | 1.837 | 0.066 | 9 |
| Random | 5.577 | -0.738 | 11.891 | 1.731 | 0.083 | |

Test for heterogeneity: Q= 8.406 on 8 degrees of freedom (p= 0.395)
Moment-based estimate of between studies variance = 4.825

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 0.00 | 0.00 | -7.00 | -36.35 | 22.35 |
| 1 Mp1 | 0.00 | 0.00 | -24.00 | -63.78 | 15.78 |
| 7 Mm1 | 0.03 | 0.03 | 2.00 | -8.71 | 12.71 |
| 7 Mp1 | 0.02 | 0.02 | 16.00 | 2.14 | 29.86 |
| 644 Ma1 | 0.00 | 0.00 | 21.00 | -99.49 | 141.49 |
| 644 Ma2 | 0.00 | 0.00 | 7.00 | -96.56 | 110.56 |
| 5407 Mm1 | 0.03 | 0.02 | 7.00 | -5.32 | 19.32 |

| | | | | | |
|---|---|---|---|---|---|
| 5407 Mp1 | 0.01 | 0.01 | 16.00 | -2.16 | 34.16 |
| 5418 Ma1 | 0.01 | 0.01 | -8.00 | -29.07 | 13.07 |

Days Open - Monsanto

### 8.3.2 Comments and Conclusions

When the data from 18 groups studied (involving all companies products) were evaluated there was a small but statistically significant (P=0.01) increase (approximately 5 days) in average days open. When only studies based on Monsanto's data were evaluated, a similar effect was observed although it was not quite statistically significant (P=0.066).

The Panel concluded that there was evidence that the average days open would be slightly increased by the use of rbST. This effect was small and amounted only to approximately 5 extra days. However, as with services per conception, days open was only computed for cows which conceived.

## 8.4 Twinning (Multiple Births)

Twinning is the birth of two calves. In the context of this review, it signifies the birth of two calves at the parturition following the lactation with rbST administration. In general, twin births are considered undesirable because they are much more likely than single births to be followed by complications.

### 8.4.1 Meta-Analysis

Two meta-analyses were carried out to evaluate the effects of rbST on the risk of twinning

- Effects of rbST on risk of twinning based on studies using all companies' products.
- Effects of rbST on risk of twinning based on studies using Monsanto's product.

. meta val cilow cihigh , ci eform pr gr(r) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(12) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6,12 ) b2("**Twinning Risk - All Companies**") t2("random effects")

**Meta-analysis (exponential form)**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.314 | 0.819 | 2.110 | 1.132 | 0.258 | 5 |
| Random | 1.767 | 0.716 | 4.362 | 1.235 | 0.217 | |

Test for heterogeneity: Q= 12.062 on 4 degrees of freedom (p= 0.017)
Moment-based estimate of between studies variance = 0.647

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 7 Mm1 | 0.94 | 0.58 | 11.68 | 1.54 | 88.51 |
| 7 Mp1 | 0.88 | 0.56 | 7.08 | 0.88 | 56.90 |
| 168 Ca2 | 5.55 | 1.21 | 1.57 | 0.68 | 3.61 |
| 5407 Mm1 | 4.68 | 1.16 | 1.45 | 0.59 | 3.59 |
| 5407 Mp1 | 5.10 | 1.19 | 0.50 | 0.21 | 1.18 |

Twinning Risk - All Companies

. meta val cilow cihigh , ci eform pr gr(r) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(12) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6,12 ) b2("**Twinning Risk - Monsanto**") t2("random effects")

**Meta-analysis (exponential form)**

**Effect of rbST on 3.5% FCM**

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.207 | 0.679 | 2.146 | 0.642 | 0.521 | 4 |
| Random | 2.083 | 0.571 | 7.602 | 1.111 | 0.267 | |

Test for heterogeneity: Q= 11.803 on 3 degrees of freedom (p= 0.008)
Moment-based estimate of between studies variance = 1.201

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 7 Mm1 | 0.94 | 0.44 | 11.68 | 1.54 | 88.51 |
| 7 Mp1 | 0.88 | 0.43 | 7.08 | 0.88 | 56.90 |
| 5407 Mm1 | 4.68 | 0.71 | 1.45 | 0.59 | 3.59 |
| 5407 Mp1 | 5.10 | 0.72 | 0.50 | 0.21 | 1.18 |

Twinning Risk - Monsanto

### 8.4.2 Comments and Conclusions

Most of the evidence for, or against, an increased risk of twinning came from the PAMP study ([12]). The results from that study are split. There appeared to be a decreased risk in primiparous cows and an increased risk of twinning in multiparous cows (although neither were statistically significant). One other study ([5]) reported a large increases in risk of twinning associated with

rbST (relative risks of 7.1 and 11.7 in primiparous and multiparous cows respectively although only the latter was statistically significant). However, cows in this latter study were injected intramuscularly and Monsanto suggests that IM injections resulted in a higher incidence of reproductive problems.

The Panel concluded that there may be an increased risk of twinning but no firm conclusions could be drawn.

### 8.4.3 Additional Information Required

The problem with assessing the impact of rbST on twinning was the limited number of studies which followed cows through to calving following treatment with the drug. Although the two main studies providing data on the risk of twinning ([5,12]) had data from a total of 791 cows, one would require data from 2000 cows (1000 cows in each treatment group) to be relatively certain of detecting a doubling of the risk (from 2.5% to 5%).

A recent study published in the Journal of Dairy Science ([29]) has reported a general increased risk of twinning in Holstein Friesian cows with a rise in the incidence from 1.4% of lactations in1983 to 2.4% in 1993. This paper also identified increased milk production and increased frequency of cystic ovarian diseases as risk factors for increasing the number of twins born. Since rbST increases milk production and appears to increase the risk of cystic ovarian disease (P= 0.11) these may both have contributed to the apparent increased risk of twinning which was observed in most of the studies reported.

## 8.5 Non-Pregnancy Risk

Many studies reported the proportion of cows which ultimately conceived during the treatment period (reported as a pregnancy rate). In order to be consistent with other health outcomes, the overall effect of rbST on pregnancy has been evaluated in this report as the risk of the cow failing to conceive (i.e. non-pregnancy).

One difficulty in analyzing these data was the problem of identifying which pregnancies occurred before the onset of treatment and which ones occurred afterwards. Whenever possible, data from the two time periods were separated and only those from the treatment period were used in the analysis.

### 8.5.1 Meta-analysis

Two meta-analyses were carried out to evaluate the effects of rbST on the non-pregnancy risk .

- Effects of rbST on the non-pregnancy risk based on studies using all companies' products.
- Effects of rbST on the non-pregnancy risk based on studies using Monsanto's product.

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Non-Pregnancy Risk - All Companies**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.434 | 1.229 | 1.674 | 4.579 | 0.000 | 20 |
| Random | 1.434 | 1.229 | 1.674 | 4.579 | 0.000 | |

Test for heterogeneity: Q= 18.968 on 19 degrees of freedom (p= 0.459)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1.56 | 1.56 | 2.73 | 0.57 | 13.10 |
| 1 Mp1 | 0.79 | 0.79 | 2.89 | 0.32 | 26.06 |
| 7 Mm1 | 20.92 | 20.92 | 1.34 | 0.87 | 2.06 |
| 7 Mp1 | 3.83 | 3.83 | 3.84 | 1.41 | 10.45 |
| 157 Um1 | 1.85 | 1.85 | 3.00 | 0.71 | 12.68 |

| | | | | | |
|---|---|---|---|---|---|
| 157 Up1 | 2.40 | 2.40 | 1.67 | 0.47 | 5.92 |
| 157 Ua2 | 5.89 | 5.89 | 2.40 | 1.07 | 5.38 |
| 168 Cm1 | 5.06 | 5.06 | 0.91 | 0.38 | 2.17 |
| 168 Cp1 | 3.30 | 3.30 | 1.24 | 0.42 | 3.65 |
| 168 Cm2 | 3.09 | 3.09 | 2.01 | 0.66 | 6.13 |
| 168 Cp2 | 1.40 | 1.40 | 0.83 | 0.16 | 4.35 |
| 291 Ua1 | 10.09 | 10.09 | 1.22 | 0.66 | 2.26 |
| 403 Cp1 | 13.76 | 13.76 | 1.10 | 0.65 | 1.87 |
| 644 Ma1 | 2.03 | 2.03 | 1.67 | 0.42 | 6.60 |
| 644 Ma2 | 2.15 | 2.15 | 1.67 | 0.44 | 6.35 |
| 5403 Ca1 | 6.34 | 6.34 | 3.33 | 1.53 | 7.25 |
| 5407 Mm1 | 37.72 | 37.72 | 1.42 | 1.03 | 1.95 |
| 5407 Mp1 | 12.19 | 12.19 | 0.97 | 0.55 | 1.70 |
| 5418 Ma1 | 25.06 | 25.06 | 1.26 | 0.85 | 1.86 |

| | | | | | |
|---|---|---|---|---|---|
| 5425 M | 1.62 | 1.62 | 3.75 | 0.80 | 17.53 |

Non-Pregnancy Risk - All Companies

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Non-Pregnancy Risk- Monsanto**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.404 | 1.163 | 1.696 | 3.525 | 0.000 | 10 |
| Random | 1.404 | 1.163 | 1.696 | 3.525 | 0.000 | |

Test for heterogeneity: Q= 8.678 on 9 degrees of freedom (p= 0.467)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 1.56 | 1.56 | 2.73 | 0.57 | 13.10 |
| 1 Mp1 | 0.79 | 0.79 | 2.89 | 0.32 | 26.06 |
| 7 Mm1 | 20.92 | 20.92 | 1.34 | 0.87 | 2.06 |

| | | | | | |
|---|---|---|---|---|---|
| 7 Mp1 | 3.83 | 3.83 | 3.84 | 1.41 | 10.45 |
| 644 Ma1 | 2.03 | 2.03 | 1.67 | 0.42 | 6.60 |
| 644 Ma2 | 2.15 | 2.15 | 1.67 | 0.44 | 6.35 |
| 5407 Mm1 | 37.72 | 37.72 | 1.42 | 1.03 | 1.95 |
| 5407 Mp1 | 12.19 | 12.19 | 0.97 | 0.55 | 1.70 |
| 5418 Ma1 | 25.06 | 25.06 | 1.26 | 0.85 | 1.86 |
| 5425 M . | 1.62 | 1.62 | 3.75 | 0.80 | 17.53 |

Non-Pregnancy Risk - Monsanto

### 8.5.2 Comments and Conclusions

Although the point estimates of the relative risk of non-pregnancy varied widely across studies, they were quite consistently greater than 1. Overall, the relative risk of non-pregnancy was approximately 1.4 (equivalent to a 40% increase in the risk of non-pregnancy).

One study ([30]) reported conception data in terms of the hazard ratio for pregnancy (which estimates the risk of a treated cow getting pregnant at a given point in time compared to the risk of a control cow). That study reported a significantly reduced hazard ratios (0.38) which indicates that treated cows were less likely to conceive.

The Panel concluded that the use of rbST in non-pregnant cows increased the risk of the cow not becoming pregnant by approximately 40%. In commercial dairy operations, failure to conceive would normally result in the cow being culled. (See Section 8.9 - Overall Assessment of Reproductive Effects)

## 8.6 Risk of Abortion

### 8.6.1 Meta-analysis

Two meta-analysis were carried out to evaluate the effect of rbST on the risk of abortion.

- Effects of rbST on the risk of abortion based on studies using all companies' products.
- Effects of rbST on the risk of abortion based on studies using Monsanto's product.

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Abortion Risk - All Companies**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.177 | 0.751 | 1.845 | 0.710 | 0.478 | 6 |
| Random | 1.165 | 0.712 | 1.905 | 0.608 | 0.543 | |

Test for heterogeneity: Q= 5.679 on 5 degrees of freedom (p= 0.339)
Moment-based estimate of between studies variance = 0.047

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Ma1 | 1.58 | 1.47 | 3.10 | 0.65 | 14.77 |
| 127 Um1 | 2.66 | 2.36 | 0.47 | 0.14 | 1.56 |
| 127 Up1 | 2.63 | 2.34 | 1.00 | 0.30 | 3.35 |

| | | | | | |
|---|---|---|---|---|---|
| 127 Um2 | 1.78 | 1.64 | 0.57 | 0.13 | 2.48 |
| 5407 Mm1 | 7.59 | 5.60 | 1.37 | 0.67 | 2.79 |
| 5407 Mp1 | 2.78 | 2.46 | 2.00 | 0.62 | 6.48 |

Abortion Risk - All Companies

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Abortion Risk - Monsanto**")

**Meta-analysis (exponential form)**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.666 | 0.945 | 2.938 | 1.765 | 0.078 | 3 |
| Random | 1.666 | 0.945 | 2.938 | 1.765 | 0.078 | |

Test for heterogeneity: Q= 0.991 on 2 degrees of freedom (p= 0.609)
Moment-based estimate of between studies variance = 0.000

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Ma1 | 1.58 | 1.58 | 3.10 | 0.65 | 14.77 |

| | | | | | |
|---|---|---|---|---|---|
| 5407 Mm1 | 7.59 | 7.59 | 1.37 | 0.67 | 2.79 |
| 5407 Mp1 | 2.78 | 2.78 | 2.00 | 0.62 | 6.48 |

Abortion Risk - Monsanto

### 8.6.2 Comments and Conclusions

The definition of abortion and how it was determined varied considerably across studies. However, most of the evidence about the effect of rbST on the risk of abortion was derived from the PAMP study ([12]) in which abortion was simply defined as "abortion indicated by dairyman".

When all studies were evaluated, there appeared to be no evidence of an increased risk of abortion. However, when only studies based on Monsanto's product were examined, the estimate of the relative risk was 1.67 (P=0.078).

"Fetal loss"was also reported in two Monsanto studies: PAMP and "Multi-location IM study"([4,12]). Although not clearly defined, this was presumably based on the loss of rectally confirmed pregnancies. Relative risk of 1.2, 1.11 and 1.78 were reported for PAMP - primiparous, PAMP - multiparous and "Multi-location IM"respectively, but none of the individual estimates were significantly greater than 1.

The overall conclusion of the Panel was that there was some evidence of an increased risk of abortion / fetal loss associated with use of the product but there were inadequate data to draw a firm conclusion.

### 8.6.3 Additional Information Required

As noted above, there were inadequate data to allow the Panel to come to a firm conclusion about the effect of rbST on the risk of abortion/fetal loss. Studies to provide those data would have to have a consistent process for defining and recording abortions and fetal losses.

## 8.7 Gestational Length

Gestation length is the time (number of days) from the breeding of conception to the subsequent calving.

### 8.7.1 Meta-analysis

Two meta-analyses were carried out to evaluate the effects of rbST on gestation length.

- Effects of rbST on gestation length based on studies using all companies' products.

- Effects of rbST on gestation length based on studies using Monsanto's product.

. meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-10) rtrunc(10)
xlabel(-10, -5, 0 , 5, 10) b2("**Gestation length - All Companies**") t2("random effects")

**Meta-analysis**

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.021 | -0.968 | 1.011 | 0.042 | 0.966 | 10 |
| Random | -0.402 | -2.459 | 1.655 | -0.383 | 0.702 | |

Test for heterogeneity: Q= 26.632 on 9 degrees of freedom (p= 0.002)
Moment-based estimate of between studies variance = 6.341

### Effect of rbST on 3.5% FCM

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 0.24 | 0.10 | -6.00 | -9.97 | -2.03 |
| 1 Mp1 | 0.26 | 0.10 | 0.00 | -3.88 | 3.88 |
| 168 Cm1 | 0.41 | 0.11 | -1.00 | -4.05 | 2.05 |
| 168 Cp1 | 0.26 | 0.10 | -1.00 | -4.88 | 2.88 |

| | | | | | |
|---|---|---|---|---|---|
| 168 Cm2 | 0.15 | 0.08 | 1.00 | -3.99 | 5.99 |
| 168 Cp2 | 0.13 | 0.07 | 1.00 | -4.54 | 6.54 |
| 5298 Ea2 | 0.03 | 0.03 | -3.00 | -13.53 | 7.53 |
| 5407 Mm1 | 1.99 | 0.15 | 1.00 | -0.39 | 2.39 |
| 5407 Mp1 | 0.30 | 0.10 | -4.00 | -7.60 | -0.40 |
| 5422 Mm1 | 0.15 | 0.08 | 8.00 | 3.01 | 12.99 |

Gestation length - All Companies

. meta val se , pr gr(r) id(std_lbl) cl xline(0) ltrunc(-10) rtrunc(10) xlabel(-10, -5, 0 , 5, 10) b2("**Gestation length - Monsanto**") t2("random effects")

## Meta-analysis

### Effect of rbST on 3.5% FCM

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 0.196 | -0.947 | 1.339 | 0.336 | 0.737 | 5 |
| Random | -0.356 | -4.026 | 3.313 | -0.190 | 0.849 | |

Test for heterogeneity: Q= 25.261 on 4 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 14.065

**Effect of rbST on 3.5% FCM**

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Mm1 | 0.24 | 0.06 | -6.00 | -9.97 | -2.03 |
| 1 Mp1 | 0.26 | 0.06 | 0.00 | -3.88 | 3.88 |
| 5407 Mm1 | 1.99 | 0.07 | 1.00 | -0.39 | 2.39 |
| 5407 Mp1 | 0.30 | 0.06 | -4.00 | -7.60 | -0.40 |
| 5422 Mm1 | 0.15 | 0.05 | 8.00 | 3.01 | 12.99 |

Gestation length - Monsanto

### 8.7.2 Comments and Conclusions

The Panel concluded that there was no consistent evidence of an effect of rbST on gestation length.

## 8.8 Retained Placenta

The proposed label for the product also refers to a possible increased risk of retained placenta in the carry-over period in treated cows. One study ([4]) which recorded the frequency of retained placenta following treatment with rbST reported a relative risk of 1.6 (P=0.1). The Panel concluded that while there appeared to be some evidence of increased risk of retained placenta, there were insufficient data on which to base a firm conclusion.

## 8.9 Overall Assessment of Reproductive Effects

The Panel concluded that the use of rbST has some negative effects on reproduction in dairy cows. Treatment was associated with a substantially increased risk of non pregnancy and a small increase in days open in cows which did conceive. The Panel concluded that although there was

some evidence of increased risks of cystic ovaries, twinning, retained placenta and abortion/fetal loss, a lack of data precluded firm conclusions being drawn about these four outcomes. Studies which employed a consistent approach to defining and recording these reproductive events would be required to provide such data. There did not appear to be any effect of rbST on the number of services required for cows which did conceive or the length of the subsequent gestation.

### 8.10 Ability to Control/Eliminate Detrimental Effects

Given that most of the cows in the studies reported were on well managed reproductive programs, the Panel did not feel that current dairy health management practices would be able to control or eliminate the apparent detrimental effects of rbST on reproductive performance if treatment started at approximately day 60 post-calving when most cows are not pregnant. However, since the detrimental effects were primarily related to the breeding of cows, an obvious solution to avoid these problems would be to delay use of the product until cows were confirmed pregnant. Delaying use of the product until after pregnancy has been confirmed would not deal with the potential increased risk of retained placenta or abortion/fetal loss, if those increased risks are confirmed.

### 8.11 Additional Information Required

In general the panel felt that there was good information available for the two most important measures of reproductive performance: days open and non-pregnancy rate. Unfortunately, there were insufficient data to confirm or rule out possible increased risks of cystic ovaries, twinning, retained placenta, and abortion/fetal loss. Delaying use of rbST until after cows conceive would remove any concern about the possible effects of the drug on cystic ovaries and twinning rates. Additional data from studies with a consistent approach to detecting abortion/fetal loss will be required before firm conclusions about the possible effects of rbST on the loss of pregnancy can be drawn.

## 9. Feet and Legs

In this section, virtually all causes of clinical lameness were combined and the overall effect of the drug on the risk of clinical lameness was examined. The increased risk of lameness was measured in terms of relative risk. There was considerable variation across studies in how lameness was defined, diagnosed and recorded.

### 9.1 Meta-analysis

Two meta-analyses were carried out to evaluate the effect of rbST on the risk of clinical lameness.

- Effects of rbST on the risk of clinical lameness based on studies using all companies products.
- Effects of rbST on the risk of clinical lameness based on studies using Monsanto's product.

. meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline (1) ltrunc (.33)rtrunc (6) xlabel (.33, .5, .75, 1, 1.5, 2, 3,6 ) b2 ("**Lameness Risk-All Companies**")

### Meta-analysis (exponential form)

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.546 | 1.295 | 1.846 | 4.820 | 0.000 | 11 |
| Random | 1.577 | 1.249 | 1.992 | 3.823 | 0.000 | |

Test for heterogeneity: Q= 13.036 on 10 degrees of freedom (p= 0.222) Moment-based estimate of between studies variance = 0.032

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 1 Ma1 | 0.52 | 0.51 | 1.05 | 0.07 | 16.09 |
| 168 Ca1 | 0.88 | 0.85 | 6.00 | 0.74 | 48.73 |
| 168 Ca2 | 1.04 | 1.01 | 1.16 | 0.17 | 7.89 |
| 281 Ca1 | 7.42 | 6.00 | 3.20 | 1.56 | 6.57 |
| 425 Ma1 | 4.23 | 3.73 | 1.53 | 0.59 | 3.97 |

| | | | | | |
|---|---|---|---|---|---|
| 1218 Ca1 | 4.06 | 3.59 | 0.66 | 0.25 | 1.75 |
| 1552 Ma1 | 34.30 | 16.39 | 1.19 | 0.85 | 1.66 |
| 5403 Ca1 | 3.54 | 3.18 | 2.75 | 0.97 | 7.79 |
| 5407 Mm1 | 39.27 | 17.44 | 1.77 | 1.29 | 2.42 |
| 5407 Mp1 | 20.81 | 12.51 | 1.44 | 0.94 | 2.21 |
| 5422 Mm1 | 6.17 | 5.16 | 1.69 | 0.77 | 3.72 |

Lameness Risk - All Companies

. meta val cilow cihigh , ci eform pr gr (f) id (std_lbl) cl xline (1) ltrunc (.33) rtrunc (6) xlabel (.33, .5, .75, 1, 1.5, 2, 3,6 ) b2 ("**Lameness Risk-Monsanto**")

### Meta-analysis (exponential form)

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.477 | 1.220 | 1.787 | 3.999 | 0.000 | 6 |
| Random | 1.477 | 1.220 | 1.787 | 3.999 | 0.000 | |

Test for heterogeneity: Q= 3.078 on 5 degrees of freedom (p= 0.688) Moment-based estimate of between studies variance = 0.000

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 Ma1 | 0.52 | 0.52 | 1.05 | 0.07 | 16.09 |
| 425 Ma1 | 4.23 | 4.23 | 1.53 | 0.59 | 3.97 |
| 1552 Ma1 | 34.30 | 34.30 | 1.19 | 0.85 | 1.66 |
| 5407 Mm1 | 39.27 | 39.27 | 1.77 | 1.29 | 2.42 |
| 5407 Mp1 | 20.81 | 20.81 | 1.44 | 0.94 | 2.21 |
| 5422 Mm1 | 6.17 | 6.17 | 1.69 | 0.77 | 3.72 |

Lameness Risk - Monsanto

## 9.2 Conclusions and Comments

The Panel concluded that the risk of clinical lameness was increased approximately 50% in cows treated with rbST.

## 9.3 Are the Effects Direct or Indirect?

While it is difficult to make biological sense of a direct effect of rbST on lameness, the Panel speculated that the mechanism may be through the increased milk production response to rbST forcing changes in the nutritional management of those cows. Higher producing cows require a diet with very high energy and protein density. Cows fed close to a 60% concentrate-forage ratio (C:F) or a high starch:low fibre diet, are more susceptible to lameness problems, especially laminitis ([31]). Laminitis is a multi-factorial disease with many predisposing factors, including: grain overload, poorly balanced rations, management (stall design and comfort) and behaviour ([32,33]). Acute laminitis is evident by reluctance to rise or to walk. The clinically apparent effects on the structure of the hoof include solar hemorrhage, claw abnormalities, white line hemorrhage and/or abscesses and sole ulceration ([34]). Consequently, cows with laminitis potentially spend more time lying down and consequently may have an increased risk of carpal, tarsal and fetlock lesions when floor surface is hard with little bedding materials to support their weight.

High producing dairy herds attempting to maximize energy intake are continually confronted with subclinical acidosis and laminitis. While management of feeding and husbandry practices

can be implemented to reduce the incidence of the disease ([35]) the control of lameness problems in dairy herds remains problematic.

### 9.4 Ability to Control/Eliminate Detrimental Effects

The two main studies contributing data to the meta-analyses were one by Wells et. al ([36]) and the PAMP study (12). In the former, the most common causes of lameness in treated cows were lesions of the carpus and tarsus, followed by interdigital swelling. In the latter, lesions of the fetlock and hoof were most commonly reported but lesions of the hock contributed the most to the number of days on treatment.

While the Panel recognized that recent improvements in stall and stall surface design may help reduce some of these problems in newer dairy facilities, in general, the Panel did not feel that current dairy cattle management techniques would be able to control or eliminate the increased risk of lameness. Additional studies would be required to better define the nature of the clinical lamenesses observed and to determine possible mechanisms by which those lamenesses had occurred.

Two specific concerns associated with increased risk of lameness were noted. The first is that lameness may have a detrimental effect on reproductive performance in that cows may be unwilling to stand for mounting. These cows would be less likely detected in heat. The second relates to the definite need for increased dry matter intake in rbST treated cows. It is important that treated cows be able to walk to and compete effectively for feed provided to the herd in free stall barns. Lame cows may have difficulty in achieving the necessary dry matter intake, resulting in further loss of body condition.

## 10. Other Health Concerns

A wide variety of health conditions could have been considered under this heading. These include problems such as abomasal displacement, hypocalcemia, diarrhea, bloat, etc. However, in general there were insufficient data in the literature to draw any conclusions for many possible health outcomes other than mastitis, lameness and reproductive diseases. First there were not many studies which reported health related outcomes. Second, there was no consistency in the method of reporting health outcomes across studies. Third, even if a health outcome was reported the numbers of animals affected in the treated and control groups was so small that it was impossible to draw any meaningful conclusions.

The PAMP study ([12]) reported the most extensive health data. While there were insufficient data in many categories to draw any firm conclusions there was some evidence of increased episodes of cows being off feed in the treated group. With only limited data from a single study the Panel did not draw strong conclusions about this risk.

Two specific "other health issues" which were considered in a bit more detail were the occurrence of injection site reactions and the effect of rbST on metabolic diseases.

## 10.1 Injection Site Reactions

One Vermont study ([37]) reported a high frequency (50 - 60%) of injection site reactions scored 2 or 3 on a scale of 0 - 3 following subcutaneous injections. (A score of 2 represented moderate swelling while 3 represented severe swelling). One other study ([4]) reported a low frequency (2 - 7%) of reactions following intramuscular injections. The Monsanto "bridging" study reported much higher average injection site scores following subcutaneous injections compared to intramuscular injections (1.1 vs 0.2 - 0.5). The evidence suggests more problems with injections site reactions following subcutaneous injections but the reason for the high frequency in the Vermont study is unknown.

An Adverse Drug Experience report for the period of February 1994 to February 1998 that was filed by Monsanto reports 212 injections site reactions, of which 176 were classified as "probably" caused by the injection of rbST. Without any information about the frequency of use of rbST or the overall proportion of reactions that are reported, it is impossible to estimate the overall frequency of reactions.

Overall, the Panel concluded that problems with injection site reactions do occur. However, there were insufficient data to adequately assess the frequency or severity of these reactions or to determine what factors might influence their occurrence (e.g. breed dispositions).

## 10.2 Metabolic Diseases

There was a significant reduction in metabolic diseases (ketosis and parturient paresis) reported in the carry-over period in the "Multi-location study" ([4]) (relative risk = 0.25, P=0.01). In addition, one single herd study ([38]) specifically designed to look at the effect of rbST on clinical ketosis reported a substantial, but not statistically significant, reduction in the risk of clinical ketosis (relative risk = 0.08; confidence interval = 0.005, 1.3) in the carry-over period.

The Panel concluded that there was a reduction in the risk of metabolic diseases during the carry-over period and that it was at least partially attributable to lower average body condition scores at the start of a lactation following one in which rbST had been used. The higher level of dry matter intake during the carry-over period in previously treated cows (see Section 5.1.2) would also contribute to a lowering of the risk of ketosis.

# 11. Culling

## 11.1 Meta-analysis

Three meta-analysis were carried out to evaluate the effects of rbST on the risk of culling.

- Effect of rbST on the risk of culling based on studies using all companies' products.
- Effect of rbST on the risk of culling based on studies using Monsanto's product.
- Effect of rbST on the risk of culling in multiparous or mixed parity groups of cows (i.e. excluding primiparous only groups).

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3, 6 ) b2("**Culling Risk-All Companies**")

### Meta-analysis (exponential form)

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.241 | 0.991 | 1.554 | 1.878 | 0.060 | 8 |
| Random | 1.241 | 0.991 | 1.554 | 1.878 | 0.060 | |

Test for heterogeneity: Q= 6.789 on 7 degrees of freedom (p= 0.451)
Moment-based estimate of between studies variance = 0.000

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 627 Ca1 | 1.06 | 1.06 | 6.00 | 0.89 | 40.38 |
| 1218 Ca1 | 0.74 | 0.74 | 0.58 | 0.06 | 5.63 |
| 5407 Mm1 | 44.80 | 44.80 | 1.38 | 1.03 | 1.85 |
| 5407 Mp1 | 11.56 | 11.56 | 0.75 | 0.42 | 1.33 |

| | | | | | |
|---|---|---|---|---|---|
| 5409 Ma1 | 0.53 | 0.53 | 1.00 | 0.07 | 14.78 |
| 5409 Ma2 | 9.69 | 9.69 | 1.18 | 0.63 | 2.22 |
| 5409 Ma3 | 5.41 | 5.41 | 1.48 | 0.64 | 3.44 |
| 5422 Mm1 | 2.07 | 2.07 | 1.02 | 0.26 | 3.99 |

Culling Risk - All Companies

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Culling Risk-Monsanto**")

### Meta-analysis (exponential form)

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.222 | 0.973 | 1.535 | 1.728 | 0.084 | 6 |
| Random | 1.222 | 0.973 | 1.535 | 1.728 | 0.084 | |

Test for heterogeneity: Q= 3.718 on 5 degrees of freedom (p= 0.591)
Moment-based estimate of between studies variance = 0.000

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 5407 Mm1 | 44.80 | 44.80 | 1.38 | 1.03 | 1.85 |
| 5407 Mp1 | 11.56 | 11.56 | 0.75 | 0.42 | 1.33 |

| | | | | | |
|---|---|---|---|---|---|
| 5409 Ma1 | 0.53 | 0.53 | 1.00 | 0.07 | 14.78 |
| 5409 Ma2 | 9.69 | 9.69 | 1.18 | 0.63 | 2.22 |
| 5409 Ma3 | 5.41 | 5.41 | 1.48 | 0.64 | 3.44 |
| 5422 Mm1 | 2.07 | 2.07 | 1.02 | 0.26 | 3.99 |

Culling Risk - Monsanto

. meta val cilow cihigh , ci eform pr gr(f) id(std_lbl) cl xline(1) ltrunc(.33)rtrunc(6) xlabel(.33, .5, .75, 1, 1.5, 2, 3,6 ) b2("**Culling Risk-Primiparous Excluded**")

### Meta-analysis (exponential form)

| Method | Pooled Est | 95% CI Lower | 95% CI Upper | Asymptotic z_value | Asymptotic p_value | No. of studies |
|---|---|---|---|---|---|---|
| Fixed | 1.358 | 1.064 | 1.734 | 2.455 | 0.014 | 7 |
| Random | 1.358 | 1.064 | 1.734 | 2.455 | 0.014 | |

Test for heterogeneity: Q= 3.333 on 6 degrees of freedom (p= 0.766)
Moment-based estimate of between studies variance = 0.000

| Study | Weights Fixed | Weights Random | Study Est | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|
| 627 Ca1 | 1.06 | 1.06 | 6.00 | 0.89 | 40.38 |
| 1218 Ca1 | 0.74 | 0.74 | 0.58 | 0.06 | 5.63 |

| | | | | | |
|---|---|---|---|---|---|
| 5407 Mm1 | 44.80 | 44.80 | 1.38 | 1.03 | 1.85 |
| 5409 Ma1 | 0.53 | 0.53 | 1.00 | 0.07 | 14.78 |
| 5409 Ma2 | 9.69 | 9.69 | 1.18 | 0.63 | 2.22 |
| 5409 Ma3 | 5.41 | 5.41 | 1.48 | 0.64 | 3.44 |
| 5422 Mm1 | 2.07 | 2.07 | 1.02 | 0.26 | 3.99 |

Culling Risk - Primiparous Excluded

(This meta-analysis was based on groups of cows which were either multiparous or "mixed"{both multiparous and primiparous}. Only one group of cows which was exclusively primiparous has been excluded.)

## 11.2 Comments and Conclusions

Relatively few studies reported the effect of rbST on culling. The primary reason for this was:

"In the pre-approval studies, the study design dictated that cows remained in the herd unless moribund or dead."([12])

Overall there appeared to be approximately a 20 - 25% increase in the risk of culling that was associated with the use of rbST but this effect did not quite achieve statistical significance (P = 0.06) in the meta-analyses. Much of the data about culling was derived from the PAMP study which reported a statistically significant increased risk of culling in multiparous cows (relative risk = 1.38) but no statistically significant effect in primiparous cows. It may be that the effects are different in primiparous and multiparous cows. Older cows may experience more adverse health effects and may experience a true increased risk of culling. When the one group of entirely primiparous cows were excluded from the meta-analysis, the relative risk of culling associated with the use of rbST rose from 1.24 to 1.36 and became significant (P=0.01)

One problem with interpreting culling data relates to the inclusion criteria for culling in the study . In one study ([34]), reproductive culls were included in the total. In two other studies (including the PAMP study)([4,12]), reproductive culls were not included. Since rbST increases the risk of non-pregnancy and cows which do not conceive are invariably culled, the overall increased risk of culling associated with rbST would be underestimated by the meta analyses above.

The Panel concluded that the use of rbST does increase the risk of culling, particularly in multiparous cows.

# 12. Animal Welfare

Any assessment of the impact of a product on animal welfare is inherently subjective in nature. However, the Panel did discuss four specific animal welfare issues.

First, the Panel addressed the question as to whether regular subcutaneous injections were likely to be an animal welfare concern. Such injections would be a category "B" procedure according to the Canadian Council on Animal Care (see Appendix 11). Tthe Panel did not feel repeating it every 14 days constituted an animal welfare concern.

Secondly, the Panel discussed the possible effects of injections site reactions. The equivocal data on injection site reactions raised concern about the possible occurrence of reactions. However, without more substantial evidence about the frequency and severity of those reactions, the Panel could not draw strong conclusions about this potential animal welfare concern.

Third, the Panel discussed the animal welfare effects of an increase in the frequency of clinical diseases (mastitis and lameness). One of the fundamental principles of animal welfare is that animals should be maintained free of disease to as great an extent as possible. The recommended code of practice for the care and handling of dairy cattle (1990) states.

"Nearly all husbandry systems impose restrictions on the stock, some of which can cause an unacceptable degree of discomfort or distress by preventing the animals from fulfilling their basic needs. Meeting these needs, and others that must be considered, includes providing the following:

- the prevention of abnormal behavior, injury, parasitic infestation, and disease, and rapid diagnosis and treatment when indicated;"

In general, the Panel felt that current health management practices for dairy cattle were inadequate to eliminate the increased risk of clinical mastitis and lameness associated with the use of rbST and consequently there is a legitimate animal welfare concern. On the other hand, rbST does appear to reduce the risk of metabolic disease in subsequent lactations when used in over-conditioned dairy cattle.

Finally, there is evidence that cows treated with rbST have a reduced life span. Both the increased risk of culling and the increased risk of non- pregnancy would contribute to a reduction in the lifespan of treated cattle.

Overall, the Panel felt that there were animal welfare concerns that were associated with the use of rbST.

# 13. Drug Interactions

There was no evidence of interactions between rbST and other commonly used pharmaceutical agents in the studies reviewed by the Panel. However, the Panel did not consider it within their mandate to review the mechanisms of action of the drug and can not comment further on this issue.

# 14. Conclusions and Recommendations

## 14.1 Efficacy

### 14.1.1 Yield

The Panel concluded that rbST does increase production. In primiparous Holsteins the production increase averaged 3 kg or approximately 11.3%. In multiparous Holsteins the increase averaged 4.4 kg or approximately 15.6%. However, these are average values and actual responses varied from study to study.

The Panel concluded that the efficacy of the drug had been clearly established.

### 14.1.2 Composition

There was a very small increases in the butterfat content of milk produced and in the protein content of milk produced by multiparous cows. However, the magnitude of these increases were not of much consequence.

## 14.2 Animal Safety

The Panel reached a number of conclusions about the safety of the drug when used in animals.

### 14.2.1 Body Condition

Treatment with rbST reduced the body condition of cows and although dry matter intake was increased, this did not appear adequate to compensate for the increased energy output associated with the increased milk yield. This body condition score reduction appeared to carry over into the early portion of the next lactation. Over several lactations, this may result in an increased proportion of animals being below a level of body condition considered optimal for good health and production.

### 14.2.2 Mastitis

There was approximately a 25% increase in the risk of clinical mastitis in treated cows. It appeared as though there was also a slight increase in the prevalence of subclinical infections. However, the data relating to subclinical mastitis was limited. Furthermore, the Panel felt that current dairy health management practices would reduce but could not eliminate the increased risk of clinical mastitis that was associated with the use of rbST.

### 14.2.3 Antibiotic Residues

Given the relatively small expected increase in the number of cases of clinical mastitis, the current awareness amongst dairy producers of the problem of antibiotic residues in milk, and current programs for regular monitoring all milk shipments to dairy processors, the Panel felt that the probability of increased antibiotic residues in dairy products was very small.

### 14.2.4 Reproductive Effects

There were a number of effects on reproductive performance that were associated with the use of rbST. These included a substantial increase in the risk of non-pregnancy and a slight increase in days open in cows which do conceive. There was also inconclusive evidence of an increased risk of cystic ovaries and twinning. All of these adverse effects could be controlled by delaying use of drug until cows were confirmed pregnant. There was some limited evidence of an increased risk of retained placenta and abortion/fetal loss in treated cows but there were insufficient data to draw a firm conclusion about this possible effect.

### 14.2.5 Lameness

The Panel concluded that there was approximately a 50 % increase in the risk of clinical lameness associated with use of rbST. Many of the cases of lameness involved joints and dairy producers and veterinarians currently have a limited ability to control or eliminate this increased risk.

### 14.2.6 Other Health Effects

The Panel noted that there was not very much information about other potential health effects of rbST but did note that use of the product may reduce the risk of metabolic diseases (ketosis in particular) in the subsequent lactation.

### 14.2.7 Culling

In general, there was an increased risk of culling associated with the use of rbST, particularly in multiparous cows. When considered along with the increased risk of non-pregnancy, the Panel concluded that the use of rbST would likely reduce the lifespan of dairy cattle.

### 14.2.8 Animal Welfare

The Panel felt that there were a number of legitimate animal welfare concerns associated with the use of rbST. These included an increased risk of clinical mastitis and lameness, and a reduction in the lifespan of treated cows. Without better data on the frequency and severity of injection site reactions, the Panel could not determine if these represented a significant animal welfare concern.

## 14.3 Additional Information

The Panel recognized that rbST is one of the most extensively studied animal pharmaceuticals ever to be reviewed. In general, the Panel felt that it was able to make a reasonably informed assessment of the effect of the drug in terms of efficacy and animal safety.

However, a few specific areas where additional information would be beneficial, particularly if the drug is licenced and the adverse effects need to be managed are as follows.

- More information is needed with regard to the etiologic agents associated with the increased incidence of clinical mastitis cases and the increased prevalence of subclinical intramammry infections.
- The effect of rbST on the risk of cystic ovaries, twinning, retained placenta and abortion/fetal loss needs clarification.
- The frequency of injections site reactions needs clarification.
- More information about the effect of rbST on a variety of health conditions would be beneficial.

Most of the items identified above affect relatively few cows. Consequently, studies to provide the data identified would have to involve large numbers of animals in commercial dairy herds and would be expensive to conduct. Such studies should only be considered if it is felt that the information missing is pivotal to making a decision about whether or not to approve the product.

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## Monsanto Submissions

Adriaens F, Bruneau P, deKerchove G, Hard DL. Evaluation of tailhead injection site swelling and sensitivity in British and French field trials (#89-168, # 90-001, #89-031, #90-110). Monsanto Submission 1990;
Reference ID: 5408

Adriaens F, Phipps RH, Weller RF, de KG, Hard DL, Hintz RL, Hartnell GF. Efficacy and safety of CP115099-F in dairy cows treated for a fourth consecutive lactation in the U.K. (#85-009D). Monsanto Submission 1991;
Reference ID: 5413

Arambel MJ, Lamb RC, Green GA, Madsen KS. Farm trials in Utah using bovine somatotropin (#87-066). Monsanto Submission 1989;
Reference ID: 5416

Bauman DE, Huber JT, Lamb RC, Samuels WA. Multi-location intramuscular single dose study (single dose IM) (#85-039, #85-038, #85-021, #86-003). Monsanto Submission 1987;
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Collier RJ. Post-approval evaluation of Prosilac bovine somatotropin in commercial dairy herds (#93-051). Monsanto Submission 1996;
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Collier RJ, McGrath MF. Injection site reaction field study (#91-072). Monsanto Submission 1998;
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Galton DM, Samuels WA, Madsen KS. Farm trials in New York using bovine somatotropin (#87-067). Monsanto Submission 1989;
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Reference ID: 137

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Reference ID: 689

Zullo. Effect of bovine somatotropin on milk composition and product yields: a review. Cult.Dairy.Prod.J. 1990;25(2):16
Reference ID: 661

Zwickl. Somatotropin antibody formation in cows treated with a recombinant bovine somatotropin over two lactations. J.Dairy.Sci. 1990;73(10):2888-95.
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# Appendix 5 - List of "Key" Articles

## Monsanto Submissions

Adriaens F, Bruneau P, deKerchove G, Hard DL. Evaluation of tailhead injection site swelling and sensitivity in British and French field trials (#89-168, # 90-001, #89-031, #90-110). Monsanto Submission 1990;
Reference ID: 5408

Adriaens F, Phipps RH, Weller RF, de KG, Hard DL, Hintz RL, Hartnell GF. Efficacy and safety of CP115099-F in dairy cows treated for a fourth consecutive lactation in the U.K. (#85-009D). Monsanto Submission 1991;
Reference ID: 5413

Arambel MJ, Lamb RC, Green GA, Madsen KS. Farm trials in Utah using bovine somatotropin (#87-066). Monsanto Submission 1989;
Reference ID: 5416

Bauman DE, Huber JT, Lamb RC, Samuels WA. Multi-location intramuscular single dose study (single dose IM) (#85-039, #85-038, #85-021, #86-003). Monsanto Submission 1987;
Reference ID: 7

Bussen SC, Collier RJ. Carcass evaluation study (#89-049). Monsanto Submission 1998;
Reference ID: 12

Cole WJ, Collier RJ, Eppard PJ, Hartnell GF, Hintz RL, Hoffman RG, Loesch TL, McLaughlin CL, McCrate MM, Selby BD, et al. Effect of Sometribove treatment of dairy cows on the incidence of clinical signs and birth abnormalities in the resulting offspring. Monsanto Submission 1992;
Reference ID: 5426

Collier RJ. Post-approval evaluation of Prosilac bovine somatotropin in commercial dairy herds (#93-051). Monsanto Submission 1996;
Reference ID: 5407

Collier RJ, McGrath MF. Injection site reaction field study (#91-072). Monsanto Submission 1998;
Reference ID: 9

DeLeon J.M., Eppard PJ, Lanza GM, Hammond BG, Cole WJ, Hudson S, Hintz RL, Miller MA, White TC, Metzger LE. Effect of CP115099-F treatment of the dam in study no.: 100-DDC-COW-PJE-85-010 on the subsequent health and reproductive performance of first generation heifers (86-024, 85-010). Monsanto Submission 1990;
Reference ID: 5423

Eppard PJ, Cole WJ. Multi-lactation chronic animal toxicity study (#85-010). Monsanto Submission 1990;
Reference ID: 4

Eppard PJ, Olsson PK, Cole WJ, Collier RJ, Hintz RL, McCrate MM, Selby BD, Sorbet RH, Veenhuizen J, Vicini JL. Effect of Sometribove treatment of the dam on health, growth, and reproduction of the resulting F1 Heifers (86-066). Monsanto Submission 1992;
Reference ID: 5424

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Reference ID: 5425

Eppard PJ. Non-clinical injection site reaction study (#91-068). Monsanto Submission 1998;
Reference ID: 10

Erdman R, Samuels WA, Madsen KS. Farm trials in Maryland and Pennsylvania using bovine somatotropin (#88-063). Monsanto Submission 1989;
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Reference ID: 1

Galton DM, Samuels WA, Madsen KS. Farm trials in New York using bovine somatotropin (#87-067). Monsanto Submission 1989;
Reference ID: 5417

Gavert HO, Pabst K, Hard DL, Kerchove G, Madsen KS, Peel CJ, Wollny C. Safety and efficacy of CP115099-F. (Sometribove) in dairy cows through three consecutive lactations of treatment (#85-

012A). Monsanto Submission 1989;
Reference ID: 5410

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Reference ID: 2

Messerole VK, Madsen KS, Hartnell GF, Cole WJ, Hintz RL, Samuels WA, Swenson GH. Response of cows to biweekly administration of sometribove (N-Methionyl Bovine Somatotropin) in a prolonged release system (CP115099-F) in commercial dairy herds in Michigan and New York (#87-065, #87-067). Monsanto Submission 1987;
Reference ID: 5415

Olson JD, Green GA, Madsen KS. Farm trials in Colorado using Somatotropin (#87-057). Monsanto Submission 1989;
Reference ID: 5414

Rijpkema YS, vanReeuwijk L, Hard DL. Responses of dairy cows to treatment with Sometribove (r-BST) during three consecutive years. Livestock Production Science 1990;26:193-216.
Reference ID: 5409

Schockmel LR, Vedeau F, Peel CJ, deKerchove G, Madsen KS, Hartnell GF. Efficacy and safety of CP115099-F in dairy cows. Report on lactations 1 and 2 of the French clinical trials performed at Sanders Experimental Centre, Saint Symphorien. (#85-16B). Monsanto Submission 1988;
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Reference ID: 5421

Vicini JL, Hudson S, Cole WJ, Miller MA, Eppard PJ, White TC, Collier RJ. Effect of acute challenge with an extreme dose of somatotropin in a prolonged-release formulation on milk production and health of dairy cattle (#86-011). J.Dairy.Sci. 1990;73(8):2093-102.
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Reference ID: 126

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Reference ID: 384

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Reference ID: 281

# Appendix 6 - Summary of material provided by Health Canada

**see end of document for description of columns**

| Binder | Our Ref. ID # | Monsanto Report # (if applic) | Monsanto Project #(s) or Journal Reference | Source | Description | Year |
|---|---|---|---|---|---|---|
| 1 - 1 | | | | BVD | Product Description | |
| 1 - 2 | | | | Mons. | Draft Labelling | |
| 1 - 3 | | | | BVD | Guidelines for Preparation of Veterinary | 1991 |
| 1 - 4 | | | Multiple | USDA | Freedom of Information Summary | 1993 |
| 1 - 5 | | | | Eu | European Union Evaluation | 1993 |
| 1 - 6 | 7 | | 93-051 | Mons. | Post-Approval Monitoring Program | 1996 |
| 2 - 1 | | | | USDA | CVM Update - PAMP | |
| 2 - 2 | | | | Mons. | Posilac Technical Info. | |
| 2 - 3 | | | | Ag Can | rbST Task Force Report - Exec Summ | 1995 |
| 2 - 4 | | | | Ag Can | rbST Task Force Report - full | 1995 |

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|---|---|---|---|---|---|---|
| | | | | | (Note: Animal & Human Health section of 2 -3 and 2 - 4 not included) | |
| 3 - 1 | 5 | | 86-032 | BVD | BVD Summary of IM / SC Bridging Study | 1998 |
| 3 - 2 | 5 | MSL[b]-9646 | 86-032 | Mons. | IM / SC Bridging Study | 1990 |
| 4 - 1 | | | | BVD | BVD Efficacy Review based on: | 1998 |
| | 1 | MSL- 9607 | 87-023, 34, 29, 24 | | Multiloc. SC Dose Response Study | 1989 |
| | 5 | MSL- 9646 | 86-032 | | IM / SC Bridging Study | 1986 |
| | 5407 | | 93-051NC | | Penn Herd in PAMP Study | 1993 |
| 4 - 2 | 1 | MSL- 9607 | 87-023, 34, 29, 24 | Mons. | Multilocation SC Dose Response Study | 1989 |
| 4 - 3 | 2 | MSL-12207 | 89-075 | Mons. | Tailhead / Postscapular Admin. Study | 1992 |
| 4 - 4 | 5408 | MLL[c]-90467 | 88-129, 89-168,<br>90-001, 89-031,<br>90-110 | Mons. | Injection Site Reaction Studies | 1990 |
| 5 - 1 | | | | BVD | BVD Summary of Effects Over Several Lactations<br>- based on: | 1998 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 1076 | | JDS 74:3807 | Jrnl. | 2 lactation study | 1991 |
| | 645 | | J Agric Sci 115:95 | Jrnl | British study | 1990 |
| | 5409 | MLL-90402 | Lvstck Prod Sci 26:193 OR<br>85-017 | Jrnl / Mons. | Dutch study | 1990 |
| | 34 | | JDS 80:2355 | Jrnl | 4 lactation study | 1997 |
| | 5410 | MLL-90406 | 85-012A | Mons. | German study | 1989 |
| | 5411 | MLL-90376 | 85-16B | Mons. | French study | 1988 |
| | 5412 | MLL-90413 | 85-009C | Mons. | 3 lactation study (UK) | 1989 |
| | 5413 | MLL-90487 | 85-009D | Mons. | 4th lactation study (UK) | 1985 |
| 5 - 2 | | | see above | | Selected journal reprints in support of Section 5-1 | |
| 5 - 3 | | | | Mons. | Revised package insert | |
| | 34 | | JDS 80:2355 | Jrnl | 4th lactation study - paper | 1997 |
| | 5413 | MLL 90487 | 85-009D | Mons | 4th lactation study (UK) | 1991 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 - 4 | 5407 | | 93-051 | BVD | BVD Summary of the Post-Approval Monitoring Program (PAMP) study | 1998 |
| 6 - 1 | | | | BVD | BVD Summary of Supporting (Non-pivotal) Efficacy Data<br>- based on: | 1998 |
| | 416 | | JDS 74:945 | Jrnl | 15 herd study | 1991 |
| | 2 | MSL-12207 | 89-075 | Mons. | Tailhead / Postscapular Admin. Study | 1992 |
| | 5414 | MSL- 9088 | 87-057 | Mons. | Colorado study | 1989 |
| | 5415 | MSL-10629 | 87-065, 67 | Mons. | Michigan, NY study | 1987 |
| | 5416 | MSL- 9089 | 87-066 | Mons. | Utah study | 1989 |
| | 5417 | MSL- 9836 | 87-067 | Mons. | NY study (part of 2 lines above) | 1989 |
| | 5418 | MSL- 9087 | 88-063 | Mons. | Maryland, Pennsylvania study | 1989 |
| 6 - 2 | | | see above | | Copies of all the above papers | |
| 7 - 1 | | | | BVD | BVD Report on Udder Health | 1998 |
| 7 - 2 | | MSL- 9558 | | Mons. | Effect of Sometribove on Mammary Gland Health | 1990 |
| 7 - 3 | | MSL- 9958 | | Mons. | Effect of Sometribove on Mammary Gland Health - Additional Analysis | 1990 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 - 4 | 5421 | MSL- 8140 | 86-023 | Mons. | 1986 IM Dose Response Study | 1988 |
| 7 - 5 | 5422 | MSL- 8193 | 85-039, 38, 21, 03 | Mons. | Long Term Evaluation - 4 Sites | 1987 |
| 7 - 6 | | MSL- 8193 | 85-039, 38, 21, 03 | Mons. | Supplement to Long Term Evaluation (corrections) | 1987 |
| 8 - 1 | 5407 | | 93-051 | Mons. | PAMP - Full Tables | 1996 |
| 8 - 2 | 5407 | | 93-051 | Mons. | PAMP - Mastitis Data (details) | 1997 |
| 8 - 3 | 137 | | JDS 77:2249 | Jrnl | Clinical Mastitis and Milk Yield | 1994 |
| | 416 | | JDS 74:945 | Jrnl | Lactating Cows and rbST (15 herds) | 1991 |
| | 329 | | JDS 75:111 | Jrnl | 2 lactation study of high dose sustained release bST | 1992 |
| | 20 | | JDS 80:3212 | Jrnl | bST and Clinical Mastitis (Incidence, Discarded Milk and Culling) | 1997 |
| | 5419 | | JDS 81:1262 | Jrnl | Culling in 32 Herds in Indiana, Michigan, Ohio | 1998 |
| | 201 | | JDS 76:3727 | Jrnl | Coliform Mastitis in Periparturient cows | 1993 |
| | | | | FAO/ WHO | Conclusions of 1998 JECFA meeting | 1998 |
| 9 - 1 | 5423[d] | MSL- 8083 | 85-010 | BVD | BVD Summary of Offspring Safety | 1998 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 5424[d] | MSL-12360 | 86-066 | | | |
| | 5425[d] | MSL-12817 | 88-009 | | | |
| | 5426[d] | MSL-12026 | 10 studies | | | |
| 9 - 2 | 5423 | MSL- 8083 | 85-010 | Mons. | Heifer Health and Reproductive Performance | 1988 |
| 10 - 1 | ?, 6 | MSL- 9648 | ?, 86-023 | Mons. | Effect on Reproductive Performance (5 studies) | 1990 |
| | ?, 5 | | ?, 86-032 | | | |
| | 1 | | 87-023,34, 29,24 | | | |
| 10 - 2 | 961 | | Therio 36:573 | Jrnl | Effect of bST on Reproductive Performance | 1991 |
| | 5423 | MSL- 9670 | 85-010 | Mons. | Heifer Health and Reproductive Performance | 1990 |
| | 5424 | MSL-12360 | 86-066 | Mons. | Heifer Growth, Health, and Reproductive Performance | 1992 |
| | 5425 | MSL-12817 | 88-009 | Mons. | Heifer Growth, Health, Repro and Milk Production | 1993 |
| | 5426 | MSL-12026 | 10 studies | Mons. | Birth Abnormalities | 1992 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 11 - 1 | | | | BVD | BVD Summary in the Safety of Nurtilac | 1998 |
| 11 - 2 | | MSL 9639 | multiple | Mons. | Effect of Sometribove on health of Dairy Cattle | |
| 11 - 3 | | MSL 11899 | multiple | Mons. | BST and Immune Responsiveness | 1995 |
| | | MSL 14344 | | | | |
| 12 - 1 | | MSL 11545 | 91-072 | Mons. | Histo of Inj. Site Reactions | 1991 |
| 12 - 2 | 261 | MSL 8734 | 86-031 | Mons. | Jersey Study | 1984 |
| 12 - 3 | | MSL 9012 | 89-049 | Mons. | Injection Sites - Supplement | 1989 |
| 12 - 4 | | MSL 9012 | 89-049 | Mons. | Injection Sites - Final | 1989 |
| 12 - 5 | | MSL 11509 | 91-068 | Mons. | Histopath Exam of Inj. Sites | 1991 |
| 12 - 6 | | MSL 10724 | 90-103 | Mons. | Histopath Exam of Inj. Sites | 1990 |
| 12 - 7 | | | 92-003 | Mons. | Injection Site Response | 1992 |
| 13 | 5423 | MSL 8133 | 85-010 | Mons. | Toxicity - two lactation study | 1988 |
| 14 - 1 | 5423 | MSL 8133 | 85-010 | Mons. | Toxicity - Clinical Pathology | 1988 |
| 15 - 1 | | MSL 7113 | 86-011 | Mons. | Acute Toxicity | 1987 |
| 15 - 2 | 5423 | | 85-010 | Mons. | Toxicity - two lactations | 1988 |
| 16 - 1 | | | | BVD | Gaps Analysis (2 reports) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Other | | | | Mons. | Adverse Drug Experience Report | 1998 |

**Binder/Section #:**

This appears as binder # - section # (eg. 4-1 is binder 4, section 1)

**Our Reference ID #:**

The reference ID # in our bibliographic database

**Monsanto Report #:**

The number which the Monsanto Company has assigned to their reports

**Monsanto Project #(s) or Journal Reference:**

The number which the Monsanto Company has assigned to their projects, or in the case of a journal, a shortened form of its reference

**Source:**

The source of the article/report/project

**Description:**

A few word description of the article/report/project

North American Reports

British or European Report

These reference numbers refer to reports rather than studies

# Appendix 7 - Cover Sheets for all "Key" Articles

## Reference #: 1

**Title:**

Response of cows throughout lactation to Sometribove in a prolonged system - a dose titration study conducted at four U.S. sites (#87-023, #87-034, #87-029, #87-024)

**Authors:**

Franson,S.E.; Cole,W.J.; Madsen,K.S.; Hartnell,G.F.; Hoffman,R.G.; Meserole,V.K.; Sprick,D.M.; Dyes,S.E.; Collier,R.J.; Hintz,R.L.

**Reference:**

Monsanto Submissions, binder 4-2, and FOI Report (binder 1-4), 1989

**Topics Covered:**

efficacy, nutrition, BCS, udder health, general health, feet and legs, reproduction

**Location:**

New York, Arizona, Florida, Utah

**Number of Herds:**

4

**# of Cows:**

255 (109 PP and 146 MP)

**Breed:**

Holstein

**Treatment:**

Drug: Sometribove

Dose: 0, 250, 500, 750 mg/14d

Route: SC

Start: +60 ± 3 days

Duration: full lactation, or -74 days

Groups: 4

**Treatment Allocation**

**Random:**

yes

**Method:**

blocking

**How was it randomized:**

by parity, calving date and milk production

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsant

Role: principle investigator

**Comments:**

- 19 cows had had some prior exposure to BST trial (control or a dose)
- Prevalence of quarter IMI determined at fifth sampling period (chosen because it was the last sample taken when most cows were still milking)
- Prevalence of injection site scores 1 in treatment cows was
  - week 1 primiparous 72% multiparous 75%
  - week 2 primiparous 73% multiparous 73%
- No apparent effect of treatment on physical exam parameters (TPR)
- Reproduction data based on days open restricted to 305 days but included cows treated prostaglandin
- There were discrepancies in data between table 1.35B and 1.37B (I used data from 1.37B)
- No evidence of any effects on calf health
- General conclusions
  - Detailed study for obtaining both production and health data

## Reference #: 2

**Title:**

Evaluation of the galactopoietic response of bovine somatotropin (Sometribove (CP115099-F), 500mg and CP115400-P, 260mg) when administered subcutaneously to lactating Jersy cows in a commercial dairy herd (#89-075, #88-192)

**Authors:**

Meserole,V.K.; Duque,J.A.; Hintz,R.L.; Peel,C.J.

**Reference:**

Monsanto Submission, binder 4-3, and FOI Report (binder 1-4), 1992

**Topics Covered:**

efficacy, udder health, BCS

**Location:**

Arizona

**Number of Herds:**

1

**# of Cows:**

138

**Breed:**

Jersey

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d in oil, 260 mg/14d in pellet

Route: SC - tailhead or postscapular

Start: +60 to 180 days

Duration: 14 wks

Groups: 5

**Treatment Allocation**

**Random:**

yes

**Method:**

**How was it randomized:**

**Blind Techniques:**

none

**Observation Period:**

18 weeks

**Company:**

Monsanto

**Role:**

principle investigator

## Comments:

- General Conclusions
  - Injection site had no effect on efficacy

- Relatively short study with no health effects

## Reference #: 4

**Title:**

Multi-lactation chronic animal toxicity study

**Authors:**

Eppard,P.J.; Cole,W.J.

**Reference:**

Monsanto Submission, FOI Report (binder 1-4), 1990

**Topics Covered:**

efficacy

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

82

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 600, 1800, 3000 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: full lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method: blocked

How was it randomized: by parity

**Blind Techniques:**

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- Reference #4 (Monsanto), #1076 (JDS-production), and #329 (JDS-health/reproduction) all report results from the same study (Multi-lactation chronic animal toxicity study). The results will be handled as follows:
  - #4 -No data extracted but comments left on cover sheet
  - #1076 -Production and nutrition data extracted but all comments left on cover sheet
  - #329 -Only clinical mastitis data extracted (too few numbers for other health parameters)
- General conclusions
  - Administration of rbST over two lactations increased production
  - IM inoculations resulted in injection site reactions
  - No culling data extracted because of very low numbers
  - Dry matter intake was significantly increased in multiparous cows but not in primiparous cows
  - Reproduction data included in pooled data analysis presented with reference #7 (Multi-location IM study)

## Reference #: 5

**Title:**

Comparison of the effectiveness of intramuscular and subcutaneous administration of CP115099-F (#86-032)

**Authors:**

White,T.C.; Collier,R.J.; Hartnell,G.F.; Dyes,S.E.; Hudson,S.; Miller,M.A.; Metzger,L.E.; Hintz,R.L.; Sorbet,R.H.; Curran,T.L.; Schurter,K.L.

**Reference:**

Monsanto Submission, binder 3-2, FOI Report (binder 1-4), 1990

**Topics Covered:**

efficacy, udder health, general health, BCS, lameness, reproduction

**Location:**

Monsanto Animal Research Center, Dardenne, MO

**Number of Herds:**

1

**# of Cows:**

64 (21 PP and 43 MP)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14 days

Route: IM or SC

Start: +60 ± 3 days

Duration: 1 lactation

Groups: 3

**Treatment Allocation**

Random: yes

Method: randomized complete block

How was it randomized: computer

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: principle investigators

**Comments:**

- Prevalence of quarter IMI determined at last sampling period
- General Conclusion
  - SC injections resulted in lower blood somatotropin levels than IM injections but comparable milk production responses

## Reference #: 7

**Title:**

Multi-location intramuscular single dose study (single dose IM) (#85-039, #85-038, #85-021, #86-003)

**Authors:**

Bauman,D.E.; Huber,J.T.; Lamb,R.C.; Samuels,W.A.

**Reference:**

Monsanto Submission, FOI Report (binder 1-4), 1987

**Topics Covered:**

reproduction, efficacy

**Location:**

New York, Arizona, Utah, Missouri

**Number of Herds:**

4?

**# of Cows:**

364

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

**Route:**

IM

**Start:**

+60 ± 3 days

**Duration:**

full lactation

**Groups:**

2

**Treatment Allocation**

Random: yes

**Method:**

block

**How was it randomized:**

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- Reproduction data were pooled from 3 IM studies (Multi-location IM single dose (ref #7); IM dose titration (ref #5421); IM/SC bridging (ref #5)), but all reported here because 71% of the cows came from this study
- Mastitis data were pooled with various other studies in the Freedom of Information (FOI) Report and could not be extracted
- General conclusions
    - Efficacy data as expected
    - Pooled IM study data showed significant adverse effects on reproductive performance

## Reference #: 9

**Title:**

Injection site reaction field study (#91-072)

**Authors:**

Collier,R.J.; McGrath,M.F.

**Reference:**

Monsanto Submission, FOI Report (binder 1-4)

**Topics Covered:**

general health (injection site reactions), welfare

**Location:**

**Number of Herds:**

5

**# of Cows:**

232

**Breed:**

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +60 days

Duration: 1 lactation

Groups: 2

**Treatment Allocation**

Random:

Method:

How was it randomized:

**Blind Techniques:**

none

**Observation Period:**

**Company's Role**

Company: Monsanto

Role: principle investigator

**Comments:**

- General Comments
  - 6% of cows had persistent injection site reactions

## Reference #: 10

**Title:**

Non-clinical injection site reaction study (#91-068)

**Authors:**

Eppard, P.J.

**Reference:**

Monsanto Submission, FOI Report (binder 1-4)

**Topics Covered:**

general health

**Location:**

Missouri

**Number of Herds:**

**# of Cows:**

5

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: not indicated

Duration: not indicated

Groups: 1

**Treatment Allocation**

Random: N/A

Method:

How was it randomized:

**Blind Techniques:**

N/A

**Observation Period:**

post mortem

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- General Conclusions
  - Histological description of injection site reactions

## Reference #: 12

**Title:**

Carcass Evaluation Study (#89-049)

**Authors:**

Bussen,S.C.; Collier,R.J.

**Reference:**

Monsanto Submission FOI Report (binder 1-4)

**Topics Covered:**

general health, welfare

**Location:**

New York, Michigan, Utah, Arizona

**Number of Herds:**

4?

**# of Cows:**

31

**Breed:**

27 Holstein, 4 Jersey

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: not indicated

Duration: not indicated

Groups: 1

**Treatment Allocation N/A**

Random:

Method:

How was it randomized:

**Blind Techniques:**

N/A

**Observation Period:**

slaughter inspection

**Company's Role**

Company: Monsanto

Role: principle investigator

## Comments:

- General Conclusions
  - 17/27 (63%) of cows had injection site lesions (time from last injection to slaughter was 1-12 days

## Reference #: 20

**Title:**

Recombinant bovine somatotropin and clinical mastitis: incidence, discarded milk following therapy, and culling

**Authors:**

Judge, L.J., Erskine, R.J., Bartlett, P.C.

**Reference:**

Journal of Dairy Science 80:3212-3218, 1997

**Topics Covered:**

udder health, culling

**Location:**

Michigan

**Number of Herds:**

4

**# of Cows:**

555

**Breed:**

Holstein

**Treatment**

Drug: Posilac

Dose: 500 mg/14 days

Route: SC

Start: +63 to 69 days

Duration: until 21 days prior to dry off, or until removal from herd

Groups: 2

**Treatment Allocation**

Random: yes

Method: blocking

**How was it randomized:**

for 3 farms - 1 week blocks

For remaining farm - alternate cow basis

**Blind Techniques:**

none

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: product

## Reference #: 34

**Title:**

Administration of recombinant bovine somatotropin to dairy cows for four consecutive lactations

**Authors:**

Huber,J.T.; Wu,Z.; Fontes,C.; Sullivan,J.L.; Hoffman,R.G.; Hartnell,G.F.

**Reference:**

Journal of Dairy Science 80:2355-2360, 1997

**Topics Covered:**

Efficacy, BCS, udder health

**Location:**

Arizona

**Number of Herds:**

1

**# of Cows:**

78

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route: IM -1 st lactation, SC -next three lactations

Start: +60 ± 3days

**Duration:**

32 weeks if tx remained the same

16 wks if tx was altered in second lactation

Groups: 4

**Treatment Allocation not indicated**

Random:

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

4 lactations

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- General Conclusions
  - Based on the six cows in each treatment group that were treated for 4 consecutive lactations
    - increased milk production was consistent
    - no negative effect on BCS or SCC
  - Results may be biased by only looking at six cows that survived each group

## Reference #: 124

**Title:**

Interval from calving to conception in high producing dairy cows treated with recombinant bovine somatotropin

**Authors:**

Esteban,E.; Kass,P.H.; Weaver,L.D.; Rowe,J.D.; Holmberg,C.A.; Franti,C.E.; Troutt,H.F.

**Reference:**

Journal of Dairy Science 77:2549-2561, 1994

**Topics Covered:**

Reproduction

**Location:**

California

**Number of Herds:**

1

**# of Cows:**

156 (77 PP and 74 MP)

**Breed:**

Holstein

**Treatment**

Drug: Somavubove

Dose: 0, 17.2, 51.6, 86.0 mg/d

Route: IM

Start: +70 days

Duration: full lactation for 2 lactations

Groups: lactation 1 - 4 groups
lactation 2 - 5 groups

**Treatment Allocation**

Random: yes

Method: randomized block

How was it randomized: by calving date

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Upjohn

Role: funded

### Comments:

- Haz ratios - based on model with rbST dose treated as categorical variable

## Reference #: 126

**Title:**

Production responses of cows to recombinantly derived bovine somatotropin and to frequency of milking

**Authors:**

Speicher,J.A.; Tucker,H.A.; Ashley,R.W.; Stanisiewski,E.P.; Boucher,J.F.; Sniffen,C.J.

**Reference:**

Journal of Dairy Science 77:2509-2517, 1994

**Topics Covered:**

Efficacy, BCS

**Location:**

Michigan

**Number of Herds:**

1

**# of Cows:**

118

**Breed:**

Holstein

**Treatment**

Drug: Somavubove

Dose: 0 (no placebo), or 14 mg/d

Route: IM

Start: +75 days

Duration: 230 days

Groups: 2 (control, treatment)

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

none

**Observation Period:**

1 lactation

**Company's Role**

Company: Upjohn

Role: co-investigator

### Comments:

- If overall values were not reported the values for the 2x milking (not 3x) were selected

## Reference #: 127

**Title:**

Reproductive performance in high producing dairy cows treated with recombinant bovine somatotropin

**Authors:**

Esteban,E.; Kass,P.H.; Weaver,L.D.; Rowe,J.D.; Holmberg,C.A.; Franti,C.E.; Troutt,H.F.

**Reference:**

Journal of Dairy Science 77:3371-3381, 1994

**Topics Covered:**

reproduction

**Location:**

California

**Number of Herds:**

1

**# of Cows:**

156 (77 PP and 74 MP)

**Breed:**

Holstein

**Treatment**

Drug: Somavubove

Dose: 0, 17.2, 51.6, 86.0 mg/d

Route: IM

Start: +70 days

Duration: full lactation for 2 lactations

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by calving date

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Upjohn

Role: funded

## Reference #: 128

**Title:**

The influence of Sometribove dose and days in lactation on behavior of cows implanted with pelleted Sometribove

**Authors:**

Arave,C.W.; Anderson,M.J.; Walters,J.L.

**Reference:**

Journal of Dairy Science 77:3365-3370, 1994

**Topics Covered:**

welfare

**Location:**

Utah

**Number of Herds:**

1

**# of Cows:**

99

**Breed:**

Holstein

**Treatment**

Drug: Pelleted bST implants

Dose: 0, 160, 320 mg/14d in one study, and 0, 120, 240, 360 mg/14d in a second study

Route: SC

Start: ?

Duration: 50 wks

Groups: at least 4

**Treatment Allocation**

Random: not indicated

Method:

How was it randomized:

**Blind Techniques:**

not indicated

**Observation Period:**

1 year

**Company's Role**

Company: Monsanto

Role: data provided

### Comments:

- No data were extracted
- Product administered through 11 guage implant needle
- Not equivalent to commercially available administration
- No strong conclusions about welfare concerns of injections

## Reference #: 136

**Title:**

The effects of a sustained-release recombinant bovine somatotropin (Somidobove) on udder health for a full lactation

**Authors:**

McClary,D.G.; Green,H.B.; Basson,R.P.; Nickerson,S.C.

**Reference:**

Journal of Dairy Science 77:2261-2271, 1994

**Topics Covered:**

udder health

**Location:**

6 states

**Number of Herds:**

6

**# of Cows:**

352 (193 PP and 159 MP)

**Breed:**

Holstein

**Treatment**

Drug: Somidobove

Dose: 0, 160 (PP only), 320, 640, 960 mg/28d (MP only)

Route: SC

Start: +36 to 49 days

Duration: 1 lactation

Groups: 5

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: parity, average daily milk yield, BW, and BCS

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Eli Lilly

Role: ?

## Comments:

- To compute the RR for prevalence of ¼ IMI, only the prev. (%) was given so I assumed that all quarters of all cows in each treatment group were at risk
- 640 mg/28d used as a comparison dose for primiparous cows, while 960 mg/28d was used as the comparison dose for multiparous cows
- General Conclusion
    - rbST had very little, if any effect on udder health

# Reference #: 137

**Title:**

Clinical mastitis in cows treated with Sometribove (recombinant bovine somatotropin) and its relationship to milk yield

**Authors:**

White,T.C.; Madsen,K.S.; Hintz,R.L.; Sorbet,R.H.; Collier,R.J.; Hard,D.L.; Hartnell,G.F.; Samuels,W.A.; de,Kerchove G.; Adriaens,F.; Craven,N.; Bauman,D.E.; Bertrand,G.; Bruneau,P.; Gravert,G.O.; Head,H.H.; Huber,J.T.; Lamb,R.C.; Palmer,C.; Pell,A.N.; Phipps,R.; Weller,R.; Piva,G.; Rijpkema,Y.; Skarda,J.; Vedeau,F.; Wollny,C.

**Reference:**

Journal of Dairy Science 77:2249-2260, 1994

**Topics Covered:**

udder health

**Location:**

World wide

**Number of Trials:**

15 full lactation trials, 70 short term trials

**# of Cows:**

3611

Full Lactation Trials

**#of Cows:**

914

**Breed:**

Holstein, Holstein-Friesian, Jersey

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route: IM or SC

Start: +60 ± 3 days

Duration: 252 days

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

Short Term Studies

**# of Herds:**

France 20

England 18

South Africa 15

S 9

Zimbabwe 4

Czechoslovakia 2

Italy 1

Malaysia 1

#of Cows: 2697

**Breed:**

**Treatment**

Drug: Sometribove

Dose: 0 (no placebo), 500 mg/14d

Route: SC

Start: after +60

Duration: 12 wks

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized: by parity, previous yield, and stage of lactation

**Blind Techniques:**

no placebo used

**Observation Period:**

partial lactation

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- A review paper - no new data
- Full Lactation Studies
  - RR of clinical mastitis was 1.39, with a confidence interval of 1.11 to 1.74, p=.004
  - ~ of cases of mastitis during the treatment period
  - IRR of clinical mastitis was 1.43 with a confidence interval of 1.20 to 1.70, p=.0000
  - Log SCC data - significant treatment X time interaction but details not given
  - Similar higher risk of clinical mastitis in pre-treatment period as during treatment period
  - Multiple analysis to adjust for level of milk production. They concluded that there was no increased risk of clinical mastitis after adjustment for milk production
- Short Term Studies
  - After adjustment for level of milk production, there was no increased risk of clinical mastitis associated with treatment
- General Conclusions
  - There is clearly a higher risk in treated cows, but...
  - Adjusting for milk production appears to remove increase in risk
  - Similar increase in risk in pretreatment period which was surprising

## Reference #: 157

**Title:**

Pregnancy incidence in high producing dairy cows treated with recombinant bovine somatotropin

**Authors:**

Esteban,E.; Kass,P.H.; Weaver,L.D.; Rowe,J.D.; Holmberg,C.A.; Franti,C.E.; Troutt,H.F.

**Reference:**

Journal of Dairy Science 77:468-481, 1994

**Topics Covered:**

reproduction

**Location:**

California

**Number of Herds:**

1

**# of Cows:**

156 (77 PP and 74 MP)

**Breed:**

Holstein

**Treatment**

Drug: Somavubove

Dose: 0, 17.2, 51.6, 86.0 mg/d

Route: IM

Start: +70 days

Duration: full lactation for 2 lactations

Groups: 4

**Treatment Allocation**

Random: yes

Method: randomized block

How was it randomized: by calving date

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Upjohn

Role: funded

### Comments:

- General Conclusions
  - rbST had a large detrimental effect on fertility

## Reference #: 160

**Title:**

Modeling response to slow-releasing somatotropin administered at 3- or 4-week intervals

**Authors:**

Gallo,L.; Cassandro,M.; Carnier,P.; Mantovani,R.; Ramanzin,M.; Bittante,G.; Tealdo,E.; Casson,P.

**Reference:**

Journal of Dairy Science 77:759-769, 1994

**Topics Covered:**

efficacy

**Location:**

Italy

**Number of Herds:**

1

**# of Cows:**

196 (62 PP and 134 MP)

**Breed:**

Holstein Friesian

**Treatment**

Drug: Somidobove

Dose: 0, 640 mg/3 wk, 640 mg/4wk

Route: SC

Start: +70 days

Duration: full lactation

Groups: 3

**Treatment Allocation**

Random: no

Method: assignment, balanced by parity, DIM, pre-treatment milk yield

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 year

**Company's Role**

Company: Eli Lilly

Role: product

### Comments:

- This paper was concerned with developing a statistical model to describe bST response, not really with documenting the effects of bST. So, actual values are not given for most parameters
- No data were extracted

## Reference #: 168

**Title:**

Multi-farm use of bovine somatotropin for two consecutive lactations and its effects on lactational performance, health, and reproduction

**Authors:**

Hansen,W.P.; Otterby,D.E.; Linn,J.G.; Anderson,J.F.; Eggert,R.G.

**Reference:**

Journal of Dairy Science 77:94-110, 1994

**Topics Covered:**

efficacy, udder health, reproduction, feet and legs, general health, BCS

**Number of Herds:**

6

**Location:**

Minnesota

**# of Cows:**

352 (124 PP and 228 MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 5.15, 10.3, 16.5 mg/d

Route: SC

Start: +8 to 35 days

Duration: full lactation for 2 lactations

Groups: lactation 1 - 4 groups
lactation 2 - 3 groups

**Treatment Allocation**

Random: yes

Method: blocking

How was it randomized: blocked into groups of 4 by parity and calving date. Within a block they were randomly assigned.

**Blind Techniques:**

placebo used

**Observation Period:**

two lactations

**Company's Role**

Company: Cyanamid

Role: co-Investigator

### Comments:

- Could not extract SCC data since it was not recorded on the log scale
- No statistically significant effect of rbST on SCC
- General Conclusions
  - Large variation between herds in production response to rbST
  - Quite low dose of rbST used
  - Reduced response to rbST in L2 compared to L1
  - rbST did reduce BCS in L1 and this was not fully regained before the start of L2

## Reference #: 215

**Title:**

Interactions of high milk yield and reproductive performance in dairy cows

**Authors:**

Nebel,R.L.; McGilliard,M.L.

**Reference:**

Journal of Dairy Science 76:3257-3268, 1993

**Topics Covered:**

Reproduction

**Location:**

**Number of Herds:**

**# of Cows:**

**Breed:**

**Treatment**

Drug:

Dose:

Route:

Start:

Duration:

Groups:

**Treatment Allocation**

Random:

Method:

How was it randomized:

**Blind Techniques:**

**Observation Period:**

**Company's Role**

Company:

Role:

### Comments:

- This paper is a review article, and no data were extracted
- Discussed interactions of high milk production vs reproductive performance (indirect effects of bST)
- Good review of factors affecting reproduction in dairy cows
- Reproductive traits have low heritability, so the effects of the environment/management are the most important factors influencing reproduction
- Reproductive performance is compromised through delayed ovarian activity and reduced conception rates, by demands of high milk yield
- When NEB, it modifies follicular population and affects the number of follicles during the first 25 DIM
- Selection for high milk production has changed endocrine profiles so that hormones favor lactation at the expense of reproduction

## Reference #: 249

**Title:**

Effects of treatment of dairy cows with recombinant bovine somatotropin over three or four lactations

**Authors:**

Oldenbroek,J.K.; Garssen,G.J.; Jonker,L.J.; Wilkinson,J.I.

**Reference:**

Journal of Dairy Science 76(2):453-467, 1993

**Topics Covered:**

efficacy

**Location:**

Holland

**Number of Herds:**

1

**# of Cows:**

177

**Breed:**

Jersey, Dutch Red and White, Friesian

**Treatment**

Drug: Somidobove

Dose: 0 (no placebo), 320, 640 or 960 mg/28 d (in most of the 6 trials)

Route: SC

Start: not specified

Duration: usually 168 days

Groups: 2 or 4

**Treatment Allocation not indicated**

Random:

Method:

How was it randomized:

**Blind Techniques:**

no placebo used

**Observation Period:**

6 different trials between Fall, 1985 to Fall 1988.

**Company's Role**

Company: Eli Lilly

Role: co-investigator

**Comments:**

- General conclusions
  - Few data were extracted because almost all results were pooled over multiple doses
  - Average production response was consistent over multiple lactations but maximum production response had low repeatability within cow (between treatment periods) (0.2) and between lactations (0.5)
  - No obvious detrimental effects on fertility or health

## Reference #: 261

**Title:**

Effects of a prolonged-release formulation of Sometribove (n-methionyl bovine somatotropin) on Jersey cows

**Authors:**

Pell,A.N.; Tsang,D.S.; Howlett,B.A.; Huyler,M.T.; Meserole,V.K.; Samuels,W.A.; Hartnell,G.F.; Hintz,R.L.

**Reference:**

Journal of Dairy Science 75:3416-3431, 1992

**Topics Covered:**

efficacy, udder health, nutrition, reproduction, general health

**Location:**

Vermont

**Number of Herds:**

1

**# of Cows:**

46

**Breed:**

Jersey

**Treatment**

Drug: Sometribove

Dose: 0,500 mg/14d

Route: SC

Start: +60 ± 3 days

Duration: full lactation, or +400 days for open cows

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- General conclusion
  - Considerable injection site reactions in these Jerseys
  - Study covers many issues from efficacy to health

## Reference #: 279

**Title:**

Lactational response of Jersey cows to bovine somatotropin administered daily or in a sustained-release formulation

**Authors:**

Jenny,B.F.; Grimes,L.W.; Pardue,F.E.; Rock,D.W.; Patterson,D.L.

**Reference:**

Journal of Dairy Science 75:3402-3407, 1992

**Topics Covered:**

efficacy, udder health, BCS, nutrition

**Location:**

South Carolina

**Number of Herds:**

1

**# of Cows:**

24 (9 PP and 15 MP)

**Breed:**

Jersey

**Treatment**

Drug: BST

Dose: 0, 15.5 mg/d or 310 mg/14d

Route: SC

Start: +98 to 105 days

Duration: until -70 ± 5 days for cows open <200 d
or +400 days for cows open >200 d

Groups: 3

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity, calving date, and anticipated yield

**Blind Techniques:**

placebo used

**Observation Period:**

42 d prior to start of tx to week 42 of lactation

**Company's Role**

Company: American Cyanamid

Role: co-investigator

### Comments:

- Effect of rbST treatment in all cows
- 24 jerseys were assigned to 3 groups - 8 cows per group (unable to determine if any cows were removed from trial

## Reference #: 281

**Title:**

Lactation, health, and reproduction of dairy cows receiving daily injectable or sustained - release somatotropin

**Authors:**

Zhao,X.; Burton,J.H.; McBride,B.W.

**Reference:**

Journal of Dairy Science 75:3122-3130, 1992

**Topics Covered:**

reproduction, lameness, efficacy, nutrition, udder health, BCS

**Location:**

Guelph

**Number of Herds:**

1

**# of Cows:**

74 (26 PP and 48 MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 10.3 mg/d, 350 mg/14d

Route: SC

Start: +28 to 35 days

Duration: 40 wks

Groups: 3

**Treatment Allocation not indicated**

Random:

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: American Cyanamid

Role: ?

### Comments:

- The overall results were increased milk production, minimal health concerns, increased feed efficiency, mild impairment of reproductive efficiency

## Reference #: 290

**Title:**

Influence of bovine somatotropin on the composition and manufacturing properties of milk

**Authors:**

Laurent,F.; Vignon,B.; Coomans,D.; Wilkinson,J.; Bonnel,A.

**Reference:**

Journal of Dairy Science 75:2226-2234, 1992

**Topics Covered:**

efficacy

**Location:**

France, England

**Number of Herds:**

3

**Herd #1**

Location: France

# of Cows: 40 (12 pp and 28 MP)

Breed: French Friesian

**Treatment**

**Drug: bST**

Dose: 0 (no placebo), 320, 640, 960 mg/28d

Route:

Start: +70 to 152 days

Duration: 12 wks

Groups: 4

**Herd #2**

Location: England

# of Cows: 32 (12 PP and 20 MP

Breed: Montbeliard

**Treatment**

Drug: bST

Dose: 0 (no placebo), 640 mg/28d

Route:

Start: +43 to 102 days

Duration: 20 wks

Groups: 2

**Herd #3**

Location: France

# of Cows: 48 (12 PP and 36 MP)

Breed: French Friesian

**Treatment**

Drug: bST

Dose: 0 (no placebo), 320 mg/14d, 320, 640 mg/28d

Route:

Start: +42 ± 7 days

Duration: 28 wks

Groups: 4

**Treatment Allocation**

Random: yes

Method: randomized block

How was it randomized: by parity

Blind Techniques:

no placebo used

**Observation Period:**

between 13 and 29 weeks

**Company's Role**

Company: Lilly?

Role: co-investigator

## Comments:

- General Conclusions
  - No data extracted
  - rbST had minimal effect on manufacturing properties of milk

# Reference #: 291

**Title:**

Milk yield, health, and reproduction of dairy cows given somatotropin (Somavubove) beginning early postpartum

**Authors:**

Stanisiewski,E.P.; Krabill,L.F.; Lauderdale,J.W.

**Reference:**

Journal of Dairy Science 75:2149-2164, 1992

**Topics Covered:**

efficacy, reproduction, BCS, udder health

**Location:**

Michigan

**Number of Herds:**

1

**# of Cows:**

210

**Breed:**

Holstein

**Treatment**

Drug: Somavubove

Dose: 0, 0 to 14 mg/d, 5 mg/d, 5 to 14 mg/d,14 mg/d

Route: IM

Start: +14 days with changes in dosage occurring on day 60

Duration: to + 130 days

Groups: 5
* comparison dose was 0mg/d up until +60 days then it was changed to 14 mg/d to +130 days

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by calving date

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Upjohn

Role: co-investigator

### Comments:

- This study uses a 130 day treatment period
- Reasons for culls from the study are recorded
- An extensive reproductive parameter analysis is included

## Reference #: 298

**Title:**

Impact of bovine somatotropin administration beginning at day 70 of lactation on serum metabolites, milk constituents, and production in cows previously exposed to exogenous somatotropin

**Authors:**

Lean,I.J.; Baldwin,R.L.; Troutt,H.F.; Bruss,M.L.; Galland,J.C.; Farver,T.B.; Rostami,J.; Weaver,L.D.; Holmberg,C.A.

**Reference:**

American Journal of Veterinary Research 53:731-741, 1992

**Topics Covered:**

efficacy, general health

**Location:**

California

**Number of Herds:**

1

**# of Cows:**

72 (All MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 17.2, 51.6, 86 mg/d

Route:

Start: +70 days

Duration: 30 days

**Treatment Allocation**

Random: yes, at start of 1 st study

Method: block

How was it randomized: the randomized block was not strictly followed due to removal and replacement of animals

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Upjohn

Role: co-investigator

## Comments:

- General Conclusions
  - The study was a detailed metabolic study of bST in a 2nd lactation, but the treatment and observation period of 30 days was too short to evaluate efficacy or health effects

# Reference #: 302

**Title:**

Effect of a prolonged-release formulation of N-methionyl bovine somatotropin (Sometribove) on milk fat

**Authors:**

Lynch,J.M.; Barbano,D.M.; Bauman,D.E.; Hartnell,G.F.; Nemeth,M.A.

**Reference:**

Journal of Dairy Science 75:1794-1809, 1992

**Topics Covered:**

efficacy

**Location:**

New York

**Number of Herds:**

1

**# of Cows:**

18 (10 PP and 8 MP)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, or 500 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: full lactation

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: co-investigators

### Comments:

- This paper presents detailed analysis of the composition of milk fat (fatty acid composition)
- Data primarily presented in graphical form and were not extracted

## Reference #: 318

**Title:**

Factors affecting response of cows to biweekly injections of Sometribove

**Authors:**

Sullivan,J.L.; Huber,J.T.; DeNise,S.K.; Hoffman,R.G.; Kung,L.; Franson,S.E.; Madsen,K.S.

**Reference:**

Journal of Dairy Science 75: 756-763, 1992

**Topics Covered:**

efficacy

**Location:**

Arizona

**Number of Herds:**

1

**# of Cows:**

78 (18 PP and 60 MP)

**Breed:**

Holstein

**Treatment**

Drug: BST

Dose: 0, 500 mg/14d

Route: IM

Start: +60 days

Duration: 36 wks

Groups:

**Treatment Allocation**

Random: yes

Method:

How was it randomized: by parity

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- Data not presented in a format suitable for extraction and comparison with other studies
- General Conclusions
  - No significant effects of pre-treatment yield, genetic index, or environmental temperature (month) on response to rbST

## Reference #: 329

**Title:**

Response of dairy cows to high doses of a sustained-release bovine somatotropin administered during two lactations. 2. Health and reproduction

**Authors:**

Cole,W.J.; Eppard,P.J.; Boysen,B.G.; Madsen,K.S.; Sorbet,R.H.; Miller,M.A.; Hintz,R.L.; White,T.C.; Ribelin,W.E.; Hammond,B.G.; Collier,R.J.; Lanza,G.M.

**Reference:**

Journal of Dairy Science 75:111-123, 1992

**Topics Covered:**

udder health

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

82

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 600, 1800, 3000 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: full lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity

**Blind Techniques:**

none

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: principle investigator

**Comments:**

- Reference #4 (Monsanto), #1076 (JDS-production), and #329 (JDS-health/reproduction) all report results from the same study (Multi-lactation chronic animal toxicity study). The results will be handled as follows:
  - #4 -No data extracted but comments left on cover sheet
  - #1076 -Production and nutrition data extracted but all comments left on cover sheet
  - #329 -Only clinical mastitis data extracted (too few numbers for other health parameters)
- General Conclusions
  - No effect of rbST on clinical mastitis risk
  - Health, lameness and culling data not extracted due to small numbers

## Reference #: 344

**Title:**

Evaluation of Sometribove in a prolonged-release system in lactating dairy cows--production responses

**Authors:**

Hartnell,G.F.; Franson,S.E.; Bauman,D.E.; Head,H.H.; Huber,J.T.; Lamb,R.C.; Madsen,K.S.; Cole,W.J.; Hintz,R.L.

**Reference:**

Journal of Dairy Science 74:2645-2663, 1991

**Topics Covered:**

efficacy, nutrition, BCS, udder health

**Location:**

Arizona, Florida, Utah

**Number of Herds:**

4

**# of Cows:**

254 (109 PP and 145 MP)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 250, 500, and 750 mg/14d

Route: SC

Start: +60 ± 3 days

Duration: 36 weeks

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity

**Blind Techniques:**

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: co-investigator

## Comments:

- 3.5% Salable FCM recorded
- Cyclic activity of 14 day production commented on but not recorded or illustrated
- Feed efficiency p and m different and should be noted
- BCS prior to treatment vs treated not illustrated - only compared with treatment groups

# Reference #: 384

**Title:**

Effect of Sometribove on rumen fermentation, rate of passage, digestibility, and milk production responses in dairy cows

**Authors:**

Winsryg,M.D.; Arambel,M.J.; Kent,B.A.; Walters,J.L.

**Reference:**

Journal of Dairy Science 74, 3518-3523, 1991

**Topics Covered:**

efficacy, general health, nutrition

**Location:**

Utah

**Number of Herds:**

1

**# of Cows:**

6

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, or 25 mg/d

Route: SC

Start: +60 ± 7 days

Duration: 6 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: single reversal switchback design

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

at least 9 weeks

**Company's Role**

Company: Monsanto

Role: none

### Comments:

- There were only 6 cows in the study therefore no data extracted

## Reference #: 385

**Title:**

Post-parturient metabolic and production responses in cows previously exposed to long-term treatment with Somatotropin

**Authors:**

Lean,I.J.; Troutt,H.F.; Bruss,M.L.; Farver,T.B.; Baldwin,R.L.; Galland,J.C.; Kratzer,D.; Holmberg,C.A.; Weaver,L.D.

**Reference:**

Journal of Dairy Science 74:3429-3455, 1991

**Topics Covered:**

efficacy, BCS, nutrition

**Location:**

California

**Number of Herds:**

1

**# of Cows:**

85 (All MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 17.2, 51.6, 86 mg/d

Route: Not specified

Start: +70 d

Duration: 1 lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: this was not strictly followed due to removal and replacement of animals.

**Blind Techniques:**

placebo used

**Observation Period:**

carry over effect (70 days of subsequent lactation)

**Company's Role**

Company: Upjohn

Role: co-investigators

## Comments:

- No data extracted since all results were presented in graphical form
- Study looked at "carry over" effects
- Serum ffa and bhb levels were higher in treated cows for 1$^{st}$ 40 days of next lactation
- No substantial effects on milk composition
- Dry matter intakes were higher in tx cows up to day 40 of next lactation
- Tx cows had lower BCS before calving but difference disappeared after calving

- General Conclusions
    - Control cows metabolized more tissue after calving which may lead to higher post-parturism milk yields (not evident in this study) but greater health risks

## Reference #: 403

**Title:**

Relationships among milk yield, metabolism, and reproductive performance of primiparous Holstein cows treated with Somatotropin

**Authors:**

Morbeck,D.E.; Britt,J.H.; McDaniel,B.T.

**Reference:**

Journal of Dairy Science 74:2153-2164, 1991

**Topics Covered:**

Efficacy, reproduction, BCS, general health, nutrition

**Location:**

North Carolina

**Number of Herds:**

1

**# of Cows:**

32 (all PP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 5.15, 10.3, 16.5 mg/d

Route: SC

Start: +28 to 35 days

Duration: to 400 DIM or when milk production <9kg/d

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: American Cyanamid

Role: none

### Comments:

- Experiments with lower dosage than label
- Efficacy
  - bST did not significantly affect any measure of milk production in growing primiparous cows
- Reproduction
  - Rate of detection of estrus was lowest in high group and decreased linearly with dose of bST
  - Overall days to first insemination and conception were affected by bSt ($p<0.05$)
- BCS
  - Cows treated with bSt lost more body condition in the first trimester than control cows suggesting that metabolism was altered (NEB) and could have contributed to the reduced detection rate of estrus
  - No difference amongst groups in BCS at the end of lactation
- General health/nutrition
  - Insulin, glucose, NEFA and BUN were not affected bt bST between 300-100 DIM eventhough cows showed a decrease in BCS (apparent NEB)

## Reference #: 406

**Title:**

Observations on intra-mammary infection and somatic cell counts in cows treated with recombinant bovine somatotropin

**Authors:**

Lissemore,K.D.; Leslie,K.E.; McBride,B.W.; Burton,J.H.; Willan,A.R.; Bateman,K.G.

**Reference:**

Canadian Journal of Veterinary Research 55:196-198, 1991

**Topics Covered:**

udder health

**Location:**

Guelph

**Number of Herds:**

1

**# of Cows:**

37

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 10.3, 20.6, 41.2 mg/d

Route: SC

Start: +28 to 35 days

Duration: 266 days

Groups: 4

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role not indicated**

Company:

Role:

### Comments:

- DHI SCC log(e) were higher in the treatment group after ~120 days of lactation
- General Conclusion
  - Higher prevalence of infection in mid lactation but not in late lactation

## Reference #: 410

**Title:**

Serum immunoglobulin profiles of dairy cows chronically treated with recombinant bovine somatotropin

**Authors:**

Burton,J.L.; McBride,B.W.; Kennedy,B.W.; Burton,J.H.; Elsasser,T.H.; Woodward,B.

**Reference:**

Journal of Dairy Science 74:1589-1598, 1991

**Topics Covered:**

general health

**Location:**

Guelph

**Number of Herds:**

1

**# of Cows:**

29 (all MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: O, 10.3, 20.6 mg/d

Route: SC

Start: +28 to 35 days

Duration: 266 days

Groups: 3

**Treatment Allocation not indicated**

Random:

Method:

How was it randomized:

**Blind Techniques:**

not indicated, but placebo used in other studies by this author

**Observation Period:**

1 lactation

**Company's Role**

Company: Cyanamid (used in other studies by this author)

Role: ?

### Comments:

- General Conclusions
  - rbST had no apparent detrimental effect on humoral immunity
  - No data extracted

## Reference #: 416

**Title:**

Responses by lactating cows in commercial dairy herds to recombinant bovine somatotropin

**Authors:**

Thomas,J.W.; Erdman,R.A.; Galton,D.M.; Lamb,R.C.; Arambel,M.J.; Olson,J.D.; Madsen,K.S.; Samuels,W.A.; Peel,C.J.; Green,G.A.

**Reference:**

Journal of Dairy Science 74:945-964, 1991

**Topics Covered:**

BCS, udder health

**Location:**

Michigan, Maryland, New York, Utah, Minnesota, Missouri

**Number of Herds:**

15

**# of Cows:**

890 (297 PP and 593 MP)

**Breed:**

Not indicated

**Treatment**

Drug: Sometribove

Dose: 0 (no placebo), 500 mg/14d

Route: SC

Start: +57 to 180 days

Duration: 12 wks (for three different stages of lactation)

Groups: 2

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by stage of lactation, and parity

**Blind Techniques:**

no placebo used

**Observation Period:**

16 wks

**Company's Role**

Company: Monsanto

Role: co-investigators

### Comments:

- This paper presents results from 15 herds, these herds are already covered in references #5415, 5416, 5417, and 5418
- Consequently, only udder health and BCS data were extracted (these were either not extracted or dropped from the other studies)
- General Conclusions
    - Moderate increased risk of clinical mastitis but results were quite variable across herds

## Reference #: 425

**Title:**

Effects of recombinant methionyl bovine somatotropin (Sometribove) in high producing cows milked three times daily

**Authors:**

Jordan,D.C.; Aguilar,A.A.; Olson,J.D.; Bailey,C.; Hartnell,G.F.; Madsen,K.S.

**Reference:**

Journal of Dairy Science 74:220-226, 1991

**Topics Covered:**

efficacy, udder health, lameness

**Location:**

Colorado

**Number of Herds:**

1

**# of Cows:**

104 (42 PP and 62 MP)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, or 25 mg/d

Route: IM

Start: 53 to 180 d

Duration: 12 wks

Groups: 2 (tx, control)

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity amd days post partum. As well the MP cows were blocked by whether or not they had received Zinpro prior to study.

**Blind Techniques:**

none

**Observation Period:**

16 wks (2 pre-tx, 12 tx, 2 post-tx)

**Company's Role**

Company: Monsanto

Role: co-investigated

### Comments:

- SCC recorded as raw cell counts (not log transformed) so data not extracted
- BCS data averaged over the 84 day treatment period (no values for end of period given)
- General conclusions
    - Significant increase in production with limited evidence of increased health risks

## Reference #: 539

**Title:**

Response of dairy cows treated with bovine somatotropin to a luteolytic dose of prostaglandin F2 alpha

**Authors:**

Kirby,C.J.; Wilson,S.J.; Lucy,M.C.

**Reference:**

Journal of Dairy Science 80:286-294, 1997

**Topics Covered:**

reproduction

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

30

**Breed:**

26 Holstein, 4 Guernsey

**Treatment**

Drug: Posilac

Dose: 0, 500 mg/14d

Route: SC

Start: +65 ± 5 days

Duration: 6 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: not indicated

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

6 weeks

**Company's Role**

Company: Monsanto

Role: none

### Comments:

- It seems that bST treated cows were less likely to have a norgestomet-synchronized estrus based on small number of cows (n=18)
- Proportion of cows ovulating from first or second wave follicles after PG injection on day 12 was similar in bST treated and control cows
- More control cows were observed in estrus than were cows treated with bST (92% vs 42%; P<.01) for the total possible estruses during the 6 weeks observation period
- In accordance with Kirby et al. (1992), bST treated cows have approximately 2d faster development of the second follicular wave. The reason for changes in follicular dynamics of treated cows is not completely understood as it seems that bST caused earlier atresia of the first wave dominant follicle (IGF-I may accelerate the normal process of granulosa cell growth)
- Treatment of lactating cows with bST causes a change in the timing of follicular waves and led to a decreased percentage of cows detected in standing heat
- No significant milk production increase in bST cows vs control cows during the 6 week observation period
- Many other specific reproduction parameters (eg. hormone levels) noted in paper but the data were not extracted

## Reference #: 605

**Title:**

Use of recombinant bovine somatotropin for up to two consecutive lactations on dairy production traits

**Authors:**

McBride,B.W.; Burton,J.L.; Gibson,J.P.; Burton,J.H.; Eggert,R.G.

**Reference:**

Journal of Dairy Science 73:3248-3257, 1990

**Topics Covered:**

Efficacy, nutrition, BCS, udder health

**Number of Herds:**

1

**Location:**

Guelph

**# of Cows:**

43(6 PP and 37 MP)

**Breed:**

Holstein

**Treatment**

Drug: rbST

Dose: 0, 10.3, or 20.6 mg/d

Route: SC

Start: +28 to 35 days

Duration: 266 days

Groups: 5

**Treatment Allocation**

Random: yes

Method: blocked by parity and yield

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: American Cyanamid

Role: co-investigator

**Comments:**

- Carry over effects looked at first 28-35 days of L2
- No carry over effects on production or milk composition
- General Conclusions
  - Cows treated in L2 had continued increased production
  - Cows treated in L1 had higher feed intakes in early L2 which reduced the gains in feed efficiency associated with treatment

## Reference #: 627

**Title:**

Overall efficacy of chronically administered recombinant bovine somatotropin to lactating dairy cows

**Authors:**

Burton J.H.; MacLeod G.K.; McBride,B.W.; Burton,J.L.; Bateman K.; McMillan I.; Eggert,R.G.

**Reference:**

Journal of Dairy Science 73:2157-2167, 1990

**Topics Covered:**

efficacy, udder health, reproduction, BCS, culling

**Location:**

Guelph

**Number of Herds:**

1

**# of Cows:**

38 (9 PP and 29 MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 10.3, 20.6, 41.2 mg/d

Route: SC

Start: 28 to 35 DIM

Duration: 38 wks

Groups: 4

**Treatment Allocation**

Random: yes

Method: blocked by age and production level

How was it randomized: MP cows balanced based on previous lactation yield. PP allotted randomly

**Blind Techniques:**

placebo used

**Observation Period:**

41 wks (3 wks prior to tx, 38 wks tx)

**Company's Role**

Company: Cyanamid

Role: funded

### Comments:

- Point estimate is based on 41.2 mg/d dose
- Statistical significance is based on comparison among all 4 treatments

## Reference #: 628

**Title:**

Effect of acute challenge with an extreme dose of somatotropin in a prolonged-release formulation on milk production and health of dairy cattle (#86-011)

**Authors:**

Vicini,J.L.; Hudson,S.; Cole,W.J.; Miller,M.A.; Eppard,P.J.; White,T.C.; Collier,R.J.

**Reference:**

Journal of Dairy Science 73:2093-2102, 1990

**Topics Covered:**

general health

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

8

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0 or 15000mg/7d

Route: SC

Start: +238 to +246

Duration: 15 days

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

15 days

**Company's Role**

Company: Monsanto

Role: principle investigator

**Comments:**

- No data to extracted
- General Conclusions
    - Very high dose of rbST produced slight increase in rectal temperature, slight decrease in dry matter intake and subcutaneous injection site reactions

## Reference #: 643

**Title:**

Use of prolonged-release bovine somatotropin for milk production in British Friesian dairy cows. 3. Effect on manufacturing properties and quality of Cheddar, Wensleydale and Cheshire cheese

**Authors:**

Phipps,R.H.; Bines,V.; Adriaens,F.

**Reference:**

Journal of Agricultural Science 115:113-116, 1990

**Topics Covered:**

efficacy (cheese production)

**Location:**

United Kingdom

**Number of Herds:**

not indicated

**# of Cows:**

not indicated

**Breed:**

British Friesian

**Treatment not indicated**

Drug:

Dose:

Route:

Start:

Duration:

Groups:

**Treatment Allocation not indicated**

Random:

Method:

How was it randomized:

**Blind Techniques:**

not indicated

**Observation Period:**

1985-1987

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- Paper looked at the effect of rbST treated milk on cheese production.
- No data were extracted

## Reference #: 644

**Title:**

Use of prolonged-release bovine somatotropin for milk production in British Friesian dairy cows. 2. Effect on health and reproduction in two consecutive lactations of treatment

**Authors:**

Weller,R.F.; Phipps,R.H.; Craven,N.; Peel,C.J.

**Reference:**

Journal of Agricultural Science 115:105-112

**Topics Covered:**

udder health, reproduction

**Location:**

United Kingdom

**Number of Herds:**

1

**# of Cows:**

90 (lactation 1)
60 (lactation 2)

**Breed:**

British Friesian

**Treatment**

Drug: Sometribove

Dose: 0, or 500 mg/14 d

Route:

Start: +60 ± 3 days

Duration: full lactation for 2 lactations

Groups: 2 (tx and control)

**Treatment Allocation**

Random: yes

Method: 2 X 2 factorial

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: co-investigator

## Comments:

- General Conclusions
  - rbST reduced fertility

- rbST appeared to increase subclinical and clinical mastitis (particularly in 2nd lactation)

## Reference #: 645

**Title:**

Use of prolonged-release bovine somatotropin for milk production in British Friesian dairy cows. 1. Effect on intake, milk production and feed efficiency in two consecutive lactations of treatment

**Authors:**

Phipps,R.H.; Weller,R.F.; Craven,N.; Peel,C.J.

**Reference:**

Journal of Agricultural Science 115:95-104, 1990

**Topics Covered:**

efficacy, nutrition, BCS

**Location:**

United Kingdom

**Number of Herds:**

1

**# of Cows:**

60

**Breed:**

British Friesian

**Treatment**

Drug: Sometribove

Dose: 0, or 500 mg/14 d

Route: IM (1 st lactation), SC (2 nd lactation)

Start: +60 ± 3 days

Duration: full lactation for 2 lactations

Groups: 2

**Treatment Allocation**

Random: yes

Method: 2 X 2 factorial design

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- General Conclusions
  - rbST significantly increased milk production in both 1st and 2nd study lactations
  - Effect of rbST on BCS was most pronounced in 1st study lactation
  - rbST increased feed efficiency (gfe measured as kg FCM/MJ ME)

## Reference #: 730

**Title:**

Health, welfare and fertility implications of the use of bovine somatotrophin in dairy cattle

**Authors:**

Whitaker,D.A.; Smith,E.J.; Kelly,J.M.;; Hodgson-Jones,L.S.

**Reference:**

Veterinary Record 122:503-505, 1988

**Topics Covered:**

udder health, efficacy, BCS, reproduction

**Location:**

Scotland

**Number of Herds:**

1

**# of Cows:**

36 (16 PP and 22 MP)

**Breed:**

Friesian and Friesian-Ayrshire cross

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route:

Start: +80 ± 7 days

Duration: 8 to 26 wks

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized: parity, previous milk yield, calving date, heifers were alternately assigned

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: none

## Comments:

- Reproduction data were not presented in a useable form

# Reference #: 802

**Title:**

The effects of long-term administration of bovine growth hormone on the lactational performance of identical-twin dairy cows

**Authors:**

Peel,C.J.; Sandles,L.D.; Quelch,K.J.; Herington,A.C.

**Reference:**

Animal Production 41:135-142, 1985

**Topics Covered:**

efficacy

**Location:**

Australia

**Number of Herds:**

1

**# of Cows:**

10

**Breed:**

? (twins)

**Treatment**

Drug: purified bovine pituitary growth hormone

Dose: 39 iu/d

Route: SC

Start: +5 to 26 days

Duration: 154 days

Groups: 2

**Treatment Allocation**

Random: yes

Method: formal

How was it randomized: simple formal random

**Blind Techniques:**

yes

**Observation Period:**

22 weeks

**Company's Role**

Company: none

Role: None

## Reference #: 931

**Title:**

Effects of recombinant bovine somatotropin (Sometribove) on ovarian function in lactating and non-lactating dairy cows

**Authors:**

De La Sota,R.L.; Lucy,M.C.; Staples,C.R.; Thatcher,W.W.

**Reference:**

Journal of Dairy Science 76:1002-1013, 1993

**Topics Covered:**

reproduction, drug interactions

**Location:**

Florida

**Number of Herds:**

1

**# of Cows:**

24

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 25 mg/d

Route: SC

Start:

Duration: 2 periods of 19 days

Groups:

**Treatment Allocation**

Random

Method: treatment crossover design

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

2 periods of 19 days each

**Company's Role**

Company: Monsanto

Role: product

### Comments:

- This paper presents many graphs of follicular measurements for lactating and non-lactating cows. No data were extracted
- General conclusions
  - rbST increased the number of follicles in lactating cows
  - rbST increased the size of the 2$^{nd}$ largest follicle

## Reference #: 961

**Title:**

Effect of recombinantly-derived bovine somatotropin on reproductive performance of dairy cattle

**Authors:**

Cole,W.J.; Madsen,K.S.; Hintz,R.L.; Collier,R.J.

**Reference:**

Theriogenology 36:572-594, 1991

**Topics Covered:**

reproduction, efficacy, general health

**Location:**

Missouri, New York, Arizona, Utah

**Number of Herds:**

5

**# of Cows:**

814 (272 PP and 542 MP)

**Breed:**

Not indicated

**Treatment**

Drug: Sometribove

Dose: 0, 250, 500, 600, 750, 1800, 300 mg/14d

Route: IM or SC depending on study

Start: +60 ± 3 days

Duration: to -70 days for pregnant cows, 50 weeks (350days) for non-pregnant cows

Groups: 7

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity

**Blind Techniques:**

placebo used

**Observation Period:**

between calving to calving, and calving to calving + 60 days, depending on study

**Company's Role**

Company: Monsanto

Role: principle investigator

**Comments:**

- All data derived from 5 other studies which have been included in the database
- No data extracted from this paper for the database
- This paper incorporates results from 5 separate studies involving IM and SC injections and using up to 6 times the label dose of bST
- Only the 500 mg dosage effects will be evaluated in these comments
- Initiation of bST (IM) soon after AI or conception has a consistent trend (NS) to result in failure to maintain pregnancy for all cows (9% increased EED)
- Cows bred within 28 days after beginning of bST (IM) have a tendency to have a numerically lower CR (5-20%) which is worst in primiparous cows
- Significant decrease in pregnancy rate (19%) and increase of .4 SPC and 25 days open in bST (IM) treated cows compared to controls in primiparous cows not repeated in titration SC study
- Milk production levels has a significant negative impact on pregnancy rate, days open, and SPC
- To limit the negative impact of bST on reproduction, it is advised to delay bST treatment until after confirmation of pregnancy especially in primiparous cows
- Reported significant increase of twinnings in cows (RR=1.9) with IM injection only (not found in SC injection)
- Negative effects of bST on reproduction are essentially indirect ones through increased demand on body stores and nutritional management

## Reference #: 1018

**Title:**

Bovine somatotropin and cow health--what are the facts?

**Authors:**

Ceelen,H.J.

**Reference:**

Canadian Veterinary Journal 36:25-29, 1995

**Topics Covered:**

udder health, reproduction, general health

**Location:**
**Number of Herds:**
**# of Cows:**
**Breed:**
**Treatment**

Drug:

Dose:

Route:

Start:

Duration:

Groups:

**Treatment Allocation**

Random:

Method:

How was it randomized:

**Blind Techniques:**
**Observation Period:**
**Company's Role**

Company:

Role:

### Comments:

- Special report summarizing the effects of rbST, therefore no data were extracted
- Udder health: no differences at labeled dosages
- Reproduction: trend toward reducing reproductive efficiency; increased calving interval; solution to start bST>60-80 DIM
- General health: no difference in incidence or severity of peripartum disease

## Reference #: 1029

**Title:**

An international perspective on bovine somatotropin and clinical mastitis

**Authors:**

Willeberg,P.

**Reference:**

JAVMA 205(4):538-541, 1994

**Topics Covered:**

welfare

**Location:**

**Number of Herds:**

**# of Cows:**

**Breed:**

**Treatment**

Drug:

Dose:

Route:

Duration:

**Treatment Allocation**

Random:

Method:

How was it randomized:

**Blind Techniques:**

**Observation Period:**

**Company's Role**

Company: none

Role: none

## Comments:

- Not a research paper
- General Conclusions (ID)

    - There is evidence of increased mastitis risk but no jurisdiction has addressed the question of whether or not this constitutes an animal welfare problem.
- General Conclusions (AP)
    - Assumption that increased mastitis is detrimental to an animal's welfare and health
    - Mastitis is manageable from a human health perspective
    - No attention paid to management of mastitis from a cow welfare perspective
    - EU takes a much different approach to welfare issues than does the US and Canada
    - As bST is used, clinical mastitis will increase, animal welfare will decrease

## Reference #: 1076

**Title:**

Response of dairy cows to high doses of a sustained-release bovine somatotropin administered during two lactations. 1. Production response

**Authors:**

Eppard,P.J.; Hudson,S.; Cole,W.J.; Hintz,R.L.; Hartnell,G.F.; Hunter,T.W.; Metzger,L.E.; Torkelson,A.R.; Hammond,B.G.; Collier,R.J.; Lanza,G.M.

**Reference:**

Journal of Dairy Science 74:3807-3821, 1990

**Topics Covered:**

Efficacy, nutrition, udder health

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

82 - lactation 1
38 - lactation 2

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, .6, 1.8, 3.0 g/14d

Route: IM

Start: +60 ± 3 days

Duration: 1 lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: principle investigator

## Comments:

- Reference #4 (Monsanto), #1076 (JDS-production), and #329 (JDS-health/reproduction) all report results from the same study (Multi-lactation chronic animal toxicity study). The results will be handled as follows:
    - #4 -No data extracted but comments left on cover sheet
    - #1076 -Production and nutrition data extracted but all comments left on cover sheet
    - #329 -Only clinical mastitis data extracted (too few numbers for other health parameters)
- Effect of bST administered at 1, 3X, 5X labeled dose during 2 lactations (subset of 38 pregnant cows continued to 2$^{nd}$ lactation
- Md reported are between 3 g/14d bST vs control
- Efficacy:
    - Overall significant improvement of milk production in bST cows by 7.2 kg/d (first year) and by 10.6 kg/d (second year)

    - Unexplained higher milk production increased for 1X bST
    - Despite an increase of clinical mastitis in the second year of study, bST treated cows had a significant increase in salable 3.5% FCM (+12.1 kg/d)
- Udder health:
    - Clinical mastitis not increased during the 2nd year follow-up at labeled dose but cows on 5X dosage had twice the risk of getting mastitis compared to controls
- Nutrition:
    - DMI was increased significantly by 3 kg during the 1st treatment period but it was not significant during the 2nd year of bST follow-up
    - GFE (kg) was significantly better for bST treated cows only during the first year of the study
    - No overall significant differences were noted in average energy balance
    - Milk composition (ie. fat, lactose, protein, ash, calcium, phosphorous, magnesium and zinc) was unaffected by bST during either lactations

## Reference #: 1218

**Title:**

Health and reproductive performance of dairy cows treated for up to two consecutive lactations with bovine somatotropin

**Authors:**

Burton,J.L.; McBride,B.W.; Burton,J.H.; Eggert,R.G.

**Reference:**

Journal of Dairy Science 73:3258-3265, 1990

**Topics Covered:**

culling, reproduction, lameness, udder health, general health, drug interactions

**Location:**

Guelph

**Number of Herds:**

1

**# of Cows:**

43

**Breed:**

Holstein

**Treatment**

Drug: rbST

Dose: 0, 10.3, 20.6 mg/d

Route: SC

Start: +28 to 35 days

Duration: 38 weeks

Groups: 3

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by age and milk yield

**Blind Techniques:**

placebo used

**Observation Period:**

44 weeks

**Company's Role**

Company: Cyanamid

Role: co-investigator

## Reference #: 1289

**Title:**

Effect of bovine somatotropin on reproductive function in lactating dairy cows

**Authors:**

Waterman,D.F.; Silvia,W.J.; Hemken,R.W.; Heersche,G.; Swenson,T.S.; Eggert,R.G.

**Reference:**

Theriogenology 40:1015-1028, 1993

**Topics Covered:**

reproduction, efficacy, nutrition

**Location:**

Kentucky

**Number of Herds:**

1

**# of Cows:**

22 (8 PP and 14 MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 40 mg/d

Route: SC

Start: +32 to 85 days

Duration: 10 to 28 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: not mentioned

How was it randomized: paired on basis of age, calving date, and relative milk producing ability

**Blind Techniques:**

placebo used

**Observation Period:**

up to 28 weeks

**Company's Role**

Company: American Cyanimid

Role: co-investigator

## Comments:

- Small number of cows may contribute to p-value>0.05
- No differences in LH secretion in cows experiencing anestrus (5 cows:1 placebo vs 4 bST)
- bST tended to reduce expression of estrus (p=0.34) and increase the number of cows with at least one anoestrus period (p=0.05)

## Reference #: 1524

**Title:**

Effect of exogenous somatotropin on hematological variables of lactating cows and their offspring

**Authors:**

Eppard,P.J.; White,T.C.; Sorbet,R.H.; Weiser,M.G.; Cole,W.J.; Hartnell,G.F.; Hintz,R.L.; Lanza,G.M.; Vicini,J.L.; Collier,R.J.

**Reference:**

Journal of Dairy Science 80:1582-1591, 1997

**Topics Covered:**

general health

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

82

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, .6, 1.8, 3.0 g/14 d

Route: IM

Start: 60 ± 3 DIM

Duration: until dry off or necropsy

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: randomized block

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- No data extracted
- rbST caused only mild reduction of most RBC parameters (mostly at higher doses)

## Reference #: 1552

**Title:**

Effect of long-term administration of a prolonged release formulation of bovine somatotropin (Sometribove) on clinical lameness in dairy cows

**Authors:**

Wells,S.J.; Trent,A.M.; Collier,R.J.; Cole,W.J.

**Reference:**

American Journal of Veterinary Research 56:992-996, 1995

**Topics Covered:**

feet and legs

**Location:**

Michigan, New York, Pennsylvania

**Number of Herds:**

8

**# of Cows:**

188

**Breed:**

Not indicated

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route: SC

Start: varied

Duration: 1 lactation

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized: by age, stage in lactation

**Blind Techniques:**

yes

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: co-investigator

## Comments:

- No evidence of increased lameness or leg lesions in treated cows after a minimum of lactation tx

# Reference #: 2104

**Title:**

Bovine ketosis and somatotrophin: risk factors for ketosis and effects of ketosis on health and production

**Authors:**

Lean,I.J.; Bruss,M.L.; Troutt,H.F.; Galland,J.C.; Farver,T.B.; Rostami,J.; Holmberg,C.A.; Weaver,L.D.

**Reference:**

Research in Veterinary Science 57:200-209, 1994

**Topics Covered:**

general Health, BCS

**Location:**

California

**Number of Herds:**

1

**# of Cows:**

156 (78 PP and 78 MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 17.2, 51.6, 86.0 mg/d

Route:

Start: +70 days

Duration: 1 lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method: block

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Upjohn

Role: co-investigator

### Comments:

- General Conclusions
  - rbST significantly reduced the risk of clinical ketosis in the first 60 days of subsequent lactation
  - Reduced risk probably due to lower BCS at the start of lactation

## Reference #: 2215

**Title:**

Effect of a prolonged-release formulation of N-methionyl bovine somatotropin (sometribove) on milk composition

**Authors:**

Barbano.D.M.; Lynch,J.M.; Bauman,D.E.; Hartnell,G.F.; Hintz,R.L.; Nemeth,M.A.

**Reference:**

Journal of Dairy Science 75:1775-1793, 1992

**Topics Covered:**

efficacy, udder health

**Location:**

Ithica, New York

**Number of Herds:**

1

**# of Cows:**

80 (24 PP and 56 MP)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: not indicated

Groups: 2

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: co-investigator

## Comments:

- Protein is increased significantly in rbST treated cows
- Production increased significantly
- No change in lactose or fat
- Cheese yield for bSt treated cows is higher
- Casein levels are not significantly higher
- SCC is > for bST treated cows than for controls
- Cyclical pattern of production with each 14 day period

# Reference #: 3056

**Title:**

Actions of bovine somatotropin on polymorphonuclear leukocytes and lymphocytes in cattle

**Authors:**

Elvinger,F.; Hansen,P.J.; Head,H.H.; Natzke,R.P.

**Reference:**

Journal of Dairy Science 74:2145-2152, 1991

**Topics Covered:**

general health

**Location:**

Florida

**Number of Herds:**

1

**# of Cows:**

24

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 12.6 mg/d

Route: SC

Start: ?

Duration: 112 days

Groups: 2

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: product

### Comments:

- No data were extracted
- No effect on PMNL function
- General Conclusion
  - Difficult paper to analyze, as there were a lot of statistics which were not very relevant

## Reference #: 3295

**Title:**

Follicular function in lactating dairy cows treated with sustained-release bovine somatotropin

**Authors:**

Kirby,C.J.; Smith,M.F.; Keisler,D.H.; Lucy,M.C.

**Reference:**

Journal of Dairy Science 80:273-285, 1997

**Topics Covered:**

reproduction

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

26 (all PP)

**Breed:**

Holstein

**Treatment**

Drug: Posilac

Dose: 0, 500 mg/14d
Group 1 7 cycles saline
Group 2 7 cycles Posilac
Group 3 3 cycles Posilac, 4 cycles saline
Group 4 3 cycles saline, 4 cycles Posilac

Route: SC

Start: +120 to 180 days

Duration: 14 wks

Groups: 4

**Treatment Allocation**

Random: yes

Method: not indicated

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

14 wks

**Company's Role**

Company: Monsanto

Role: technical assistance

## Comments:

- General Conclusions
  - Second follicular wave was 2 days earlier in rbST treated cows
  - Residual effect of rbST on follicular function for up to three weeks

- rbST increased the number of follicles developing

## Reference #: 4744

**Title:**

Health management of dairy herds treated with bovine somatotropin

**Authors:**

Kronfeld,D.S.

**Reference:**

JAVMA 204(1):116-130, 1994

**Topics Covered:**

welfare, culling, udder health, general health

**Number of Herds:**
**Location:**
**# of Cows:**
**Breed:**
**Treatment**

Drug:

Dose:

Route:

Duration:

**Treatment Allocation**

Random:

Method:

How was it randomized:

**Blind Techniques:**
**Observation Period:**

### Comments:

- Review paper
- General conclusion (ID):

  - The author concludes that there are increased adverse health effects associated with the use of rbST and attributes these primarily to a longer period of negative energy balance at the start of the lactation.
  - Some of the analyses, based on expected linear trends, are quite suspect.
- General conclusion (AF):
  - Metabolic stress during periods of tissue mobilization is accompanied by higher rates of disease
  - rbST treated cows are not like genetically superior cows. Shape of the lactation curve is changed with rbST resulting from a second or prolonged catabolic period
  - Current methods for increasing a cow's maximal energy intake have not mitigated the rbST stimulated catabolic response
  - "Burn out" is not recognized as such
  - Other stresses should be reduced during rbST administration
  - Heat tolerance is affected by greater heat production in bST treated cows
  - Effect on rbST on abortion rate has not been studied
  - Reduced reproductive performance is linked to stress
  - Mean duration of and number of cows treated with antibiotics for mastitis is increased with treatment
  - Higher post treatment mastitis
  - Higher culling and mortality rates in treated cows

## Reference #: 5135

**Title:**

Effect of dietary energy and previous bovine somatotropin on milk yield, mastitis, and reproduction in dairy cows

**Authors:**

Hemken,R.W.; Harmon,R.J.; Silvia,W.J.; Tucker,W.B.; Heersche,G.; Eggert,R.G.

**Reference:**

Journal of Dairy Science 74:4265-4272, 1991

**Topics Covered:**

efficacy, BCS, udder health, nutrition

**Location:**

Kentucky

**Number of Herds:**

1

**# of Cows:**

30 (all MP)

**Breed:**

Holstein

**Treatment**

Drug: bST

Dose: 0, 20,6 mg/d

Route: SC

Start: +28 to 35 days

Duration: 39 wks

Groups: 2

**Treatment Allocation**

Random: yes

Method: randomized complete block

How was it randomized: 2X3 factorial arrangement according to time of calving

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: American Cyanamin

Role: co-investigator

### Comments:

- All results pooled over ration groups
- bST cows in lactation 2 may have recieved 0, 10.3, 20.6, or 41.2 mg/d in previous lactation
- Both L1 and L2 cows compared against common control group

## Reference #: 5298

**Title:**

Effects of a 28-day sustained-release formulation of recombinant bovine somatotropin (rbST) administered to cows over two consecutive lactations

**Authors:**

Leonard,M.; Gallo,G.; Gallo,M.; Block,E. Reference: Canadian Journal of Animal Science 70:795-809, 1990

**Topics Covered:**

efficacy, udder health, reproduction, nutrition

**Location:**

Quebec

**Number of Herds:**

1

**# of Cows:**

60 (12 PP and 48 MP)

**Breed:**

Holstein

**Treatment**

Drug: rbST

Dose: 0, 320, 640 (only dose used in L2),
960 mg/28d (comparison dose for L1)

Route: SC

Start: early, middle, or late lactation

Duration: 252 (time period for comparison), 168, or 84 d depending on commencement period for lactation 1, and 252 d for 2 $^{nd}$ lactation

Groups: 4 (1 $^{st}$ lactation)
2 (2 $^{nd}$ lactation)

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Eli Lilly

Role: product

### Comments:

- SCC data were not log transformed so were not extracted for further analysis
- Peak response obtained between 8 and 12 days post injection
- Reproduction and health data from L1 not summarized since it was based on three different durations of administration
- General Conclusions
  - rbST worked well in multiparous cows and to a lesser extent in primiparous cows
  - Overall body condition score was not adversely affected (could not extract BCS data)

## Reference #: 5403

**Title:**

Responses of dairy cows supplemented with somatotropin during weeks 5 through 43 of lactation

**Authors:**

**Chalupa,W.; Vecchiarelli,B.; Galligan,D.T.; Ferguson,J.D.; Baird,L.S.; Hemken,R.W.; Harmon,R.J.; Soderholm,C.G.; Otterby,D.E.; Annexstad,R.J.; Linn,J.G.; Hansen,W.P.; Ehle,F.R.; Palmquist,D.L.; Eggert,R.G.**

**Reference:**

Journal of Dairy Science 79:800-812, 1996

**Topics Covered:**

efficacy, udder health, reproduction, lameness, BCS, nutrition

**Location:**

Kentucky, Minnesota, Pennsylvania, Ohio

**Number of Herds:**

4

**# of Cows:**

136 (36 PP and 100 MP)

**Breed:**

Holsteins(116), Jerseys(12), Brown Swiss(4), Ayrshires(4)

**Treatment**

Drug: Cyanamid

Dose: 0, 10.3, 20.6, 41.2 mg/d

Route: SC

Start: 28 to 35 d

Duration: 38 wks

Groups: 4 (control and 3 treatments)

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: blocked by breed, parity, calving date

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Cyanamid

Role: co-investigated

## Comments:

- All results (p-values) based on comparisons among 4 groups
- All results (point estimates) based on comparison of 41.2 mg/d vs control
- My estimates of RR for mastitis and non-pregnancy (etc.) Do not match the values they report

- I assumed the health data presented in table 10 were based on # of cows (not # of cases)
- BCS data not used - scale reversed from normal scale
- General conclusions
    - rbST improved productivity but there was significant negative health and reproduction effects at 41.2 mg/d dose. These negative effects were less noticeable at lower doses.

## Reference #: 5407

**Title:**

Post-approval evaluation of Posilac bovine somatotropin in commercial dairy herds (93-051)

**Authors:**

Collier, R.J.

**Reference:**

Monsanto Submission, binder 1-6, 1996

**Topics Covered:**

udder health, reproduction, general health, lameness, culling

**Location:**

Northeastern, southeastern, upper midwest, and western United States

**Number of Herds:**

28

**# of Cows:**

1213

**Breed:**

various

**Treatment**

Drug: Posilac

Dose: 0 or 500 mg/14d

Route: Subcutaneous

Start: +57 to +70

Duration: until the end of lactation

Groups: two (control and tx)

**Treatment Allocation**

Random: yes

Method:

How was it randomized: by starting order (DIM) and parity

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- No increase in twinning (data not extracted)
- No increase in cystic ovaries (data not extracted)
- All data extracted are pooled across all herds
- Crude RR and stratified (by herd) RR for mastitis are virtually identical
- Poisson reg$^{n}$ used to evaluate effect of treatment on mastitis sick days. No significant effects found in primiparous or multiparous cows
- General Conclusions
    - A good study for providing data on health and reproduction effects of rbST

## Reference #: 5408

**Title:**

Evaluation of tailhead injection site swelling and sensitivity in British and French field trials (#89-168, # 90-001, #89-031, #90-110)

**Authors:**

Adriaens,F; Bruneau,P.; deKerchove,G; Hard,D.L.

**Reference:**

Monsanto Submissions, binder 4-4

**Topics Covered:**

general health, welfare (injection site reactions)

**Location:**

United Kingdom and France

**Number of Herds:**

28

**# of Cows:**

704

**Breed:**

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: not specified

Duration: not specified

Groups: 2

**Treatment Allocation not specified**

Random:

Method:

How was it randomized:

**Blind Techniques:**

none

**Observation Period:**

**Company's Role**

Company: Monsanto

Role: ?

**Comments:**

- General Conclusions
  - Tailhead injections resulted in small, firm, painless nodules in 30% of cows but these regressed over time
  - Tailhead injections resulted in fewer serious lesions than post-scapular injections

## Reference #: 5409

**Title:**

Responses of dairy cows to treatment with Sometribove (r-BST) during three consecutive years

**Authors:**

Rijpkema,Y.S.; vanReeuwijk,L.; Hard,D.L.

**Reference:**

Livestock Production Science 26:193-216, 1990

**Topics Covered:**

efficacy, udder health, culling

**Location:**

Holland

**Number of Herds:**

1

**# of Cows:**

64 (16 PP and 48 MP)

**Breed:**

Friesian and Friesian-Holstein

**Treatment**

Drug: Sometribove

Dose: 0, or 500 mg/14 d

Route: IM (1 st lactation), SC (2 nd & 3 rd lactation)

Start: 63 DIM (1 st & 2 nd lactation), 91 DIM (3 rd lactation)

Duration: 36 wks (1 st lactation), up to 42 wks (2 nd lactation), 30 wks (3 rd lactation)

Groups: 2

**Treatment Allocation**

Random: yes

Method: 2 X 3 factorial (1 st year), 2 X 2 (2 nd year)

How was it randomized: by lactation

**Blind Techniques:**

placebo used

**Observation Period:**

3 lactations

**Company's Role**

Company: Monsanto

Role: co-investigator

### Comments:

- Tend toward poorer reproductive performance in tx group but no SE of estimates given to allow data to be extracted
- Tend toward higher SCC in tx group but values not given on a log scale
- General Conclusions
    - rbST continued to increase milk production over all 3 lactations although increase was not significant in L2 or L3
    - rbST treated cows maintained body weight equal to or greater than control cows
    - Higher feed intake by treated cows during the pre-treatment period meant that gross feed efficiency over the whole lactation was lower in treated cows in L2 and no different in L3
    - Lower fat yields in years L2 and L3 in treated cows

## Reference #: 5410

**Title:**

Safety and efficacy of CP115099-F. (Sometribove) in dairy cows through three consecutive lactations of treatment (#85-012A)

**Authors:**

Gavert,H.O.; Pabst,K; Hard,D.L.; Kerchove,G; Madsen,K.S.; Peel,C.J.; Wollny,C.

**Reference:**

Monsanto Submissions, binder 5-1, 1989

**Topics Covered:**

efficacy, nutrition

**Location:**

Germany

**Number of Herds:**

1

**# of Cows:**

60 - lactation 1
40 - lactation 2
27 - lactation 3

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: IM - lactation1
SC - lactations 2 & 3

Start: +98 - lactation 1
+63 - lactations 2 & 3

Duration: full lactation

Groups: 2

**Treatment Allocation not specified**

Random:

Method:

How was it randomized

**Blind Techniques:**

?

**Observation Period:**

3 lactations

**Company's Role**

Company: Monsanto

Role: ?

**Comments:**

- General Conclusions
  - Sometribove had either no effect or a negative effect on productivity and feed efficiency

## Reference #: 5411

**Title:**

Efficacy and safety of CP115099-F in dairy cows. Report on lactations 1 and 2 of the French clinical trials performed at Sanders Experimental Centre, Saint Symphorien. (#85-16B)

**Authors:**

Schockmel,L.R.; Vedeau,F.; Peel,C.J.; deKerchove,G; Madsen,K.S.; Hartnell,G.F.

**Reference:**

Monsanto Submission, binder 5-1, 1988

**Topics Covered:**

efficacy, BCS, nutrition

**Location:**

France

**Number of Herds:**

1

**# of Cows:**

58 - lactation 1
39 - lactation 2

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route:
IM - lactation 1
SC - lactation 2

Start: +63 d

Duration: 1 lactation

Groups: 2

**Treatment Allocation not specified**

Random:

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

2 lactations

**Company's Role**

Company: Monsanto

Role: ?

### Comments:

- General Comments
  - Sometribove increased production and feed efficiency over both lactations

## Reference #: 5413

**Title:**

Efficacy and safety of CP115099-F in dairy cows treated for a fourth consecutive lactation in the U.K. (#85-009D)

**Authors:**

Adriaens,F.; Phipps,R.H.; Weller,R.F.; de,Kerchove G.; Hard,D.L.; Hintz,R.L.; Hartnell,G.F.

**Reference:**

Monsanto Submissions, binder 5-1, UK study - 3 rd and 4 th lactations, 1991

**Topics Covered:**

efficacy, nutrition

**Location:**

United Kingdom

**Number of Herds:**

1

**# of Cows:**

90 - lactation 1
60 - lactation 2
43 - lactation 3
28 - lactation 4

**Breed:**

British Friesian

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +60 ± 3 d

Duration: 1 lactation

Groups: 2

**Treatment Allocation not specified**

Random:

Method:

How was it randomized:

**Blind Techniques:**

none

**Observation Period:**

4 lactations

**Company's Role**

Company: Monsanto

Role: ?

**Comments:**

- Data from lactations 1 & 2 presented in Ref #644 and 645 (not repeated here)
- General Conclusions
  - Sometribove consistently increased milk production and feed efficiency over 4 lactations
  - No evidence of carry over effect into first 8 weeks of subsequent lactation
  - Losses from study groups appeared roughly equal but no details on reasons for removal given
  - No health and reproduction data presented

## Reference #: 5414

**Title:**

Farm trials in Colorado using Somatotropin (#87-057)

**Authors:**

Olson,J.D.; Green,G.A.; Madsen,K.S.

**Reference:**

Monsanto Submission, binder 6-2, 1989

**Topics Covered:**

Udder Health

**Location:**

Colorado

**Number of Herds:**

2

**# of Cows:**

152

**Breed:**

Not specified

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: Not specified

Start: +57 to 188 days

Duration: 12 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: blocked

How was it randomized: by parity and herd

**Blind Techniques:**

none

**Observation Period:**

16 weeks

**Company's Role**

Company: Monsanto

Role: ?

### Comments:

- Data presented by individual herd - only the incidence of clinical mastitis data could be pooled across the herds in the study
- Relatively short treatment period

## Reference #: 5415

**Title:**

Response of cows to biweekly administration of Sometribove (N-Methionyl Bovine Somatotropin) in a prolonged release system (CP115099-F) in commercial dairy herds in Michigan and New York (#87-065, #87-067)

**Authors:**

Messerole,V.K.; Madsen,K.S.; Hartnell,G.F.; Cole,W.J.; Hintz,R.L.; Samuels,W.A.; Swenson,G.H.

**Reference:**

Monsanto Submission Binder 6-2

**Topics Covered:**

efficacy, udder health, BCS

**Location:**

Michigan, New York

**Number of Herds:**

7

**# of Cows:**

462

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0 (no placebo), 500 mg/14d

Route: SC

Start: +57 to 189 days

Duration: 12 wks

Groups: 2

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by parity and stage of lactation

**Blind Techniques:**

no placebo used

**Observation Period:**

14 wks

**Company's Role**

Company: Monsanto

Role: co-investigators

### Comments:

- See also reference #416
- Clinical mastitis data included the 2 week post treatment observation period

## Reference #: 5416

**Title:**

Farm trials in Utah using bovine somatotropin (#87-066)

**Authors:**

Arambel,M.J.; Lamb,R.C.; Green,G.A.; Madsen,K.S.

**Reference:**

Monsanto Submission Binder 6-2

**Topics Covered:**

efficacy, BCS

**Location:**

Utah

**Number of Herds:**

3

**# of Cows:**

154

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +57 to 180 days

Duration: 12 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by herd, parity, and stage of lactation

**Blind Techniques:**

none specified

**Observation Period:**

18 weeks

**Company's Role**

Company: Monsanto

Role: co-investigator?

### Comments:

- See also reference #416
- SCC data were not log transformed (so not used)
- No health data

## Reference #: 5417

**Title:**

Farm trials in New York using bovine somatotropin (#87-067)

**Authors:**

Galton,D.M.; Samuels,W.A.; Madsen,K.S.

**Reference:**

Monsanto Submission, binder 6-2

**Topics Covered:**

efficacy, BCS, udder health

**Location:**

New York

**Number of Herds:**

4

**# of Cows:**

231

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +57 to 189 days

Duration: 12 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: blocked

How was it randomized: by herd, parity, and stage of lactation

**Blind Techniques:**

none

**Observation Period:**

16 weeks

**Company's Role**

Company: Monsanto

Role: co-investigator?

**Comments:**

- See also reference #416
- Relatively short treatment period
- No health data presented

## Reference #: 5418

**Title:**

Farm trials in Maryland and Pennsylvania using bovine somatotropin (#88-063)

**Authors:**

Erdman,R.; Samuels,W.A.; Madsen,K.S.

**Reference:**

Monsanto Submission, binder 6-2, 1989

**Topics Covered:**

efficacy, udder health, reproduction

**Location:**

Maryland and Pennsylvania

**Number of Herds:**

2

**# of Cows:**

76

**Breed:**

Not specified

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +57 to 180 days

Duration: 12 weeks

Groups: 2

**Treatment Allocation**

Random: yes

Method: block

How was it randomized: by herd, parity, and start of lactation

**Blind Techniques:**

none

**Observation Period:**

16 weeks

**Company's Role**

Company: Monsanto

Role: co-investigator?

### Comments:

- See also reference #416
- BCS data were mot used since the values for the end of treatment period were not presented
- Reproduction data is only based on cows that were not pregnant before the start of the study

## Reference #: 5419

**Title:**

Effect of the use of bovine somatotropin on culling practices in thirty-two dairy herds in Indiana, Michigan, and Ohio

**Authors:**

Ruegg,P.L.; Fabellar,A; Hintz,R.L.

**Reference:**

Journal of dairy Science 81:1262-1266, 1998

**Topics Covered:**

Culling

**Location:**

Indiana, Michigan, Ohio

**Number of Herds:**

32

**# of Cows:**

5468

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +63 days

Duration: 1 lactation

Groups: 2

**Treatment Allocation**

Random: none

Method:

How was it randomized:

**Blind Techniques:**

none

**Observation Period:**

1 year

**Company's Role**

Company: Monsanto

Role: principle investigator

## Comments:

- Study has very low power (n=32)

- Only data extracted was that which relates to culling density
- Only 25-64% of eligible cows in "adopter" herds were put on bST
- General Conclusions (ID)
    - Trend towards higher culling in adoption herds but low power of study limits ability to draw conclusions
- General Conclusions (PD)
    - Culling patterns in herds that use bST are unaffected for at least the first year of use
    - Weak study because farmer decided on use of bST within a herd - and this varied

## Reference #: 5421

**Title:**

Assessment of the effective range of CP115099-F in lactating primiparous and multiparous dairy cows (86-023)

**Authors:**

Vicini,J.L.; Eppard,P.J.; Lanza,G.M.; Hudson,S.; Miller,M.A.; Cole,W.J.; White,T.C.; Nemeth,M.A.; Abel,K.M.; Duque,J.A.; Hintz,R.L.; Hartnell,G.F.; Madsen,K.S.; Ribelin,W.E.; Ganguli,S.; Sprick,D.M.

**Reference:**

Monsanto Submission, binder 7-4 and FOI Report (binder 1-4), 1988

**Topics Covered:**

efficacy, nutrition, udder health, reproduction, BCS

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

84

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 250, 500, 750 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: full lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method: randomized block

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation

**Company's Role**

Company: Monsanto

Role: principle investigator

## Comments:

- SE of estimates not given, so no confidence interval was calculated for efficacy data
- BCS data during treatment period was presented as change in Bcs so the data was not extracted but there was slightly higher BCS gain in tx primiparous cows (compared to controls) and lower BCS gain in multiparous cows
- Mastitis data refers to "infected cows" without a clear definition. I assume these were clinical cases
- Injection site reaction data not extracted since they were IM injections
- Reproduction data was combined in pooled analysis presented with Ref #7 (Multi-location IM study)
- General conclusions
    - Significant production effects and moderate health and reproduction effects

# Reference #: 5422

**Title:**

Long term evaluation of zinc methionyl bovine somatotropin treatment in a prolonged release system for lactating multiparous cows at four U.S. clinical trial sites (85-039, 85-038, 85-021, 85-003)

**Authors:**

Huber,J.T.; Bauman,D.E.; Samuels,W.A.; Lamb,R.C.; Hard,D.L.

**Reference:**

Monsanto Submission, binder 7-5, 1990

**Topics Covered:**

Efficacy, udder health, reproduction, nutrition, general health, lameness, culling

**Location:**

New York, Arizona, Utah, Missouri

**Number of Herds:**

4?

**# of Cows:**

272 (all MP)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 0, 500 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: full lactation

Groups: 2

**Treatment Allocation**

Random: yes

Method: blocking

How was it randomized: by site

**Blind Techniques:**

placebo used

**Observation Period:**

1 lactation and start of second

**Company's Role**

Company: Monsanto

Role: ?

### Comments:

- Reproductive data extracted for limited breeding periods (170-230 days)
- Injection site scores recorded on a scale of 0-3
- General Conclusions
  - Significant production effect and moderate health and reproduction effects
  - Study has good health and reproduction data

## Reference #: 5423

**Title:**

Effect of CP115099-F treatment of the dam in study no.: 100-DDC-COW-PJE-85-010 on the subsequent health and reproductive performance of first generation heifers (86-024, 85-010)

**Authors:**

DeLeon J.M.; Eppard,P.J.; Lanza,G.M.; Hammond,B.G.; Cole,W.J.; Hudson,S.; Hintz,R.L.; Miller,M.A.; White,T.C.; Metzger,L.E.

**Reference:**

Monsanto Submission, binder 10-2, 1990

**Topics Covered:**

reproduction

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

17 (F1 heifers)

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 600, 1800, 3000 mg/14d

Route: SC

Start: +60 days

Duration: 1 lactation

Groups: 4

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

heifer calves - up to 16 months

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- No effect of treatment on heifer calf growth, health or reproductive performance
- Only non-pregnancy rate data extracted

## Reference #: 5424

**Title:**

Effect of Sometribove treatment of the dam on health, growth, and reproduction of the resulting F1 Heifers (86-066)

**Authors:**

Eppard,P.J.; Olsson,P.K.; Cole,W.J.; Collier,R.J.; Hintz,R.L.; McCrate,M.M.; Selby,B.D.; Sorbet,R.H.; Veenhuizen,J.; Vicini,J.L.

**Reference:**

Monsanto Submission, binder 10-2, 1992

**Topics Covered:**

reproduction

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

39 - F1 heifers

**Breed:**

Holstein

**Treatment**

Drug: Sometribove

Dose: 500 mg/14d

Route: SC

Start: +60 ± 3 days

Duration: 1 lactation

Groups: 2

**Treatment Allocation**

Random: yes

Method: not specified

How was it randomized:

**Blind Techniques:**

?

**Observation Period:**

28 days to pregnancy (up to 18 months)

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- General conclusions
  - No effect of treatment on growth or reproductive performance of heifers
  - Few health effects detected but study has limited power
  - Slight evidence of increased vaginal/cervix disorders in calves from treated cows
  - Data not extracted due to small numbers (except non-pregnancy rate)

## Reference #: 5425

**Title:**

Effect of bST treatment of the dam on health, growth and reproduction and milk production of the resulting F1 heifers (88-009)

**Authors:**

Eppard,P.J.; Metzger,L.E.; Hintz,R.L.; Cole,W.J.; Collier,R.J.; McCrate,M.M.; Olsson,P.K.; Selby,B.D.; Sorbet,R.H.; Vicini,J.L.; Veenhuizen,J.; White,T.C.

**Reference:**

Monsanto Submission, binder 10-2, 1993

**Topics Covered:**

Reproduction

**Location:**

Missouri

**Number of Herds:**

1

**# of Cows:**

50 (F1 heifers)

**Breed:**

Not indicated

**Treatment**

Drug: Sometribove

Dose: 500, 600, 1800, 3000 mg/14d

Route: IM

Start: +60 ± 3 days

Duration: 1 lactation

Groups: 5

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

placebo used

**Observation Period:**

F1 lactation and F2 calves

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- General Conclusions
  - No effect of treatment on F1 production
  - Minimal health effects (+ and -)
  - No effect on F2 calves
  - Only concern is reproductive performance in F1 heifers

## Reference #: 5426

**Title:**

Effect of Sometribove treatment of dairy cows on the incidence of clinical signs and birth abnormalities in the resulting offspring

**Authors:**

Cole,W.J.; Collier,R.J.; Eppard,P.J.; Hartnell,G.F.; Hintz,R.L.; Hoffman,R.G.; Loesch,T.L.; McLaughlin,C.L.; McCrate,M.M.; Selby,B.D.; Sorbet,R.H.; Veenhuizen,J.J.; Vicini,J.L.; White,T.C.

**Reference:**

Monsanto Submission, binder 10-2

**Topics Covered:**

reproduction

**Location:**

Various

**Number of Herds:**

6

**# of Cows:**

548 (F1 calves)

**Breed:**

Various

**Treatment**

Drug: Sometribove

Dose: various

Route: various

Start: +60 ± 3 days

Duration: various

Groups: various

**Treatment Allocation**

Random: yes

Method:

How was it randomized:

**Blind Techniques:**

not specified

**Observation Period:**

0 - 56 days of age

**Company's Role**

Company: Monsanto

Role: principle investigator

### Comments:

- General Conclusions
  - Very few health effects detected
  - Slight evidence of increased risk of birth abnormalities (particularly umbilical hernias) in offspring from primiparous cows
  - No data extracted

## Reference #: 5428

**Title:**

Impact of bovine somatotropin on genetic evaluation of dairy sires and cows

**Authors:**

Weigel,K.A.; Fisher,T.M.; Van der Linde,C.; Gianola,D.; Rekaya,R.

**Reference:**

Journal of Dairy Science 81:2045-2051, 1998

**Topics Covered:**

efficacy

**Location:**

**Number of Herds:**

222

**# of Cows:**

51 986

**Breed:**

Holstein

**Treatment**

Drug:

Route:

Start:

Duration

Groups:

**Treatment Allocation NA**

Random:

Method:

How was it randomized:

**Blind Techniques:**

NA

**Observation Period:**

multiple lactations

**Company's Role**

Company: none

Role:

### Comments:

- Use of rbST had very little effect on genetic selection decisions

# Appendix 8 - Data Extraction Guidelines

The following are a list of data extraction guidelines to assist you in your review of the articles.

## Cover Sheet

There have been a few changes made to the cover sheet (a copy of which is included with the template document which I sent you via e-mail) The changes are:

- the addition of "Reference"
- the addition of "start" and "groups" to the treatment section
- the addition of "Company's Role" with one of the following as a response:
    - PI - Principle Investigator
    - CI - Co-investigator
    - F - Funded
    - P - Product
    - N - None.

### Comments Section

In the case of an article with many flaws or if it is a review article, etc. we will simply note this in the comments section of the cover sheet and will not use the information from it in the data review. It was also suggested that the reviewer provide overall comments about an article.

### Outcomes Measured Table

With respect to the "Outcomes Measured" table:

- "Category" refers to the areas which the Panel had decided needed to be addressed (ie. efficacy, udder health, etc.)
- "Parity" refers to what parity group was included in this particular parameter (ie. p - primiparous, m - multiparous, a - all)
- "Outcome" refers to what has been measured (eg. 3.5 % FCM, days open). A list of codes for key outcomes measured have been provided. Fro all other outcomes simply write in a description.
- "Dx Criteria" refers to the criteria used, by the authors, for a particular outcome.
- "Measure of Effect" refers to the type of outcome. The most common measures we are using are mead difference (for continuous data) and RR or OR (for categorical data).
- "Value" refers to the value either given in the article or calculated for the particular outcome measured.
- "CI low and high" refer to the lover and upper boundaries of the confidence interval.
- "p-value" refers to the p-value either given in the article or calculated.
- "Adj for Prodn" refers to whether or not the result has been adjusted for level of milk production.

### Multi-dose Studies

The following are guidelines which we agreed to use for multi-dose studies.

- With multi-dose studies we will use the data from whichever dose is closest to the Monsanto label dose (500 mg/14d = 36 mg/d) and we will identify this as the "comparison dose" (Please circle this dose on the cover sheet). Our evaluations will compare the "comparison dose" to the control dose.
    - In these cases Panel members can simply extract the raw data (directions to appear below) and Nicky will do the necessary calculations.
- If a single p-value is reported for comparison among all groups we will report this and will make note of it.
- If disease data have been pooled across multiple doses then we will not use those data in our summary.

Extracting Data for RR or OR Calculations

The Panel members need only to extract the following data and Nicky will do the necessary calculations.

**set up a 2X2 table**

| | **D+** | **D-** |
|---|---|---|
| Tx | a | b |
| Control | c | d |

Where:

- **D+:** cows with undesirable outcome (eg. clinical mastitis, non-pregnancy, lameness)
- **D-:** cows without undesirable outcome
- **Tx:** cows treated with bST
- **Control:** cows not treated with bST
- **a, b, c, d:** # of cows in each group

With these data we can calculate the RR (or OR) and a confidence interval.

## Extracting Data for Mean Difference Calculations

The Panel members need only to extract the following data and Nicky will do the necessary calculations. Sample data from reference # 126 appears below.

| | mean | standard error | n |
|---|---|---|---|
| Tx | 36.2 | 0.8 | 30 |
| Control | 31.9 | 0.7 | 33 |

Where:

- **mean:** mean (average) value for each group
- **standard error (SE):** standard error of the mean value (note - if standard deviation is given instead of the standard error make sure you highlight this)
- **n:** # of cows in each group

With these data we can calculate the mean difference and a confidence interval for that difference.

# Appendix 9 - Listing of Full Database

(ARCHIVED - PDF Version - 59 KB)

# Appendix 10 - Calculations of Cases of Mastitis

## Assumptions:

1. Incidence rate of clinical mastitis = 45 cases / 100 lactations

   Estimate based on the three major studies which provided data on clinical mastitis incidence rates (5407, 5422, 20). In the control cows in these studies, there were 441 cases in 975 lactations = 45 cases / 100 lactations.

2. Proportion of cases during treatment period = 78%

   Of the 441 cases reported above, 345 (78%) occurred during the treatment period.

3. rbST increases risk of clinical mastitis by 25%

In Section 7.1.2 of this report the estimate of the increased risk of clinical mastitis associated with rbST use was 25% - 30%. 25% represents a slightly conservative estimate.

4. 77% of milk production occurs after day 60

   This estimate is based on a standard lactation curve with peak production of 39Kg/day and a persistency value of 0.133

5. rbST increases milk production by 10%

   In section 4.1.2 the increase in FCM was estimated to be 11.4% in primiparous cows and 15.6% in multiparous cows. However, it was noted that these results were obtained in institutional herds under very intensive nutritional management. Consequently, a more conservative estimate of 10% has been selected.

6. 100 cow dairy herd producing, on average, 8000 l per lactation

   This is just a hypothetical herd for the purpose of the following calculations.

### Additional Cases of Mastitis if Producer Keeps Milking 100 cows:

45 cases distributed as:

10 cases before 60 days
35 x 1.25 = 43.75 cases after day 60
Total = 53.75 cases

If the producer keeps milking 100 cows, we can expect an extra 8.75 cases of mastitis per 100 lactations. This represents an overall increase of 19.4%

### Additional Cases of Mastitis if Producer Keeps Constant Milk Production:

100 cows would produce:

100 x 8000 x 0.23 = 184,000 l before day 60
100 x 8000 x .77 x 1.1 = 677,600 l after day 60
Total production = 861,600 l (or an overall increase of 7.7%)

If the producer reduce the herd size by 7.7% to keep milk production constant, he would expect to have:

53.75 / 1.077 = 49.9 cases of clinical mastitis for a net increase of 4.9 cases of mastitis per 100 lactations. This represents an overall increase of 10.9%