

**Report on
Animal Welfare Aspects
of the
Use of Bovine Somatotrophin**

**Report of the
Scientific Committee on Animal Health and Animal Welfare**

Adopted 10 March 1999

REPORT ON ANIMAL WELFARE ASPECTS OF THE USE OF BOVINE SOMATOTROPHIN

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CHAPTER 1. INTRODUCTION:

1.1 Request for an Opinion

1.1.1 Mandate

The Scientific Committee on Animal Health and Animal Welfare is asked to examine the use of bovine somatotrophin (BST).

In particular, the Committee is invited to assess the effects and risks of using BST under normal conditions including the following aspects:

- the incidence of mastitis and other disorders in dairy cows;

- other aspects of the welfare of dairy cows.

In a parallel exercise, the Scientific Committee on Veterinary Measures related to Public Health is asked to report on possible direct and indirect adverse effects on consumer health caused by the use of BST.

1.1.2. Background

Council Decision 94/936/EC of 20 December 1994 amending decision 90/218/EEC concerning the placing on the market and administration of bovine somatotrophin (BST) prohibited the marketing and the use of BST in the EU until 31 December 1999.

The Council asked the Commission to entrust a Working Party of independent scientists with the task of assessing the effects of using BST, in particular as regards the impact of the use of this product on the incidence of mastitis. In this request, it is stated that "BST is an issue which gives rise to considerable interest among consumer, agricultural and industry interests. In this context concerns have been expressed about the safety to humans, animals and the

environment, the quality of milk, the economic and social consequences in agriculture, the climate for research and development, industrial competitiveness and trade implications".

The production of this report is therefore one of the steps requested by the Council prior to the review of the prohibition on the use of BST which should take place before 31 December 1999.

1.1.3 Previous Opinion

The Animal Welfare Section of the Scientific Veterinary Committee examined the general question of the use of substances administered to animals for non-therapeutic and non-prophylactic purposes in 1991. As a result it adopted the following statement;

“STATEMENT (1991) BY THE SCIENTIFIC VETERINARY COMMITTEE ON THE USE OF SUBSTANCES ADMINISTERED TO ANIMALS FOR NON-THERAPEUTIC AND NON-PROPHYLACTIC PURPOSES.

The Committee is concerned that in discussion about the use of products resulting from biotechnology procedures, such as recombinant bovine somatotrophin, insufficient attention is paid to effects on the welfare of animals treated with the product. Such a new product should not be licensed for general use unless adequate information from scientific studies of the welfare of animals treated with the product has been obtained and considered. Such studies should include measurements of welfare such as those of disease incidence, physical disorders, injuries, behaviour and physiology. These studies should be carried out over a period of the animal's life at least as long as the longest time that such an animal would be kept on a farm and in a variety of management conditions. Studies in commercial farm conditions should be included.

No comprehensive studies of the welfare of animals treated with recombinant bovine somatotrophin have been reported. Work on the effects on the incidence of mastitis and other production-related diseases indicates that some welfare problems may exist but more comprehensive studies are desirable to clarify the extent of the problems.”

1.2 Outline of Report

The subject of chapter 2 of this report is a brief account of animal welfare and its scientific assessment. Chapters 3 to 5 review the biology of high yielding dairy cows, the usage of BST and the biology of BST action in cows. Chapters 6-12 provide and discuss data on the effects of BST on animal welfare. Conclusions and recommendations of the report are presented in chapter 13 and, finally, references are listed.

In this report the abbreviation BST is generally used to indicate recombinant bovine somatotrophin¹.

¹ Tropic factors affect direction or extent of body movement while trophic factors affect growth so 'somatotropin', which is often used, is a misnomer.

CHAPTER 2. Welfare Concepts and Assessment in relation to BST

2.1 The concepts of animal welfare

There is widespread belief that people have moral obligations to the animals with which they interact, such that poor welfare should be minimised and very poor welfare avoided. This has led to animal welfare being on the political agenda of European countries. In addition to political debate, the amount of information based on the scientific study of animal welfare has increased. Scientists have added to knowledge of the physiological and behavioural responses of animals and philosophers have developed ethical views on animal welfare. All agree that decisions about animal welfare should be based on good scientific evidence (Duncan, 1981, Ödberg, 1996; Simonsen, 1996).

The fact that farm animals are reared for commercial purposes should not cause us to forget that they are living and sensitive creatures which need to regulate their lives and avoid suffering. The concept of welfare has to be defined in such a way that it can be scientifically assessed and the term can be used in legislation and in discussion amongst animal users and the public. Welfare is clearly a characteristic of an individual animal and is concerned with the effects of all aspects of its environment on the individual. Broom (1986) defines it as follows: “the welfare of an animal is its state as regards its attempts to cope with its environment.” Welfare therefore includes the extent of: success in coping, failure to cope which may lead to disease, injury and death, ease of coping or difficulty in coping and the associated pleasurable mental states and unpleasant states such as fear and frustration (Dantzer et al., 1983; Broom, 1988). Good welfare can occur providing the individual is able to adapt to or cope with the constraints it is exposed to. Hence welfare varies from very poor to very good and can be scientifically assessed (Broom, 1996, 1998, Broom and Johnson 1993). The word stress is used when there is failure to cope.

The welfare of a farm animal can be considered in relation to the housing and management conditions to which it is submitted. Welfare is good when all of needs associated with the maintenance of good health and needs to show certain behaviours to be met. Health is an important part of welfare and behaviour is important in many regulatory systems.

How this concept applies to animals which are submitted to an exogenous hormonal treatment aimed at increasing their productivity and having no direct benefit for the individuals to which it is administered is considered in the next sections.

2.2 The assessment of farm animal welfare

Farm animal welfare is assessed by a combination of indicators of its physical and mental components (Smidt, 1983). The scientific methods that are available for selecting these indicators, and establishing and interpreting scores, are detailed in several reviews (Moberg, 1985; Wiepkema and van Adrichem 1987; Broom, 1993; Broom and Johnson, 1993). In general, minimum early mortality, low morbidity, little or no risk of injury, good body condition, the ability to express species-specific activities including social interactions, exploration and play, and the lack of abnormal behaviour and of physiological signs of stress, including alterations of immune responses, indicate that there is no major animal welfare problem.

2.3 The assessment of the potential impact of BST on animal welfare

Any exogenous treatment that modifies the physiology of an organism with the objective of increasing its productivity is likely to impair welfare if the individual is not able to adapt to the physiological and metabolic changes this treatment induces. In addition, the treatment can impact on welfare indirectly, via its effects on body structure and function and factors that regulate behaviour at the sensory, perceptual, motivational and motor levels. The treatment under consideration could also increase mortality and morbidity risks, for example because of failure of basic regulatory physiological functions or the physiological function targeted by the treatment. All these possibilities need to be taken into account when assessing the possible effects on welfare of a new treatment.

If the treatment is administered by injection, it is important to verify that the injected product does not cause much pain or discomfort at the site of injection during or after the injection procedure.

In the case of BST, the following points must be considered for a proper assessment of the effects of this treatment on animal welfare:

(i) Injection site: Injected materials may cause localised or wide ranging painful effects. Comparative studies should involve normal test injections and placebo injections or no injection. Behavioural and physiological responses should be measured with and without human manipulation of the injection site area.

(ii) Mortality and morbidity: Early mortality or culling because of disease, injury or physiological system failure shows that the welfare has been poor. Hence the mortality rate on farm and the rate of culling for all but human error reasons are welfare indicators. In addition, welfare is poor if the incidence of production related diseases is higher in treated animals than in placebo-treated animals. If some weakness or abnormality means that the individual would be more likely to succumb to pathogen challenge, respiratory failure, poison accumulation, injury, etc. then the welfare is poorer than in an animal which does not have this weakness or abnormality. In a group of animals, such as a flock, house, herd or any other population unit, the amount of poor welfare caused by disease is a function of its incidence, severity and duration, as described by Willeberg (1991). Health indicators of animal welfare must also be studied with a broad population perspective. If the metabolic condition created by a treatment were responsible for an increased use of preventive or therapeutic veterinary medicines, the welfare would be poorer. Animals which may have leg pain or other pain should be compared with unaffected controls or the same individual after analgesic application or disappearance of all clinical signs.

(iii) Body condition and Reproduction: Welfare is poorer if body condition score is too low or if, at the other extreme, there is unbalanced organ function or damaging muscle hypertrophy. Reproduction is given high priority in the allocation of resources within an animal so, if given adequate fertilisation opportunities, individuals which are not already involved in reproductive processes are less likely to conceive or less likely to carry young to term, poor welfare is indicated.

(iv) Behaviour: Animals use behaviour as one of the important means of adapting to their physical and social environment. If such adaption is prevented, welfare will be poor. Various

behaviours including abnormalities of behaviour are indicators of pain, fear or other poor welfare. Some behaviours are indicators of good welfare.

(v) Physiology: Physiological indicators of metabolic stress or disturbance of the main regulatory functions, such as heart rate and adrenal hormones and signs of malfunction of the immune system are all indicators of poor welfare. Some physiological changes in brain and body may indicate good welfare. BST treatment should not create a state of metabolic stress nor interfere with the main physiological regulatory functions.

For an adequate assessment of welfare a wide range of indicators must be used, although single indicators can show that welfare is poor.

2.4 Conclusion

Animal welfare can be assessed in a scientific way and indicators of welfare include those of physiological states, behaviour and health. A proper assessment of the effects of BST on the welfare of dairy cows must be based on the whole range of indicators that are available to measure welfare in these animals.

CHAPTER 3 WELFARE PROBLEMS IN HIGH YIELDING DAIRY COWS

3.1 Biological functions which are modified when milk yield is high

The biology of dairy cows in relation to the high levels of milk production required from them in the modern dairy herd has been described in a variety of text books (e.g. Webster 1993). The cow is well adapted to eat fibrous plants whose energy and protein content are not high, for example grasses. The pasture plants preferred by modern cattle are those which are long enough for comfortable grasping with the tongue, are composed more of leaf than of stalk and contain an adequate proportion of water, fibre, protein and utilisable energy (Stobbs 1974, Fraser and Broom 1990, p.90).

If insufficient energy or protein are ingested by a lactating cow, which is the case at the beginning of lactation, she will utilise her body reserves (mainly adipose tissue) and, subsequently, body tissues such as muscle in order to continue lactation. If too much concentrate feed is given to a lactating cow, the accumulation of metabolites such as volatile fatty acids leads to a greatly increased risk of digestive problems and metabolic disorders. These may occur at the same time that a high milk yield is being produced so a high yield does not indicate the absence of problems. As Webster (*loc. cit.*) explains, ruminal overload and unstable fermentation can lead to acidosis and laminitis, whilst increased tissue mobilisation leads to, on the one hand weight loss and anoestrus and, on the other hand ketosis, which like acidosis, can result in fatty liver. Other clinical disease conditions are also more likely when digestive disorders occur. Disorders associated with an inappropriate dietary balance and prolonged high levels of milk secretion are mediated via a wide range of physiological changes in the cow.

3.2 Welfare problems in dairy cows

The major welfare problems in dairy cows are mastitis, foot and leg problems, conditions which lead to impaired reproduction, inability to show normal behaviour, emergency physiological responses or injury.

For a recent review of lameness, including the extent to which it is a welfare problem, see Greenough and Weaver (1996). Almost all animals which walk with a limp, or reduce walking to a low level, or avoid walking whenever possible suffer from some leg or foot pain. In some cases, walking is reduced because of pain in all four feet but the animal may not limp. The ability of cows with foot and leg problems to carry out various preferred behaviours is generally impaired and there may be adverse consequences for various other aspects of their normal biological functioning. Clinical disorders of feet and legs in dairy cows always mean some degree of poor welfare and sometimes means that there is very poor welfare indeed.

Measurements of the extent to which some degree of lameness occurs in dairy cows include 35 - 56 cases per 100 cows per annum in the USA, 59.5 cases per 100 cows per annum in the UK and more than 83% prevalence in cows kept in loose housing systems in the Netherlands (Frankena et al. 1991). The actual figures depend upon the method of assessment and most of these cases were not treated by veterinary surgeons but there is no doubt that lameness is often a severe welfare problem.

Clinical mastitis in mammals is a painful condition. The sensitivity to touch of the affected tissues (i.e. udder and teats) is clearly evident, particularly at milking time and there is obvious damaging of normal function. Mastitis incidence should have declined greatly with improved methods of prevention and treatment but it has not declined in the expected way, or has not declined at all (Barkema et al 1998, Schukken et al. 1998). In Denmark and in the Netherlands mastitis involving *Streptococcus uberis* or *Staphylococcus aureus* has not declined in incidence. Webster (1993) reports 40 cases of mastitis per 100 cows per year as an average for the UK

Other conditions of dairy cows which result in abnormalities of behaviour, emergency physiological responses, injury or impaired reproductive function also involve poor welfare. Reproductive problems in dairy cows have become very common in recent years with large numbers of cows being culled because of failure to get in calf (Esslemont and Kossaibati, 1997). Indeed culling policy has a significant effect on measurements of the prevalence or incidence of leg and foot problems, mastitis and reproductive disorders. Those farmers who cull at first signs of problems, or who cull at a fixed, early age will report fewer problems. The practice in the dairy industry is to cull at a considerably earlier age now than was the case 10 or 20 years ago.

3.3 Milk yield and welfare in dairy cows

In 1999, the dairy cow may produce up to 18,000kg or more of milk per annum with a peak milk yield of 75kg per day and in several countries a mean of over 8000 kg per annum is obtained. This compares with UK figures of 6,000kg per annum and 30kg per day 10 years ago (Webster, 1993) and a beef cattle average of 1,000 — 2,000kg and 10kg per day. The dairy animal is producing considerably more than its ancestor would have. This raises questions concerning what is the maximum mean production level in a herd beyond which there will always be welfare problems.

The peak daily energy output of the dairy cow per unit body weight is not very high in comparison with some other species such as seals or dogs but the product of daily energy output and duration of lactation is very high. Hence long term problems are the most likely to occur (Nielsen, 1998). There are long term adverse consequences of high yield because, although some cows seem to be able to produce at high levels without welfare problems, the risk of poor welfare indicated by lameness, mastitis or fertility problems is greater as milk yield increases (Pryce et al. 1997,1998)

The steady increase in reproductive problems, some of which indicate poor welfare, as milk yields have increased is well known. As Studer (1998) states, "despite programmes developed by veterinarians to improve reproductive herd health, conception rates have in general declined from 55-66% 20 years ago to 45-50% recently (Spalding et al 1975, Foote 1978, Ferguson 1988, Butler and Smith 1989). During the same periods, milk production has greatly increased."

Studies showing that milk yield is positively correlated with the extent of fertility problems have come from a range of different countries (van Arendonk et al 1989, Oltenacu et al 1991, Nebel and McGilliard 1993, Hoekstra et al 1994, Pösö and Mäntysaari 1996, Pryce et al. 1997, Pryce et al 1998). Studer (1998) suggests that high producing cows which are thin, and whose body condition score declines by 0.5 to 1.0 during lactation, often experience anoestrus. A loss of condition score of about 1.0 during lactation was considered to be very frequent in the review presented by Broster and Broster (1998). Data on the relationships

between milk yield and reproduction measures from two large scale studies are presented in Table 1.

In some studies, effects of health problems on reproduction are evident, for example Peeler et al. (1994) showed how cows which were lame in the period before service were less likely to be observed as being in oestrus. Such lameness is more likely in high producing cows.

Direct links between level of milk production and extent of disease conditions are also evident from a range of studies, positive correlations being reported by Lyons et al (1991), Uribe et al (1995) and Pryce et al (1997, 1998 see Table 1). In addition to mastitis and leg and foot problems, which are often measured in such studies, the occurrence of other clinical conditions can also be affected by production level. Modern, high producing cows with good body condition have a high incidence of milk fever, retained placenta, abomasal displacement, metritis, fatty liver and ketosis (Studer 1998) and of digestive disorders (Seegers et al., 1997). The extended calving interval and the greater number of days to first service as milk production level increases (e.g. Table 1) could be related to a small extent to different management practices with higher producing cows but most of the effect is likely to be because there are more reproductive problems occurring in the higher producing animals and hence poorer welfare.

Table 1 :Relationship between milk production level and other variables in two studies. Correlation coefficients and standard errors
For all correlations p is less than 0.05 and for most it is very much less.

MEASURE	Pryce et al, 1997		Pryce et al, 1998	
Number of lactation records	33,732		10,569	
Calving interval	0.50	±0.06	0.28	±0.06
Days to first service	0.43	±0.08	0.41	±0.06
Mastitis	0.21	±0.06	0.29	±0.05
Foot problems	0.29	±0.11	0.13	±0.06
Milk fever	0.19	±0.06		
Somatic cell count			0.16	±0.04

Mastitis, foot disorders, reproductive disorders etc. occur more in higher yielding members of a herd irrespective of the mean yield of the group so it seems that the individuals which are working hardest metabolically in a group may be the most vulnerable.

The high yields of modern dairy cows are a consequence of genetic selection and feeding. Webster (1993) emphasised that ancestral cows were adapted to high fibre, low density diets. Despite changes resulting from breeding, most of the traits of the ancestor animals still remain. For example, cows do not adapt easily to high grain diets or to diets with high protein and low fibre (Webster 1993).

3.4 Conclusions

There is already evidence of welfare problems in dairy cows, for instance more than 50 cases of foot disorders and more than 40 cases of mastitis per 100 dairy cows can typically occur in Europe per year. Some of these animals and others in the herd may have reproductive disorders and other production related diseases.

There is clear evidence from several countries of significant positive associations between milk yield and mastitis, foot disorders, reproductive disorders and other production related diseases.

CHAPTER 4 HOW BST IS USED

4.1 The substance

Commercially produced BST is very similar to naturally occurring BST found in the bovine pituitary, with only a single amino acid difference or a few amino acid differences according to the manufacturers. It is produced by biotechnological methods involving the fermentation of *E. coli* strains containing the gene for the production of BST.

In the US it is estimated that 1.44 million cows were treated in the two year period from February 1994 to February 1996. Sales in the US are reported to have increased by 30% in 1997 over 1996. In 1998 over 100 million doses have been sold since it was commercialised almost 5 years ago. Thirty percent of the 9 million dairy cows in the U.S. are in herds supplemented with BST. A veterinary prescription is not required in the U.S.A. in order to obtain or administer BST.

4.2 The technique

Dairy cows are usually injected subcutaneously in the ischiorectal fossa (depression beside the tailhead) or behind the shoulder (post scapular). The volume of injectate of a commonly used formulation in the U.S.A. is 1.4ml.

The injection is typically repeated every 14 days.

4.3 Uses of BST

BST has been used for the following purposes;

- to increase milk production – in this case BST is given from the ninth or tenth week after calving until the end of lactation. In the US the generally claimed responses are from 2.25 l to 6.6 l of milk/cow/day.

- to extend the lactation of cows that would otherwise be culled because of inability to breed or other health reasons. BST can be used to keep a cow in production for 30 to 100 days extra.

These will permit a decrease in the number of cows necessary to produce the same quantity of milk.

The maximum increase in milk production occurs after three or four injections. The response to BST can vary from cow to cow. It is not possible to predict which cows will show large increases in milk yield in response to BST administration.

Manufacturers of BST list the conditions in which BST should and should not be used and the possible side effects of the treatment.

4.4 Conclusion

Commercially produced BST is very similar in structure to naturally occurring BST. It is recommended by a manufacturer that dairy cows should be given an injection of 500mg of BST once every 14 days.

CHAPTER 5 BIOLOGY OF BST ACTION IN DAIRY COWS

5.1 Introduction

Growth hormone (GH) is a component of a complex neuro-endocrine and metabolic system which maintains physiological homeostasis in the body. It is a protein composed of 191 or 190 amino acid residues and it is released from the anterior pituitary gland as four molecular variants: smaller fragments have also been reported. Pre-formed GH, stored in pituitary somatotroph cells, is released by exocytosis in response to several stimuli, including GH releasing factor (GRF) and somatostatin (SS) from the hypothalamus, blood concentrations of glucagon, insulin-like growth factors (IGFs) and oestrogen, and psychological stimuli, such as stress and sleep. Somewhat paradoxically, in view of the galactopoietic effects of increased blood concentrations of GH, low milk yields in underfed animals are associated with high concentrations of GH in blood (Bauman and Vernon, 1993).

Natural episodic release of GH from the anterior pituitary is chiefly controlled by the hypothalamic neuro-secretory peptides GRF (stimulatory) and SS (inhibitory), whose secretion into the hypothalamo-hypophyseal portal system is regulated by numerous neurotransmitters, including noradrenaline, dopamine and acetylcholine. Raised concentrations of GH in peripheral blood feed back onto the hypothalamus, inhibiting GRF and stimulating SS secretion, and these two peptides also exert acute negative feedback effects on the hypothalamus. In well-fed animals increased plasma concentrations of GH are associated with increased secretion from the liver of IGF1 and its binding proteins, and chronic inhibitory control of GH secretion is regulated by IGF1 feedback on central neural and hypothalamic systems (Prosser and Mepham, 1989; Burton et al, 1994; Etherton and Bauman, 1998).

Control of GH action on its target tissues is mediated by a wide range of factors, such as: concentrations in blood of hormones and metabolites; the type and level of blood plasma binding proteins; tissue distribution and concentration of GH receptors; and transmembrane signalling mechanisms. The major physiological actions of bovine GH (BGH) are to increase lipolysis, diabetogenesis, protein accretion, bone development, gluconeogenesis, mammatogenesis and, in lactating animals, galactopoiesis.

5.2 Injection of exogenous GH (BST)

Based on the discovery in Russia in the 1930s that injection of extracts of anterior pituitary gland increased milk yield in cattle, the use of recombinantly derived BGH has now been established in several countries, most notably the USA. In Europe, it is more usually designated 'recombinant somatotrophin' - abbreviated to rBST or BST. Commercially produced rBST consists of a single molecular species which differs from pituitary (p) BGH by 0-9 amino acid residues (depending on the manufacturer). For example, the Monsanto product, Posilac, has double the potency of pBGH, from which it is immunologically distinct and exhibits several pharmacokinetic differences (Kronfeld, 1997).

Injected rBST also differs from endogenous pBGH in other significant ways, viz. i) blood concentrations are substantially higher than those achieved physiologically; ii) the pattern of release of slow-release preparations into the circulation differs markedly from the physiological pattern of episodic release; iii) feedback processes induce chronic inhibition of endogenous pBGH synthesis and secretion (Adriaens et al, 1995).

In principle, disruption of normal relationships between the elements of the neuroendocrine system described above by elevating supply of a *single* element of the complex might be expected to precipitate adverse effects, as for example in the human disease acromegaly, which is due to excessive secretion of GH from the pituitary. Despite this, some describe BST's galactopoietic action in cattle in ways which suggest the "orchestrated" enhancement of physiological control, e.g. " somatotropin is a homeorhetic controller that affects numerous target tissues in ways that are highly coordinated" (Bauman, 1992); (Etherton and Bauman, 1998). Strictly speaking, this is a misuse (or re-definition) of the term 'homeorhesis', which was introduced by Waddington in the 1950s to describe "an equilibrium (which) is not centred on a static state but rather on a pathway of (developmental) change" (Waddington, 1967).

5.3 Milk yield responses

Official estimates of the yield response to BST administration have varied from 10-25% (AHI, 1987) to 10-15% (CAST, 1993). However, responses can be variable and may depend on management factors to achieve a maximal response. Indeed, independent studies suggest that a third of treated herds will have less than a 10% increase (e.g. Chilliard, 1988), while there is at least one full report in which BST administration produced no significant yield increase (Kim et al, 1991).

In the USA, the Office of Technology Assessment (OTA) assumed a mean increase of 12% (approx. 5 kg/day), with variations being attributed to the quality of management (OTA, 1991). According to Etherton and Bauman (1998) "greater increases occur when the management and care of the animals are excellent". This claim might have some validity if it could be shown that high yielding cows prior to BST injection show consistently greater yield responses, but according to Kronfeld it is not sustained by examination of the literature (Kronfeld, 1994).

In low yielding cattle, dramatic effects on BST have been reported, e.g a 288% increase in yield in *Bos indicus* cows (Phipps et al, 1991) treated on days 75-95 of lactation, although between days 96 and 120 there was no significant effect on yield.

The production response increases with increasing dose of BST up to a maximum response at 30-40 mg/day (Bauman, 1992). The commercial preparation in use in the USA is a slow-release formulation in which 500 mg are administered every 2 weeks.

Although responses to BST are often described as 'smooth' (Bauman, 1992), periodic injections produce an unphysiological lactation curve. Thus, the results of Eppard et al (1991) show that the milk yield curve has a distinctly 'saw-tooth' appearance: during the 2 week period between injections the yield increased approximately 50% in the first 7 days, declining to baseline by day 14, before being sharply stimulated again by the next injection. In the case of 28 day injection cycles a lower than expected milk yield can be obtained in the fourth week (Vérité et al, 1989).

Claims for the increased efficiency of milk production when using BST, i.e. in terms of conversion of feed to milk, by means of lower maintenance costs per unit of milk produced. According to Kronfeld (1994), the claim may not apply for more than one lactation, particularly if a broader definition of efficiency, encompassing the lifetime performance of cows, is employed.

5.4 Milk composition

Significant effects on milk composition have been reported. For example, a decrease in casein concentration (mean 6.9%), which persisted over the 31 weeks of treatment, was reported by Kindstedt et al (1991). In this study of 26 Jersey cows receiving BST injections every two weeks throughout a complete lactation, casein expressed both as a percentage of total and true protein was significantly lower ($p<0.05$) than in the control group. According to the authors, at midlactation, concentrations of casein in the BST cows “decreased sharply and remained lower than the control group throughout the remainder of lactation”. Following the same time course of change, nonprotein nitrogen expressed as a percentage of total nitrogen was significantly higher in the BST treated group ($p<0.05$).

Baer et al (1989) reported a sustained increase in long chain fatty acids (mean 11.5%) and a decrease in short chain fatty acids (mean 9.4%) over 28 weeks of BST treatment. Variations have also been described in response to a single injection of BST, e.g. milk fat increased by a maximum of 6% and milk protein decreased by the same amount (Chilliard et al, 1998) (See Figure 1). Somatic cell counts and IGF1 levels are also increased. Such changes appear to fall within the broad spectrum of concentrations which applies to milk of clinically normal cows as a whole (Kronfeld, 1994), although it is possible that BST could push concentrations of milk constituents beyond normal limits if they were already at those limits.

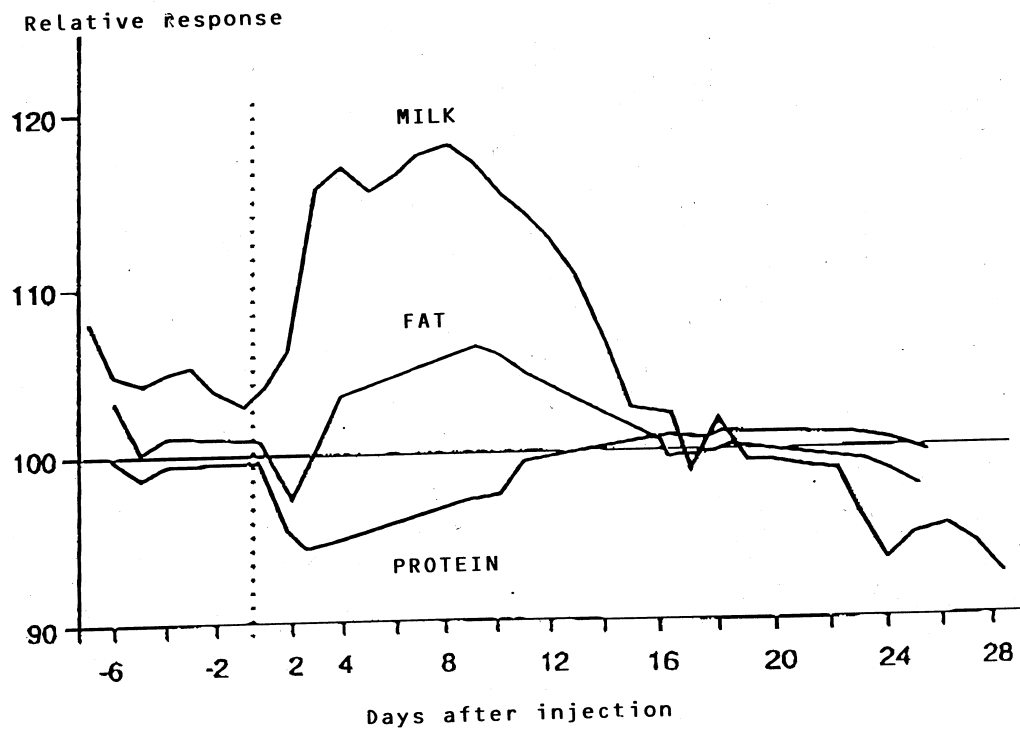


Figure 1: Changes in milk yield and composition following prolonged release somatotrophin injection (Verité et al. 1988)

Generally speaking, in the early phase of BST treatment, when the cow is in negative energy balance, milk fat concentrations increase and those of protein decrease, whereas these concentrations revert to normal as the cow attains positive energy balance (Bauman and Vernon, 1993).

5.5 Physiological actions of injected BST

Injection of exogenous BST is associated with marked elevations of circulating IGF1, small increases in thyroxine concentration and variable responses in circulating insulin, which may be related to blood sampling regimes or nutritional status (Prosser and Mepham, 1989).

As for other peptide hormones, the initial step of BST action involves binding with receptors on target tissues. GH receptors have been described on several cell types, e.g. hepatocytes,

adipocytes, lymphocytes, macrophages, fibroblasts, chondrocytes, β islet cells and osteoblasts (Burton et al, 1994). There appear to be at least two classes of GH receptor in the bovine liver and hepatic production of IGF1 seems to be associated with the high-affinity receptor. There is much evidence that mammary tissue does not possess receptors for GH so that its galactopoietic effects are mediated largely by other factors (Etherton and Bauman, 1998).

Effects of BST can be considered under three headings: nutrient partitioning; cardiovascular effects; and alterations of mammary function.

5.5.1 Nutrient partitioning

When cows are treated with BST the increase in milk yield occurs very rapidly whereas the increase in voluntary feed intake is delayed until the 5-7th week of treatment. Thus, in the initial stages of treatment the requirement for extra nutrients to support lactation is met by mobilization of body stores or other tissues (Bauman and Vernon, 1993). Evidence that GH is instrumental in this process of nutrient partitioning is provided by studies which show that, in response to BST, mammary uptake of glucose and non esterified fatty acid (NEFA) is increased while that of muscle is reduced (Prosser and Mepham, 1989).

The lag in feed intake in the initial stages of treatment implies that the cows are in negative energy balance, and this is more marked when the yield response is greater. Eventually, as feed intake increases, the animal attains positive energy balance. Consequently, the adaptations in whole body metabolism which support the additional milk yield, and the factors which control these processes, must vary during prolonged treatment periods. This may account for the often conflicting reports of changes in circulating metabolite concentrations and in the concentrations of milk constituents.

Changes in fat content of milk are related to the potent effects of BST on adipose tissue. The response was formerly considered two-fold, i.e. decreased lipid synthesis (which thus 'saves' acetate and glucose) and increased lipolysis, releasing NEFAs (Bauman and Vernon, 1993) However, a more recent theory is that BST has no direct effects on lipogenesis or lipolysis but that it alters lipid metabolism on a chronic basis by reducing adipocyte sensitivity to insulin stimulation of lipid synthesis and increasing the responsiveness to catecholamine stimulation of

lipolysis (McGuire and Bauman, 1995). Recent data of Boisclair et al. (1997) has suggested that the elevated blood concentrations of NEFA observed in BST-treated heifers, and the marked elevations in NEFA in response to "intensive handling" of BST-treated steers, imply that BST sensitises adipose tissue to adrenergic stimulation. Whatever the ultimate explanation, the net result is that treated cows have reduced body fat and body condition. Generally, blood plasma NEFA concentrations are increased in cows in negative energy balance but do not change when they are in positive energy balance. When plasma NEFAs increase, milk fat concentration increases and the composition of the milk fat shifts to a greater content of long chain fatty acids, derived from the blood plasma.

Milk lactose concentration does not change appreciably in response to BST, due to the fact that, as the major osmole, it determines water flow into milk. The increased output of lactose is met by increased diversion of glucose to the mammary glands, and it has been suggested that this is effected by increased hepatic gluconeogenesis and decreased glucose oxidation in peripheral tissues (Prosser and Mepham, 1989).

5.5.2 Cardiovascular effects

There are several reports describing the increased rate of mammary blood flow in BST-treated ruminants, and the increased uptake from the blood of milk precursors appears to be partly accounted for by this increased flow (Fullerton et al. 1989). However, the precise role of the hyperaemic response remains uncertain. For example, it is unknown whether it is the cause or consequence of increased mammary activity.

Short term BST treatment has also been shown to increase cardiac output (Fleet et al. 1988); (Davis et al. 1988) and, in the few studies in which it has been recorded, heart rate is increased (Heap et al. 1989; Soderholm et al. 1988).

5.5.3 Alterations in mammary function

Evidence that BST affects mammary metabolism *per se*, albeit indirectly, is provided by studies of the mammary extraction of blood metabolites, i.e. by measurement of arterio-venous differences (Δ AV) across the mammary gland. For example, BST injections have been shown to increase mammary Δ AVs of glucose, acetate and triacylglycerols (Heap et al. 1989).

Strong evidence for BST-induced changes in mammary function is also provided by measurements of mammary blood flow. For example, in one study the pretreatment ratio of 'blood flow/milk yield' was about 700, whereas following BST treatment it decreased to 415 (Heap et al. 1989). This indicates that the extraction of substrates from blood perfusing the mammary gland increased substantially (although blood flow also increased).

Hence, effects on mammary tissue involve both increases in milk secretion rate per cell and increased maintenance of cell numbers (McGuire and Bauman, 1995).

However, by comparison with the large number of studies on BST aimed at assessing its galactopoietic effect there is a relative paucity of publications reporting the basis of its physiological action.

5.6 Mediation of effects by IGF1

The apparent absence of GH receptors in mammary tissue, and the lack of any galactopoietic effect when BST is infused directly into the mammary artery of lactating ruminants, suggests that alterations to mammary function are mediated by other factors. There is much evidence that in cows IGF1 performs this role (Prosser and Mepham, 1989, Burton et al, 1994).

Attempts to confirm this hypothesis by administration of IGF1 have been complicated by the fact that circulating IGF1 is largely (95%) bound to specific binding proteins (six in total), the major form of which has a molecular weight of 150 kDA. In treated cows, not only do blood concentrations of IGF1 increase but also that of IGFBP-3, while that of IGFBP-2 decreases. When animals are in negative nutritative balance, the effects of IGF1 are greatly reduced and

the galactopoietic effect impaired (McGuire and Bauman, 1995). IGF1 may not act exclusively as an endocrine factor but also as an autocrine or paracrine factor (Prosser and Mepham, 1989), so that blood levels may reflect the cumulative production by different tissues. Nevertheless, the liver seems likely to be a major site of IGF1 production (Etherton and Bauman, 1998).

The galactopoietic effect of BST injections is accompanied by increased secretion of IGF1 in milk, which slightly precedes the increase in milk secretion rate (Prosser et al, 1991). Data on the magnitude of the increase in milk IGF1 concentration are sparse. The earliest report indicated a 3.7-fold increase as result of seven days of BST treatment (Prosser et al, 1989), while the Monsanto Company, in its submission to the European Community Committee on Veterinary Medicinal Products cited an "about five-fold increase" (CEC, 1993), but few reports have appeared in refereed publications and there have been questions about the accuracy of the IGF1 assays in some reports (Burton et al, 1994).

Direct evidence that IGF1 acts on mammary tissue is substantial. Thus: i) IGF receptors are present in mammary tissue and increase at lactogenesis (Burton et al. 1994); ii) IGF1 stimulates casein synthesis and glucose uptake in cultured mammary cells (Burton et al. 1994); iii) close unilateral intra-arterial mammary infusion of IGF1 in goats stimulated milk secretion to a significantly greater degree in the infused gland than in the non-infused gland (Prosser et al, 1990). IGF1 may also be responsible for the hyperaemic response to BST because the mammary blood flow of the infused gland was significantly increased by IGF1 infusion (Prosser and Davis, 1992).

According to Kronfeld (1994), many of the adverse health effects of BST are best viewed as a consequence of extending the phase of metabolic stress which normally accompanies the onset of lactation. Since the maximal response to BST is achieved within 2-5 days but the increase in feed intake takes 5-7 weeks to match the requirement for extra milk synthesis, the body goes into negative energy and protein balance, with associated changes in live weight, body composition and condition score. Consequently, BST administration extends the period of metabolic stress from 2-3 months to 4-6 months (see Figure 2).

As this situation differs from that in which milk yield has been increased by selective breeding,

the often made comparison between yield increases due to genetic improvements and BST (Bauman, 1992) is of dubious validity. Thus, it has been claimed that pathological lesions evident in BST-treated cows are merely the result of increased yield. However, Kronfeld's analysis (Kronfeld, 1994) shows that, while milk yield increases with increasing BST dose up to twice the recommended commercial dose, there are continuing increases in the frequency of several lesions up to (at least) five times the commercial dose, viz. kidney cysts, lung-pleural adhesions, kidney fibrosis, muscle fibrosis and joint inflammation.

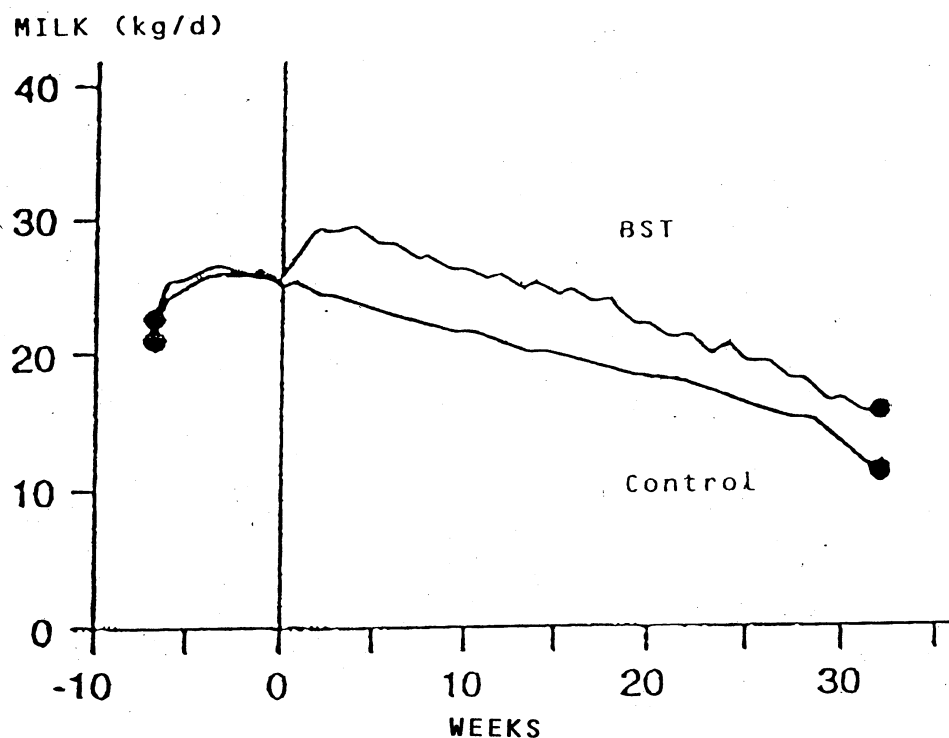


Figure 2: The lactation curve in cows receiving BST, first administered after the attainment of peak milk yield (Chilliard, Colleau et al, 1998)

5.6.1 Neurocrine and neuroendocrine actions of BST

The neural actions of GH were first documented in 1941, but these have been largely ignored until recently. Although pGH is synthesised principally in the pituitary gland, it is also now known to be produced at several ectopic sites, including the brain. GH receptors or binding

proteins also occur in the brain, where GH is involved in cell proliferation and maturation, neurotransmission and central behaviour. Consequently, as well as exerting endocrine effects “GH should also now be considered as a *bona fide* neuropeptide” (Harvey et al, 1993). Moreover, the occurrence of GH binding proteins throughout the pituitary gland and within pituitary cells implies that GH may have, previously unrecognised, endocrine, paracrine, autocrine and/or intracrine roles in hypophyseal regulation (Harvey et al, 1993).

In view of these neural actions of GH, the welfare implications of increasing blood concentrations of BST by injection would appear to require extensive investigation. Currently, there is a dearth of information on this aspect of BST’s physiological effects.

5.6.2 Behavioural and other implications

There appears to be only a single refereed publication on the effects of BST on cow behaviour (Arave et al, 1994) - and that reports the frequency of various aversive behaviour patterns during implantation of a pelleted form of BST, rather than injection of the oil-based preparation which is used commercially. The 99 cows in the study were observed when they were implanted with 0, 120, 160, 240, 320 or 360 mg of BST. Flinching and lungeing were both observed in about 50% of cases and head-bobbing and a sagging of the back in 30-40% cases. Cows kicked at the handler or chute 11% of the time, and kneeling, indicating “extreme agitation”, was observed in 5% of cases. Kicking, kneeling and ears back were significantly affected by BST dose. The extent of the swollen area around the implant was greater as implant dose increased. The implantation occurred in a handling chute and some behaviours decreased or disappeared with repeated implantations but others did not.

The fact that Boisclair et al (1997) reported that "BST caused a substantial rise in (blood) NEFA concentration ... when animals were subjected to intensive handling", suggests that, by sensitising adipose tissue to adrenergic stimulation, BST exacerbates the stress response. Whether this is merely a clinical response or has implications for animal welfare remains to be investigated.

Because of its anti-apoptotic effects, IGF1 could promote cell proliferation in cows to a stage of tumour neogenesis (see Report from the Scientific Committee on Veterinary measures in relation to Public Health). However, in general, cows on modern dairy farms do not live long enough for such effects to be of any significance.

There are other possible consequences of IGF1 which do not appear to have been investigated e.g. effects on calves in utero or feeding on milk containing high levels of IGF1.

5.7 Conclusions

The primary galactopoietic effect of BST in cows appears to be altered nutrient utilisation and mobilisation of non-mammary tissues, sparing nutrients for milk synthesis. This is achieved by effects on liver and adipose tissue but also by alterations in the responsiveness of other tissues to metabolic hormones.

BST increases cardiac output and heart rate and this is associated with an increase in the rate of mammary blood flow. Mammary metabolic activity is increased, involving greater substrate uptake and synthesis of milk-specific components. IGF1 seems to be largely responsible for such effects. In consequence, when BST is used, milk yields increase by about 10%, with compositional changes depending on the cow's energy status, e.g. IGF1 increases approximately five fold.

It appears that BST extends the period of metabolic stress which normally accompanies the onset of lactation. The cow remains in negative energy balance, utilising food reserves or other tissues, for some weeks after the commencement of BST usage.

The consequences of BST, acting as a neuropeptide, on the brain and on behaviour are not known.

Questions about the effects of elevated IGF1 levels in the cow on the welfare of the cow, or the welfare of the calf in utero, appear not to have been investigated. Neither have questions about the effects of elevated IGF1 levels in milk on the welfare of calves which drink the milk.

CHAPTER 6 BST AND MASTITIS

6.1 Introduction

The questions associated with the potentially increased incidence of clinical mastitis in BST treated cows and the resulting increased usage of antibiotics have been in the forefront of discussions for a long time. These issues have animal welfare aspects as well as public health aspects, and have been covered in previous reviews by various committees and organisations.

6.1.1 The European Union

In 1993 the CVMP (Committee for Veterinary Medicinal Products) as an advisory committee to the EU Commission issued final scientific reports on two applications for marketing authorisation of veterinary medicinal products containing bovine somatotrophin. In these reports the CVMP expressed the view relative to target animal safety of the products, that although the clinical trial data provided by the applicants shows an increased incidence of mastitis in treated animals as compared with the control animals this increase is an indirect effect resulting from the increased milk yield of the treated animals. It was furthermore recommended by the CVMP that, in order to take account of the prevailing practical animal husbandry conditions being less optimal than the conditions in the trial herds, the health and welfare of the target animals should be investigated in two-year post-marketing studies to include e.g. the incidence of mastitis.

At the end of 1994 the EU Council decided, however, to extend the moratorium on marketing and use of BST until the end of 1999. In 1998 a report by independent scientists should be prepared, "... in particular as regards the impact of the use of this product on the incidence of mastitis" (Council Decision 94/936/EC).

6.1.2. The situation in the USA

The mastitis issue has also been discussed relative to the US situation and by other international bodies. In 1993 the FDA decided to approve use of BST (POSILAC from Monsanto) on the US market effective February 1994. The documentation of the data behind the decision has been made publicly available through the Freedom of Information Summary (FOI) from 1993 (FDA 1993). Here data on mastitis is found in the section on Animal Safety (the data will be reviewed as part of the literature review) and in the conclusions on this topic the FDA sums up the facts as follows:

Use of BST increases:

- the risk of clinical and sub-clinical mastitis;
- the number of cases of clinical mastitis;
- milk somatic cell counts in some herds.

During the process the United States General Accounting Office (GAO) in 1992 called on the FDA to particularly study the potential risk to human food safety posed by a possible increase in drug residue in milk before approving the drug (GAO 1994). From the FDA FOI summary it appears that no animal welfare concerns were considered at all, and there was no mentioning of potential increase in antibiotic resistance caused by the increased use of antibiotics for mastitis treatment.

As a result of the FDA decision the label/package insert does contain a recommendation to precede the use of BST by the implementation of e.g. a comprehensive and ongoing mastitis control program, as well as a series of precautions and side effects including a section on mastitis, in which the FOI findings listed above are explained. However, animal welfare does not appear to have been an issue in the decision making process on BST in the U.S.A.

A post approval monitoring program (PAMP) was subsequently carried out by the company, to determine if mastitis incidence and antibiotic use was manageable under actual use conditions. The key components of the PAMP were the following three parts:

- A proactive system of collecting Adverse Drug Experience Reports
- A program of tracking milk residues by key dairy states before and after the approval
- A 28-herd study to evaluate the product under actual conditions of use.

A fourth part was designed to compare milk discarded from BST-using and non-using herds (Biotech Education 1998), but data from this part has never been reported, and the study was not mentioned in the final report.

The results of the PAMP (Monsanto 1996) will be reviewed in the literature review section.

6.1.3. The situation in Canada

Over the years there has been a great deal of debate over this item in Canada, including the mastitis issue. Recently, the Canadian authorities made a submission to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) meeting in 1998 which e.g. refers to the risk of antibiotic residues resulting from treatment of mastitis in BST cows and to the expression of the opinion that: “ The greatest hazard is the emergence and spread of antibiotic resistant bacteria through the food chain, as an iatrogenic effect of treating mastitis in BST cows” (Canada, 1997).

In 1998 there was a report by scientists from Health Protection Branch, Health Canada which critically reviewed previous reports by Canadian authorities on the public health and human safety evaluations made. This included a conclusion that antibiotic resistance in farm-borne human pathogens associated with the increased risk of mastitis associated with the use of BST was not properly addressed so far, although it has obvious human health implications (Health Canada, 1998).

As recently as January 1999 the Canadian authorities finally decided, that BST should not be approved for use in Canada due to “ a sufficient and unacceptable threat to the safety of dairy cows”. This was substantiated by a scientific report from a committee of veterinary experts headed by an internationally recognised veterinary epidemiologist, in which increased risks of mastitis, infertility and lameness were found (Health Canad, 1999).

6.1.4. International organisations

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) in their preliminary report on the 50th. meeting in February 1998 expresses the view that the risk of mastitis induced by BST is an issue of animal health that is not within the terms of reference of the Committee. However, the possible increased use of antibiotics was considered. This was done by strictly referring to the PAMP data from the US and the conclusions from this data, i.e. "that the use of BST will not result in higher risk to human health due to the use of antibiotics to treat mastitis and that the increased potential for drug residues in milk could be managed by practices currently in use by the dairy industry and by following label directions for use" (JECFA 1998).

6.2. Mastitis in dairy cows

As already mentioned in Chapters 3, there are welfare aspects associated with high milk yield in dairy cows and the resulting higher risk of mastitis.

In this section some more details on the topic of mastitis in dairy cows will be presented as an aid in evaluating the importance of subsequently reviewed data on occurrence of mastitis in BST treated cows. Particular emphasis will be given to those items which seem important to the evaluation of animal welfare and public health aspects of mastitis in dairy cows.

6.2.1. General aspects

Mastitis is by far the most common disease of dairy cows. When veterinary surgeons describe the occurrence of clinical mastitis, they vary in the extent of clinical signs which must exist before they state that mastitis is present. In a precise study, the term clinical mastitis implies that there are signs of mastitis which can be detected by a veterinary surgeon conducting an examination of an animal. The prevalences of clinical mastitis reported in careful studies carried out in the EU have often been 40 or more cases per 100 cows per year, but with great variation between individual farms (Wilesmith et al. 1986, Plym Forshell et al. 1997, Schukken

et al. 1998, Seegers et al. 1998). Prevalence rates of sub-clinical mastitis vary even more between herds and also greatly depend on the methodology used in the diagnosis. Prevalence figures of around 50% of cows being clinically or subclinically infected are not uncommon in certain herds.

Mastitis is also the most costly disease to dairy farmers, and the number one cause of antibiotic use in dairy cows in spite of the fact that current treatment protocols are not necessarily clinically or cost effective (Radostits et al. 1994, Sandholm et al. 1995, Leslie and Keefe 1998).

Mastitis is an inflammation of the mammary gland, characterised by increased somatic cell counts (SCC) in the milk and by pathological change in the mammary tissue. The disease is usually caused by pathogenic micro-organisms entering the gland through the teat duct. Many different bacteria cause mastitis, some being considered as specific udder pathogens, others being merely opportunistic organisms that cause disease when there is a increased susceptibility of the udder for some reason. Among the common bacteria causing clinical mastitis are *Staphylococcus aureus*, *Streptococcus* spp., *E. coli*, as well as other minor and major pathogens (Bramley 1992, Wilesmith et al. 1986).

Mastitis has been described as being of different types, although the nomenclature is neither exclusive nor necessarily standardised. Furthermore, individual cases tend to quickly develop and thereby change between the categories, which is also why classification of cases and statistical data may be difficult to compare across different studies, unless a common protocol has been used.

The following general classification system exists for different types of mastitis:

- *sub-clinical*
- *clinical*
 - *chronic*
 - *acute /hyper-acute*
 - *mild* *or severe*

Sub-clinical mastitis can only be detected by the application of some sort of diagnostic test to a milk sample. The tests used are either tests aimed at directly revealing the micro-organisms involved or indirect tests to present evidence of inflammatory reactions in the udder tissue and/or milk. Somatic cell counts (SCC) may be considered among the latter, although increased cell counts may be caused by physiological processes, which are not inflammation due to infection by micro-organisms (Coulon et al., 1998). In any case increased SCC becomes a quality issue, since SCC standard values are used in quality and price evaluation of milk delivered for consumption.

Clinical mastitis exists when a cow shows clinical signs of udder infection in one or more of the quarters. The different types of clinical mastitis mentioned in the following may sometimes be seen as different phases which occur when the characteristics of a case change over time.

Chronic mastitis often involves an insidious appearance of long duration, which gradually leads to morphological changes in the udder (fibrosis, change in size or shape). *Acute /hyper-acute* generally refers to a sudden onset of signs.

Mild cases merely show changes in the milk (flakes, clots, watery appearance) (Grade 1 cases). *Severe* cases show clinical signs of inflammation in the udder (heat, swelling, pain, etc) (also called Grade 2 cases) and sometimes even fever and depression in the cow (Grade 3 cases).

6.2.2. Animal welfare aspects

As mentioned in Chapter 2, clinical mastitis is a painful condition, at least in the proportion of cases which has been referred to in 6.2.1. as *severe acute clinical mastitis*. This category is defined by the local reaction in the udder including pain, and in some of these cases, fever and depression would add to the distress of the affected animal.

Unfortunately, very few reports are available on the distribution of acute clinical mastitis cases between the *severe* and the *mild* categories. Wilesmith et al. (1986), defined *mild cases* as those involving milk or quarter, while *severe* and *very severe* were used for defined degrees of systemic disturbance. They reported that 58 - 62% of the clinical cases were *mild* over a three year period. It should be noted, that according to these definitions, an unknown proportion of the classified mild cases could have had some pain and discomfort due to local reactions in the affected quarter, while probably the large majority of the classified severe cases had experienced such or more likely more pronounced pain and discomfort. There was a fatality rate of 0.3 - 0.6% among the cases of clinical mastitis. The annual incidence rates were 25 - 31% of cows affected, but with 1.5 - 1.6 cases per cow per year for a total of 41 - 55 cases per 100 cows per year. They comment that their results suggest that severe cases have been more common in recent years, possibly due to an increase in the proportion of clinical cases due to *E. coli*. Further work in the UK (Blowey and Edmondson 1995) on the economics of mastitis assumes a proportion of mild cases to be 70% with reference to previous UK studies (refs. to be given later).

Qualitative information on pain and discomfort associated with clinical mastitis is very scarce. Alban (1995) in a subjective ranking of cattle diseases according to their presumed welfare consequences scores clinical mastitis as having on average a moderately painful character. In a subsequent paper by Alban and Agger (1997) discrimination between the various types of mastitis gives different scores for pain, ranging from "very painful" in necrotising mastitis to "minor pain" in mild mastitis.

Hillerton (1998), in promoting the needs to treat clinical cases with antibiotics in spite of current efforts to reduce the amount of antibiotics used in animal production, states that: "Mastitis is a painful condition causing moderate to severe distress" and "Primary consideration is that all animals with clinical mastitis are suffering".

The classification of pain associated with clinical mastitis is being applied by Alban (1995) and Alban and Agger (1997) in the further characterisation of welfare associated with disease according to the notion that also the duration of the disease episode is important. This model refers to earlier work by Morton and Griffith (1985) and by Willeberg (1991).

The duration of cases of clinical mastitis obviously varies, but the acute episodes which are most relevant to welfare considerations are on average measured in days (Alban 1995). In many of the cases there will be a gradual recovery during the course of the episode, so that the pain and discomfort will decrease throughout the duration of the episode. On the other hand, fatal cases will deteriorate with progressively poorer welfare throughout the course of the episode.

Statistical data on the duration of cases of clinical mastitis in dairy cows are not readily available outside of controlled studies such as those later reviewed on the use of BST. Such data will therefore appear as results for the untreated control groups from those studies that reported such results (see Section 6.3).

The importance of the incidence of clinical mastitis in dairy cows to the assessment of the welfare consequences of this condition has already been highlighted in the previous sections of this chapter, as well as in Chapters 2 and 5. The more formal presentation of the arguments for this importance can be found in Willeberg (1991), who expressed the welfare importance of disease as a function of its incidence, duration and the intensity of pain or discomfort. The incidence of the disease in a population of animals must also be taken into consideration. Clearly, the more frequently a disease condition occurs in a population, the more important is this condition to the overall welfare of animals in this population.

Although sub-clinical mastitis does not *per se* cause pain or discomfort for the cow and therefore has no direct welfare consequences, it is generally thought that cows with sub-clinical mastitis are at higher risk of getting subsequent episodes of clinical mastitis.

6.2.3 Treatment and prevention of mastitis in dairy cows

Treatment of clinical mastitis cases with antibiotics is not limited to those cases which according to the previous classification may be classified as *severe*, although such cases are probably more likely to receive systemic treatment. Also *mild* clinical cases are often treated with local application of antibiotics, such as intra-mammary tubes. Even cases of *subclinical mastitis* are sometimes treated with antibiotics, depending on other factors in the herd. Cows

are often treated on being dried off before calving (Radostits et al. 1994). The result is that mastitis in dairy cows is associated with a very large usage of antibiotics.

6.2.3.1. Antibiotic resistance

The possible effects of residues in milk on human health are discussed in the report of the Scientific Committee on Veterinary Public Health. Antibiotic resistance may have important consequences for farm animals. Microbial resistance to antibiotics could result in less effective control of disease in cattle and other species and hence lead to poor welfare and increased costs for farmers.

6.3 Comparative studies on mastitis in BST treated and non-treated cows

This section will describe the results of studies aimed at documenting if and how mastitis aspects may differ between BST treated and non-treated cows. A large number of studies have been carried out, which among their primary or secondary aims have had such aspects, being either qualitative or quantitative or both.

It should be noted here, that due to missing detailed identification of individual studies and to the nature of some of the reports being reviewed in the following sections, it is not possible to ensure that data from a study do not appear again as data in other reports, especially when it comes to the meta-analyses. This will unintentionally cause some non-independence among results presented in different reports including this report.

6.3.1. Qualitative aspects

6.3.1.1. Types of clinical mastitis

There is no information from the available comparative studies to describe changes following BST treatment in the proportional composition of clinical mastitis cases with respect to type, i.e. acute *versus* chronic and mild *versus* severe based on the clinical signs.

6.3.1.2. Microbiology

6.3.1.2.1. Clinical mastitis

In the Technical Manual on Posilac (Monsanto 1993) a summary table of microbiological findings from 10 comparative studies is presented. From this table it appears that *Staphylococcus aureus* and coliforms are relatively more frequently isolated from clinical mastitis cases among the BST treated cows than among the control cows (18% *versus* 11% and 26% *versus* 19%, respectively). The Manual concludes that the relative distribution is not affected by the treatment but no statistical data were presented. Cole et al. (1992) also found these two groups of pathogens to account for the majority of cases.

Pell et al. (1992) described a herd of Jersey cows in which chronic cases of clinical mastitis caused by *Staphylococcus aureus* occurred among the BST cows but not among the control cows. In the study by Weller et al. (1990) *Streptococcus uberis* was the most common bacterium isolated. The paper by White et al. (1994) mentions that microbiological identification was not uniformly determined at all trial locations, and data were not summarised. In Judge et al. (1997) fewer isolates of *Staphylococcus aureus* and coliforms were found among clinical mastitis cases in treated than in controls, while *Streptococcus* spp. were more frequent in the former than in the latter group.

6.3.1.2.2. Prevalence of sub-clinical infections

McBride et al. (1988) showed results indicating that the prevalence of infected cows was significantly greater in mid-lactation in BST-treated compared to control cows. Lissemore et al. (1991) observed a higher prevalence of infected cows and quarters in mid-lactation in BST-

treated compared with control cows. Both these studies used different dosages of BST and the differences were most apparent for the high dosages.

McClary et al. (1994) found only few differences among the bacteria isolated from sub-clinical mastitis cases (so-called IMI: Intra Mammary Infections) between treated and non-treated cows. Only for *Staph.* spp. were there more cases in treated cows than in controls.

The FOI-summary indicates that sub-clinical mastitis identified by growth of bacteria from milk samples showed at least 50% excess risk in BST-treated cows. These differences were statistically significant. The difference appeared to be caused by differences originating in the bacteriological sub-groups of “pathogen” and “coagulase negative *Staphylococcus*”.

6.3.2. Quantitative aspects

In this section duration and incidence of mastitis from comparative studies will be reviewed. It is important to note, that since BST is most often administered only in part of the lactation period (i.e. from approximately 60 days after calving to dry-off), incidence figures will implicitly refer to this period of risk. If such a figure is compared with an incidence based on the entire lactation period, the former incidence will of course tend to be lower than the latter, if such were available. For the same reason, control cows from BST studies will show an incidence of mastitis which is lower than that of a “normal” non-treated cow for an entire lactation period. Due to the higher risk of mastitis in the first 60 days of lactation, the risk for the remaining part of the lactation is probably only about half of the total lactation incidence.

6.3.2.1. Duration of clinical mastitis

The duration of episodes of clinical mastitis is important for at least two reasons, for the impact on welfare of the cows and for the total use of antibiotics in the treatment of cases.

McClary et al. (1994) found no difference in duration between treatment groups, and Judge et al. (1997) found no difference between treated and non-treated cows in the average number of

days for which milk was discarded when antibiotics were used (10.0 and 11.5 days, respectively).

In his review of the literature, Kronfeld (1994) found three studies with strong evidence for a prolonged duration of clinical episodes in treated over non-treated cows. One of these reports (Thomas et al. 1991) was based on 871 cows from 15 herds and this report shows that the proportion of cow days with antibiotic treatment for clinical mastitis in BST treated cows were more than twice that in non-treated cows (0.36 % versus 0.16%). Average case length also varied considerably in the study of Cole et al. (1992), but no consistent pattern was apparent. The third study reviewed by Kronfeld (1994) is that of Pell et al. (1992) in which, on average, control cows were treated for clinical mastitis for 1.5 days, while BST cows were treated for 8.9 days. This was probably confounded by the problem of chronic infections by *Staph. aureus* mentioned above. Burton et al. (1994) reported that the total number of treatment days for mastitis were close to three times higher in BST treated than in control cows. In the FOI summary there was no difference in the average number of days affected between BST and control cows with clinical mastitis, but there was a significant difference in number of days affected per 252-days lactation periods between treated and control cows due to the increased risk of clinical mastitis in BST treated cows. In the PAMP study no difference was found. In general, the most substantial studies on the duration of treatment for mastitis indicate that this was greater after BST usage but not every study showed this effect.

In experimental studies by Vandeputte-Van Messom and Burvenich (1993) BST was shown to influence the recovery after experimental coli-mastitis. Recovery was measured mainly in terms of return to milk production. There was better recovery in some BST treated cows, but not in others. The effect was found both when BST was given before and after the onset of infection.

6.3.2.2. Incidence of clinical mastitis

Reports published since the 1980's on the efficacy of BST in increasing milk yield have often had as a minor secondary aim to evaluate any adverse health effects of the treatment. Only a limited number of these reports, however, have documented their findings with actual

numerical information, while most have merely commented, that no obvious health problems were observed. Given the often small number of cows in these studies, such undocumented statements are of little value.

Published reports up through 1991-92 containing actual data on cases of clinical mastitis have been reviewed by Willeberg (1993). In the review data from 11 individual studies and from 6 meta-analyses of series of studies were analysed. The data from individual studies illustrate the wide variability in the ratio of the risk of clinical mastitis in treated and non-treated cows from individual herds in which BST was used, ranging from 0.36 to 1.8. In meta-analyses the ratio varies between 1.17 and 1.47. The difference between the two series of estimates are due to the large sampling variability in the studies based on small numbers of cows as well as the variability in risk between individual herds, which is averaged in the meta-analyses. It was concluded, that the more reliable estimates from the meta-analyses indicate that BST treatment results in an excess risk of clinical mastitis of 15-45 % over that in non-treated cows, that this effect may be partly due to an indirect effect through increased milk yield, and that this increase is of concern regarding the welfare of future populations of dairy cows.

Since this review a number of relevant publications have become available. In a general review, Bauman (1992) supports the observation that data from many cows are needed to substantiate what he calls a “subtle health effect”, and he cites only the study by Phipps (1989), which claims no observed effect in a summary of data from 1300 cows. However, these data were re-analysed in two of the meta-analyses in Willeberg (1993) with resulting estimates of excess risk of 27 and 47%, respectively.

Pell et al. (1992) observed an increased number of cases of clinical mastitis in BST treated cows in a study of only 46 cows, but came to no conclusions due to the small number. Data from more than 600 cows (FDA’s POSILAC Freedom of Information Summary –FOI-, 1993) enabled the estimation of a statistically significant 79% excess risk of clinical mastitis in BST treated cows compared with non-treated cows, when analysed by the same meta-analysis technique as used by Willeberg (1993). Also sub-clinical mastitis was shown to be significantly more common in treated cows than in controls, as well as treated cows having an increase in the number of somatic cells in the milk (SSC). No mention was made of any animal welfare

concerns. Hansen & Otterby (1993) in a short review indicate that the risk of clinical mastitis may be increased in BST-treated cows.

White et al. (1994) made meta-analyses of data from a number of individual studies, and estimated the excess risk of clinical mastitis in treated over non-treated cows to be 42%. In logistic regression analysis, however, the introduction of milk yield as an explanatory variable caused the association between BST and clinical mastitis to become non-significant. Based on these data the authors conclude that the excess clinical mastitis is an indirect effect of BST mediated by the increased milk yield, which is regarded as a direct causal factor. McClary et al. (1994) found no effect of BST on clinical and sub-clinical mastitis in a study of 352 cows during one lactation, while there was an increase in the SCC. Neither could Hansen et al. (1994) demonstrate any increased risk of clinical mastitis in another study on 352 cows over two lactations. Burton et al. (1994) in a review concluded that there may be an apparent adverse health effect of BST treatment in the case of clinical mastitis, since some studies have found an increase in cows treated with higher doses or over multiple lactations.

In the post-approval monitoring program (PAMP) of POSILAC an evaluation of clinical mastitis in 28 herds was performed (Collier 1996). The study confirmed the occurrence of a statistically significant increase in clinical mastitis in BST treated cows, although at a lower level (23%) than at the FOI estimate described above (79%). Judge et al. (1997) reported a 22% non-significant overall increase in risk of clinical mastitis in a study involving 555 cows from 4 herds. However, very marked herd differences were apparent, so that in one herd there was a statistically significant increased risk of 330 % in BST-treated cows. However, the mastitis incidence in control cows from these herds was low compared to reported average values, which could make the results less representative for herds of average background risk of mastitis. Fontes et al. (1997) reported on 58 Brazilian cross bred cows and found a tendency to more mastitis in BST-treated cows.

Kronfeld (1997), in a review of some of the published studies as well as the FOI and PAMP reports, criticises the apparent inconsistencies and weaknesses in the reports on clinical mastitis, and he also points to the animal welfare aspects of the continued use of BST in spite of the controversy over interpretation of the published data. Ruegg et al. (1998) reported on culling rates in 19 herds using BST and they found no statistically significant increase in

overall culling over that in 13 non-BST herds. However, they do report higher proportion of culling due to mastitis in BST herds compared to controls, but this was not significant due to low power of the statistical testing of the small number of herds. In a recent Canadian review (Health Canada 1999) the conclusion of several meta-analyses was that there was an increased risk of clinical mastitis by about 25%.

6.3.2.3. Sub-clinical mastitis

Since sub-clinical mastitis can be diagnosed only by testing of milk samples the measures of the frequency of sub-clinical mastitis are technically speaking prevalence figures. When SCC is used to indicate sub-clinical mastitis the results may be presented either as prevalence of high somatic cell counts or as average SCC for the cows in the group.

6.3.2.3.1. Somatic cell counts (SCC)

McBride et al. (1988) showed that the mean SCC was significantly greater throughout the treatment period in high-dose-BST-treated compared with control cows. Peel et al. (1988) found that the SCC was significantly increased in BST treated cows in two out of eight studies reviewed; in five others the SCC were non significantly elevated and in one it was non significantly lowered.. Craven (1990) observed a statistically significant increase in SCC towards the end of the lactation period in some locations. Lissemore et al. (1991) observed a higher SCC for some months in BST-treated compared to control cows. Thomas et al. (1991) found no differences in SCC during treatment. In the study by Cole et al. (1992) the levels of SCC generally reflected the level of clinical mastitis, which increased with increasing dosage of BST. Some of these studies used different dosages of BST and differences were most apparent for the high dosages.

McClary et al. (1994) found increased SCC in BST-treated cows with a significant dose-response trends for both primiparous and multiparous cows. White et al. (1994) found only slight associations between treatment and SCC. Masoero et al. (1998) found no effect of BST on SCC in BST-treated compared to control cows. Similar conclusions were obtained by Monsallier (1991).

Millstone et al. (1994) published results from meta-analysis of data from 8 studies, and the results indicated a statistically significant increase of 19% in mean SCC in BST-treated over control cows across the 8 studies. In 3 individual studies there was a significant difference, while 5 studies showed insignificant differences.

The FOI (1996) found that SCC were elevated in some herds when BST was used. It is possible that this was due to higher sub-clinical infection rate in these study locations. In the PAMP study there were no significant differences in SCC. A similar conclusion was reached in the Canadian review (Health Canada 1999), although tendencies were found in some instances.

In general it appears that cell count data does not give reliable information about BST effects, but where there are differences, the SSC was found to be higher in BST treated animals.

6.4. Discussion of epidemiological issues in the studies reviewed

A number of epidemiological issues can be raised relative to the field studies of BST which form the basis for the animal safety evaluations by the various agencies involved in the scrutiny of the product as part of the authorisation for marketing (Willeberg 1993, 1994 and 1997). The following epidemiological points will be considered relative to the incidence of clinical mastitis. However, the general principles here are also relevant to studies on lameness and fertility problems.

- sample size and resulting power of the individual study to identify excess clinical mastitis due to BST treatment;
- importance of different mastitis rates during the pre-treatment period between cows belonging to the BST group and to the non-treated group;
- herd effects and representativeness of experimental herds;
- relevance and correctness of the “indirect effect through milk yield” explanation.

6.4.1 Sample size and resulting power to identify treatment effects

Willeberg (1993) has dealt with this issue extensively. The point to be made is that the many published papers on individual BST studies, which typically include 40 - 60 cows in each of the treatment and non-treatment groups, have far from sufficient statistical power to detect a realistic difference in the risk of clinical mastitis between the two groups. Assuming a base-line risk of 20 cases per 100 non-treated cows for the relevant part of the lactation period and hypothesising an increase by 35% in this risk from BST, it would require approximately 600 cows in each group for this difference to become statistically significant (95% confidence level and 80% power). Consequently, the great majority of single study reports conclude, that there is no significant increase in clinical mastitis due to BST. However, the absence of significance is often the result of a low sample size. Subsequent meta-analyses have corrected for this problem of low power, and consequently estimates of increase in risk ranging from 17% to 47% due to BST treatment were obtained (Willeberg 1993).

In a previous paper the issue was dealt with indirectly by pointing out, that examination of “subtle health effects such as mastitis incidence” will require large number of animals treated for several lactations under a range of environmental and management conditions (Eppard et al. 1987). In the paper by Millstone et al. (1994) a similar discussion has been presented with respect to mean SCC figures from individual BST studies.

The point made above concerning studies of the effects of BST treatment on the incidence of mastitis is also relevant to other causes of poor welfare such as foot disorders (Chapter 7), reproductive disorders (Chapter 9) and to health in general and welfare in general. It is not possible to conclude whether or not BST treatment affects the incidence of problems unless a sufficient sample size is used. Some published studies and other reports have concluded that BST had no effect on disease incidence or other indicators of welfare when the data sample was insufficient to allow such a conclusion.

6.4.2 Different pre-treatment mastitis rates in the BST group and the non-treated group

Phipps (1989) comments on the fact that: “in certain circumstances there appears to be an increased incidence of clinical mastitis in treated cows yet in other cases there is no indication of increased clinical mastitis as a result of BST treatment”. He goes on: “However, the overall incidence of clinical mastitis was notably also higher before BST treatment commenced in cows already allocated to the treatment group and thus the relative incidence of mastitis was not affected by BST treatment”.

Also White et al. (1994) found that the mastitis incidence during the pre-treatment period was significantly higher in the to-be-treated group than in the to-be-non-treated group. This paper suggests that this may be due to a greater predisposition to mastitis in the treatment group than in the non-treatment group, i.e. the randomisation procedure used in allocating the cows to either group had not been successful on this point. Nevertheless, in White et al. (1994) the statistical analyses of the treatment effects were carried through ignoring the potential bias introduced by this unfortunate event. This appears to be a case of “randomise and close-your-eyes”, i.e. to rely on the supposedly beneficial effect of randomisation even though the data itself shows that the randomisation procedure had failed on a critical point.

In important studies such as these for resolving the controversy over the BST-mastitis issue the scientifically most sound solution might have been to analyse separately the information from those herds or individual studies with no differences in pre-treatment mastitis rates. This, however, was not attempted.

6.4.3. Herd effects and representativeness of experimental herds

The incidence of clinical mastitis varies greatly among dairy herds, and consequently published meta-analyses (Phipps 1989, Craven 1991, Thomas et al. 1991, White et al. 1994) contain evidence of a considerable herd effect in terms of differences among herds in the risk of clinical mastitis in non-treated cows, and in differences in the risk ratios between treated and non-treated cows. Adjustment for these herd effects, however, was not always made in the published analyses and no information was given on how representative the selected herds were for the population of potentially BST-using herds. Neither has any formal study been

made to identify factors which may be responsible for these differences in the effect of BST among herds.

Furthermore, some reports mention the need for larger field studies to be carried out under a range of environmental and management conditions in order to detect “any subtle health effects” (Eppard et al. 1987, Bauman 1992). The Committee on Veterinary Medicinal Products (CVMP) advising the European Commission said in its final report on two BST applications that it is important to verify that the overall level of risk to the health and welfare of the target animal is not increased when the product is used under practical farming conditions where standards of animal husbandry may not be as high as those in the experimental herds. The CVMP recommendation is therefore that, if BST should be allowed in the EU, then a wide-ranging study of at least two years duration should be undertaken to determine the effects of BST on the incidence of mastitis and associated metabolic disorders under practical conditions of use (European Commission 1993).

The argument that the excess risk associated with BST is of no public health concern because it is smaller than the variation caused by herd effects and other factors such as season (FDA 1993) does not hold for animal welfare concerns. Antibiotic residue avoidance programs were stated to be adequate to detect and prevent the potential public health effects of treatment, but no additional safeguard exists to prevent animal suffering in clinical cases of mastitis. Therefore, all factors which decrease the risk of clinical mastitis are relevant as potential preventive measures to improve animal welfare. The main issue in choosing among them is the possibility of managing the exposure to the respective factors. While one has full control over whether or not to use BST, in practice very little control can be exerted over seasonal and herd factors, as long as the causal factors behind their effects have not been identified in more detail.

6.5. Conclusions

Clinical mastitis is often a painful disease. The welfare of most cows with mastitis is poor, the

extent of poor welfare being dependent on the severity of the condition.

It has been stated in certain published papers and reports that BST has no effects on some welfare measures e.g. mastitis, foot disorders, health in general, or welfare in general. However, in many cows the sample sizes used were too small to justify such conclusions and meta-analyses have revealed that there are effects.

The duration of episodes of treatment for clinical mastitis were longer in BST-treated than in non-treated cows.

BST usage increases the risk of clinical mastitis above the risk in non-treated cows. The magnitude of this increase has been variously estimated by meta-analyses or large scale studies at 15- 45%, 23%, 25 %, 42% and 79%.

These estimates describe an increase due to BST which is not only statistically significant but also biologically relevant and of considerable welfare concern. Whether this effect is direct or indirect does not alter the welfare concerns.

CHAPTER 7 EFFECTS OF BST ON LEG AND FOOT DISORDERS (LAMENESS)

7.1 Introduction

Lameness in dairy cattle has been considered as one of the major causes of poor welfare and economic losses in dairy farming. As explained in section 2.2, assessment of leg and foot problems is not always straightforward. One of the major problems is that in order to get a proper insight into the prevalence and incidence of claw disorders in particular, one has to lift the feet and examine them thoroughly.

The effect of BST on health of dairy cattle has been scrutinised for years now. No direct acute toxic effects of BST on the claws or legs of dairy cattle have been described. There are few planned studies on the effects of long term administration of BST on the incidence or prevalence of foot or leg disorders.

7.2 Foot and leg disorders

A possible association between BST treatment and an increased incidence of lameness has been reported by several authors (Zhao et al.,1992; Cole et al., 1992; Kronfeld, 1997; PAMP, 1996). Cole et al. (1992) described a higher incidence of clinical lameness in the BST treated animals in the first and second year of the BST administration. In the high treatment group (3.0g/14 d) lameness had a more chronic character. Lameness was diagnosed by clinical daily health observations. Clinical lameness diagnoses included foot rot, hock problems, sole abscesses, lameness due to injuries, lameness due to limb and joint problems such as swelling of the foot, hock, knee or leg, and "undiagnosed". The results did not give an explanation of the different lameness diagnoses. During the study, animals were kept in tie stall confinement housing. The housing system might explain in part the overall low incidence of claw disorders compared with studies where dairy cattle are housed in a loose housing system. Wells et al. (1995) described the long term effect of the administration of BST in 94 pairs of high producing cows. The prevalence of gait abnormalities and visual evaluation of the limb was estimated at a single farm visit, but the feet were not lifted. A high

prevalence of lameness was recorded, 39.4% of untreated animals and 46.9% of BST treated animals ($p > 0.05$). Limb lesions significantly associated with long term BST treatment were superficial laceration of the tarsus, superficial swelling of the metatarsophalangeal joint. In this study treated animals had a lower risk for femoral lesions and superficial lacerations. Kronfeld (1997) described the results of a FDA-PAMP study. Kronfeld emphasised in particular the high incidence of laminitis in treated cows. This high incidence of laminitis has been attributed to diet i.e. the use of more grain to increase energy density and minimise loss of body condition. PAMP data (Monsanto, 1996) indicated that cows injected with BST had approximately 50% more days observed of foot and leg disorders. There was an association between the use of BST and incidence and duration of hock disorders, knee calluses and lesions of the foot. These were primarily associated with lacerations and bruises associated with infections. These observations were also associated with altered gait. Sample size, definition of diagnoses and pre-treatment incidence rates of several foot and leg disorders might have influenced the outcome of this study. As a consequence some possible associations between the increased incidence of, for example, foot rot and laminitis and the use of BST were not significant. The PAMP data are summarised in Table 2 below. The FOI summary for BST showed the same association between the use of BST and an increased incidence and duration of knee calluses, hock disorders and foot disorders. More multiparous treated cows were lame and suffered over a longer period of time. Pell (1992) and Oldenbroek (1990) could not find an increased incidence of lameness associated with the use of BST.

7.3 Skeletal and joint problems

Cole (1992) described a slight increase of femur length associated with BST treatment in primiparous cows. Several reports of the same or similar study have been presented. Cole (1992) described that the incidence of macroscopic and microscopic lesions of bone and cartilage was unaffected by BST treatment. However no data were presented. The FOI summary part 3 indicated that post-mortems of five cows, that were chronically treated with BST 500 mg/14 days, revealed that in all animals multiple articular (subchondral) erosions and other joint pathologies were observed in multiple joints. However the authors concluded

that environmental factors might be responsible for the articular lesions rather than any direct effect of BST.

The PAMP study carried out in the USA has provided clear evidence for the effects of BST treatment on foot disorders and other musculo-skeletal problems. Data were collected on a daily basis on farm and by veterinary surgeons who attended for injections.

Table 2 Foot disorders and other problems with the musculoskeletal system assessed daily and by veterinarians in control and BST-treated cows (PAMP data)

Disorder		Daily Inspection			Veterinarian Inspection		
		Control	BST Treated	P if <0.05	Control	BST Treated	P if <0.05
Hock Primiparous	Cows	0	1		5	14	0.013
	Days	0	1		10	72	<0.001
Hock Multiparous	Cows	1	4		20	28	
	Days	1	10	0.003	42	84	<0.001
Foot Primiparous	cows	25	34		18	25	
	Days	49	117	0.001	34	43	
Foot Multiparous	cows	31	68	<0.001	32	49	0.035
	Days	117	247	<0.001	45	112	<0.001
Gait Primiparous	cows	13	19		29	29	
	Days	26	40		77	76	
Gait Multiparous	cows	24	41	0.025	72	90	
	Days	123	83	0.003	179	284	<0.001
All Musculo-skeletal Primiparous	Cows	29	42		39	58	0.008
	Days	100	148	0.004	115	178	<0.001
All Musculo-skeletal Multiparous	cows	50	88	<0.001	105	126	
	Days	253	322	0.007	283	462	<0.001

Number of cows =(primiparous) 209 control, 210 BST daily; 200 control, 203 BST veterinarian (multiparous) 356 control, 313 BST daily; 341 control, 340 BST veterinarian.

The PAMP tables from which table 2 is extracted include many musculoskeletal disorders but most of these occurred at a very low incidence.

The daily inspection and veterinary inspection data are generally similar in direction but some conditions e.g. hock disorders were more likely to be detected during veterinary inspection. The figures for gait disorder in multiparous cows are surprising because the daily inspection and veterinary inspection data were significantly different in opposite directions and it seems improbable that, for the daily inspection, increased foot disorders was associated with reduced gait disorders.

Foot disorders make up the majority of cases and these are of great importance in relation to the welfare of the animals. The daily inspection data showed that the number of multiparous cows with foot disorders was 2.2 times higher in BST-treated than in control cows and the number of days affected was 2.1 times higher in BST-treated cows.

7.4 Conclusions

An increased incidence of foot and leg disorders associated with the long term administration of BST has been described by several authors. In the largest scale study, the number of multiparous cows with foot disorders was increased by a factor of 2.2 and the number of days affected was increased by a factor of 2.1.

As a consequence of the nature of the different foot and leg disorders there will be pain and other suffering in these animals. Hence welfare will be seriously and adversely affected as a consequence of the BST treatment.

8.1 Analysis

Since BST is administered by injection in the form of a pellet or a suspension, there is the possibility that pain or discomfort could be caused to the animal by this action.

Pooled data from three studies conducted by Monsanto and published in the United States Food and Drugs Administration (FDA) Freedom of Information Summary (FDA, 1993: Table 41) show that one week post-injection 24% of cows (maximum of 43% in one study) had visible injection-site swellings 10-16 cm long or 1-2 cm high (category 2), while 4% (max. 8%) had swellings >16 cm long or >2 cm high or other complications (draining lesion, lameness, haematoma etc) (category 3). Only 26% had no visible swelling at this time - as was the case for 93% cows injected with placebo, indicating that it was the injectate which was responsible for the lesions rather than the physical process of injection.

Swellings tended to subside over time, e.g at week 2, the category 2 swellings in the worst case study had declined from 43% to 20%, while the category 3 swellings fell from 8% to 2%. According to the Freedom of Information Summary: "over 95% of scores were completely resolved within 5 weeks of injection". However, given that cows would normally receive BST injections on a two-weekly cycle, it is likely that any adverse effects on their welfare would increase progressively along with the increasing number of swollen sites on the body (at various stages post-BST injection).

Swelling Severity Score

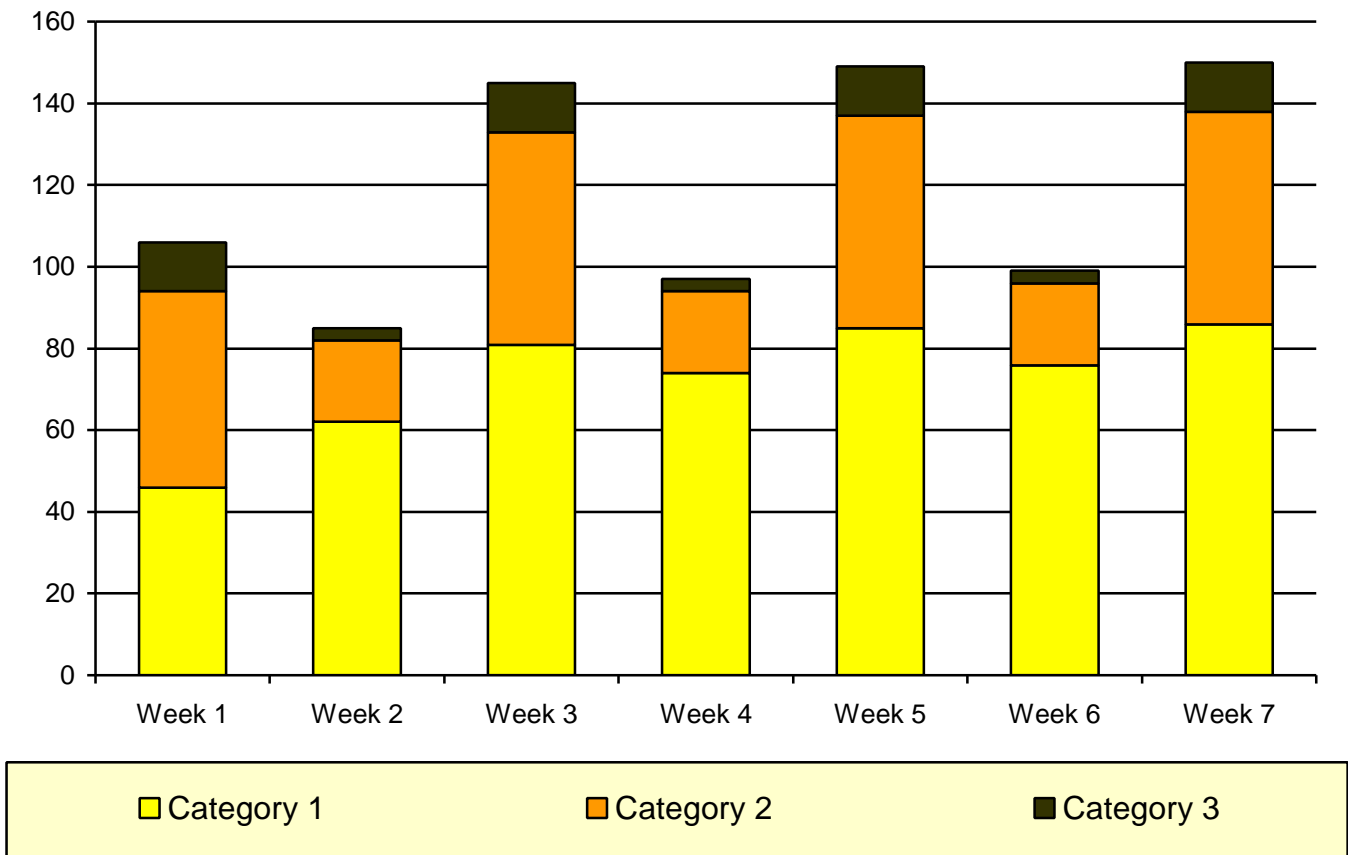


Figure 3: The ‘Swelling Severity Score (SSS) attributable to injection site swellings following repeated two-weekly injections of BST (based on the data in Table 41 of the FDA ‘Freedom of Information’ report on Monsanto’s Posilac.

Category 1: swelling <10cm long or <1cm high,

Category 2: swelling 10-16cm long or 1-2cm high,

Category 3: swelling >16cm long or >2cm high or other complications

Thus, assigning a Swelling Severity Score (SSS) of 3 to each percentage point of category 3 swellings, SSS of 2 to each % category 2 swellings and an SSS of 1 to each % category 1 swellings, it can be shown with reference to the pooled data from the three studies (see Figure 3) that the total SSS score per hundred cows following the start of a two-weekly BST injection cycle would change weekly as follows: 106, 85, 145, 97, 149, 99, 151..... Although

in the second week post-injection matters improve, as the next cycle of injections is given there is an underlying trend towards increasingly poor welfare.

In a more detailed study of a clinical field study involving 232 cows (FDA, 1993), 13 animals were selected because of persistent injection site problems. Four of these cows had injection sites scoring 2 or 3 which were at least 30 days old. Of 19 samples examined for microbial contaminants, 5 were contaminated, two with *Actinomyces pyogenes*.

Further studies were conducted on two cows that showed chronic injection site reactions (i.e. persisting for 6-12 months) and on three cows “with more typical reaction sites” (FDA, 1993). “Microscopically, granulomatous inflammation was found at nearly all sites characterised by multifocal areas containing macrophages, lymphocytes, polymorphonuclear leukocytes and giant cells. The overall reaction was supported by fibrous connective tissue while the foci of residual sometribove [i.e. the BST preparation] were apparent.” By comparison with the “more typical reaction sites”, in chronically reacting cows there was a “notable ... increase in the presence of polymorphonuclear leukocytes in the sites”.

In what appears to be the only quantified report of injection-site lesions in a peer-reviewed scientific publication, Pell et al (1992) reported that out of 367 injections of 23 cows, ten days post-injection 10.1% cows had 'severe' (i.e. category 3) lesions, while 49.9% had 'moderate' (i.e. category 2) lesions. Out of 358 placebo injections of 23 cows in the same group, none had severe reactions and 0.6% had moderate reactions. It is clear that the BST or another component of the preparation, excluding the vehicle, is causing the problem.

According to the FDA Two Year Report on BST, between February 1994 and February 1996 there were 156 reports relating to injection-site reactions in cows treated with BST, from which the estimated percentage of cows with this clinical manifestation was 0.1% (CVM, 1996) As noted above, farmers are not likely to report such problems and any reports may refer to a proportion of category 3 swellings only. Whatever the explanation, the number of adverse reactions implied by these data is much lower than would be anticipated from the data released in the Freedom of Information Summary (FDA, 1993) and in the report of Pell et al (1992).

The dangers of BST in causing injection-site lesions are acknowledged by the manufacturers of Posilac, who recommend in their advice to users: "use of Posilac in cows in which injection site swellings repeatedly open and drain should be discontinued". Moreover, users are warned that "injection site swellings ... may remain permanent" (Monsanto, 1994)

A potential welfare problem with the injection site recommended by manufacturers i.e. the ischiorectal fossa (the tailhead) in their submission to the CVMP (CEC, 1993) has been identified. There are dangers that such a site would not only make detection of swellings more difficult but that in an area which is frequently encrusted with faecal matter the risks of infection might be increased. It is also possible that painful swellings in this area might adversely affect the usage of the tail e.g. removing flies.

Welfare might also be adversely affected by the restraining procedures accompanying injection, quite apart from the effects of the injection itself. It is difficult to define such effects accurately because they will depend partly on legal provisions (e.g. on who is allowed to administer BST) and partly on the injection procedures on a particular farm. If, as in the USA, farmers are allowed to inject their cows, concerns must arise due to some farmers' lack of training and expertise and their inability to cope with emergencies which might ensue.

8.2 Conclusion

Injection site problems occur in most cows injected with BST, but not with placebo injections, and are exacerbated by repeated injections. In 4% of cows the swelling is severe and there are occasionally chronic infections. The pain associated with this problem has not been adequately assessed.

CHAPTER 9 EFFECTS OF BST ON REPRODUCTION PROBLEMS IN COWS.

9.1 Mechanisms and preliminary studies of BST effects

The possibility that BST treatment interferes with reproduction was already evident from the first studies on the effects of BST on milk yield in dairy cows. In their report of the effects of different doses of BST on milk yield of primiparous Holstein cows, Morbeck et al (1991) noted that although days from parturition to first detected oestrus, days open, and services per conception were not affected, days from parturition to first service increased with the dose of BST, and rate of detection of oestrus decreased. Thus there was some evidence of reduced birth weight in calves and increased incidence of multiple births (Bauman et al., 1987). In a similar way, Cole et al (1992) reported that although reproductive health generally was not affected by BST treatment, delayed conception and increased incidence of abortion might occur. They also pointed out that decreased reproductive performance was an health issue requiring further evaluation. Interference of BST treatment with ovulation and oestrus detection was confirmed by several other groups (Hemken et al, 1991; Lefebvre and Block, 1992; Stanisiewski et al, 1992). These effects were not due to the handling stress accompanying BST injection since the effects of sustained-release BST did not differ from those of daily injection of BST (Zhao et al, 1992). BST did not have significant long term effects since the reproductive problems of cows treated with BST during the first lactation did not carry over upon cessation of treatment. Cows treated with BST at the first lactation and exhibiting reproduction problems at that time had a higher pregnancy rate during the second lactation, when they were no longer treated (Esteban et al, 1994a). There was no evidence of any habituation to the effects of BST on reproduction since repetition of the BST treatment during a second lactation induced the same problems as during the first lactation (Esteban et al, 1994b).

The mechanisms of effects of BST on reproduction have been investigated in both lactating and non lactating animals. BST had no effect on pituitary functions, as assessed by plasma levels of gonadotropins (Adriaens et al, 1995). The ovary is the most likely target of the effects of BST. BST increased the number of small size antral follicles (Gong et al, 1991, 1993; Kirby et al, 1997), although negative results have also been reported (Andrade et al,

1996). In lactating dairy cows, BST increased the weight of corpora lutea and the levels of IGF-I and IGFBP in the follicular fluid (Lucy et al, 1995). The effects of BST on ovarian follicular dynamics have been confirmed by De la Sota et al (1993). These authors showed that BST-treated lactating cows developed dominant follicles that were larger and less oestrogenic than those in nonlactating cows. Examination of the response of BST-treated dairy cows to a luteolytic dose of PGF2-alpha led Kirby et al (1997) to propose that BST reduces FSH, increases the turnover of dominant follicles, and induces differences in the timing of follicular waves.

9.2 Monitoring studies

The FOI summary and Post Approval Monitoring Program in the USA provide detailed information about effects on reproduction. The significant differences listed in Table 3 refer to various sample sizes and *denotes small data set.

Table 3 Significant effects on reproduction from FOI summary and PAMP survey.					
Source	Measure	Primiparous / Multiparous	Control	500mg BST	p value
FOI	Pregnancy rate	primip	90%	63%	0.002
PAMP	Pregnancy rate	multip	82 ± 2.7	73 ± 3.0	0.039
PAMP	Days open	primip	134 ± 7	150 ± 7	0.048
FOI	Gestation length	primip	280.4 ± 0.8	277.9 ± 0.9	0.028
FOI	Gestation length	multip	280.5 ± 0.8	277.4 ± 0.9	0.02
PAMP	Gestation length	primip	279 ± 1.3	275 ± 1.3	0.001
FOI	Multiple births	primip	2.9%	20.8%	0.016 *
FOI	Multiple births	multip	1.2%	13.6%	0.003

There is evidence that BST treatment can adversely affect reproduction. Pregnancy rate dropped by 7-9% in multiparous cows and by up to 27% in primiparous cows, gestation length was shortened by 2-4 days, the number of days open increased in primiparous cows and the frequency of multiple births was substantially increased. Multiple births cause various welfare problems both for the cow and the calf. Failure to conceive by cows given appropriate opportunity, is an indicator that the cow is having difficulty in attempting to cope with the conditions in which it finds itself and hence that its welfare is poor. In the allocation of

resources within an animal, reproduction is given high priority so conditions must be stressful before conception is inhibited. Hence the measure "pregnancy rate" which indicates the proportion of animals inseminated which become pregnant reveals how many animals are so severely affected by metabolic demands and external effects on the individual that they cannot conceive. Similarly, "days open" is longer if conception is delayed so, provided that management of reproduction is adequate, a high figure for "days open" indicates poor welfare. Both of these measures showed significant differences between BST-treated and control cows. Gestation length can be shorter than normal because of the temporal advancement of parturition and this can be brought about by poor welfare. However, cows with twins usually show temporally advanced parturition and BST-treatment increased the frequency of twinning in this study so this change could have caused the changes in gestation time in the table.

Some of the effects of BST on reproduction are mediated by BST action on ovarian function via IGFI. The effects do not continue after cessation of treatment.

Concern has also been expressed about an increased incidence of retained placenta, abortion/foetal loss and cystic ovaries in BST treated animals (Canada 1999). However, more data on these possible effects are needed.

9.3 Conclusion

There is evidence that BST treatment can adversely affect reproduction. Pregnancy rate dropped from 82 to 73% in multiparous cows and from 90 to 63% in primiparous cows, gestation length was shortened by 2-4 days and the number of days open increased in primiparous cows. The effects do not carry over after cessation of treatment. The frequency of multiple births which can cause welfare problems, was substantially increased by BST. Failure to conceive is an indicator of poor welfare and multiple births lead to poor welfare.

CHAPTER 10 EFFECTS OF BST ON IMMUNOLOGY, PATHOGEN REPLICATION AND ON INFECTIOUS DISEASE IN CATTLE.

This Chapter considers experimental studies of the effects of natural Growth Hormone (GH) and BST.

10.1 Immune effects of GH

Advances in the understanding of the regulatory influences of non immune factors on immunity have revealed that in addition to its classical endocrine effects, GH is critically involved in the maintenance of lymphoid organ size and cellularity. GH receptors are present on peripheral blood monocytic cells, thymocytes and possibly lymphocytes (see for a general review Arkins et al, 1992).

10.1.1. Thymic function and hematopoiesis

GH sustains thymus growth, influences migration of T cell precursors to the thymus, and promotes the differentiation of double negative T cells (CD4⁻ CD8⁻) into the double positive phenotype (CD4⁺ CD8⁺), certainly via its ability to stimulate the synthesis of thymulin from thymic epithelial cells. GH also plays an important role in the development of hematopoietic precursors and augments the in vitro maturation of erythrocytes.

10.1.2. Lymphocyte function

GH consistently augments the in vitro proliferation of lymphoid cells, possibly by acting as an autocrine factor. GH also augments a number of immune responses in vivo, including antibody synthesis and skin graft rejection, the development of adjuvant arthritis, the activity of natural killer cells, and lectin-induced T-cell proliferation and IL-2 synthesis. However, these effects are in general more easily observable in animals whose pituitary has been experimentally removed or where it is underfunctioning for pathological reasons (hypopituitary animals) than in normal animals.

10.1.3. Phagocytosis

Phagocytic cell function is influenced by GH. GH-treated macrophages acquire morphological and functional characteristics of activated macrophages. The same applies to polymorphonuclear leukocytes, and results in the enhanced synthesis of reactive oxygen intermediates (superoxyde anion). IGF-1 has similar effects on phagocytic cell functions to those of GH, including the production of oxygen reactive intermediates and tumor necrosis factor-alpha and the oxygen-dependent killing of bacteria.

10.1.4. Summary

Based on the large body of in vitro and in vivo data available concerning the effects of GH and IGF-1 on immune function, it is apparent that GH and IGF-1 are able to stimulate many components of the immune response, and specially phagocytosis. However, these effects are always more marked in hypopituitary than in normal animals, and it is important to note that the enhancement of phagocytosis that is obtained in response to GH and IGF-1 is not apparent in the absence of triggering stimuli for the activation of phagocytosis.

10.2 Immune effects of BST

Compared with what is known on the immune effects of GH and IGF-1, there have been relatively few investigations of the effects of BST administration on cattle immunity, and most of these investigations have been carried out by only two research groups, one in Canada and one in Belgium. They have used repeated daily injections of BST.

10.2.1 Haematopoiesis

Long term BST treatment in dairy cows induces a significant increase in the neutrophil fraction in peripheral blood, but reduces haematocrit, perhaps because of an increase in plasma volume (Burton et al, 1990, 1992).

10.2.2 Lymphocyte function

Treatment of dairy cows with BST enhances T cell proliferation response induced by concavalin A (Burton et al, 1991), and results in higher serum IgG and IgA concentrations (Burton et al, 1991). However, there is no change in the delayed type hypersensitivity response to dinitrochlorobenzene (Burton et al, 1992). In addition, BST reduces the inhibitory effect of high temperature on mitogen-induced proliferation in vitro, but it has no effect on the depressed lymphoproliferative response that occurs in lactating dairy cows submitted to heat stress nor does it alleviate the decreased migration of leukocytes to the mammary gland after chemotactic challenge (Elvinger et al, 1992).

10.2.3 Phagocytosis

BST treatment stimulates polymorphonuclear leukocyte (PMN) adhesiveness and release of oxygen reactive intermediates in PMN from milk and peripheral blood (reviewed in Arkins et al, 1992). These results indicate that PMN bacterial killing can be enhanced in vivo, which may result in increased resistance to mastitis. BST treatment has mixed effects on resistance to experimental models of disease in cows (mastitis; metabolic disease, response to endotoxin) but in all cases, there is no evidence for a worsening of the condition in BST-treated animals compared to controls. In an experimental model of coliform mastitis, Vandeputte-van Messom and Burvenich (1993) showed that pretreatment with BST normalises milk production and composition, but only in those animals which respond very intensively to intramammary inoculation of *E. coli* with a respiratory burst activity of blood neutrophils. In calves injected intravenously with endotoxin, BST treatment decreased the impact of endotoxin on metabolic variables (Elsasser et al, 1996).

10.2.4 Summary of immune effects of BST

BST enhances several aspect of the immune response and tends to enhance resistance to experimental models of disease. However, the effects of BST treatment on an ongoing inflammatory response have not been assessed.

10.3 BST and viral replication

Because human recombinant GH has been reported to enhance lentivirus replication in vitro (Laurence et al, 1992), the importance of such an effect for BST and its possible adverse consequences on viral propagation within the herd have attracted attention

10.3.1 Lentiviruses

Preliminary results indicate that BST can enhance and prolong the production of Maedi Visna virus in milk macrophages of seropositive ewes and trigger the expression of caprine arthritis encephalitis virus in goat. This might be due to the presence of GH-induced transcription factors on the nucleic acid of these viruses, or to a non specific enhancement of the multiplication of virus containing epithelial cells in the mammary gland (Chilliard et al, 1998).

10.3.2 Other viruses and non conventional transmissible agents

GH alone or in combination with progesterone, oestrogens or corticoids, augments by 2 to 10 the replication of murine cytomegalovirus in vitro (Chong et Mims, 1984). GH and IGF-1 can also induce the expression of messenger RNA of PrP, the prion protein that is associated with bovine spongiform encephalopathy, in rat pheochromocytome cells in vitro. This effect, however, requires enormous doses of GH and IGF-1 that are far above those used in dairy cows.

10.4 Conclusion

The immuno-stimulatory effects of BST observed experimentally have not been confirmed clinically.

Very preliminary results indicate that GH might enhance the production of pathogenic agents that develop intracellularly, such as viruses. However, the importance of this effect for BST treatment and its functional consequences in vivo remain largely unknown.

CHAPTER 11 EFFECTS OF BST ON OTHER HEALTH PROBLEMS

11.1 Body condition

The mechanism of action of BST involves a whole range of changes in the metabolism of body tissue so that more nutrients can be used for milk production. These changes involve direct effects on tissue metabolism (e.g, adipose liver). Several papers have been published on body condition and body tissue composition. Most papers show poorer body condition in cows treated with BST. Those cows have a lower body condition score (BCS) at the end of lactation than the control animals. The difference between BC of treated and control animals varied between 0.2 and 0.5 points (FOI part 4, Wells 1995, Chilliard 1988, Phipps 1990, FOI 1993). On the other hand, BST treated cows might have an increased voluntary feed intake starting 4 - 6 weeks after the onset of the treatment (FOI 1993, Oldenbroek 1990)

The body weight of a BST treated animal has been recorded as approximately 40 kg higher than control animals at the end of the lactation. However, body composition changed and this effect may be largely due to an increase in body water. (Oldenbroek, 1990; Wells, 1995; Chilliard, 1991).

11.2 Metabolic and digestive disorders

Several studies have focused on the potential adverse effect of the long-term exogenous administration of BST on health aspects of dairy cattle. Not all studies were very informative concerning study design, diagnoses etc. Conclusions such as "no health effects were noted" have been stated regularly (Phipps 1990, Hartnell, 1991, Burton 1994, Oldenbroek 1990). In general health effects are difficult to detect, because symptoms are often non specific and therefore, the prevalence and incidence of different health diagnoses, based only on visual or physical examinations are of limited value. Moreover, to study the potential adverse effect of BST on different health disorders requires large numbers of animals as most disorders occur commonly during the rising phase of lactation.

During BST treatment an increased number of cows experienced periods "off feed" (reduced

feed intake) (Monsanto 1996, Kronfeld 1994, Cole 1992, Pell 1992) There is no indication in the literature that BST-treated animals might have an increased incidence of ketosis (Burton 1994)

Several studies showed an increased incidence of bloat, indigestion and diarrhoea in BST treated cows (FOT NADA 14-872 1993, Monsanto 1996) In addition, the incidence of left displaced abomasum tended to increase BST-treated animals (Monsanto 1996). In general the control animals had more miscellaneous health problems during the pre-treatment period than the BST-treated animals. This difference might have influenced the outcome of the study (Monsanto 1996)

Several authors have described increases in laboured breathing, body temperature and heart rates in BST treated animals (Cole 1992, FOI #140-872 1993, Monsanto 1996).

One manufacturer of BST warns that udder oedema is more likely in BST-treated cows, especially when BST use is commenced in mid-lactation.

11.3 Heat Stress

The increased metabolic activity associated with BST-induced galactopoiesis also involves an increase in heat production by the body, which challenges thermoregulatory processes. The effect can be pronounced, as illustrated by the report that, of 18 cows receiving BST and subjected to heat stress, two cows died and four suffered from ataxia, whereas no such responses were observed in 16 control cows (Elvinger et al, 1992).

11.4 Culling

Concern has been expressed that cows might be metabolically overworked when treated during their lactation with BST. Therefore, life-expectation of the BST treated cows might be reduced. This effect of BST might be visible in an increased percentage of involuntary culling in herds However, the decision to cull dairy cows is complex and affected by many cow and farm factors.

Only limited information is available on culling rates associated with BST treatment. This is because of the above described reason and the fact that culling was prohibited in several of the studies.

PAMP data (1996) showed that more cows had been removed from the BST treated herds than from the control herds. The difference was significant in multiparous cows.

Ruegg et al (1998) focussed in their study on the culling practices of 32 herds. In 19 herds cows were BST treated. During the course of the study, 4 farms discontinued or restricted the use of BST and two control herds commenced BST treatment. These farms were excluded from the study. Culling rate was higher in the BST treated herds than in the control herds, although the difference was not significant. In the BST treated herds, more cows were culled because of mastitis and sickness and less cows were culled for reason of production or death, than in the control herds. A problem with this study was that the control and BST-treated herds appeared to have considerable differences in herd size, milk production levels and age at first calving.

Cole et al (1992) presented a study on health and reproduction of BST-treated dairy cows. No culling was conducted during the study and cows were only removed for scheduled necropsies or unscheduled necropsies when a cow died or was declared moribund. Eight cows had unscheduled deaths, and all these animals were BST treated. The following diagnoses were included, four mastitis cases, two pneumonias, one abomasal displacement and one case of Johnes disease.

Other studies did not reveal a high culling incidence of BST treated animals compared with control animals (Oldenbroek 1990).

11.5 Medicine usage and milk composition

BST increases the frequency of certain disease conditions such as mastitis and foot problems in cows. These conditions are normally treated using veterinary medicines. Hence BST is leading, on average to the increased use of veterinary medicines. This increased use allows more opportunity for the development of resistance to antimicrobials in pathogens on farms. It

may also result in increased residues of antibiotics in milk. These residues could result in further resistance to antimicrobials when the milk is fed to calves or other animals. This topic is the subject of another Scientific Committee report.

11.6 Conclusions

BST usage increases the incidence of several disease conditions and hence is likely to increase the usage of veterinary medicines. Increased antimicrobial usage may lead to resistance to antimicrobials with consequences for the health of humans, cattle and other animals. This topic is the subject of report of another Scientific Committee.

BST treated cows often have a lower than normal body condition at the end of lactation and experience increased "off-feed" periods

The incidence of bloat, indigestion and diarrhoea has been shown to increase in BST-treated cows.

BST lowers the ability to cope with high temperatures which in certain conditions can result in poor welfare.

The Post-Approval Monitoring Program study in the USA reported a higher culling rate in multiparous cows treated with BST.

CHAPTER 12 BST AND WELFARE: RESEARCH METHODOLOGY AND ANALYSIS

12.1 Introduction

The effects on animal welfare of all new biotechnology products used on animals, or biotechnology procedures involving genetic modification of animals, should be properly studied. In 1991 the E.U. Scientific Veterinary Committee pointed out that comprehensive studies of the welfare of cattle treated with BST had not been carried out. Some studies have now been carried out and the conclusions stated in this report have been reached but wide ranging studies of animal welfare are still needed.

A problem with published research on BST is that many studies were made only on animals injected with BST for one or two lactations. The long-term effects of BST usage are not adequately known and there could be exacerbation of the effects discovered so far, or new effects. Other problems with published research are summarised in section 6.4.1

12.2. Interpretation of data linking BST, welfare and milk yield

Poor welfare such as that associated with mastitis, foot or leg problems, some reproductive disorders or other production-related diseases can be caused by high milk yields (see Chapter 3). BST increases milk yield and also thereby increases these problems. The problems in interpretation of BST effects which this raises will now be discussed.

Results of meta-analyses, including those of Willeberg (1993), White et al. (1994), FOI (1996), Monsanto (1996) and Health Canada (1999) show that there is a significant excess risk of mastitis in the BST-treated group over the non-treated group during the treatment period equivalent to 15 - 79%, when the BST effect is estimated across individual studies. Similarly, foot disorders can be doubled and the proportion of cows which fail to conceive increased by 50-70% in BST treated cows. Some or most of these effects might be expected as a consequence of increased milk yield.

White et al. (1994), used logistic regression analysis to examine the effect of BST treatment on the risk of clinical mastitis, while milk yield, parity and study were included as co-variates. There was a significant linear relationship between milk yield and clinical mastitis during treatment, and when the increase in milk production was controlled for, the BST effect

became statistically insignificant. No parameter estimates of the effects, however, were provided. These results were used by White et al. (1994) to argue that the effect of BST on clinical mastitis is due to an indirect causal effect mediated through the increase in milk yield:

BST -----> milk yield increase -----> clinical mastitis increase

This was taken as evidence for no harmful effect of BST as such on the occurrence of clinical mastitis. The argument has also been presented that other milk production enhancing factors, e.g. genetic improvement, will have similar mastitis etc. increasing properties, but such measures are not being similarly investigated and questioned. It has been argued that, if instead of using BST one could genetically increase the milk yield by the same amount, the number of clinical mastitis, foot disorder and reproductive disorder cases would increase similarly without any official concern.

The indirect effect has been quoted by some as the ultimate explanation and the main reason for accepting that the issue of mastitis etc. has been resolved (CVMP 1993). However, the FDA has not accepted this argument and therefore such analysis has not been introduced among the FOI and PAMP analyses or in the Health Canada analyses. The study by White et al. (1994) showed that BST increases milk yield which increases the risk of clinical mastitis. It should be noted, therefore, that the analysis which included milk yield as a co-variate violated the basic epidemiological rule, that an intermediate variable in a causal pathway should never be considered as a confounder and should therefore not be introduced as a co-variate in a multivariate analysis (see e.g. Greenland & Neutra 1980, Weinberg 1993, Joffe & Greenland 1994). Kleinbaum et al. (1982) wrote :” A pure intervening variable (B in: A † B † C) should not be considered as a potential confounder, since its control can spuriously reduce or eliminate any manifestation in the data of a true association between exposure (A) and disease (C)”. The rationale behind this is, that epidemiology has the practical purpose of discovering relations which offer possibilities of disease prevention and for this purpose a causal association may be defined as an association between categories of events or characteristics in which an alteration in the frequency or quality of one category is followed by a change in the other (MacMahon & Pugh 1970). If one wants to make sound epidemiological estimation of the causal effects of an exposure, it is therefore wrong to try to distinguish or separate indirect from direct effects - they both count in estimating the disease promoting effect of exposure to the primary variable in question (BST). Therefore, the combined effect is the best estimate of that caused by introducing BST and similarly of the preventive effect of abolishing BST treatment once it may have been introduced. Accordingly, the total effect of BST is the only meaningful parameter and this effect is unbiasedly estimated only by the risk difference

(attributable risk), which in the study of White et al. (1994) amounts to 8.3 cases of clinical mastitis per 100 BST treated cows, equivalent to 42 % above the risk in non-treated cows.

A proper and critical epidemiological evaluation of the indirect effect argument thus results in the conclusion, that such analysis and the conclusions drawn from it have confused the issue, not resolved it.

Two further, very significant flaws in the argument that increases in mastitis, foot disorders, reproductive problems etc. are acceptable because they are just a consequence of increased milk yield are: (i) that the poorer welfare would not occur in these animals if the BST were not used and (ii) that BST usage often results in such poor welfare, associated with serious mastitis, foot disorders and some reproductive problems, that there is severe and unnecessary pain, suffering and distress. Methods of dairy cow management which have such avoidable effects are not acceptable. The cow which has severe, clinical mastitis suffers, irrespective of whether or not the causal factors are direct or indirect (Willeberg 1994).

The relationships between BST use, milk yield and production related welfare problems such as mastitis, foot disorders and reproductive disorders are as follows. 1. An increase in milk yield leads to a steepening increase in mastitis etc. as the upper end of the range of possible milk yields is approached. 2. BST increases the milk yield and hence causes a small effect on the risk of mastitis etc. in low producing cows but an increasingly large effect on mastitis etc. as the pre BST treatment yield increases high producing cows. 3. Most farmers use BST to make high yielding cows into very high yielding cows. 4. Hence BST causes a substantial increase in the risk of mastitis etc. on most farms and this risk, with associated poor welfare, would not occur if BST were not used.

12.3 Management factors and the use of BST

Quality of management is a major factor determining milk yield response as is the quantity and quality of feed provided. As an example, good management measures recommended by a product manufacturer to ensure a high response in milk yield to BST administration include;

- Cows should not be overcrowded

- Additional ventilation or cooling systems may be needed if not adequate.
- Flooring should be kept clean and provide adequate traction
- Feeding areas should be designed to facilitate feeding
- Adequate water must be provided
- Cows should be protected from the effects of heat in hot weather and adequate shade should be provided.
- High quality feed should be available
- Fly control is imperative.

It is evident that such measures would improve cow welfare. However, use of BST in the absence of such measures would exacerbate welfare problems.

It has been suggested that, if there are adverse effects in cows treated with BST, the farmers are not managing their animals well enough. Hence farmers who do find that their cows have mastitis, foot disorders, reproductive disorders or other problems specified as a potential risk when bovine somatotrophin is used may be reluctant to report the occurrences. Any failure of farmers to report problems would affect the results of follow-up studies after BST use.

12.4 Conclusions

It remains to be discovered whether injection of cows with BST over the long-term, i.e. over a lifetime of lactations, will result in more severe or new effects on welfare than those reported so far.

Where BST increases milk yield and also thereby increases mastitis, foot or leg problems, reproductive disorders or other production-related disease, then BST is causing poor welfare which would not occur if it were not used. The conclusion which should be drawn is that avoidable actions which result in poor welfare, such as BST usage, should not be permitted.

It has been suggested that, if there are adverse effects in cows treated with BST, the farmers are not managing their animals well enough. As a consequence, adverse effects are likely to be under-reported by farmers.

CHAPTER 13 CONCLUSIONS AND RECOMMENDATION

The Conclusions to this report have been grouped into four sections:

- The welfare of high yielding dairy cows.
- The use of BST, the mechanisms of BST action in cows and effects of BST which do not necessarily affect the welfare of cows.
- The scientific quality of conclusions reached in papers which might seem relevant to cow welfare or which are about possible effects on cow welfare that appear not to have been investigated.
- Animal welfare and the effects on welfare of dairy cows when BST is used.

The welfare of high yielding dairy cows.

1. There is already evidence of welfare problems in dairy cows, for instance more than 50 cases of foot disorders and more than 40 cases of mastitis per 100 dairy cows can typically occur in Europe per year. Some of these animals and others in the herd may have reproductive disorders and other production related diseases.
2. There is clear evidence from several countries of significant positive associations between milk yield and mastitis, foot disorders, reproductive disorders and other production related diseases.

The use of BST, the mechanisms of BST action in cows and effects of BST which do not necessarily affect the welfare of cows.

3. Commercially produced BST is very similar in structure to naturally occurring BST. It is recommended by one manufacturer that dairy cows should be given an injection of BST once every 14 days.
4. It has been suggested that, if there are adverse effects in cows treated with BST, the farmers are not managing their animals well enough. As a consequence, adverse effects are likely to be under-reported by farmers.
5. The primary galactopoietic effect of BST in cows appears to be altered nutrient utilisation and mobilisation of non-mammary tissues, sparing nutrients for milk synthesis.

This is achieved by effects on liver and adipose tissue but also by alterations in the responsiveness of other tissues to metabolic hormones.

6. BST increases cardiac output and heart rate and this is associated with an increase in the rate of mammary blood flow. Mammary metabolic activity is increased, involving greater substrate uptake and synthesis of milk-specific components. IGF1 seems to be largely responsible for such effects. In consequence, when BST is used, milk yields increase by about 10%, with compositional changes depending on the cow's energy status, IGF1 increases approximately five fold in cow's milk.
7. Based on the large body of in vitro and in vivo data available concerning the effects of GH and IGF-1 on immune function, it is apparent that GH and IGF-1 are able to stimulate many components of the immune response, and specially phagocytosis. However, these effects are always more marked in hypopituitary than in normal animals, and it is important to note that the enhancement of phagocytosis that is obtained in response to GH and IGF-1 is not apparent in the absence of triggering stimuli for the activation of phagocytosis.
8. It appears that BST extends the period of metabolic stress which normally accompanies the onset of lactation. The cow remains in negative energy balance, utilising food reserves or other tissues, for some weeks after the commencement of BST usage.
9. The consequences of BST, acting as a neuropeptide, on the brain and on behaviour are not known.

The scientific quality of conclusions reached in papers which might seem relevant to cow welfare or which are about possible effects on cow welfare that appear not to have been investigated.

10. It has been stated in certain published papers that BST has no effects on some welfare measures e.g. mastitis, foot disorders, health in general, or welfare in general. However, these are misleading statements because the sample sizes used were too small to justify such conclusions.
11. Questions about the effects of elevated IGF1 levels in the cow on the welfare of the cow, or the welfare of the calf in utero, appear not to have been investigated. Neither have questions about the effects of elevated IGF1 levels in milk on the welfare of calves which drink the milk.

12. It remains to be discovered whether injection of cows with BST over the long-term, i.e., over a lifetime of lactations, will result in more severe effects on welfare than those reported so far, or new effects.

Animal welfare and the effects on welfare of dairy cows when BST is used.

13. Animal welfare can be assessed in a scientific way and indicators of welfare include those of physiological states, behaviour and health. A proper assessment of the effects of BST on the welfare of dairy cows must be based on the whole range of indicators that are available to measure welfare in these animals. As reviewed in the rest of this report some evidence concerning the welfare of cows treated with BST exists but studies using a wide range of welfare indicators have not been carried out.
14. BST usage increases the risk of clinical mastitis above the risk in non-treated cows. The magnitude of this increase has been variously estimated by meta analyses or large scale studies at 15 to 45%, 23%, 25%, 42% and 79%. Clinical mastitis is often a painful disease. The welfare of cows with mastitis is poor, the extent of poor welfare being dependent on the severity of the condition.
15. The duration of treatment for mastitis in BST treated cows was longer than in non BST treated cows.
16. An increased incidence of foot and leg disorders associated with the long term administration of BST has been described by several authors. In the largest scale study, the number of multiparous cows with foot disorders was increased by a factor of 2.2 and the number of days affected was increased by a factor of 2.1.
17. As a consequence of the nature of the different foot and leg disorders there will be pain and other suffering in these animals. Hence welfare will be seriously and adversely affected as a consequence of the BST treatment.
18. Injection site reactions occur in most cows injected with BST, but not with placebo, and are exacerbated by repeated injections. Studies have shown severe reactions in at least 4% of cows. The pain associated with this problem has not been adequately assessed.
19. There is evidence that BST treatment can adversely affect reproduction. Pregnancy rate dropped from 82 to 73% in multiparous cows and from 90-63% in primiparous cows,

gestation length was shortened by 2-4 days and the number of days open increased in primiparous cows. The effects do not carry over after cessation of treatment. The frequency of multiple births which can cause welfare problems, was substantially increased by BST. Failure to conceive is an indicator of poor welfare and multiple births lead to poor welfare.

20. The immuno-stimulatory effects of BST observed experimentally have not been confirmed clinically.
21. Very preliminary results indicate that GH might enhance the production of pathogenic agents that develop intracellularly, such as viruses. However, the importance of this effect for BST treatment and its functional consequences in vivo remain largely unknown.
22. BST treated cows often have a lower than normal body condition at the end of lactation and experience increased "off-feed" periods
23. The incidence of bloat, indigestion and diarrhoea has been shown to increase in BST-treated cows.
24. BST lowers the ability to cope with high temperatures which in certain conditions can result in poor welfare.
25. The Post-Approval Monitoring Program study in the USA reported a higher culling rate in multiparous cows treated with BST.
26. BST usage increases the incidence of several disease conditions and hence is likely to increase the usage of veterinary medicines. Increased antimicrobial usage may lead to resistance to antimicrobials with consequences for the health of humans, cattle and other animals. This topic is the subject of a report of another Scientific Committee.

General conclusion

BST is used to increase milk yield, often in already high-producing cows. BST administration causes substantially and very significantly poorer welfare because of increased foot disorders, mastitis, reproductive disorders and other production related diseases. These are problems which would not occur if BST were not used and often results in unnecessary pain, suffering and distress. If milk yields were achieved by other means which resulted in the health disorders and other welfare problems described above, these means would not be acceptable. The injection of BST and its repetition every 14 days also causes localised swellings which are likely to result in discomfort and hence some poor welfare

Recommendation

BST use causes a substantial increase in levels of foot problems and mastitis and leads to injection site reactions in dairy cows. These conditions, especially the first two, are painful and debilitating, leading to significantly poorer welfare in the treated animals. Therefore from the point of view of animal welfare, including health, the Scientific Committee on Animal Health and Animal Welfare is of the opinion that BST should not be used in dairy cows.

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Acknowledgements

This report of the Scientific Committee on Animal Health and Animal Welfare is substantially based on the work of a working group of the Committee.

The working group was chaired by Prof. D. Broom. The members of the group were as follows; Prof. D. Broom, Dr. R. Dantzer, Prof. P. Willeberg, Prof. B. Mephram, Prof. E Noordhuizen-Stassen.