

Improving feed conversion efficiency and carcass composition in barrows 2F104

Report prepared for the
Co-operative Research Centre for an Internationally Competitive
Pork Industry

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Executive Summary

The major disadvantage encountered when male piglets are castrated to meet the market demands for chilled pork in countries where pork from entire males is not consumed relates to the loss of gonadal steroids for the duration of the growth phase to slaughter. This results in a loss in production efficiency through a decrease in muscle protein deposition, an increase in fatness and an increase in feed:gain as barrows are grown beyond 60kg liveweight (Higgins, 1999; Smits 2006). Ideally we require product from animals without testes but which retain the capability of the high efficiency of feed utilisation and low fat status found in intact boars. Such a product would service specific markets in Asia and the US industry, which relies heavily on barrows for pork.

The gonadal steroids testosterone and oestrogen both potentiate the synthesis and release of growth hormone (GH) releasing factors from the hypothalamus and also play a role in their activity on the pituitary GH secreting cells.

It was hypothesized that the programming of the hypothalamic-pituitary GH secretary axis with these steroids at farrowing may improve the lifelong productivity of treated piglets through an increase in the sensitivity of the GH secretary axis. Anabolic steroids are unlikely to be registered for veterinary use in the pig industry, and so alternative molecules were investigated. The non-steroidal selective androgen receptor modulators (SARM's) have been developed for the treatment of hypogonadal conditions in humans as an alternative to testosterone analogues as they retain their androgenic influence without causing prostate cancer. Pfizer Animal Health kindly provided significant quantities of 2 SARM's, CE-284821 and PF-03207245-00 which were highly androgenic and not converted to oestrogen, which is the case with endogenous testosterone.

In all, 5 studies were conducted with castrate male piglets in which the impact of neonatal injection of testosterone propionate (which mimics the native molecule and is convertible to oestrogen) was compared to the effect of dihydrotestosterone (not convertible to oestrogen) and the most promising SARM (also not convertible to oestrogen), CE-284821, on growth performance to weaning: a group of entire animals was always used as a positive control.

In experiment 1, conducted at Rivalea piggery in which the SARM was not included, testosterone propionate administered at 8mg/kg bodyweight gave significant improvement in growth performance to weaning which was associated with an elevation in circulating levels of the metabolic indicator IGF1. In experiment 2 this experimental design was replicated and animals carried through to slaughter. No production responses were observed, nor were GH secretary profiles different in the testosterone programmed piglets post-weaning. At this point the PhD student and the contracted commercial piggery withdrew from the studies. However an honours student joined the team.

The remaining 3 trials were all conducted on the much smaller production unit at Wildridge Farms at Young and through to weaning. The same castration model was used in all 3 studies: also on two occasions we conducted comparable studies with female piglets as androgenization of the GH secretary axis in females may also be important in boosting life-time growth efficiency. The size and therefore statistical power of these trials was greatly reduced because of lower piglet availability. In some of these studies we included the the SARMS, CE-284821 and PF-03207245-00 . None of these studies yielded a significant result with the same molecule used in study 1, Testosterone propionate, however there was a trend for higher productivity in 2 of these 3 studies with this molecule in both male castrate and female piglets. Neither the SARM's, CE-

284821 or PF-03207245-00 , nor dihydrotestosterone gave any response in either growth or circulating IGF1.

The heritable programming of piglets to promote growth efficiency through epigenetic processes will be a subject of great importance to the pig industry in future research. The use of steroids and their non-steroidal derivatives for this process is limited by the variability of the response. These studies are hampered by the variability between litters, which in future work of this nature must be screened in the previous parity for similar lactational performance. We feel more reliable responses may be obtained through the use of targeted nutrients and nutrigenomics in mid and late gestation to achieve similar responses.

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1. Introduction

1.1 *The issue*

The castration of pigs is not conducted routinely in the Australian industry as removal of the gonads results in a decrease muscle growth, an increase in fatness and a loss of efficiency of conversion of feed to liveweight. (Higgins, 1999; Smits, 2006). Yet markets for fresh pork from surgically castrate animals can be accessed by the Australian industry. Immunoneutralisation of GnRH through the use of Improvac in part addresses the problem, but the presence of a residual testis still excludes pork from these animals from these markets. Ideally, we require product from animals without testes but which retain the capability of the high efficiency of feed utilisation and low fat status found in intact boars. Thus, any alternative strategy to achieve this goal would service specific markets in Asia and the technology would be applicable to the US industry, which relies heavily on barrows for pork products.

1.2 *Gonadal steroids and the GH regulatory axis*

Testosterone and oestrogen potentiate the actions of the GH releasing factor GHRH (and most likely also ghrelin) in rodents (Wehrenberg, 1985) and pigs (Field, 1971; Knudson *et al.* 1985) through androgen/oestrogen receptors in the mid-hypothalamus corresponding to nuclei that secrete these GH regulatory factors. These receptors are also associated with GH secretory cells in the pituitary, although the role of these steroids in regulating GH secretion at this level is not well understood.

1.3 *The importance of the neonatal period*

The timing of surgical castration is important relative the development of the animal through to attain slaughter weights. We have shown previously (Gallagher 2000) that changes in management of piglets on days 1-3 post-farrowing can alter the metabolic responsiveness of animals through to weaning and beyond. Yet the industry has been dictated to by animal welfare regulatory bodies to castrate animals earlier to minimise pain. However, clearly this is likely to have a chronic adverse effect by programming animals to grow more slowly, since the source of the small, but biologically significant, testosterone concentrations is removed through surgery. These steroids are intimately associated with a continuum of developmental events controlling growth through to slaughter liveweights. The attainment of puberty is important for changing growth velocity and carcass composition, however gonadal steroids also exert more subtle, but significant, effects at other stages of the growth cycle, particularly through foetal life in both sheep and pigs (Gill and Hosking, 1996, Hosking, 1996). Thus castration on day 1 post farrowing may be less painful, but the testosterone required to program the GH secretory mechanisms in the mid-hypothalamus at this time will be removed. Thus the lifelong production of GH is reduced and therefore so is the growth efficiency of the piglet.

1.4 Programming piglets with gonadal steroids or alternative molecules

The steroid receptors are the largest class of eukaryotic transcription factors with 49 members that regulate the processes of growth and development. Drug targets for these factors comprise 15% of all pharmaceutical sales world-wide. The cytoplasmic receptors held in a quiescent state by heat shock proteins HSP-70 and HSP-90 are activated by the ligand and the complex recruits associated or co-regulatory proteins. Although their role is poorly understood it is thought that selective activation of these may be implicated in the progression of prostate cancer, while the activation of others does not.

The development of molecules that activate the receptor without causing this prostate malignancy have long been a target for treatment of hypogonadism in humans. Since 1998 a series of non-steroidal molecules have been developed based on the aryl propionamides, bicyclic hydantoins, quinolinones and the tetrahydroquinolinones. The important factor is that they demonstrate tissue specificity, with some showing distinct anabolic effects in muscle and bone, but are only partial agonists in the prostate and seminal vesicles. Importantly these molecules are not substrates for aromatase or 5 α -reductase and so are not converted to oestrogen in these tissues.

1.4.1 Molecules provided by Pfizer:

The first molecule is code named CE-284821: IUPAC Name: 1-(4-(methyl-1H-imidazol-1-yl)benzyl)-3-ethyl-2-(4-fluorophenyl)-1H-indole-5-carbonitrile. MW 434.52.

It has been shown to cause a doubling in muscle mass following a dosing at 10mg in feed/kg daily for 2 weeks. In these studies GnRH was reduced resulting in decreased testosterone production through negative feedback. Importantly this molecule also caused androgenisation of females which could potentially provide a major boost for the pig industry. This molecule was assessed as being micronucleus positive in an *in vitro* assay.

The second molecule was PF-03207245: the IUPAC name was not provided but the structure of the molecule was based on a formula of C₂₇H₃₃N₃O₂.

This was administered orally as medication in feed at a much lower dose of either 0.03 or 0.3mg/kg bodyweight/day for 27 days.

The duration of dosage of these molecules to exert their anabolic effects may be an important factor in determining their efficacy as an androgenic molecule capable of programming GH secretory capacity in neonates.

2. Methodology

2.1 Trial 1

2.1.1 Objective

The aim of this study was to firstly investigate the physiological effects of testosterone propionate (TP) treatment on neonatal piglets and secondly to determine whether neonatal imprinting altered the functionality of the stress reactive H-P adrenal axis through cortisol secretion and metabolic status through IGF-1 concentrations. TP was chosen as it will act through androgen

receptors as well as being partially converted to estrogen through the actions of the enzyme aromatase.

2.1.2 Design

Ninety male piglets were cross-fostered onto 10 multiparous sows at farrowing. There were 9 treatments with a single piglet receiving each treatment within each litter of 9. The treatments were:

1. Carrier oil only plus oil injection on day 25
2. Carrier oil only plus TP (8mg/kg bodyweight) on day 25
3. TP at 0.08mg/kg bodyweight plus oil injection on day 25
4. TP at 0.08mg/kg bodyweight plus TP (8mg/kg bodyweight) on day 25
5. TP at 0.8mg/kg bodyweight plus oil injection on day 25
6. TP at 0.8mg/kg bodyweight plus TP (8mg/kg bodyweight) on day 25
7. TP at 8.0mg/kg bodyweight plus oil injection on day 25
8. TP at 8.0mg/kg bodyweight plus TP (8mg/kg bodyweight) on day 25
9. Entire (not castrated) plus oil injection on day 25

At <18 hours post-birth, neonates were administered the treatments above. On day 4 all piglets were castrated with the exception of group 9 which had received no TP. On day 24, castrated groups received either an injection of oil or 8.0mg/kg TP to activate the endocrine system. On day 25, blood samples were taken via venipuncture within 30 seconds of capture to determine the basal cortisol concentration. Piglets were then held for a further 2.5 minutes to activate the H-P adrenal axis before a second blood sample was collected. Data were subjected to an analysis of variance and means were separated by least significant difference ($P < 0.05$).

2.1.3 Results

The dose of TP that yielded the only significant result was 8mg/kg liveweight. The liveweight gain of this group was similar that of the gonadally intact entire group (Figure 1).

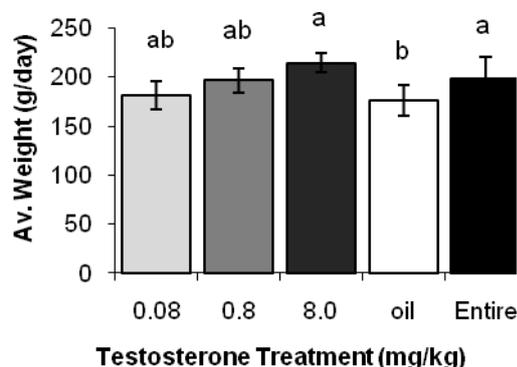


Figure 1- Mean (\pm SEM) average daily weight gain (g) of barrows treated with oil, 0.08, 0.8, 8.0mg/kg TP or remaining entire. Means with different letter differ significantly ($P < 0.05$).

Circulating IGF1 concentrations were stimulated significantly in the same 8mg/kg liveweight treatment group relative to all other treatment groups (Figure 2)

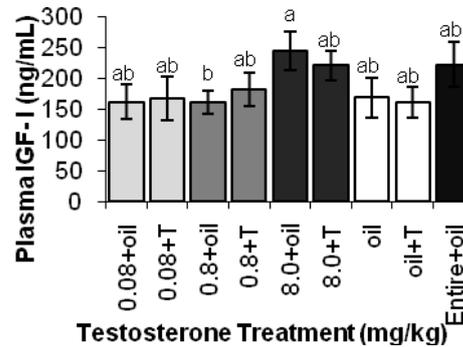


Figure 2 - Mean (± SEM) plasma IGF1 levels (ng/ml) of barrows treated with oil, 0.08, 0.8, 8.0mg/kg TP or remaining entire. Means with different letter differ significantly ($P < 0.05$)

Plasma cortisol levels did not vary between any of the treatment groups after the imposition of acute restraint stress.

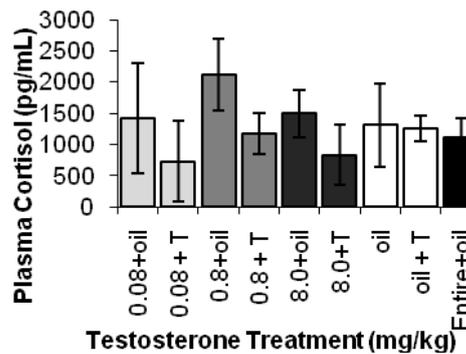


Figure 3 - Mean (± SEM) plasma cortisol levels (ng/ml) in barrows treated with oil, 0.08, 0.8, 8.0mg/kg TP or remaining entire and following acute restraint at day 24 post-partum

2.1.4 Conclusion

This experiment demonstrated the principle of neonatal programming of the growth of piglets to weaning at day 24 and this was supported by the concomitant increase in IGF1 status. However there were no long term effects on the stress axis as determined by cortisol responses to restraint.

Possibly these effects could be exerted through either the androgen or the oestrogen receptor as some of the TP will have been aromatized to oestrogen at the site of action.

2.2 Trial 2

2.2.1 Objective

Following the success of trial 1, trial 2 was designed to replicate trial 1, but this time to carry animals through to slaughter to determine the effects with the dose of 8mg/kg bodyweight on carcass characteristics. The second aim was

to determine if the neonatal treatment resulted in any differences in basal GH secretion post-weaning.

2.2.2 Design

Three litters each of 10 male piglets were established at the beginning of the trial. Animals received either TP at 8mg/kg bodyweight or the oil carrier (2ml) or were left as entire animals which received the oil carrier only. Animals were castrated on day 3 by normal commercial practice. The remaining piglets in each litter were off trial.

Thus the 3 treatments were:

- Castrated + Injected (8mg/kg TP); n=9
- Castrated + Vehicle; n=9
- Sham operation (entire) + vehicle; n=9

At day 105, ear vein catheters were inserted into each animal and on day 106 animals were subjected to a serial bleed in which blood samples (3ml) were collected every 20 minutes for 9 hours commencing at 0800h.

At day 154, animals were slaughtered and carcass composition assessed.

2.2.3 Results

Growth of animals to weaning was not significantly different between groups, although the TP imprinted animals tended to grow faster than the castrate controls (Figure 4)

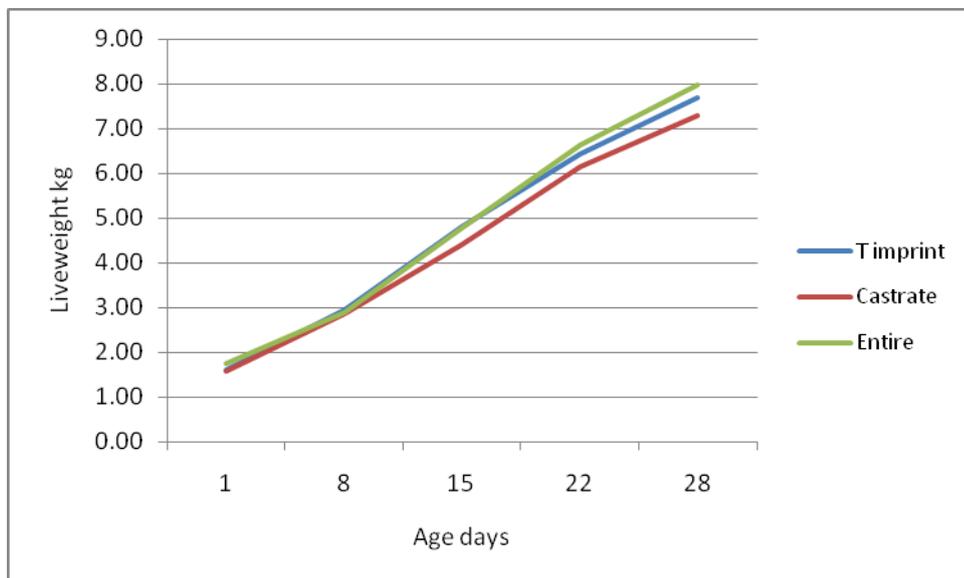


Figure 4 - Mean daily weight gain (g) of barrows treated with oil, 8.0mg/kg TP or remaining entire

Live weight gain, however, did not vary between treatments in the last 50 days of the trial (Figure 5).

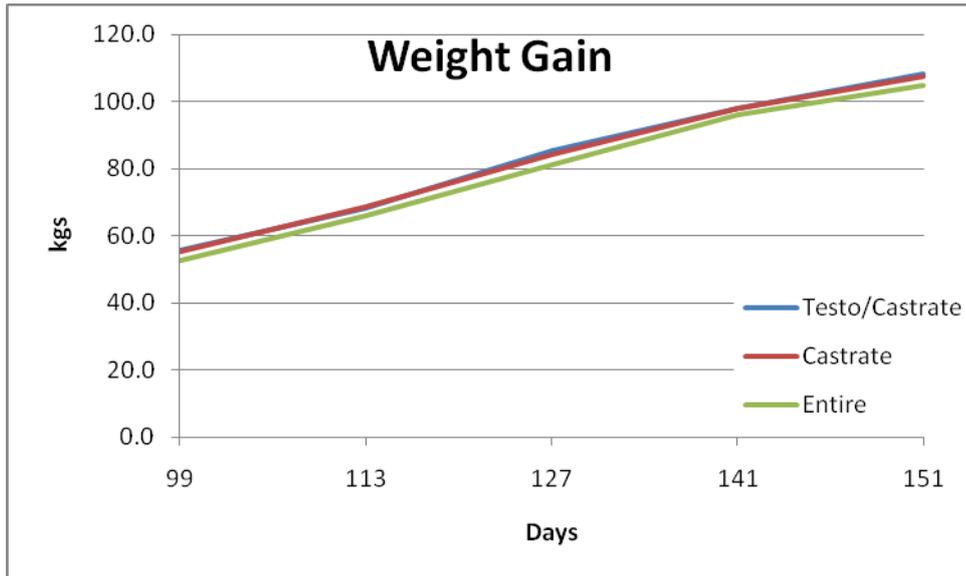


Figure 5 - Mean daily weight gain (g) of barrows treated with oil, 8.0mg/kg TP or remaining entire

Carcass analysis showed that entire animals contained less backfat than either the TP imprinted or the control castrate group (Figure 6). Thus the programming of animals with TP made no difference to the development of fat depots in the carcass.

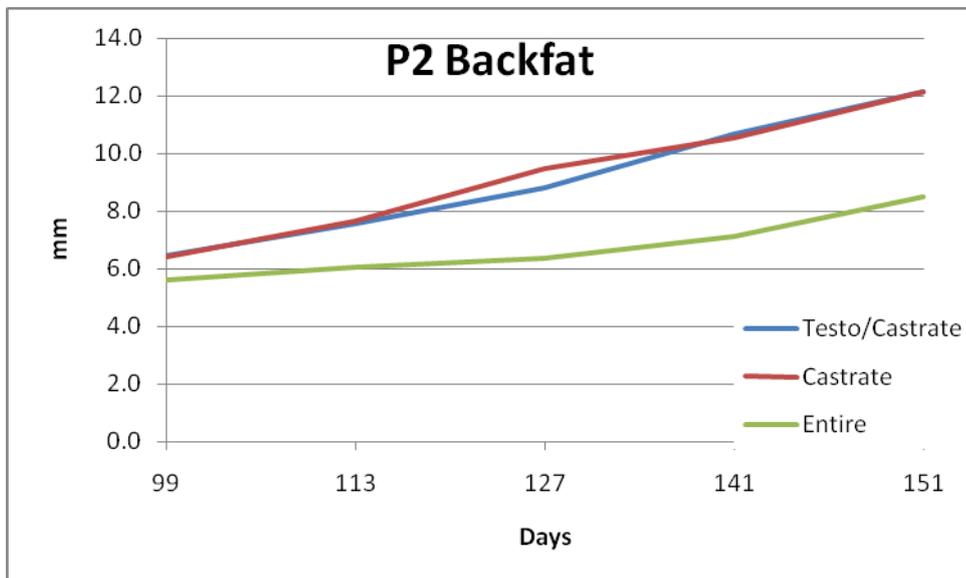
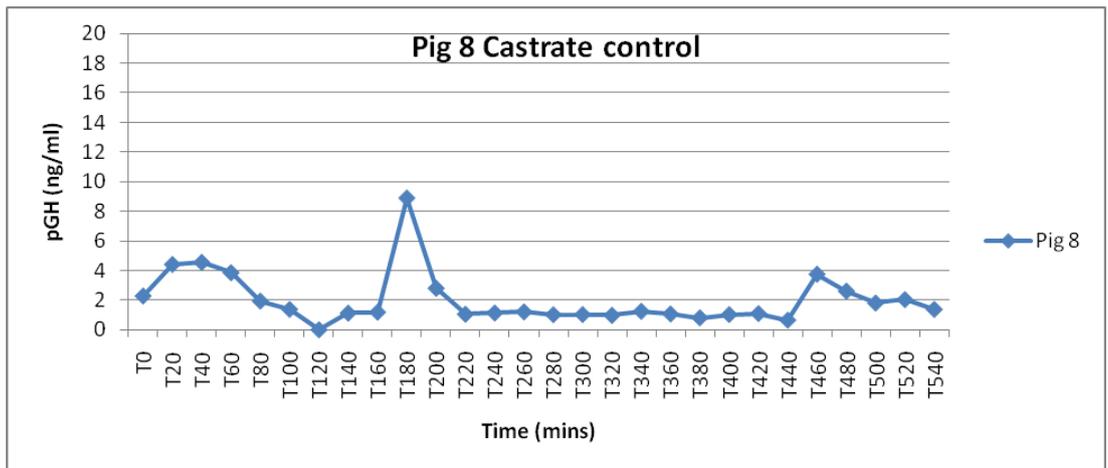
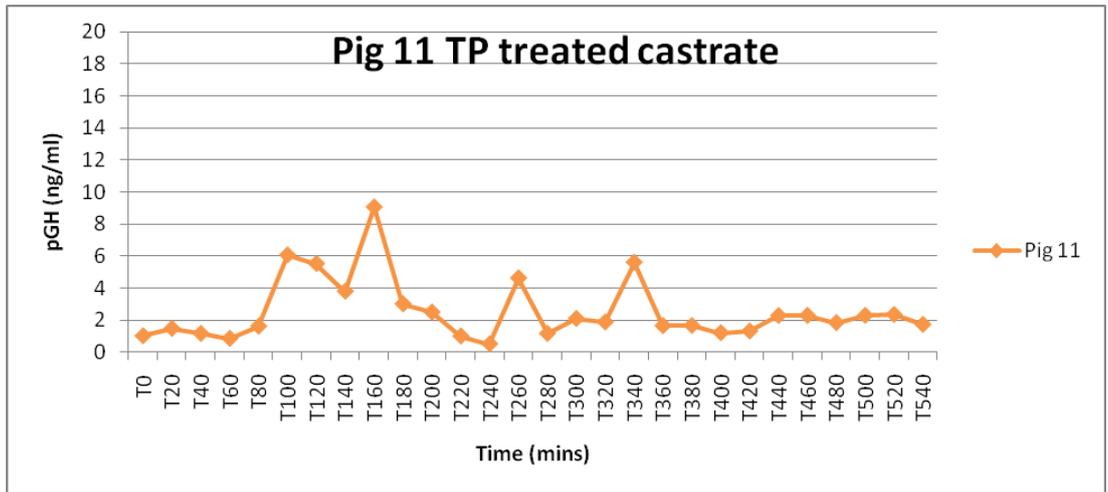
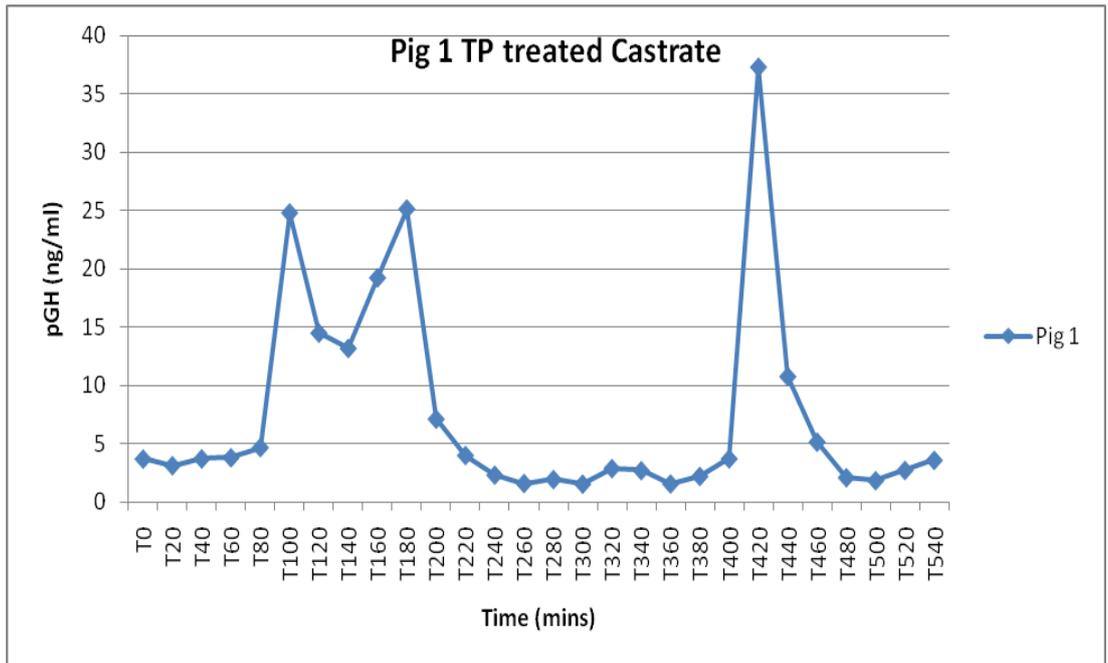


Figure 6 - Mean carcass backfat (mm) measured by ultrasound of barrows treated with oil, 8.0mg/kg TP or remaining entire from days 99 to 151 of the study.

GH analyses were conducted on blood samples collected from ear vein catheters for 8h from 0800h at day 106 of the study. Many of the catheters did not remain patent for the 8hour duration of the study. The most complete representative profiles are provided in figure 7. Some of the peaks may be related more to acute stress during the sampling procedure than to endogenous spikes in GH secretion. There is no difference between treatments.



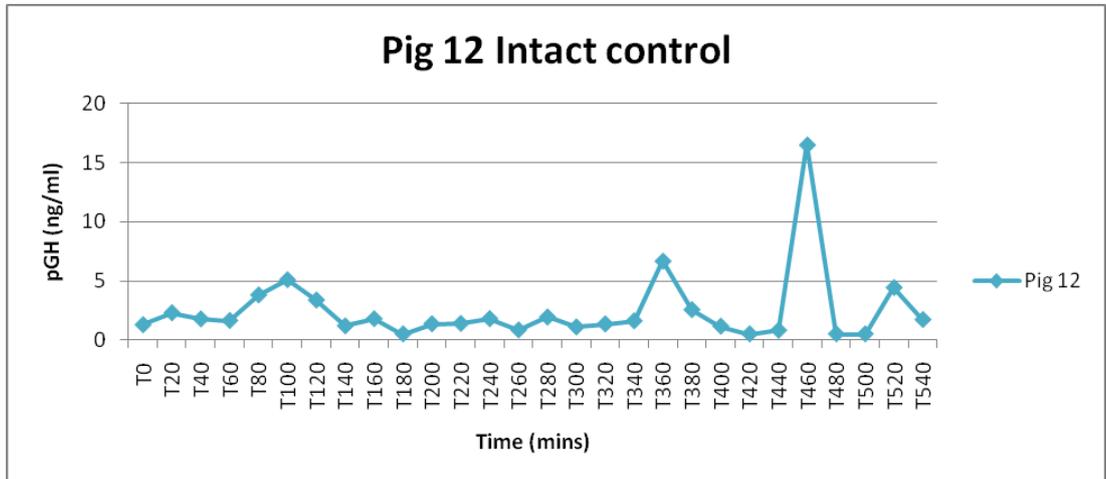
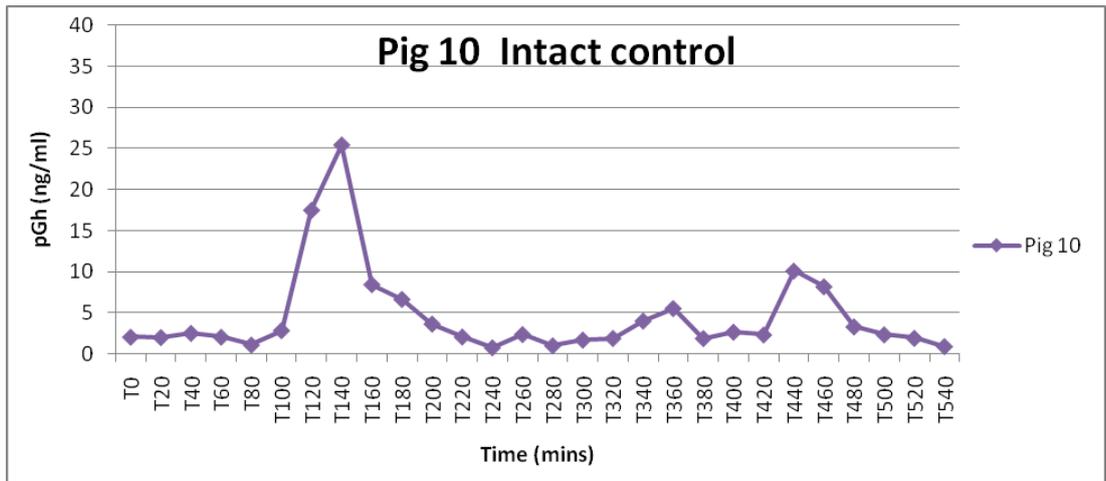
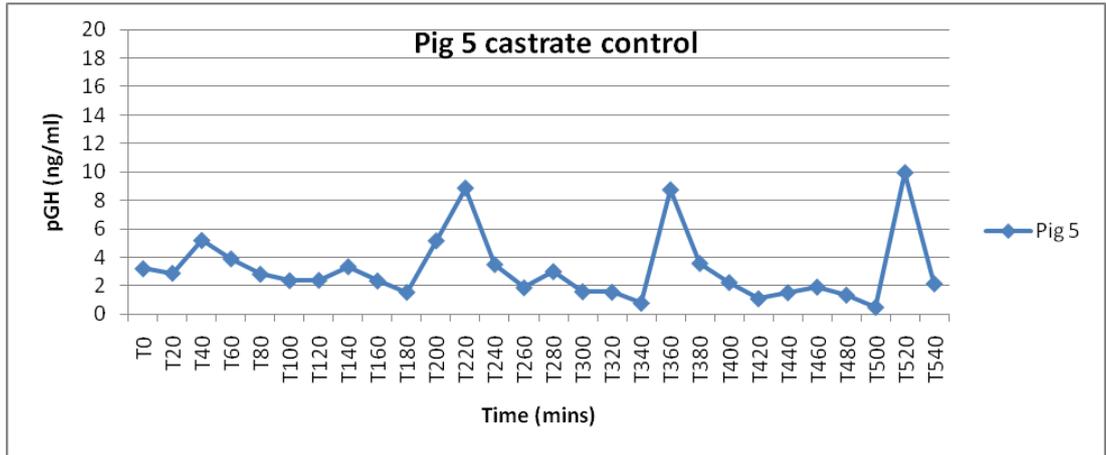


Figure 7 - Circulating GH levels in barrows treated with 8.0mg/kg TP (Pigs 1 and 11), oil (pigs 5 and 8), or remaining entire (pigs 10 and 12) . These are representative profiles which demonstrate the variability in GH status.

2.2.4 Conclusions

This trial did not yield the production response hoped for. Nowhere in the data set was there an indication of a response in either growth efficiency, carcass characteristics or GH profile. We therefore resorted to replicate the result achieved in experiment 1. At this point in time Rivalea withdrew from the research program, as did the PhD student.

2.3 Trial 3

2.3.1 Objective

The failure to replicate the positive production responses to neonatal imprinting with 8mg/kg TP in trial 2 resulted in us replicating this study but then assessing the impact of the highly androgenic SARM CE284821 and the non aromatizable testosterone analogue dihydrotestosterone (DHT) on growth performance to weaning. The latter two molecules should operate directly through the androgen receptor, whereas part of the effect of TP may be through its conversion to oestrogen. We chose weaning as the time for assessing liveweight as nutrient supply for each piglet should be relatively constant to this time point.

2.3.2 Design

Our studies from hereon in were conducted at Windridge Farms, Young, NSW.

Newborn male piglets (n=30) were cross-fostered to 3 multiparous sows (n=10 piglets per litter). Two piglets from each litter received injections of either (1) TP: 8mg/kg bodyweight: BW; (2) DHT: 8mg/kg BW; (3) SARM 1 (CE-284821, 3mg/kg BW) (4) peanut oil vehicle only: 2ml castrate or (5) vehicle only, entire. At 24 hours *post-partum* the animals in groups 1-4 were castrated while group 5 remained as an intact control. Animals were weighed on days 1, 13 and at weaning (Day 24). A blood (5ml) was collected by venipuncture (vacutainer 19G needle) on day 24 for analysis for GH and for IGF1. The data were analysed using linear mixed models (REML) in GenStat13.1 to allow for the repeated measures nature of the data. The fixed effects were day, treatment and day * treatment while the random effects were dam/piglet/day.

An important difference from the previous trials was that castration was now conducted on day 1 in accord with the Windridge commercial protocol. The dose for SARM 1 was the same dose used by Pfizer to obtain significant increases in anabolic responses to treatment on a daily basis.

2.3.3 Results

No responses in liveweight gain to weaning were recorded in this trial were recorded (Table 1). This related to the high degree of variability between the lactation performance of the sows. In view of the fact that there was no production response we do not provide the circulating IGF1 data here.

Treatment Day	TP/ castrated	DHT/ castrated	SARM1/ castrated	Vehicle only/ castrated	Vehicle only/ entire
1	1.68 ^a	1.77 ^a	1.88 ^a	1.83 ^a	1.87 ^a
13	4.28 ^b	3.65 ^b	4.81 ^b	4.16 ^b	4.61 ^b
24	6.50 ^c	5.68 ^c	7.11 ^c	6.80 ^c	6.53 ^c

Table 1 - The effect of neonatal androgens and castration on live weight (kg) change of piglets to weaning.

Mean SED for day: 0.60. Mean SED for Treatment 0.45. Values with different superscripts were significantly different: $p < 0.05$

The variation in the growth responses are shown in Figures 8, 9 and 10 in which the growth data for TP castrated, the SARM1 castrated and the vehicle only entire group are presented.

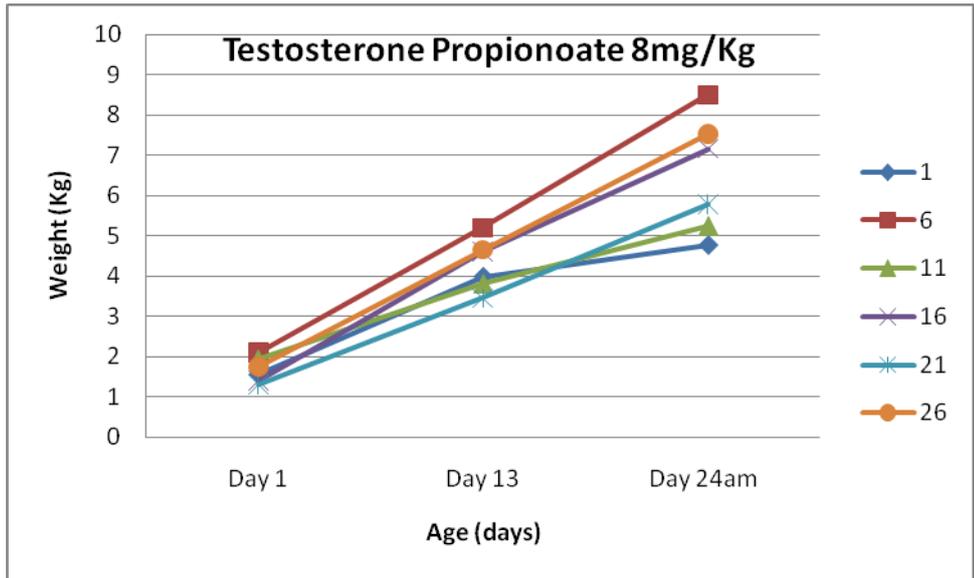


Figure 8 - Growth responses in piglets treated on day 1 with TP at 8mg/kg live weight

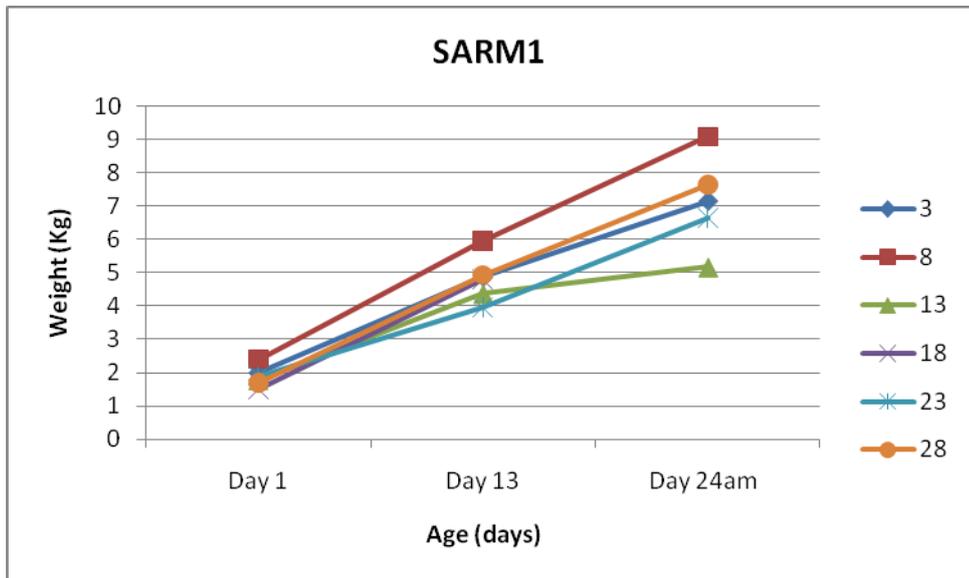


Figure 9 - Growth responses in piglets treated on day 1 with SARM1 at 3mg/kg live weight

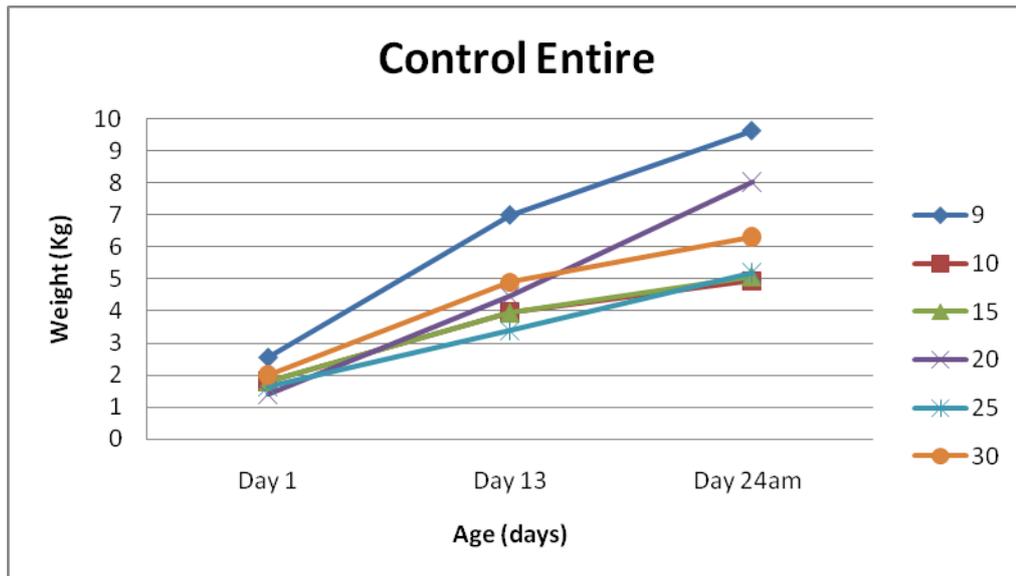


Figure 10 - Growth responses in piglets treated on day 1 with the oil vehicle only

The mean GH concentrations measured at day 24 did not vary significantly between groups, while IGF1 status was higher in the TP treated and control castrate groups. This cannot be related to treatment.

Treatment	TP/ castrated	DHT/ castrated	SARM1/ castrated	Vehicle only/ castrated	Vehicle only/ entire
GH ng/ml	4.1	3.7	4.6	4.2	4.3
IGF ng/ml	55.7*	25.1	32.5	64.4*	32.8

Table 2 - The effect of neonatal androgens and castration on circulating GH and IGF1 concentrations in blood samples collected on day 24 (weaning) * Values were significantly different ($p < 0.05$) from the others for each parameter.

2.3.4 Conclusions

The high level of variability in growth responses across treatments makes it difficult to achieve significant results. The major issue here is the small number of piglets available from sows of similar parity and farrowing on the same day at the Windridge Farm. No positive responses were recorded.

2.4 Trial 4

2.4.1 Objective

Following the failure of trial 3 we replicated the study again using a similar experimental design, but this time investigated responses to the same programming molecules in female neonates. In addition it was important to include the second SARM PF-03207245-00 in the study as this had not been evaluated previously.

2.4.2 Design

a) Newborn male piglets (n=30) were cross-fostered to 3 multiparous sows (n=10 piglets per litter). Two piglets from each litter received injections of either (1) TP: 8mg/kg bodyweight: BW; (2) SARM 1 (CE-284821, 3mg/kg BW)

(3) SARM 2 (PF-03207245-00, 0.03mg/kg BW) (4) peanut oil vehicle only castrate: 2ml or (5) vehicle only entire. At 24 hours *post-partum* the animals in groups 1-4 were castrated while group 5 remained as an intact control. Animals were weighed on days 1, 13 and at weaning (Day 24). A blood (5ml) was collected by venipuncture (vacutainer 19G needle) on day 24 for analysis for GH and for IGF1 The data were analysed using linear mixed models (REML) in GenStat13.1 to allow for the repeated measures nature of the data. The fixed effects were day, treatment and day * treatment while the random effects were dam/piglet/day.

Castration was again conducted on day 1 in accord with the Windridge commercial protocol. The dose for SARM's 1 and 2 were the same dose used by Pfizer to obtain significant increases in anabolic responses to the provision in feed on a daily basis.

b) Newborn female piglets (n=30) were cross-fostered to 3 multiparous sows (n=10 piglets per litter). Two piglets from each litter received injections of either (1) TP: 8mg/kg bodyweight: BW; (2) SARM 1 (CE-284821, 3mg/kg BW) (3) SARM 2 (PF-03207245-00, 0.03mg/kg BW) (4) dihydrotestosterone, 8mg/kg BW or (5) peanut oil vehicle only. A blood (5ml) was collected by venipuncture (vacutainer 19G needle) on day 24 for analysis for GH and for IGF1 The data were analysed using linear mixed models (REML) in GenStat13.1 to allow for the repeated measures nature of the data. The fixed effects were day, treatment and day * treatment while the random effects were dam/piglet/day.

2.4.3 Results

a) Male piglets: No significant differences in growth response were observed between the treatment groups as illustrated in Figure 11.

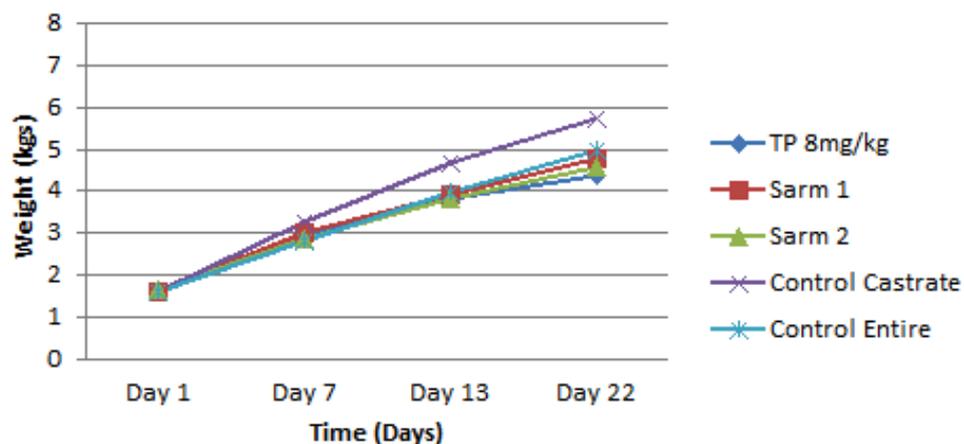


Figure 11 - The effect of neonatal androgens and castration on live weight (kg) change of male piglets to day 24 (weaning).

b) Female piglets: No significant differences in growth response were observed between the treatment groups as illustrated in Figure 12. However the liveweight gain tended to be higher in the TP treated group. Again neither of the SARMS gave a response.

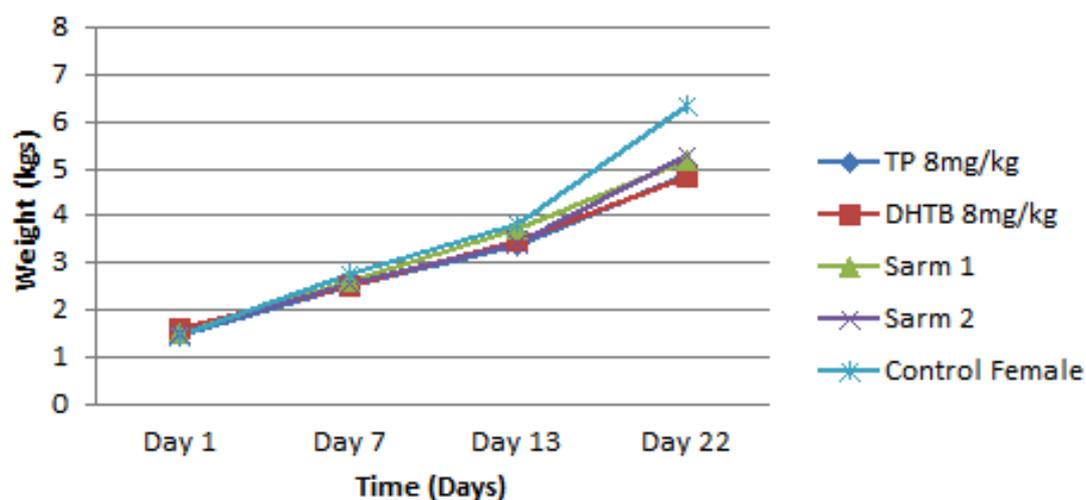


Figure 11- The effect of neonatal androgens on live weight (kg) change of female piglets to day 24 (weaning).

Given that we have not been able to find growth responses we do not report the IGF1 concentrations.

2.4.4 Conclusions

Neither the steroidal androgens nor the non-steroidal molecules yielded a significant response in growth rate to weaning.

2.5 Trial 5

2.5.1 Objective

Given that this was the last study that the project could finance and that Carla Giles had already left the project, we replicated the previous study using a similar experimental design. Again both SARM molecules were assessed. Since we had treated animals on 3 successive days in previous endocrine programming protocols, in this study animals received the same dose on days 1, 2 and 3 post-farrowing.

2.5.2 Design

a) Newborn male piglets (n=30) were cross-fostered to 3 multiparous sows (n=10 piglets per litter). Two piglets from each litter received injections of either (1) TP: 8mg/kg bodyweight: BW; (2) SARM 1 (CE-284821, 3mg/kg BW) (3) SARM 2 (PF-03207245-00, 0.03mg/kg BW) (4) peanut oil vehicle only castrate: 2ml or (5) vehicle only entire. The treatments were administered on days 1, 2 and 3 *post-partum* by intramuscular injection. At 24 hours *post-partum* the animals in groups 1-4 were castrated while group 5 remained as an intact control. Animals were weighed on days 1, 13 and at weaning (Day 24). A blood (5ml) was collected by venipuncture (vacutainer 19G needle) on day 24 for analysis for GH and for IGF1. The data were analysed using linear mixed models (REML) in GenStat13.1 to allow for the repeated measures nature of the data. The fixed effects were day, treatment and day * treatment while the random effects were dam/piglet/day.

Castration was again conducted on day 1 in accord with the Windridge commercial protocol. The dose for SARM's 1 and 2 were the same dose used by

Pfizer to obtain significant increases in anabolic responses to the provision in feed on a daily basis.

b) Newborn female piglets (n=30) were cross-fostered to 3 multiparous sows (n=10 piglets per litter). Two piglets from each litter received injections of either (1) TP: 8mg/kg bodyweight: BW; (2) SARM 1 (CE-284821, 3mg/kg BW) (3) SARM 2 (PF-03207245-00, 0.03mg/kg BW) (4) dihydrotestosterone, 8mg/kg BW or (5) peanut oil vehicle only. The treatments were administered on days 1, 2 and 3 *post-partum* by intramuscular injection. A blood (5ml) was collected by venipuncture (vacutainer 19G needle) on day 24 for analysis for GH and for IGF1. The data were analysed using linear mixed models (REML) in GenStat13.1 to allow for the repeated measures nature of the data. The fixed effects were day, treatment and day * treatment while the random effects were dam/piglet/day.

2.5.3 Results

Analysis of the growth responses to weaning again showed that there was no significant treatment effect. The growth responses for both male and female piglets are provided in Figures 12 and 13 respectively.

However interestingly with both the studies with males and females the TP treatment tended to induce a faster growth rate. This suggests that the programming of neonate needs to occur over a longer period than the 3 days of treatment in this trial and the single treatments used in trials 1-4.

The 2 SARMS has been used by Pfizer as "in feed" additives and possibly the kinetics of their release from muscle dictated that they were not present in the circulation for sufficient time to trigger the anabolic response that we sought in this and previous trials.

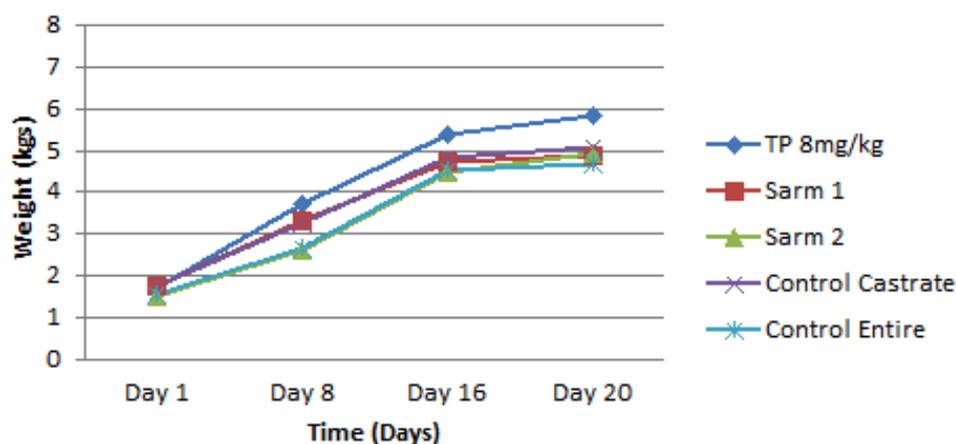


Figure 12 - The effect of neonatal androgens and castration on live weight (kg) change of male piglets to day 24

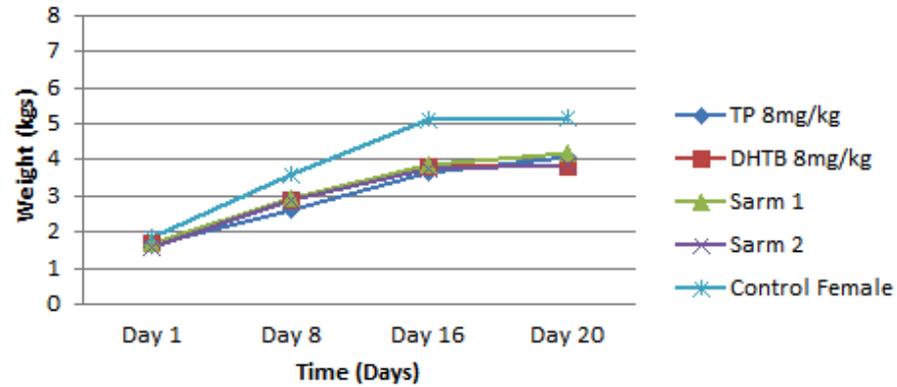


Figure 13 - The effect of neonatal androgens on live weight (kg) change of female piglets to day 24 (weaning)

Given that we have not been able to find growth responses, we do not report the IGF1 concentrations.

2.5.4 Conclusions

Increasing the treatment to a 3 day period made no difference to the lack of growth response to weaning reported from trail 4. However the prolonged period of treatment tended to improve the growth response to weaning more with the TP administered at the dose of 8mg/kg BW.

3. Application of Research

The research undertaken in this program has not yielded results that would lead to commercial application for the industry. However the process of epigenetic programming is of extreme importance to the pig industry, particularly as there is a component that is heritable and therefore passed through the generations. These studies are easily conducted in rodents in which the intergenerational period is short, but harder to conduct in pigs with a gestation period of 115 days.

Neonatal manipulation of animals is an attractive production target for improving growth, since any treatment occurs a long time (150 days) from the consumption of the product by the consumer. The possibility of residues in the product is remote.

Research in this field from now should involve a nutritional component, since the areas of fatty acid supplements to alter cell membrane fluidity and therefore cellular metabolic sensitivity will alter the way in which the piglet responds to endocrine stimuli. Similarly insulin sensitivity can be altered by nutritional manipulation of sow gestation diets.

The neonatal programming responses that we have recorded to date over a period of 10 years are most often detectable at weaning, but then homeostatic mechanisms take over post-weaning and any advantage is most often lost by the time that the animal reaches the fattening phase.

The Pork CRC should continue working in this broad developmental field since the heritable epigenetic component of production responses may mean the difference between pig production failing or succeeding commercially.

Any such technologies are easy for users to adopt if it involves use of a slow release implant, a single injection or an in feed additive. Simple adjustments to dietary factors are also easy to formulate for longer duration treatments.

4. Conclusion

This research program has not been able to deliver a product with commercial application for the producer. The positive results achieved in some of these trials have not been replicated. Where possible the immunocastration response of Improvac is the technology of choice if the residual gonads are not a limitation to a specific chilled pork market.

5. Limitations/Risks

The major limitation to this field of research is the variability in between the performance of litters on sows even from the same parity. In studies of this nature we need to evaluate the lactational performance of sows in their previous parities to minimize variation in production responses and therefore the number of animals required for any treatment group.

The SARM molecules we have evaluated here did not provide a positive response, but then we were unable to assess their androgenic actions in an *in vitro* system involving a transfected cell line expressing the androgen receptor.

We had suggested that we would assess the efficacy of these molecules in such a system, but management issues prevented this from happening.

6. Recommendations

We conclude that epigenetic programming is a high priority area for future research and products for the pork producer to adopt readily.

Our results suggest that any androgen programming to provide a growth response requires an input through the oestrogen receptor.

The results also suggest that neonatal programming may require longer term treatments to achieve the more permanent physiological and genetic adjustments required to achieve production gains.

Future work should continue to develop ways of achieving the production responses possible through repeated porcine somatotropin administration without having to resort to repeated injection of animals.

This research will involve investigating the interaction between target nutrients and other regulatory molecules.

7. References

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