Nutritional and Other Factors Affecting Efficacy of &Agonists in Pigs.

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Introduction

Genetic selection and increased understanding of nutrition over the last decade or so has led to tremendous improvements in the efficient production of high-quality lean pork. A characteristic of these leaner pigs is that they have higher levels of the naturally occurring hormone, somatotropin (or growth hormone). It has been known for several decades that injection of pigs with tissue extracts containing porcine somatotropin (pST) results in increased lean tissue deposition and decreased fat accretion in growing pigs. Advances in biotechnology have now provided a means of producing pST on a commercial scale and the efficacy of daily injection of recombinantly-derived pST for improving productive performance of swine is beyond doubt.

Administration of pST has to be via daily injection, or as a slow release device because pST is a peptide hormone and is digested if given in the feed. However, a group of orally-active compounds which alter the ratio of lean to fat deposition have recently become available for research purposes and currently being trialed for commercial use. This group of compounds, which includes ractopamine, salbutamol, cimaterol, clenbuter-01, Ro 16-87 14, BRL-47672 and L-644,969, are broadly called R-agonists because they all act through the ß-receptors on the target tissues. Hence, one of the acute actions of ß-agonists on fat tissue is to decrease fat synthesis and to increase fat breakdown. The actions on lean tissue are less well documented but probably the ß-agonists decrease skeletal muscle protein breakdown. The actions of ß-agonists have been the subject of recent reviews (Reeds and Mersmann, 199 1; Dunshea, 1993) and therefore the aim of this paper is not to cover this area again but rather to discuss some of the factors which may interact with D-agonists and influence their efficacy. These factors include non-nutritional factors such as dose, genotype, sex, duration of treatment and age of the animals and nutritional factors such as dietary protein and energy. The structure of the D-agonist also determines efficacy and the reader is referred to the review by Timmerman (1987) for the attributes of potential nutrient partitioning agents.

Non-Nutritional Factors

1. Dose

Numerous dose studies have been performed to determine optimal doses of specific ß- agonists. Cole et *al.* (1987) found progressive improvements in average daily gain (ADG), carcass gain, feed to gain (F/G) and fat thickness with increasing levels of salbutamol up to 8 ppm. Experiments with cimaterol have revealed dose-dependent responses up to 1 ppm cimaterol (Jones et *al.* 1985; Moser et *al.* 1986). Bracher-Jakob *et al.* (1990) observed improved performance in pigs treated with up to 180 ppm Ro 16-87 14. Watkins *et al.* (1990) presented a comprehensive summary of 6 dose response trials covering the range of 0 to 30 ppm of the ß-agonist ractopamine (RAC). All RAC levels improved ADG and F/G over those of controls. Levels of RAC above 10 ppm improved carcass leanness and dressing percentage. Based on these observations it was concluded that the optimum level of inclusion of RAC in the diet of finisher pigs was 10 to 20 ppm (see Figure 1). Obviously, the ranges over which performance responses occur varies with the structure of the ß-agonist and the response criteria but most response curves are quadratic in nature and an optimum dose can be determined for each compound. As with any drug administration there is a danger of abuse by those who feel that "more is better". Although economics will generally ensure that this practice would not be widespread or persist, it is fortunate that no clinical signs of toxicity were observed in pigs fed diets supplemented with up to 500 ppm RAC for 8 weeks (Williams *et al.* 1989a). One area of concern arises from anecdotal reports that in some countries there is widespread use of R-agonists produced and/or procured illegally. These compounds may be based on the chemical structures of therapeutic drugs rather than D-agonists specifically designed as growth promotants for the animal industries and thus may have long half lives. The long half life combined with indiscriminant dosages and limited screening procedures could create residue problems with consequent human health risks.

Fig.1 Effect of inclusion rate of dietary ractopamine on ADG and F/G of finisher pigs (Watkins *et al.* 1990).

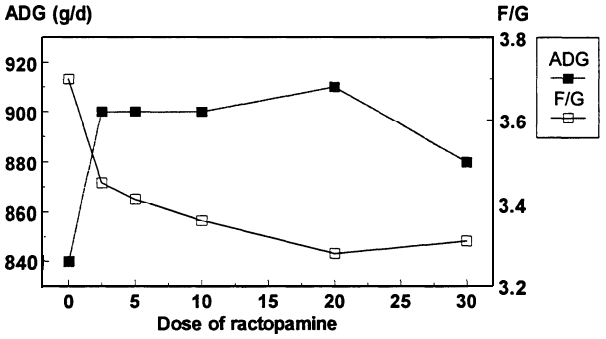
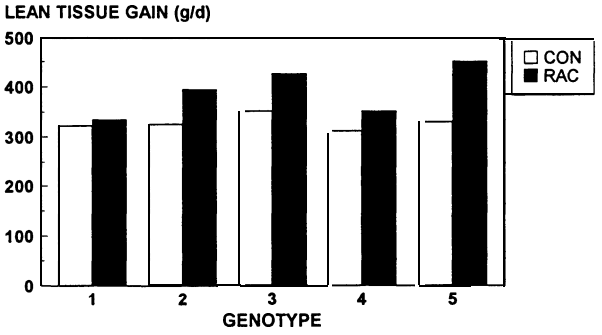


Fig. 2 Effect of dietary ractopamine (RAC) on lean tissue deposition in finisher pigs of 5 different genotypes. Genotypes are: 1. Hampshire (H) x [H x Duroc (D)]; 2. Synthetic sire line; 3. (H x D) x {[Landrace (L) x [Yorkshire (Y) x D]}; 4. L x (Y x D); 5. Y x L. (Gu *et al.* 1991).



2. Genotype

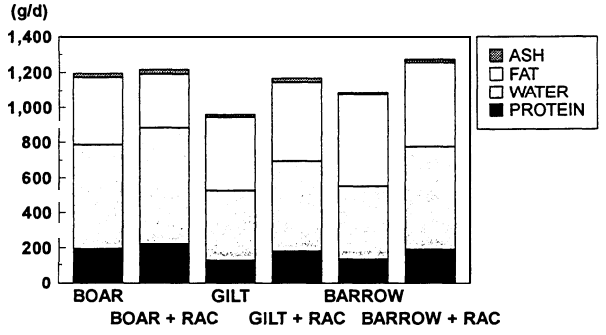
Genotype may also effect response to ß-agonist supplementation. Yen *et al.* (1990a,b) investigated the effects of cimaterol and RAC in genetically lean and obese pigs. Dietary ß-agonist supplementation improved performance in both lean and obese pigs and there were no B-agonist x genotype interactions for any traits. Bark *et al.* (1992) also compared the responses of lean and obese pigs to RAC, finding no interactions for ADG, F/G and linear measures of body composition. However, the magnitude of improvement in muscle accretion and muscle accretion efficiency was greater in pigs of the lean genotype. A RAC x genotype interaction was also observed for fatty tissue accretion with lean pigs gaining less fatty tissue than the obese pigs. Conversely, Warriss *et al.* (1990) studied the effects of the B-agonist salbutamol on performance and meat quality in two genotypes with different propensities to fatten (lean and moderate) and found greater improvements in ADG and backfat in the more moderate genotype. Gu *et al.* (199 1 a) investigated the effects of RAC in 5 genotypes and did not detect any interactions for economically important traits such as ADG, F/G or any lean quantity measures of carcass composition. However, significant ß-agonist x genotype interactions were observed for lean tissue gain (Figure 2, Gu *et al.* 199 1 b) and as with the results of Bark *et al.* (1992), RAC had greater effects in the genotypes with higher lean growth rates.

3. sex

Almost all studies with &agonists have utilised barrows or gilts. Although in general, D-agonist x sex interactions have not been observed and thus pooled data has been reported, some exceptions do exist. For example, Bekaert *et al.* (1987) reported that cimaterol increased loin eye area to a greater extent in barrows compared to gilts. Similarly, clenbuterol tended to improve carcass composition in barrows to a greater extent than in gilts (Dalrymple *et al.* 1984). Also, greater improvements in F/G were found in barrows versus gilts treated with salbutamol, whereas the converse was true for backfat reduction (Cole *et al.* 1987). Ractopamine reduced ADG in gilts but not barrows while the proportion of muscle in the carcass was increased for both sexes (Kephart and Yates, 1990). Williams *et al.* (1994) found that dietary RAC improved growth performance, body composition and lean tissue gain similarly in gilts and barrows.

There is limited information however on the effects of ß-agonists in boars, which generally out perform both gilts and barrows. Pig producers in many countries, including Australia and New Zealand, take advantage of these sex differences and do not castrate male pigs. In order to provide information on the possible interactions between sex and ß-agonists, we conducted an experiment to examine the effects of sex and RAC on performance of finisher pigs with a high potential for growth (Dunshea *et al.* 1993c). Performance of these pigs is summarised in Figure 3.

Fig. 3 Effect of sex and dietary ractopamine (RAC) on lean tissue, fat and bone deposition of finisher pigs (Dunshea *et al.* 1993c).



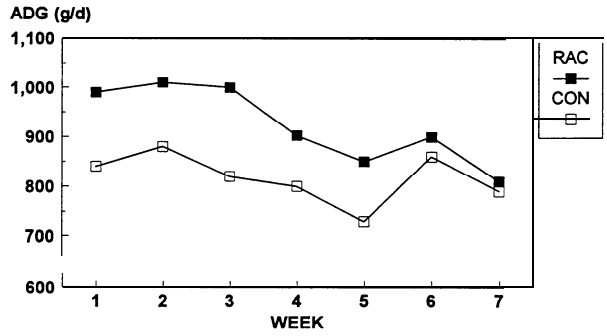
Ractopamine improved ADG in gilts and barrows but not in boars. As RAC had no effect on feed intake, these improvements in ADG were achieved through improved F/G Whole body lean (protein and water) tissue deposition was increased by RAC in all sex groups. The proportionate improvements in ADG, F/G and lean tissue (protein and water) deposition were greatest for barrows and least for boars. Although carcass fat was decreased in all sexes, the rate of fat deposition was not decreased overall, but did tend to decrease in the boars receiving RAC. In a subsequent experiment to investigate the interactions between energy intake, sex and dietary RAC we again demonstrated that RAC increased lean tissue deposition without effecting the rate of fat deposition (Dunshea *et al.*1993a). Responses were proportionately greater for gilts than boars, particularly at ad libitum feed intakes.

3. Duration of treatment

A phenomenon which occurs during repeated exposure to a variety of stimuli is down-regulation, ie. chronic exposure leads to muted responses. Down-regulation and de-sensitisation probably occurs for all ß-agonists but there may be tissue and structural differences. Therefore the period of administration of the ß-agonist will have to accommodate any down-regulation.

Data on the temporal nature of performance responses during chronic ß-agonist treatment suggest a diminution of response with time on treatment. Wallace *et al.* (1987) investigated the temporal pattern of response to the b-agonist L-644,969 and reported that cumulative ADG and F/G responses were greatest for the first week of treatment, gradually diminishing over the next few weeks. In the case of pigs fed 1 ppm L-644,969 ADG over the first week was 24% higher than the controls. Although cumulative ADG was still 15% higher than the controls at the end of the third week of treatment, the current ADG had returned to control values and was declining. We examined the temporal pattern of response to RAC in ad libitum fed pigs over the weight range from 60 to 90 kg and' found that the growth responses were greatest during the first week of treatment, after which time the response declined in a linear fashion (Dunshea *et al.*1993c). In another study, where gilts were restrictively fed diets containing 6 different levels of protein there was evidence of reduced response with time on treatment (Dunshea *et al.* 1993b). For the protein adequate diets (> 17.1% CP) ADG over the first 3 weeks was 11% higher in the RAC supplemented gilts. However, ADG between weeks 3 and 6 was not different between treatment groups. Nevertheless, responses were such during the first 3 weeks that ADG was still significantly higher (6 %) over the entire 6 weeks. In a comprehensive study of the temporal nature of response to RAC, Williams *et al.* (1994) quite clearly demonstrated that the response in ADG was greatest during the first 3 weeks of treatment and declined over the next 4 weeks (Figure 4) such that there was no difference in ADG after 6 weeks of treatment. Sainz *et al.* (1993a) found that RAC increased ADG over the first 3 weeks of treatment but not over the second 3 weeks of treatment. Skeletal muscle D-receptor numbers and affinity were reduced after at least 3 weeks of dietary RAC treatment (Sainz *et al.* 1993b). However, Smith (1989) reported that ß-adrenergic receptor binding capacity was reduced in skeletal muscle obtained from pigs treated with cimaterol for 6 weeks but not for those treated with RAC. Culture of myotubes in media containing RAC for 24 h did result in down-regulation of receptors. Spurlock *et al.* (1994) found that ß-adrenergic receptor numbers were reduced in adipose tissue but not skeletal muscle from pigs treated with RAC. Lipolytic response to the $ß_2$-agonist fenoterol is reduced after only 4 d of dietary RAC treatment suggesting down-regulation of adipose tissue ß-adrenergic receptors (Dunshea and King, 1995). The diminution of response with extended treatment may be related to failure of the D-agonist to stimulate bone deposition rather than a down-regulation of skeletal muscle ß-adrenergic receptors.

Fig. 4 Effect of duration of treatment and dietary ractopamine (RAC) on ADG of finisher pigs (Williams *et al.* 1994).



Registration of orally active ß-agonists may require a withdrawal period before slaughter. Consequently, the absence of exogenous ß-agonists in combination with the down-regulation of adipose tissue D-receptors would favour increased fat deposition during the withdrawal period. For example, although Jones *et al.* (1985) found no effect of a 7 d withdrawal period on most performance and carcass characteristics of cimaterol-treated pigs, pigs withdrawn from treatment increased feed intake above that of controls and backfat measures returned to control values. Similarly, the data of Jones *et al.* (199 1) and Watkins *et al.* (199 1) clearly show that performance during 5 and 4 d withdrawal periods respectively, after 42 d of feeding RAC is greatly reduced. On the other hand, we did not see any difference in performance during a 7 d withdrawal period in pigs previously treated with RAC for 24 d (Dunshea and King, 1994). By 7 d after withdrawal, lipolytic responses to fenoterol had returned to control values suggesting a rapid return to normal adipose

tissue adrenergic response (Dunshea and King, 1995). If withdrawal periods are required for registration of ß-agonists then attention will need to be paid to performance during this period. For example, strategic measures such as restricting feed intake may need to be imposed during withdrawal periods to minimise fat deposition.

4. Age

Age or growth phase will also govern response to ß-agonists. Most studies have probably quite rightly concentrated on the finisher stage (ie between 50 and 110 kg) when pigs are depositing considerable amounts of fat. In one of the few studies conducted over the grower phase (others have studied the entire grower-finisher phase), Mersmann et *al.* (1987) did not detect any differences in effect of cimaterol treatment between 10 and 60 kg live weight on growth performance or carcass characteristics. Bekaert *et al.* (1987) also failed to detect any differences in ADG or F/G of pigs treated with cimaterol over the grower phase (30 to 60 kg live weight) but they also did not observe any performance changes with cimaterol treatment over the finishing stage (60 to 100 kg live weight). It is likely that the lack of response of younger animals to ß-agonist treatment is because feed intake is the major factor limiting performance over this phase of growth. In this context, positive responses were observed in young lambs fed ad libitum milk replacer containing cimaterol (Williams *et al.* 1989b).

Nutritional Factors

1. Dietary protein

Nutrition, particularly dietary protein or amino acid level and composition may play an important part in the efficacy of ß-agonist supplementation, particularly in light of the increases in protein deposition of almost 50% observed over the finishing stage (Dunshea *et al.* 1993c). Mowrey *et al.* (1990) studied the effect of RAC in finishing swine fed either 14 or 16% CP. While F/G and loin eye area were higher for pigs fed 16% CP there were no interactions between RAC and dietary protein for any trait. With the exception of F/G, increasing the dietary protein from 14 to 16%, with or without supplemental synthetic lysine, did not improve responses to RAC (Ott *et al.* 1989). Ractopamine improved performance to a similar extent in pigs fed diets containing either 16, 20 or 24% CP (Jones *et al.* 1988). Bracher-Jakob and Blum (1990) investigated the effect of the R-agonist Ro 16-87 14 in pigs receiving 11 and 14% dietary protein. Significant interactions were observed for ADG, F/G and protein deposition with the R-agonist only enhancing performance in the pigs receiving 14% CP (Figure 5). These latter data support the notion that improvements in performance during ß-agonist supplementation are not due to improved biological value of dietary protein. ,

Fig. 5 Effect of dietary protein and the &agonist Ro 16-8714 (ß-Ag) on carcass protein and fat deposition in finisher pigs (Bracher-Jakob and Blum, 1990).

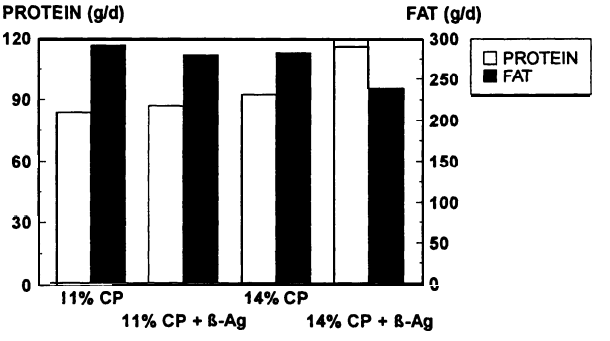
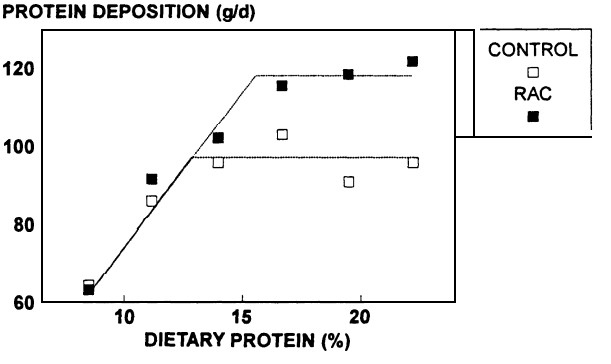


Fig. 6 Effect of dietary ractopamine (RAC) and protein on protein deposition in gilts restrictively-fed (30 MJ DE/d) over the liveweight range 60 to 90 kg (Dunshea *et al.* 1993b).



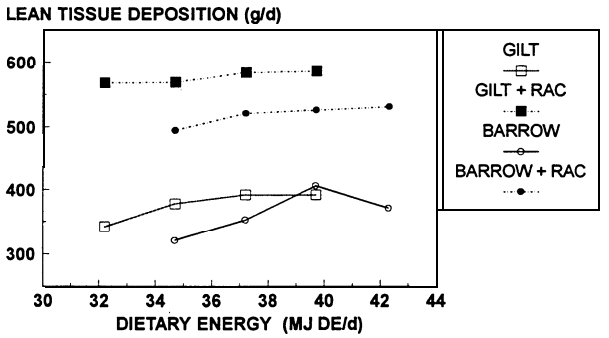
We have tested this hypothesis by examining the effect of RAC and 6 levels of "ideal" dietary protein (ARC, 198 1) in gilts which were restrictively-fed (30 MJ DE/d) between 60 and 90 kg live weight (Dunshea *et al.* 1993b). The relationship between empty body protein deposition and dietary ideal protein content (Figure 6) clearly demonstrates that the rate of protein deposition is influenced by both dietary protein and RAC. The relationship between protein deposition and dietary protein intake for both the control and RAC-treated gilts was of a linear/plateau nature. Protein deposition increased with dietary protein content at the same rate for both the control and RAC-treated gilts over at least the two lowest levels of dietary protein (< 11.2% CP), most likely because protein intake was insufficient to support any stimulation of protein deposition by RAC. Thus, the biological value of dietary protein was unchanged. However, at higher dietary protein levels, the plateau or maximal protein deposition rate was 23% higher in the gilts receiving

RAC (96.3 vs 118.4 g/d for control and RAC-treated gilts, respectively). The dietary protein contents required to support maximum protein deposition were 12.7 and 15.8% CP for the control and RAC-treated gilts, respectively. Therefore, in order to maximise performance and protein deposition in pigs treated with dietary RAC and other ß-agonists there needs to be an increase in dietary protein commensurate with the increase in protein deposition.

2. Dietary energy

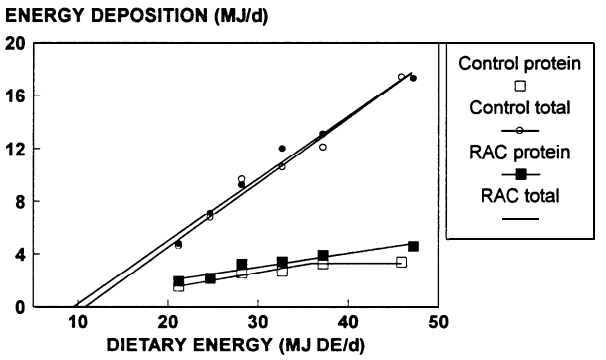
It is generally accepted that an increased maintenance energy requirement (MER) is an inevitable consequence of increased protein deposition and this is certainly the case for pigs treated with pST. However, the ratio of energy deposited to energy intake shows no change in the efficiency of energy deposition during RAC treatment under both ad libitum and restricted feeding conditions (Dunshea *et al.* 1993b,c). Conversely, Mitchell *et al.* (1990) found that the efficiency of utilisation of DE was 19% less in RAC-treated pigs. Subsequent work in the same laboratory demonstrated no difference in the efficiency of use of DE, although regression analysis suggested a small (8%) increase in MER of RAC-treated pigs (Mitchell *et al.* 1991). Also, fasting heat production was not altered in RAC-treated pigs (Yen *et al.* 199 1). Therefore, it is important to understand the relationship between dietary intake and performance in pigs treated with R-agonists.

Fig. 7 Effect of dietary ractopamine (RAC) on lean tissue deposition in finisher gilts and barrows (Williams *et al.* 1994).



Williams *et al.* (1994) investigated the interactions between energy intake, sex (gilt and barrow) and dietary RAC (44.7 ppm) in fmisher pigs. They fed-energy levels from 32 to 40 MJ DE/d to the gilts and from 35 to 42 MJ DE/d to the barrows. While there was no overall effect of energy intake on lean tissue gain, for the control pigs lean tissue deposition did tend to be lower at the lowest level of energy intake for both sexes (Figure 7). Dietary RAC increased lean tissue deposition in both sexes and at every level of energy intake. In addition, there was a significant energy intake x RAC interaction such that the response to RAC was greater at the lower energy intakes. However, based on the performance of these pigs and our knowledge of the relationships between protein deposition and dietary energy intake, it is most likely that the ranges in dietary energy intakes investigated in this experiment were above that which maximises protein deposition, particularly for the control pigs. Since energy intake can limit protein deposition in improved genotypes (Campbell and Taverner, 1988) it is imperative that the effects of B-agonists be investigated under conditions where energy is limiting.

Fig. 8 Effect of dietary energy and ractopamine (RAC) on protein energy and total energy deposited in finisher gilts (Dunshea *et al.* 1993a).



Our previous research with an improved genotype demonstrated that dietary RAC did not increase protein deposition in gilts restricted to approximately 70% of ad libitum intake (2 1 g/d; Dunshea *et al.* 1993b) to as great an extent as it did in ad libitum fed gilts (5 1 g/d; Dunshea *et al.* 1993c) suggesting that energy intake may limit response to RAC. Therefore, we decided to investigate the interactions between energy intake and RAC in finisher gilts and boars (Dunshea *et al.* 1993a). The relationship between protein deposition and DE intake for the control gilts was of the linear/plateau form with carcass protein deposition reaching a plateau at 140 g/d at an energy intake of 36 MJ DE/d (Figure 8). However, in RAC-treated gilts protein deposition increased linearly with increasing energy intake up to a maximum of 191 g/d at an ad libitum DE intake of 47.2 MJ DE/d. As with the study of Williams *et al.* (1994), RAC increased protein deposition at every level of energy intake. The slope of the linear ascending portions of the curve were not different and the improvement in protein deposition due to dietary RAC was 21 g/d up until a DE intake of 36 MJ/d. For boars receiving either 0 or 20 ppm of RAC the relationship between protein deposition and energy intake was linear up until ad libitum DE intakes of approximately 45 MJ/d (Dunshea *et al.* 1993a) While the slopes of these lines were the same, the benefit to protein deposition in boars

(19 g/d) was similar to that observed in gilts. Therefore, dietary RAC increases protein deposition in both gilts and boars at every level of energy intake but ad libitum intakes are necessary to maximise protein deposition in improved genotypes treated with RAC. Also, the differences in protein deposition between boars and gilts are still evident during RAC treatment.

Conclusion

Clearly, B-agonists improve performance in the finisher pig with the magnitude of responses depending upon dose, genotype, sex, duration of treatment, age and nutrition. If these compounds are approved for use in the pig industry then producers must be aware of these interactions. Responses will be greatest for gilts and barrows although even in boars substantial improvements in protein deposition can be achieved. The effect of genotype is less clear although it does appear that responses are greatest in leaner genotypes. These compounds will need to be used strategically during the finisher period since the response decreases with time on treatment. Responses appear to be maintained for up to 4 weeks of treatment. If responses to dietary ß-agonists are to be maximised then particular attention must be given to nutrition. Dietary R-agonists have no effect upon the biological value of dietary protein. Therefore, in order to maximise performance and protein deposition in pigs treated with dietary RAC and other D-agonists, there needs to be an increase in dietary protein commensurate with the increase in protein deposition. While S-agonists increase protein deposition across a wide range of energy intakes, dietary energy should be maximised to obtain the full benefits in improved genotypes.

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