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HGP Literature Review

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Abstract

A review of the literature relevant to public health issues associated with the use of hormonal growth promotants (HGPs) in cattle was undertaken, particularly considering previous reviews and new research findings published in the last few years.

Overall, the balance of international opinion is that there is no increase in the risk of adverse health risks associated with consumption of meat from animals treated with HGPs according to good agricultural practice. Although oestradiol-17beta, in particular, is recognised as potentially carcinogenic, these affects are associated with its hormonal action and the doses present in meat from HGP treated cattle are insufficient to exert any tumorigenic effect. In addition, hormone levels in beef from treated cattle are well below levels in other common dietary constituents and from endogenous production. Oral bio-availability of these hormones is also low.

The above views are not supported by the European Union, which has expressed the view that any increase in dietary hormone levels associated with consumption of HGP-treated meat poses an unacceptable (but unquantified) increase in risk of adverse health consequences such as cancer.

HGPs have been through a rigorous evaluation and registration process and are registered for use in cattle in many countries. In these countries they provide a substantial benefit in terms of cost and efficiency of production. Although some recent research has raised concerns about an apparent association between diets high in red meat (and speculated on the possible role of HGPs) and adverse health consequences, the evidence for HGP involvement is not strong and there is currently no need for changes in MLA or industry support for the continued use of HGPs in beef production.

Executive Summary

Hormonal Growth Promotants (HGPs) are slow-release implants that contain one or more of a group of steroidal sex hormones or their synthetic analogues and which are used for increasing growth rates and feed conversion efficiency in cattle. Although HGPs are widely used throughout Australia and many other countries, their use has been banned in the European Union (EU) and for all animals or animal products imported into the EU since 1988. This ban has been supported by arguments that HGPs pose a risk to human health through increased exposure to bio-active hormone residues in the meat and offal of treated animals, posing a potential increase in the risk of cancer and mutagenic effects. Despite the EU position, many countries continue to use HGPs, particularly Australia and North America, supported by a number of reviews and scientific committees that have found no evidence to support increased health risks associated with hormone residues in meat.

Based on information from these reviews and committees, MLA has supported the responsible use of HGPs in the Australian beef industry. However, the continuing EU ban and several recent research papers suggesting a link between red meat consumption and adverse health outcomes has prompted MLA to commission this literature review to ensure that its position is based on the latest scientific information.

HGPs are currently used in most major beef-producing countries in the world, with the notable exception of the European Union, Brazil and Argentina. In Australia, about 6.1 million doses were sold in 2006, with sales increasing progressively over the last 5-10 years. Assuming that about 50% of animals were implanted twice, these figures correspond to about 4 million head implanted, or up to 50% of the national beef kill. In addition, given that HGPs are primarily used in young animals and not in culled cows or bulls, the proportion of steers and heifers slaughtered with implants would be much higher. Although reliable statistics on enterprise type are not publicly available, the great majority of doses sold are used in feedlots.

HGPs provide significant improvements in growth rate and feed conversion efficiency in treated animals compared to untreated animals, resulting in improved efficiency and profitability for enterprises which use them. Although there are also a number of other products that can be used to improve growth rates and feed conversion efficiency, these effects are additive with HGPs, rather than an alternative. Therefore, HGPs provide a significant benefit to the industry and their loss would result in reduced efficiency and profitability for the industry, with no alternative technologies currently available to replace them.

Public health concerns over the use of HGPs have been debated for many years. Diethyl stilboestrol (DES) was first used as a hormonal growth promotant as early as the 1950's, but its use was discontinued in the USA in 1979 and in the EU in 1987 following concerns about the carcinogenic potential of residues in meat. Subsequently, the EU also placed a ban on the use of all HGPs in food producing animals in 1988, with the EU also requiring that all animals or animal products imported into the EU be similarly free of HGPs. This ban was introduced by the EU on the basis of potential adverse impacts of hormone residues in meat from HGP-treated cattle on human health. This stance has been supported by several risk analyses and reviews undertaken by the EU since the ban was initially introduced.

In summary, the EU position appears to be as follows:

- Oestradiol-17beta, in particular, is carcinogenic and is carcinogenic;
- Zeranol and Trenbolone acetate may also have weak carcinogenic effects;
- There is still insufficient data to be confident that the other hormones used are not carcinogenic;
- Bioavailability and activity of some products (particularly synthetic hormones) is uncertain but may be higher than previously assumed;
- Activity of these hormones in prepubertal children is still not well understood;
- Residue levels in meat may be considerably higher than represented due to misuse of implants (multiple implantations and/or inappropriate locations), so that dietary exposure is significantly higher than assumed; and
- Because of the above, any increase in human exposure to these compounds above natural levels poses a potential increase in the risk of adverse effects to human health and is therefore unacceptable.

Conversely, numerous other reviews and evaluations of safety and public health risks associated with HGP usage have been undertaken since the mid 1990s with consistently favourable results (in distinct contrast to the EU position). These reviews include reviews by the Joint FAO/WHO Expert Committee on Food Additives, the Veterinary Products Committee of the Department for Environment, Food and Rural Affairs (UK), the Committee for Veterinary Medicinal Products for the European Medicines Agency and the Chemical Review and International Harmonisation Section, Office of Chemical Safety, Therapeutic Goods Administration of the Australian Department of Health and Aging. They have also passed rigorous safety and efficacy evaluations by national registering authorities such as the US Food and Drug Administration and the Australian Pesticides and Veterinary Medicines Authority.

The consensus of these reviews and agencies is that:

- hormone levels in meat from treated animals are higher than in meat from untreated animals, but are still well within physiological limits for normal cattle (and well below MRLs for synthetic products);
- meat from HGP-treated animals contributes a relatively small proportion of total dietary intake of these compounds and levels in meat are well below endogenous daily production;
- although oestrogenic compounds may be carcinogenic, these effects appear to be related to hormonal activity and the levels present in diet are unlikely to result in any increase in risk to consumers;
- there is no clear evidence for adverse health effects associated with consumption of meat from HGP treated animals; and
- HGPs, when used according to good agricultural practice pose no additional health risk to consumers.

Overall, the balance of international opinion is that there is no increase in the risk of adverse health risks associated with consumption of meat from animals treated with HGPs according to good agricultural practice. Although oestradiol-17beta, in particular, is recognised as potentially carcinogenic, these affects are associated with its hormonal action and the doses present in meat from HGP treated cattle are insufficient to exert any tumorigenic effect. In addition, hormone levels in

beef from treated cattle are well below levels in other common dietary constituents and from endogenous production. Oral bio-availability of these hormones is also low.

The above views are not supported by the European Union, which has expressed the view that any increase in dietary hormone levels associated with consumption of HGP-treated meat poses an unacceptable (but unquantified) increase in risk of adverse health consequences such as cancer.

HGPs have been through a rigorous evaluation and registration process and are registered for use in cattle in many countries. In these countries they provide a substantial benefit in terms of cost and efficiency of production. Although some recent research has raised concerns about an apparent association between diets high in red meat (and speculated on the possible role of HGPs) and adverse health consequences, the evidence for HGP involvement is not strong and there is currently no need for changes in MLA or industry support for the continued use of HGPs in beef production.

Contents

1 Background

Hormonal Growth Promotants (HGPs) are a group of veterinary drugs that contain one or more of a group of steroidal sex hormones or their synthetic analogues and which are used for increasing growth rates and feed conversion efficiency in cattle. HGPs are delivered as slow-release implants, implanted beneath the skin on the back of the ear, so that they continuously release low doses of the hormones over a prolonged period.

Although HGPs are widely used throughout Australia and many other countries, their use has been banned in the European Union (EU) since 1988. Since that time, all beef and beef products exported to the EU must come from cattle that have not been treated with HGPs at any stage of their lives. This ban has been supported by arguments that HGPs pose a risk to human health through increased exposure to bio-active hormone residues in the meat and offal of treated animals, posing a potential increase in the risk of cancer and mutagenic effects. These assertions by the EU have been supported by a risk assessment undertaken in 1999 (SCVPH, 1999), and were re-iterated following subsequent reviews to consider dissenting reports and new research findings in 2000 and 2002 (SCVPH, 2000; SCVPH, 2002).

Despite the EU position, many countries continue to use HGPs, particularly Australia and North America, supported by a number of reviews and scientific committees that have found no evidence to support increased health risks associated with hormone residues in meat.

Based on information from these reviews and committees, MLA has supported the responsible use of HGPs in the Australian beef industry. However, the continuing EU ban and several recent research papers suggesting a link between red meat consumption and adverse health outcomes has prompted MLA to commission this literature review to ensure that its position is based on the latest scientific information.

2 Project Objectives

The purpose of this project was to conduct a review of current HGP usage in Australia and the world and provide MLA with the information for use in preparing background briefings, brochures and other publications.

Specifically, the objectives of the literature review were to collect information on:

- Links between HGP usage and food safety (illustrations and up-to-date facts are most important);
- Public health impacts;
- Current status of HGP usage in Australia and the world in general; and
- Pros and cons of HGP usage for the industry.

3 Methodology

This project was undertaken as a review of the relevant literature. Documents for inclusion in the review were identified in several different ways in order to try and get a comprehensive coverage of the topic. Information sources used included:

- Searching of the medical and life sciences literature using the PubMed search engine with various combinations of 'hormones', 'meat', 'estradiol' and 'beef' as keywords. Titles and abstracts were then scanned to identify publications relevant to this review.
- Similar searches of the broader internet using the same keywords in the Google® and Scirus® search engines to identify more general information and relevant documents and reports.
- Searches of specific websites for relevant reports and information, including Food and Agricultural Organisation of the United Nations, US Food and Drug Administration, UK Veterinary Products Committee, the European Commission, Australian Pesticides and Veterinary Medicines Authority and others.
- Discussions with, and information provided by, Animal Health Alliance (Australia) and representatives of member pharmaceutical companies who distribute HGPs in Australia.

4 Results and Discussion

4.1 Role and usage of HGPs

HGPs are a group of products containing natural or synthetic hormones which are used to improve growth rates and feed conversion efficiency in cattle. The active components are supplied in a slow-release implant which is implanted in the back of the ear, where it can be easily identified and removed at slaughter. Active ingredients include the naturally occurring hormones Oestradiol-17beta, progesterone and testosterone and the synthetic oestrogenic analogues Zeranol and Trenbolone acetate. These hormones are used either singly or in various combinations depending on the target age and sex of animals for the particular product.

HGPs are veterinary medicines and require registration through the Australian Pesticides and Veterinary Medicines Authority (APVMA). They are also subject to a strictly audited control program to ensure their correct use and that all treated animals are clearly identified and excluded from the European market, where the use of HGPs is banned. There are currently 18 different HGP preparations registered for use in Australia under five different brand names (Ralgro, Compudose, Progro, Revalor and Synovex), as listed in Table 1.

Table 1: Hormonal growth promotants registered in Australia

Product Name	Actives
Coopers Ralgro Cattle Growth Promoter	Zeranol
Elanco AH 0323 Oestradiol Compudose 200	Oestradiol 17 Beta
Elanco AH 0343 Oestradiol Compudose 400	Oestradiol 17 Beta
Elanco AH 0351 Oestradiol Compudose 100	Oestradiol 17 Beta
Elanco AH 0359 Compudose-G Growth And Finishing Implants For Steers And Heifers	Oestradiol / Trenbolone Acetate
Progro H Growth And Finishing Implants For Heifers	Oestradiol Benzoate / Testosterone Propionate
Progro S Growth And Finishing Implants For Steers	Oestradiol Benzoate / Progesterone
Progro Te-S Growth And Finishing Implants For Steers	Oestradiol / Trenbolone Acetate
Progro T-S Growth And Finishing Implants For Steers	Trenbolone Acetate
Progro Te-H Growth And Finishing Implants For Heifers	Oestradiol / Trenbolone Acetate
Revalor-S Steer Growth Promotant And Finishing Implants	Oestradiol 17 Beta / Trenbolone Acetate
Revalor-H Growth Promotant And Finishing Implants	Oestradiol 17 Beta / Trenbolone Acetate
Revalor-G Growth Promotant For Grass Fed Heifers And Steers	Oestradiol 17 Beta / Trenbolone Acetate
Revalor -I Growth Promotant For Non Breeding Cattle	Oestradiol 17 Beta / Trenbolone Acetate
Synovex With Trenbolone Acetate Growth And Finishing Implants For Steers And Heifers	Oestradiol Benzoate / Trenbolone Acetate
Synovex C Calf Growth Promotant	Oestradiol Benzoate / Progesterone
Synovex H Heifer Growth And Finishing Implants	Oestradiol Benzoate / Testosterone Propionate
Synovex S Steer Growth And Finishing Implants	Oestradiol Benzoate / Progesterone

4.1.1 Why use HGPs?

The hormones used in HGPs have an androgenic effect in implanted animals, resulting in more rapid growth and improved feed conversion efficiency in implanted animals. Actual improvements in weight gain and feed conversion vary depending on many factors, but improvements of 10% to 30% in average daily weight gain, 5% - 15% in feed conversion efficiency and 5% - 8% in carcase leanness can be achieved (reviewed by Preston RL, 1999). This translates into a return of between USD 20 and USD 75 over and above the cost of implantation (Preston RL, 1999). Under Australian conditions, product literature suggests an economic advantage of between $11.50 and $80 across a number of trials for Compudose® in heifers. An economic advantage of $34 for Compudose® over 400 days and $43 for Revalor® over 90 days, were claimed for steers (Compudose® and Revalor® product literature).

4.1.2 Alternatives to HGPs

A range of alternative products, including ionophores (such as monensin, narisin, salinomycin, lasalocid and bambermycin) and digestive enzymes (amylase and others), do provide some improvements in both growth rates and feed conversion. However, these products have different mechanisms of action to HGPs and as a result their effects tend to be additive (see for example Goodrich RD et al., 1984; Potter EL et al., 1986), rather than as an alternative to HGPs. They are also more limited in use, because they are all (except Rumensin® ant-bloat capsules) provided as feed supplements rather than as animal treatments.

Melangestrol acetate (MGA) is an alternative hormonal growth promotant that is used in North America, but is not currently registered in Australia. MGA is used as a feed additive rather than an implant. Because MGA is hormonal in action, it is subject to the same restrictions as implantable products in the EU but is more difficult to control usage and clearly identify treated animals at slaughter. Therefore, MGA does not provide an alternative to current HGP products and is unlikely to be registered in Australia.

Therefore, at present there are no real alternatives to HGPs that provide the same benefits and practicality to industry.

4.1.3 HGP Usage in Australia and internationally

HGPs are used extensively in most major beef-producing countries in the world, with the notable exception of Europe. Effectively, HGPs have been registered for use in virtually every country where registration has been sought, with the exception of the European Union, Brazil and Argentina. Products are currently registered in Australia, New Zealand, USA, Canada, Mexico, South America (except Argentina and Brazil), South Africa, Japan and possibly others. One reviewer suggested that one or more HGP products were approved in as many as 30 countries internationally (Preston RL, 1999).

In Australia, about 6.1 million doses were sold in 2006, with sales increasing progressively over the last 5-10 years (based on industry figures). As many cattle may receive more than one implant during a year, these figures cannot be related directly to the number of animals implanted. Assuming that about 50% of animals were implanted twice, these figures correspond to about 4 million head implanted, or up to 50% of the national beef kill (about $8 million head in 2006 – ABS, 2007). In addition, given that HGPs are primarily used in young animals and not in culled cows or bulls, the proportion of steers and heifers slaughtered with implants would be much higher.

Usage of HGPs is strictly controlled in Australia. Users must be registered in order to purchase implants and must keep records to account for usage of all implants purchased. In addition, the HGP status of all cattle sold must be declared on a National Vendor Declaration and the cattle must be appropriately identified by coloured tags. Severe penalties are in place for misrepresenting HGP-treated cattle as being untreated.

Because HGPs are used primarily for improved growth rates in young cattle, the main market for their use in Australia is in feedlots. Usage is also tightly controlled to ensure that the EU markets for untreated cattle are protected. Reliable statistics on usage according to enterprise type are not available.

4.2 HGPs and public health

Public health concerns over the use of HGPs have been debated for many years. Diethyl stilboestrol (DES) was first used as a hormonal growth promotant as early as the 1950's, but its use was discontinued in the USA in 1979 and in the EU in 1987 following concerns about the carcinogenic potential of residues in meat (VPC, 2006; Swan SH et al., 2007). Subsequently, the EU also placed a ban on the use of all HGPs in food producing animals in 1988, with the EU also requiring that all animals or animal products imported into the EU be similarly free of HGPs. This ban was introduced by the EU on the basis of potential adverse impacts of hormone residues in meat from HGP-treated cattle on human health. This stance has been supported by several risk analyses and reviews undertaken by the EU since the ban was initially introduced.

Despite the EU stance, HGPs remain registered for use in many countries, based on the conclusion by registering authorities that any residues in meat from proper use of HGPs are insufficient to adversely affect human health. Again, these positions have been supported by numerous reviews and analyses.

The following sections summarise the opposing points of view on the human health risks associated with HGP residues in meat.

4.2.1 The case against HGPs (the EU perspective)

The initial EU ban on use of HGPs and on HGPs in imported meat or products was challenged as a non-tariff trade barrier by the USA and Canada in the World Trade Organisation. This challenge was upheld, on the basis that the EU had not undertaken a risk analysis to justify their position. As a result the EU was required to pay countervailing duties to the USA and Canada in compensation for lost trade. Following this decision, the EU then commissioned an "*Assessment of the potential risks to human health from hormone residues in bovine meat and meat products*" (SCVPH, 1999), as well as 17 additional research projects aimed at resolving identified knowledge gaps following the WTO ruling (SCVPH, 2002).

The 1999 risk assessment undertaken by the EU's Scientific Committee on Veterinary Measures relating to Public Health (SCVPH, 1999) considered six specific hormonal products used as growth promotants in cattle. These products were the natural hormones oestradiol-17beta, testosterone and progesterone; and the synthetic analogues zeranol, trenbolone acetate and melengestrol acetate. The major conclusions of the report were:

- *In consideration of the recent concerns relating to the lack of understanding of critical developmental periods in human life as well as the uncertainties in the estimates of endogenous hormone production rates and metabolic clearance capacity, particularly in prepubertal children, no threshold level and therefore no ADI can be established for any of the 6 hormones.*

- *As concerns excess intake of hormone residues and their metabolites, and in view of the intrinsic properties of hormones and epidemiological findings, a risk to the consumer has been identified with different levels of conclusive evidence for the 6 hormones in question.*

- *In the case of 17 β oestradiol there is a substantial body of recent evidence suggesting that it has to be considered as a complete carcinogen, as it exerts both tumour initiating and tumour promoting effects. The data available does not allow a quantitative estimate of the risk.*

- *For the other 5 hormones, in spite of the individual toxicological and epidemiological data described in the report, the current state of knowledge does not allow a quantitative estimate of the risk.*

- *For all six hormones endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects could be envisaged. Of the various susceptible risk groups, prepubertal children is the group of greatest concern. Again the available data do not enable a quantitative estimate of the risk.*

- *In view of the intrinsic properties of the hormones and in consideration of epidemiological findings, no threshold levels can be defined for any of the 6 substances.*

Another review (perhaps related to the EU assessment), also published in 1999, also reached the conclusion that "*possible adverse effects on human health cannot be excluded*" (Andersson AM and Skakkebaek NE, 1999).

The EU reconfirmed their position in 2000 in response to dissenting responses to their 1999 assessment by the Veterinary Products Committee (VPC) of the UK Department for Environment, Food and Rural Affairs and the Committee for Veterinary Medicinal Products (CVMP) of the European Medicines Agency (VPC, 1999; CVMP, 1999; SCVPH, 2000). They concluded that these reviews did not provide convincing arguments requiring revision of their previous conclusions. They also made the point that, "*if endogenous levels of hormones are associated with life-time risk of disease, for example, human breast cancer, then continuous additional exposure, even at low doses, is likely to add to this risk, but, as yet, cannot be quantified.*"

Finally, in 2002, the EU issued a review of their previous opinions, taking into consideration the findings of the 17 research projects previously commissioned and any other new research findings (SCVPH, 2002). Based on their considerations of the new research findings, the SCVPH reaffirmed their previous opinions and stated that no amendments to those opinions were justified. In this opinion, they also noted that convincing data have now been published confirming the mutagenic and genotoxic potential of oestradiol-17beta. They also noted a dose-dependent increase in residue levels and high residues at the implant site, so that misplaced or multiple implants could result in a "*considerable risk that highly contaminated meat could enter the food chain*".

In summary, the EU position appears to be as follows:

- Oestradiol-17beta, in particular, is carcinogenic and is capable of causing mutagenic (can induce mutations) and genotoxic (damages DNA, potentially leading to mutations or cancer) effects;

- Zeranol and Trenbolone acetate may also have weak mutagenic or genotoxic effects;
- There is still insufficient data to be confident that the other hormones used are not mutagenic or genotoxic;
- Bioavailability and activity of some products (particularly synthetic hormones) is uncertain but may be higher than previously assumed;
- Activity of these hormones in prepubertal children is still not well understood;
- Residue levels in meat may be considerably higher than represented due to misuse of implants (multiple implantations and/or inappropriate locations), so that dietary exposure is significantly higher than assumed; and
- Because of the above, any increase in human exposure to these compounds above natural levels poses a potential increase in the risk of adverse effects to human health and is therefore unacceptable.

4.2.2 The case for HGPs

In addition to the EU reviews, numerous other reviews and evaluations of safety and public health risks associated with HGP usage have been undertaken since the mid 1990s with consistently favourable results (in distinct contrast to the EU position). These reviews include:

1. JECFA Review

The Joint FAO/WHO Expert Committee on Food Additives "*is an international scientific expert committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO)*". It has a role in the evaluation of the safety of additives, contaminants, naturally occurring toxicants and residues of veterinary drugs in food and the determination of Acceptable Daily Intake levels (ADIs). In 1999, JECFA considered estradiol, progesterone and testosterone and concluded that setting of ADI and acceptable residue levels were unnecessary, as the hormones were produced endogenously at variable levels in human beings. They also concluded that "*residues from use in accordance with good animal husbandry practice* [are] *unlikely to pose a hazard to human health*" (JECFA, 2000). JECFA previously also evaluated zeranol and trenbolone acetate and established ADIs and Acceptable Residue Levels for these compounds, which they concluded would not be exceeded in meat from animals treated according to good husbandry practice (JECFA, 2001b; JECFA, 2001a). JECFA also noted that:

- although hormone levels found in treated animals were generally higher than levels in untreated controls, they were within the normal physiological range for these hormones in cattle; and
- the oral bio-availability of dietary hormones was generally low.

2. Veterinary Products Committee

The Veterinary Products Committee (VPC) of the UK Department for Environment, Food and Rural Affairs reviewed the public health implications of HGP usage in 1999 and again in 2006, both times in response to the EU risk assessments of 1999 and 2002. On both occasions VPC undertook a critical evaluation of the scientific reasoning and methods of argument in the key sources cited by the SCVPH and *were unable to support the conclusion reached by the SCVPH that the risks associated with the consumption of meat from hormone-treated cattle may be higher than previously thought* (VPC, 1999; VPC, 2006). The VPC also:

- Noted that hormone concentrations in meat from treated animals were low compared to endogenous production and other food sources, so that any increase in exposure from consumption of treated meat was likely to be small;
- Noted that under normal usage oestradiol-17beta doesn't pose any risk to human health unless an active implant site is ingested;
- Noted that there are still many knowledge gaps that have not been adequately addressed (and should be); and
- Expressed some concerns about the scientific reasoning in a number of areas of the SCVPH evaluation. The main areas of concern were that the VPC:
    - *concluded that none of the publications reviewed in the Opinion provide any substantive evidence that Oestradiol is **mutagenic/genotoxic** at relevant levels of exposure from residues in meat. For the other five compounds there is no substantive evidence for mutagenic/genotoxic activity;*
    - *had concerns about the validity and selective application of **a key analytical approach cited in the Opinion**, which was based on an assay for apparent oestrogenic activity done in genetically engineered yeast. The concerns were sufficient to throw doubt upon the values derived from this analytical technique and therefore also on the conclusions of the Opinion;*
    - *found that much of the information cited on **'immunity'** and hormonally active substances comes from experiments and clinical observations in man and animals of uncertain significance; that it relied in part on unproven hypotheses, old studies or experiments, now superceded; and that questions of species specific effects and dose or exposure were largely ignored. References cited by the report as evidence of the role of sex hormones do not reflect modern physiological understanding of the immune system. Furthermore, the additional exposure to sex hormone activity represented by the residues of the 6 compounds in meat would be far below the level at which any relevant activity on the immune system and its functions has been demonstrated;*
    - *found the SCVPH mentioned a possible link between certain common **cancers** and hormonally active residues in meat. The Group found the epidemiological evidence shows a link between overall meat and fat consumption and the occurrence of these neoplasms, but a link with small traces of hormones has not been directly examined. However, the tumours are found both in men and women, and they occur widely in countries where hormonal growth promoters are not permitted;*

- *found that the SCVPH suggests that many aspects of **human development and reproduction** could be affected by hormone residues in meat. The Group found that there is no evidence for such effects. The publications cited in the report to support this suggestion did not investigate low level residues, but instead studied the actions of high levels of exogenous hormones injected into animals. Contrary to current experience, the report suggests that there are no thresholds for developmental effects, but does not give any evidence. Epidemiological studies of human exposure that do not show an effect of exogenous hormones on the outcome of pregnancy are ignored in the report. The significance of endocrine disruption for human reproduction and development is still being intensely researched, but the available data do not support the particular suspicions raised in the report, which are based on an incomplete review of the information.*

3. Committee for Veterinary Medicinal Products

The Committee for Veterinary Medicinal Products (CVMP), a committee of the European Medicines Agency, also reviewed usage of oestradiol-17beta and progesterone, in particular considering the findings of the 1999 SCVPH review (CVMP, 1999). CVMP concluded that any carcinogenic effect of these hormones was receptor mediated in endocrine-responsive tissues, rather than being due to direct genotoxic effects. They also concluded that substantial exogenous exposure would be required before carcinogenic effects would be detectable in humans and hence the contribution to exposure from meat residues of the hormones was negligible.

4. Commonwealth Department of Health and Ageing

The Australian Commonwealth Department of Health and Ageing undertook a review of HGP safety in 2003 (Anonymous, 2003), following the SCVPH review in 2002. This review considered 42 published papers covering a wide range of relevant issues, including several review articles. They concluded that *there is unlikely to be any appreciable health risk to consumers from eating meat from cattle treated with HGPs according to good veterinary practice*. They also noted that: *to adequately determine the incremental risk associated with very low levels of HGP residues in meat, the total dietary intake of hormones from all sources would need to be evaluated.*

5. Food Research Institute

The Food Research Institute of the University of Wisconsin also published a brief review on human safety of HGPs in 2000 (Doyle, 2000). Key conclusions from this review included:

- Other (non-hormonal) dietary constituents (for example: fat, fibre or caloric content), as well as age, sex, exercise and reproductive status can all substantially influence circulating hormone levels (as well as health outcomes);
- Oestradiol has a low bioavailability (<12%) when administered orally;
- There is some disagreement among scientists regarding the genotoxic potential of oestradiol under normal physiologic conditions;

- Carcinogenocity of oestradiol and testosterone is related to their hormonal activity and at low levels (where no physiological effects are apparent) do not promote tumour growth.
- Hormone levels in HGP-treated cattle are significantly higher than in untreated contemporaries, but the differences are small and well below recommended limits; and
- Meat and fish provide only 15-20% of dietary oestrogens.

6. Regulatory approval authorities

In addition to the above reviews, HGPs must be approved for use in any country wishing to make use of them. To achieve this, the manufacturer must satisfy the appropriate regulatory authority as to their safety and efficacy. These approval processes are usually quite stringent and products will not be approved if there is any doubt as to their safety. For example, the relevant authority in Australia is the Australian Pesticides and Veterinary Medicines Authority (APVMA), and for any new product to be registered APVMA must be satisfied that when the product is used according to the label directions it will not result in any appreciable risk to:

- consumers;
- other persons handling, applying or administering the chemical;
- the environment;
- target crops or animals; or
- trade in any agricultural commodity (APVMA, 2004).

The US Food and Drug Administration (FDA) has a similar requirement, and noted in a fact sheet on HGPs that (USFDA, 2002):

- "*Consumers are not at risk from eating food from animals treated with these compounds because the amount of added hormone is negligible compared to the amount normally found in the edible tissues of untreated animals and that are naturally produced by the consumer's own body*", relating to natural hormones; and
- "*FDA required that the manufacturers demonstrate that the amount of hormone left in each edible tissue after treatment is below the appropriate safe level*", for synthetic hormones.

Summary of the case for continued use of HGPs

In summary, the various reviews and analyses undertaken (other than the EU reviews) have concluded that:

- hormone levels in meat from treated animals are higher than in meat from untreated animals, but are still well within physiological limits for normal cattle (and well below MRLs for synthetic products);
- meat from HGP-treated animals contributes a relatively small proportion of total dietary intake of these compounds and is well below endogenous daily production;
- although oestrogenic compounds may be carcinogenic, these effects appear to be related to hormonal activity and that the levels present in diet are unlikely to result in any increase in risk to consumers;
- there is no clear evidence for adverse health effects associated with consumption of meat from HGP treated animals; and

- HGPs, when used according to good agricultural practice pose no additional health risk to consumers.

To highlight the differences in hormone levels of treated and untreated beef, other dietary components and natural endogenous hormone production, the National Cattlemen's Association produced the following tables (National Cattlemen's Beef Association, 2006):

Comparison of Oestrogen content of 90-gram servings of common food items	*Oestrogen content (nanograms)*
beef from a steer treated with growth promotants	1.9
beef from a steer raised without growth promotants	1.3
Soybean oil	168,000,000
Milk	11
Potatoes	225
Peas	340
Ice cream	520
Wheat germ	3,400

Normal oestrogen production in humans	*Daily Oestrogen production (nanograms)*
Non-pregnant woman	480,000
Pregnant woman	3,415,000
Man	136,000
Male child (before puberty)	41,500
Female child (before puberty)	54,000

4.2.3 More recent research

The reviews discussed above have considered all of the relevant research up until about 2002. Since then, there have been a small number of additional studies that are relevant to public health considerations of HGP usage.

There have been a number of *in vitro* studies into the role of oestrogenic compounds in human breast tissue, including both normal and cancerous cells. Most of these studies looked at biochemical and or genomic effects of these compounds. In particular, one study (Liu S and Lin YC, 2004) demonstrated that repeated exposure to oestradiol or Zeranol was capable of inducing neoplastic transformation in normal breast tissue. These findings support previous findings discussed in earlier reviews that oestradiol and other oestrogenic compounds are potentially carcinogenic. However, these findings do not provide a direct link between HGPs and human cancer

cases, particularly given the low residue level in meat from treated animals and the wide variety of other sources of these and related chemicals both in the body and exogenously.

A second paper (Cho E et al., 2006), speculates on the possible role of HGPs in increasing the risk of human breast cancer, but provides no substantive evidence to support the speculation, other than an apparent association between red meat consumption and incidence of beast cancer. These researchers reported the findings of a longitudinal study looking at the association between red meat intake and breast cancer risk. They found that women with a high (> 5 servings per week) red meat intake were at greater risk of a particular type of breast cancer (ER+/PR+) than were those with a low intake (≤ 3 servings per week). Cancer incidence was low (about 1% of 90,000 women overall, with about half of these, or 0.5% overall being ER+/PR+) and relative risks were also low, varying from 1.2 to 2.0, depending on intake level. Interestingly, when red meat intake was examined in more detail, relative risks for pork as a main meal, hot dogs (1.4-1.8) and hamburgers (1.4-1.7) were all higher than for beef/lamb as a main meal (1.1-1.3), suggesting that factors other than HGPs are likely to be involved. The study also focused primarily on red meat intake and did not consider other dietary components or life-style factors such as exercise and physical activity. In summary, while this paper does demonstrate some association between red meat intake and ER+/PR+ breast cancer, relative risks were quite low and there was no evidence to support a role for HGPs in the increased risk.

A third paper has also considered the potential health risks associated with red meat intake and speculated about the potential role of HGPs (Swan SH et al., 2007). This research investigated the association between semen quality in fertile US males and red meat intake by their mothers during pregnancy. They found that semen concentration was inversely related to the mother's beef consumption (meals/week). Sons of high beef consumers were also more likely to have a previous history of sub-fertility. In fact all of the men involved were fertile partners of pregnant women, so although sperm concentration was reduced they were not infertile. As with the previous study, there was no clear evidence for involvement of HGPs in this study, although the authors did speculate on this possibility. There was also a clear potential for recall bias in this study, as the questionnaire was administered to the mother by the son, and asked her to recall (quite specific) dietary habits from many years previously. This approach also allows opportunity for important confounders and other risk factors to be present and not accounted for. For example, many of these men would have been born at a time when diethylstilboestrol (now well recognized for its detrimental effects on male and female reproductive systems) was still widely used.

In summary, these papers have heightened awareness about possible adverse health effects of consuming HGP treated meat, without providing any strong evidence to support their speculations.

4.3 Pros and Cons of HGP usage for the beef industry

HGPs provide an important benefit for the beef industry, particularly for the feedlot sector. They provide significant increases in weight gain and feed conversion efficiency for treated cattle compared to untreated cattle, resulting in reduced feed consumption for cattle to achieve target weights and hence increased profitability for producers. Currently, although there are other products available which provide some improvements in growth rates and feed conversion, these effects are additive to HGPs and they cannot be seen as an alternative to HGPs. The importance of HGPs to

the beef industry is highlighted by the high (and increasing) level of usage in Australia, with about 6 million doses sold in 2006, compared to about 8 million cattle slaughtered.

The main negative concerns for HGP usage in the beef industry are:

- that cattle treated at any time in their life are not eligible for the EU market;
- the potential for consumer concern about public health impacts if there is a perceived (or demonstrated) increase in risk of adverse health effects for consumers of HGP treated meat; and
- potential for public concern about increased hormone levels in the environment from effluent from treated cattle (Soto AM et al., 2004). This study found elevated levels of androgens and oestrogens in water downstream from a feedlot, compared to unexposed sites. However, the environmental or public health impacts of these levels are unclear, and background hormone levels were also detected in apparently unexposed sites.

5 Success in Achieving Objectives

The objectives of the literature review were to collect information on:

- Links between HGP usage and food safety;
- Public health impacts;
- Current status of HGP usage in Australia and the world in general; and
- Pros and cons of HGP usage for the industry.

These objectives have all been achieved and addressed in the previous section.

6 Impact on Meat & Livestock Industry – now & in 5 years time

Based on this review, there is no reason for the beef industry to change its current usage of HGPs. There is no evidence to support any significant adverse health effects from consuming meat from HGP-treated animals. Cessation of HGP usage could un-necessarily cost the industry many millions of dollars in increased feed consumption and lost efficiency.

7 Conclusions and Recommendations

Overall, the balance of international opinion is that there is no increase in the risk of adverse health risks associated with consumption of meat from animals treated with HGPs according to good agricultural practice. Although oestrogen, in particular, is recognised as potentially carcinogenic, these affects are associated with its hormonal action and the doses present in meat from HGP treated cattle are insufficient to exert any tumorigenic effect. In addition, hormone levels in beef from treated cattle are well below levels in other common dietary constituents and from endogenous production. Oral bio-availability of these hormones is also low.

The above views are not supported by the European Union, which has expressed the view that any increase in dietary hormone levels associated with consumption of HGP-treated meat poses an unacceptable (but unquantified) increase in risk of adverse health consequences such as cancer.

HGPs have been through a rigorous evaluation and registration process and are registered for use in cattle in many countries. In these countries they provide a substantial benefit in terms of cost and efficiency of production. Although some recent research has raised speculation about an apparent association between diets high in red meat (and hence in HGPs) and adverse health consequences, the evidence for HGP involvement is not strong and there is currently no need for changes in MLA or industry support for the continued use of HGPs in beef production.

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9 Appendix – Quotes from selected reviews

Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2000)
… residues from use in accordance with good animal husbandry practice [are] *unlikely to pose a hazard to human health.*

The Committee noted that, although the hormone concentrations found in specific populations of treated animals were often statistically significantly higher than the corresponding values for concurrent controls, they were within the physiological range of concentrations of these substances in cattle and that the calculated excess intakes contributed only a small additional amount of hormone to the intakes resulting from consumption of other foods of both animal and plant origin.

Veterinary Products Committee (VPC, 1999; VPC, 2006)
… the Group were unable to support the conclusion reached by the SCVPH that the risks associated with the consumption of meat from hormone-treated cattle may be higher than previously thought.

Specifically, it is very unlikely that the presence of 17β-oestradiol and its metabolites in meat from treated animals would significantly increase the risk of adverse effects in consumers. This is due to their low concentrations in comparison to those arising from endogenous production and from other dietary sources. Any increase would be likely to be small in the context of the whole food basket.

There is ample information to show that zootechnical and therapeutic uses of 17β-oestradiol do not pose any risk to humans unless an active implant site is ingested.

Committee for Veterinary Medicinal Products (CVMP, 1999)
… epidemiological evidence suggests that an exogenous exposure to hormones would need to be substantial (i.e. in the order of post-menopausal therapy levels) before carcinogenic effects would be detectable in humans. … Hence, and in view of the poor biological availability of the compounds, the contribution from exposure to therapeutic and zootechnical doses of natural hormones was considered negligible.

Australian Commonwealth Department of Health and Ageing (Anonymous, 2003)
… there is unlikely to be any appreciable health risk to consumers from eating meat from cattle treated with HGPs according to good veterinary practice.

… to adequately determine the incremental risk associated with very low levels of HGP residues in meat, the total dietary intake of hormones from all sources would need to be evaluated.

… the level of 17β-oestradiol in an egg is greater than that in meat from both treated and untreated animals.

The Food Research Institute (University of Wisconsin – Doyle, 2000)
…low estradiol concentrations, where no normal physiological effects of the hormone are observed, do not promote tumor growth. This low hormone concentration has been called the no-observed-effect level (NOEL).

Meat and fish provide about 5% of progesterone, 20–30% of testosterone, and 15–20% of estrogens in the diet. Eggs and plant foods are responsible for the remainder of the dietary hormone intake.

US Food and Drug Administration
Consumers are not at risk from eating food from animals treated with these compounds because the amount of added hormone is negligible compared to the amount normally found in the edible tissues of untreated animals and that are naturally produced by the consumer's own body (relating to natural hormones)

FDA required that the manufacturers demonstrate that the amount of hormone left in each edible tissue after treatment is below the appropriate safe level (relating to synthetic hormones)

Residue levels of these hormones in food have been demonstrated to be safe, as they are well below any level that would have a known effect in humans (for all HGPs)

USDA fact sheet (original source: http://www/fas.usda.gov/itp/policy/hormone2.html - no longer available)

A person would need to eat over 6 kilograms of beef from animals treated with these hormones in order to equal the amount of these hormones in one egg.

For example, a hen's egg (about 50 grams) contains about 45 times as many estradiol equivalents as 250 grams of steer meat raised with this natural hormone.

A one pint glass of milk from an untreated cow contains about 9 times as much estradiol as a 250 gram portion of meat from a steer raised using hormones.

Wheat germ and soybean oil contain phytoestrogens at several thousand times higher hormone equivalent concentrations than a serving of beef from a steer raised with growth promotants.

Even a young boy would need to eat more than 7,000 grams of beef raised using estradiol daily in order to produce a one percent increase in his production of this hormone.

A 500-gram portion of beef raised using estradiol contains approximately 15,000 times less of this hormone than the amount produced daily by the average man, and about nine million times less than the amount produced by a pregnant woman.

Other industry documents and fact sheets (NCBA, 2006, and others)

One birth control pill contains the same amount of estrogen (35,000 nanograms) as about 1,570 kilograms of beef from cattle that had been given a growth promotant containing estrogen during feedlot finishing.

A serving of milk contains 9 times the level of hormones as a serving of beef from an implanted steer – a serving of cabbage 710 times an soybean oil 7466 times.

An adult woman (not pregnant) produces about 253,000 times more oestrogen every day than is found in a 3-ounce (90 grams) serving of beef from an implanted steer