

## Review: Effects of Ractopamine Hydrochloride (Paylean) on welfare indicators for market weight pigs<sup>1</sup>

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**ABSTRACT:** This review summarizes the effects of ractopamine hydrochloride (RAC) dose (5, 7.5, 10, and 20 mg/kg) on market weight pig welfare indicators. Ractopamine hydrochloride (trade name Paylean) is a  $\beta$ -adrenergic agonist that was initially approved in the U.S. in 1999 at doses of 5 to 20 mg/kg to improve feed efficiency and carcass leanness. However, anecdotal reports suggested that RAC increased the rate of non-ambulatory (fatigued and injured) pigs at U.S. packing plants. This led to the addition of a caution statement to the Paylean label, and a series of research studies investigating the effects of RAC on pig welfare. Early research indicated that: (1) regardless of RAC administration, fatigued (non-ambulatory, non-injured) pigs

are in a state of metabolic acidosis; (2) aggressive handling increases stress responsiveness at 20 mg/kg RAC, while 5 mg/kg reduces stress responsiveness to aggressive handling. Given this information, dosage range for Paylean was changed in 2006 to 5 to 10 mg/kg in market weight pigs. Subsequent research on RAC demonstrated that: (1) RAC has minimal effects on mortality, lameness, and home pen behavior; (2) RAC fed pigs demonstrated inconsistent prevalence and intensity of aggressive behaviors; (3) RAC fed pigs may be more difficult to handle at doses above 5 mg/kg; and (4) RAC fed pigs may have increased stress responsiveness and higher rates of non-ambulatory pigs when subjected to aggressive handling, especially when 20 mg/kg of RAC is fed.

**Key words:** beta-agonist, handling, ractopamine, swine, welfare

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Transl. Anim. Sci. 2017.1:533–558  
doi:10.2527/tas2017.0060

### INTRODUCTION

Ractopamine (RAC) is a synthetic  $\beta$ -adrenergic agonist ( $\beta$ -agonist) approved for use in swine in 27 countries located in North and South America, and the Asia-Pacific regions (Elanco Animal Health, 2012). Ractopamine is marketed under the trade names of Paylean (Elanco Animal Health, Greenfield, IN) and Engain (Zoetis Inc., Kalamazoo, MI). Ractopamine is fed to improve feed efficiency and carcass leanness with minimal effects on fresh pork quality traits (Apple et al., 2007; Bohrer et al., 2013). Improvements in feed efficiency can lead to substantial reductions in natural

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Received September 1, 2017.

Accepted October 20, 2017.

resources used in pork production (Reese and Bitney, 2001; Capper, 2011; Woods et al., 2011). Sustainable swine production must balance efficient production, food safety, quality and security, environmental stewardship, and swine welfare (Velarde et al., 2015).

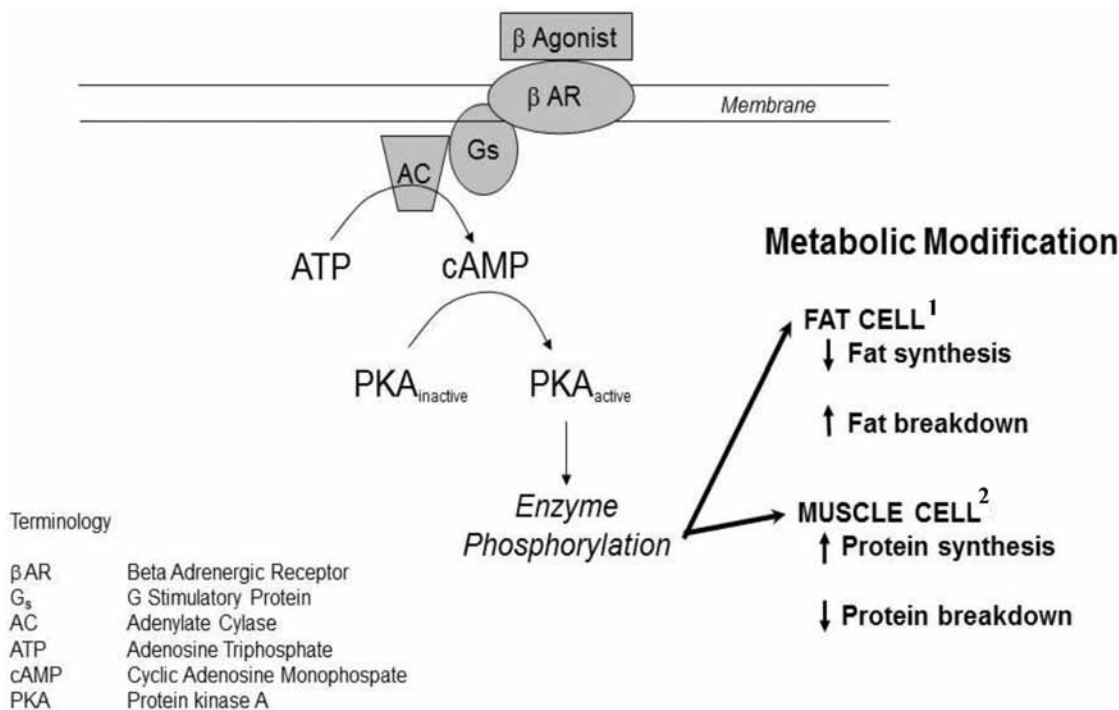
The use of  $\beta$ -agonists in swine (ractopamine) and beef (ractopamine and zilpaterol) production have recently been questioned due to reports of increased rates of non-ambulatory (i.e., fatigued and/or injured) pigs at packing plants (FDA, 2002), increased beef feedlot mortality (Loneragan et al., 2014), and abnormal cases of hoof sloughing at U.S. beef packing plants (Thomson et al., 2015). Although the economic and performance/carcass benefits of ractopamine are well known in swine (Apple et al., 2007), a comprehensive literature review on the effects of RAC on market weight pig welfare is needed for producers, veterinarians, food industries, and the general public to consider RAC's production benefits and perceived swine welfare risks. Therefore, the objective of this paper was to review the effects of RAC on market weight pig welfare.

### Ractopamine - Mode of Action

Ractopamine is a phenethanolamine and is similar in structure to natural (epinephrine and norepinephrine) and synthetic (cimiterol, clenbuterol, salbutamol, and zilpaterol)  $\beta$ -agonists (Mersmann, 1998; Moody et al.,

2000). These compounds bind to  $\beta$ -adrenergic receptors and redirect nutrients intended for fat growth toward muscle growth. There are 3 known  $\beta$ -adrenergic receptor subtypes:  $\beta$ 1,  $\beta$ 2, and  $\beta$ 3. These receptor sub-type densities vary by species and tissue type. For example, the  $\beta$ 1 receptor is the predominant subtype of swine adipose tissue and skeletal muscle, whereas  $\beta$ 2 is the predominant subtype found in beef cattle (Mersmann, 1998; Moody et al., 2000; Mills, 2002). Furthermore, each  $\beta$ -agonist shows preferential binding to either  $\beta$ 1 (ractopamine) or  $\beta$ 2 (cimiterol, clenbuterol, salbutamol, and zilpaterol) receptor subtypes. Therefore, the effects of  $\beta$ -agonists on growth and carcass traits varies across species and is dependent on the predominant  $\beta$ -receptor subtype of the animal and the preferential binding of the  $\beta$ -agonist fed (Moody et al., 2000).

When  $\beta$ -agonists bind to  $\beta$ -adrenergic receptors in adipose tissue, the G protein linked signaling system is activated, which elicits a cascade of events that results in increased lean muscle content in the animal's body (Fig. 1). Research has confirmed that RAC stimulates lipolysis and reduces lipogenesis in swine adipocytes through  $\beta$ 1 and  $\beta$ 2 receptors when protein kinase A activates hormone sensitive lipase and inactivates acetyl CoA carboxylase (Moody et al., 2000; Mills, 2002). Beta-agonists also increase carcass muscling through muscle fiber hypertrophy. Three studies have reported that RAC promotes a shift in muscle fiber type in market weight

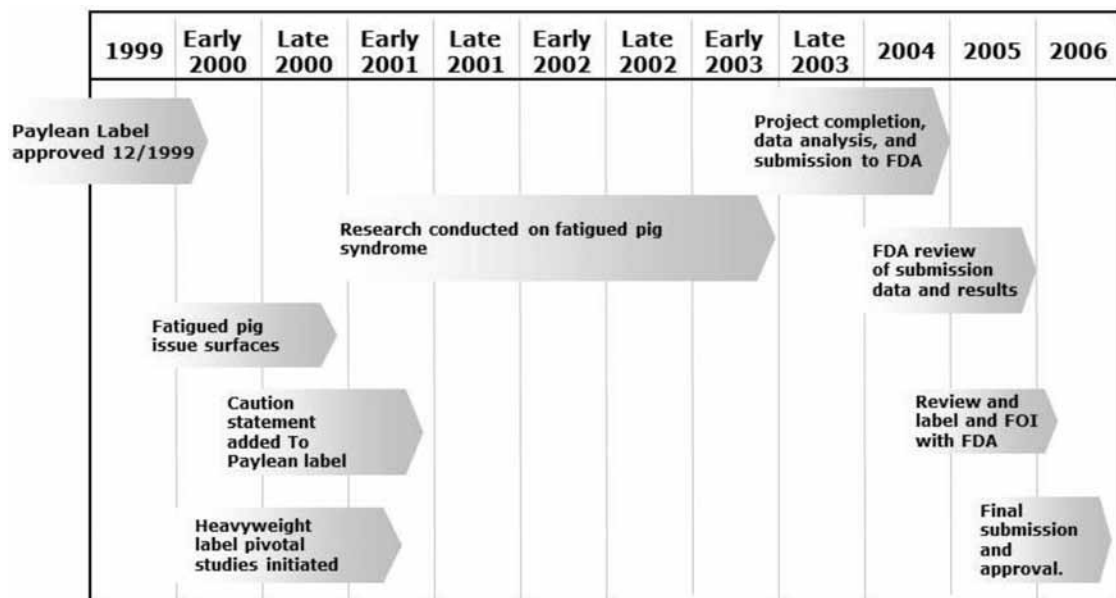


**Figure 1.** Mode of action of Ractopamine in swine (Adapted from Moody et al., 2000). <sup>1</sup> Protein kinase A stimulates lipolysis by activating hormone sensitive lipase and reduces lipogenesis by inactivating acetyl CoA carboxylase (Moody et al., 2000; Mills, 2002). <sup>2</sup> $\beta$ -agonists increase carcass muscling through muscle fiber hypertrophy (Moody et al., 2000; Mills, 2002). Muscle hypertrophy can be accomplished by increasing the rate of protein synthesis and/or by decreasing the rate of protein degradation (Moody et al., 2000; Mills, 2002).

pigs from Type IIA (fast-twitch, oxidative, glycolytic) to larger Type IIB (fast-twitch, glycolytic) muscle fibers (Aalhus et al., 1992; Depreux et al., 2002; Gunawan et al., 2007), and a more recent study showed that RAC (7.5 mg/kg over 28 d) increased muscle fiber IIX cross-sectional area (Li et al., 2015). Beta-agonists induce muscle hypertrophy by increasing the rate of protein synthesis and/or by decreasing the rate of protein degradation (Moody et al., 2000; Mills, 2002). It is currently believed that  $\beta$ 2-agonists increase the rate of protein synthesis and decrease the rate of protein degradation, while  $\beta$ 1-agonists, like RAC, increase the rate of protein synthesis (Moody et al., 2000). Ractopamine is more effective at improving carcass muscling than reducing carcass fat in market weight pigs, as the effects of RAC on carcass backfat varies across studies (Apple et al., 2007). Differences in RAC effectiveness on improving carcass muscling vs. reducing carcass fat is likely due to changes in downregulation or desensitization of  $\beta$ -adrenergic receptors in skeletal muscle and adipose tissue after prolonged use of RAC. Spurlock et al. (1994) found that  $\beta$ -adrenergic receptors were downregulated in subcutaneous fat by 30 to 53% in market weight pigs that were fed RAC for 8 d. This suggests that RAC may increase lipolysis and decrease lipogenesis in market weight pigs only for a short period of time. Meanwhile,  $\beta$ -adrenergic receptor density decreased by only 23% in *longissimus* muscle in market weight pigs fed RAC for 28 d, and this finding is consistent with recent work by Hinson et al. (2012) who reported that RAC increases loin muscle area linearly in market weight swine as RAC feeding duration increases from 7 to 35 d.

### ***Ractopamine - Approval and Launch in the U.S.***

Ractopamine (Paylean) was approved for use in market weight swine (68 to 109 kg) by the U.S. Food and Drug Administration (FDA) in December 1999 at doses of 5 to 20 mg/kg for improved rate of gain, improved feed efficiency, and increased carcass leanness (FDA, 1999). Paylean became commercially available in the summer of 2000, and producers began feeding RAC at 20 mg/kg for 42 d prior to harvest (T. Marsteller, Elanco Animal Health, Greenfield, IN, personal communication). Shortly thereafter, producers, transporters, and pork processors reported increased rates of non-ambulatory pigs at the packing plant (FDA, 2002; Fig. 2). Non-ambulatory pigs are defined as pigs that are unable to move or keep up with the rest of the group at the packing plant, and these pigs can be classified as either injured or fatigued (Anderson et al., 2002; Ritter et al., 2009a). Injured pigs include those that are lame or have a structural injury, whereas fatigued pigs are defined as pigs without obvious injury, trauma, or disease that refuse to walk at any stage of the marketing process from loading at the farm to stunning at the plant (Ritter et al., 2009a). Elanco Animal Health reported these adverse events to the FDA and worked with the FDA to modify the Paylean label. On June 1, 2001 the following cautionary statement was added to the label: "Caution: Pigs fed Paylean are at an increased risk for exhibiting the downer pig syndrome (also referred to as "slows", "subs", or "suspects"). Pig handling methods to reduce the incidence of downer pigs should be thoroughly evaluated prior to initiating use of Paylean" (FDA, 2002; Fig. 2).



**Figure 2.** Timeline depicting the chain of events after the approval and launch of Paylean.

### Ractopamine - Addressing Pig Welfare Concerns

After the cautionary statement was added to the Paylean label, a series of controlled studies (Fig. 2) were conducted to: a) understand the metabolic differences between normal and fatigued pigs at the packing plant; b) develop an animal handling model for researching predisposing factors associated with the fatigued pig syndrome; and c) evaluate the effects of feeding 20 mg/kg RAC on the physiological responses of market weight pigs.

**Metabolic Differences between Normal and Fatigued Pigs.** In January 2001, Elanco initiated a study at a Midwestern packing plant to compare the physiology of normal and fatigued pigs (Ivers et al., 2002). In this study, 35 trailer loads of pigs at the packing plant were utilized and within each load a fatigued pig and a normal pig were selected for physiological comparisons. Nineteen of the trailer loads evaluated contained pigs fed RAC (dosages not specified) and the remaining 16 loads did not receive RAC. The physiological comparisons between fatigued and normal pigs at the packing plant are summarized in Table 1. Fatigued pigs exhibited physical indicators of acute stress more frequently than normal pigs as evident by higher rates of skin discoloration, open-mouth breathing, muscle tremors, and abnormal vocalizations. Fatigued pigs demonstrated increased blood serum cortisol, epinephrine, norepinephrine, glucose, lactate, and creatine kinase values, and decreased liver and muscle glycogen stores, blood pH, blood bicarbonate, and blood base-excess values compared to clinically normal pigs. However, metabolic acidosis and physiological differences observed between normal and fatigued pigs were consistent regardless of RAC use (Ivers et al., 2002).

**Quantifying the Fatigued Pig Syndrome through an Animal Handling Research Model.** The incidence of non-ambulatory pigs was estimated to be approximately 0.75% at US packing plants in the early 2000s (Ellis et al., 2003). Therefore, animal handling models were developed to induce metabolic acidosis and fatigued pigs in controlled settings (Benjamin et al., 2001; Anderson et al., 2002; Hamilton et al., 2004). In these studies, RAC-free market weight pigs were moved approximately 300 m with aggressive (moved rapidly with 20 to 32 applications of an electric prod) or gentle (moved slowly without electric prods) handling (Benjamin et al., 2001; Anderson et al., 2002; Hamilton et al., 2004). Fatigued pigs were defined as non-ambulatory, non-injured and/or pigs showing physical indicators of acute stress (open-mouth breathing, skin discoloration, and/or muscle tremors) with rectal temperatures  $\geq 40.6^\circ\text{C}$ . The aggressive handling treatment induced metabolic acidosis and resulted in approximately 20% of the pigs being classified as fatigued (Benjamin et al., 2001; Anderson

**Table 1.** Physiological comparisons between fatigued and normal pigs at the packing plant<sup>1</sup>

Measurement	Fatigued <sup>2</sup>	Normal
Number of pigs	35	35
Physical indicators of acute stress, %		
Skin discoloration	77.1 <sup>a</sup>	0.00 <sup>b</sup>
Open-mouth breathing	44.1 <sup>a</sup>	0.00 <sup>b</sup>
Muscle tremors	82.9 <sup>a</sup>	2.86 <sup>b</sup>
Abnormal vocalizations	30.0 <sup>a</sup>	0.00 <sup>b</sup>
Rectal temperature, °C	38.4	38.9
Blood serum parameters		
Cortisol, ng/mL	230 <sup>a</sup>	141 <sup>b</sup>
Epinephrine, nmol/dL	365 <sup>a</sup>	9 <sup>b</sup>
Norepinephrine, nmol/dL	396.4 <sup>a</sup>	5.9 <sup>b</sup>
Creatine kinase, IU/L	20,674 <sup>a</sup>	4339 <sup>b</sup>
Blood plasma parameters		
Glucose, mmol/L	106.0 <sup>a</sup>	86.0 <sup>b</sup>
Lactate, mmol/L	33.1 <sup>a</sup>	11.5 <sup>b</sup>
pH	7.11 <sup>a</sup>	7.35 <sup>b</sup>
Bicarbonate, mmol/L	14.5 <sup>a</sup>	28.8 <sup>b</sup>
Base-excess, mmol/L	-16 <sup>a</sup>	2.1 <sup>b</sup>
Glycolytic potential, $\mu\text{mol/g}$		
Liver	66 <sup>a</sup>	196 <sup>b</sup>
<i>Longissimus</i> muscle	125 <sup>a</sup>	152 <sup>b</sup>
<i>Semitendinosus</i> red muscle	70 <sup>a</sup>	90 <sup>b</sup>
<i>Semitendinosus</i> white muscle	89	121

<sup>1</sup>Adapted from Ivers et al. (2002).

<sup>2</sup>Fatigued pigs are defined as non-ambulatory, non-injured pigs.

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

et al., 2002). These model studies demonstrate that pig handling methods have a major effect on market weight pig physiological responses and non-ambulatory rates, and this is supported by the findings of a recent commercial trial (Correa et al., 2010).

**Effects of 20 mg/kg RAC on the Physiological Responses of Market Weight Pigs.** A series of controlled studies were conducted to evaluate feeding RAC at 20 mg/kg on the physiological responses and transport losses (dead and non-ambulatory pigs at the packing plant) of market weight pigs. James et al. (2013) fed 384 pigs 0 or 20 mg/kg RAC for 28 d and then subjected them to gentle (moved at a moderate pace with a sorting board) or aggressive (moved rapidly with electric prods) handling. In the aggressive handling treatment, pigs fed 20 mg/kg RAC had higher rectal temperatures, higher blood lactate, and lower blood pH values than control pigs. However, there were no effects of RAC on physiological responses when pigs were moved with gentle handling procedures.

An internal Elanco study (K. D. Miller, unpublished data) evaluated the physiological responses of 150 market weight pigs fed either 0 or 20 mg/kg RAC for 31 d and then subjected the pigs to the gentle or aggressive handling treatments as described by Hamilton et al.

(2004). The investigators reported that feeding 20 mg/kg of RAC increased the fatigued pig percentage at the end of the aggressive handling procedure, however, feeding RAC did not affect the rate of fatigued pigs when gentle handling was used (Table 2). The results of Miller (unpublished data) are confirmed by another internal Elanco study (Ivers, unpublished data), who fed 144 pigs either 5 or 20 mg/kg RAC for 31 d and then subjected them to the gentle or aggressive handling described by Anderson et al. (2002). Ivers (unpublished data) found that pigs fed 20 mg/kg of RAC had a higher percentage of fatigued pigs during aggressive handling than pigs fed 5 mg/kg, but there was no effect of RAC dose on fatigued pigs during gentle handling procedures (Table 2). Collectively, these handling model studies suggest feeding RAC at 20 mg/kg and the subsequent physiological responses and fatigued pig rates are dependent on handling procedures. Furthermore, the effects of feeding 20 mg/kg RAC may be mitigated by using gentle handling procedures and/or by feeding a lower RAC dose (5 mg/kg).

### Paylean Label Change: Dose and Live Weight

The U.S. national average market pig slaughter weight in 1999 was 117.5 kg (USDA-NASS, 2012), which exceeded the range of approved live weights (68 to 109 kg) for Paylean usage (FDA, 1999). Therefore, a heavy weight label change was initiated by Elanco in the early 2000s, which resulted in the 20 mg/kg dose being removed from the Paylean label (Fig. 2). Clinical trials by Elanco (FDA, 2006) were then initiated to demonstrate RAC safety and efficacy in heavier weight market pigs at doses of 5 to 10 mg/kg. As part of the label change requirements, a target animal safety study (Gillis et al., 2007) and a post-approval safety surveillance study (Swan et al., 2007) were conducted to determine RAC effects on physiological responses to handling and transport losses (dead and non-ambulatory pigs) at the packing plant.

Gillis et al. (2007) fed RAC at 0, 5, or 10 mg/kg for 35 d and then subjected pigs to either low or high stress handling procedures from loading at the farm to stunning at the plant (Table 3). The authors concluded that RAC had minimal effects on physiological responses to handling and transport losses (dead and non-ambulatory pigs), but may affect the number of “Injured, ambulatory” pigs when high stress handling procedures are used to move market weight pigs during the final drive from the lairage pen to the stunning area.

In a year-long study, Swan et al. (2007) monitored the incidence of dead and non-ambulatory pigs in the Midwestern and Southeastern regions of the U.S. (Table 4). Pigs were fed 0, 5, or 10 mg/kg RAC for 21 to 35 d prior to harvest. Within each region, the effects of RAC were evaluated on pigs from 4 different swine farms that were marketed to the same packing plant. Ractopamine increased total transport losses (dead and non-ambulatory pigs) in the Midwest region, but not in the Southeast. The inconsistent effects of RAC on transport losses across regions may be attributed to regional differences in climate, management practices, facility designs, and pig handling/transportation practices (Table 5). The results from this study suggest that the effects of RAC on transport losses are dependent on handling and transportation procedures, which are known stressors for market weight pigs (Schwartzkopf-Genswein et al., 2012; Johnson et al., 2013).

Overall, RAC heavy weight clinical trials demonstrated that RAC can be safely fed to market weight pigs at doses of 5 to 10 mg/kg for up to 35 d prior to market and RAC may increase the rate of non-ambulatory pigs at the packing plant, especially under aggressive handling and adverse transport conditions. It is important to note that the U.S. Paylean label was amended in April 2006 to reflect that (1) RAC can be fed to market weight pigs weighing greater than 109 kg and (2) the maximum approved RAC dose was reduced from 20 to 10 mg/kg. The U.S. Paylean label now states that (a) doses of 5

**Table 2.** Effects of ractopamine (RAC) and handling treatment on the percentage of fatigued pigs in handling model studies<sup>1</sup>

Study	Pigs, #	RAC duration, d	RAC × Handling treatment subclasses <sup>2</sup>					
			Gentle handling <sup>3</sup>			Aggressive handling <sup>4</sup>		
			0 mg/kg	5 mg/kg	20 mg/kg	0 mg/kg	5 mg/kg	20 mg/kg
Miller, unpublished data	150	31	0.0% <sup>a</sup>	–	0.0% <sup>a</sup>	0.0% <sup>a</sup>	–	39.0% <sup>b</sup>
Ivers, unpublished data	144	31	–	0.0% <sup>a</sup>	5.6% <sup>a</sup>	–	25.0% <sup>b</sup>	61.1% <sup>c</sup>

<sup>1</sup>Fatigued pigs were defined as non-ambulatory, non-injured, and/or pigs showing clinical signs of acute stress (open-mouth breathing, skin discoloration, and/or muscle tremors) with rectal temperatures  $\geq 40.6^{\circ}\text{C}$ .

<sup>2</sup>RAC × handling interactions existed for the percentage of fatigued pigs ( $P < 0.05$ ).

<sup>3</sup>Gentle handling: pigs were moved slowly without electric prods.

<sup>4</sup>Aggressive handling: pigs were moved rapidly with 18 (Ivers, unpublished data) or 32 (Miller, unpublished data) applications of an electric prod.

<sup>a-c</sup>Means with different superscripts differ ( $P < 0.05$ ).

**Table 3.** Effects of ractopamine (RAC) dose and handling methods on dead and non-ambulatory pigs<sup>1,2</sup>

Measurement	RAC dose			P-values		
	0 mg/kg	5 mg/kg	10 mg/kg	0 vs. 5	0 vs. 10	5 vs. 10
Number of pigs	96	95	96	–	–	–
Loading observations <sup>3</sup>						
Dead, %	0.00	0.00	0.00	–	–	–
Fatigued, % <sup>4</sup>	0.00	0.00	0.04	1.00	0.25	0.25
Injured, non-ambulatory, % <sup>5</sup>	0.00	0.00	0.00	–	–	–
Injured, ambulatory, % <sup>6</sup>	0.04	0.07	0.04	0.49	1.00	0.49
Unloading observations <sup>7</sup>						
Dead, %	0.04	0.00	0.00	0.25	0.25	1.00
Fatigued, % <sup>4</sup>	0.00	0.04	0.00	0.25	1.00	0.25
Injured, non-ambulatory, % <sup>5</sup>	0.00	0.00	0.00	–	–	–
Injured, ambulatory, % <sup>6</sup>	0.11	0.25	0.22	0.14	0.22	0.78
Final drive observations <sup>8</sup>						
Dead, %	0.00	0.00	0.00	–	–	–
Fatigued, % <sup>4</sup>	0.00	0.00	0.00	–	–	–
Injured, non-ambulatory, % <sup>5</sup>	0.00	0.00	0.00	–	–	–
Injured, ambulatory, % <sup>6,9</sup>						
Low stress handling	0.00	0.35	0.07	0.01	0.38	0.01
High stress handling	0.07	0.26	0.33	0.09	0.03	0.47

<sup>1</sup>Adapted from Gillis et al. (2007).

<sup>2</sup>A total of 288 market weight pigs were used in a 3 × 2 factorial arrangement of treatments consisting of ractopamine dose (0 vs. 5 vs. 10 mg/kg) fed for 34 to 36 d and handling method (low stress vs. high stress handling).

<sup>3</sup>Loading observations were made as pigs were moved with either low stress or high stress handling from their home pen through a handling course and during loading onto a trailer.

<sup>4</sup>Fatigued was defined as a pig that became unwilling or unable to move in response to the handler's inputs for no physically apparent reason (i.e., no obvious injury).

<sup>5</sup>Injured, non-ambulatory was defined as pigs that were recumbent and unwilling or unable to move due to an obvious injury such as a broken leg or trauma.

<sup>6</sup>Injured, ambulatory was defined as pigs able to move and keep up with the contemporary group, but were obviously injured (obvious limp; i.e., foot, leg, or shoulder injury).

<sup>7</sup>Unloading observations were made as pigs were unloaded after a 3 h journey and moved with either low or high stress handling from the trailer to a lairage pen.

<sup>8</sup>Final drive observations were made after the pigs were allowed to rest in lairage (low stress = 4 h; high stress = 2 h) and during movements from the lairage pen to the stunning pen with either low stress or high stress handling procedures.

<sup>9</sup>Indicates a ractopamine × handling method interaction ( $P < 0.05$ ).

**Table 4.** Effects of ractopamine (RAC) and U.S. region on the rate of transport losses from loading at the farm to stunning at the packing plant<sup>1</sup>

Transport losses <sup>2</sup>	RAC dose			P-values	
	0 mg/kg	5 mg/kg	10 mg/kg	0 vs. 5	0 vs. 10
Midwest Region					
Number of pigs loaded	5577	5580	5568	–	–
Fatigued, %	0.86	1.66	1.32	0.01	0.10
Injured, %	0.26	0.53	0.59	0.05	0.03
Dead, %	0.15	0.38	0.33	0.05	0.12
Total transport losses, %	1.33	2.63	2.26	< 0.001	0.01
Southeast Region					
Number of pigs loaded	5795	5778	5776	–	–
Fatigued, %	0.63	0.48	0.61	0.40	0.93
Injured, %	0.43	0.30	0.61	0.35	0.28
Dead, %	0.21	0.12	0.32	0.33	0.35
Total transport losses, %	1.35	0.85	1.55	0.07	0.58

<sup>1</sup>Adapted from Swan et al. (2007).

<sup>2</sup>Transport loss classifications during loading at the farm, unloading, and moving through the plant included fatigued (defined as pig that became unwilling or unable to move in response to the handler's inputs for no physically apparent reason (i.e. no obvious reason), injured (defined as a pig that was recumbent and unwilling to move due to an obvious injury such as a broken leg or trauma), and total transport losses (included all fatigued, injured, and dead pigs recorded during transportation procedures).

**Table 5.** Summary of handling and transport conditions by U.S. region<sup>1</sup>

Measurements	Region	
	Midwest	Southeast
Number of trailer loads	96	96
Distance pigs moved, m		
Loading	49	67
Unloading	133	78
Final drive	103	66
Electric prod usage, % loads <sup>2</sup>		
Loading	100	100
Unloading	52	0
Final drive	97	0
Event times, min <sup>3</sup>		
Loading	47	47
Transportation	111	50
Wait at plant	69	45
Unloading	53	20
Lairage	106	300

<sup>1</sup>Adapted from Swan et al. (2007).

<sup>2</sup>Electric prod usage was measured during transportation procedures that were defined as the exit from the farm pen to loading onto the truck (Loading), animals exiting the truck through arrival at the holding pen (Unloading), and exit from the lairage pen to the stunning area (Final drive).

<sup>3</sup>Duration of loading, transportation, waiting time prior to unloading, unloading time, and lairage time.

to 10 mg/kg are approved for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in market weight swine, (b) swine must not weigh less than 68 kg and must be fed a complete ration containing at least 16% crude protein for the last 20 to 41 kg of live weight gain prior to slaughter, and (c) the following caution statement was added: “Ractopamine may increase the number of injured and/or fatigued pigs during marketing” (FDA, 2006).

## RESULTS

Determining an animals' welfare can include both animal- and resource-based measures. When considering the animal, we determine how well an animal copes when presented with internal and external stressors. A multimodal approach is often taken that includes physiological, behavioral, and immunological responses to challenges (OIE, 2015). When considering resource-based measures, housing and management practices are reviewed and an assessment is completed.  $\beta$ -agonist use has raised concerns regarding negative impacts to pig welfare (BBFAW, 2014); for example, concerns have been raised about the effects of  $\beta$ -agonists on swine behavior (Marchant-Forde and Poletto, 2015), ease of handling (Grandin, 2015; Marchant-Forde and Poletto, 2015) and an increased incidence non-ambulatory pigs at the packing plant (Grandin, 2015). Therefore, the following sections summarize the effects of RAC on (a) mortality, (b) lameness and injury, (c) general in-pen behavior, (d) agonistic behavior, (e) ease of handling, (f) fatigued pig symptoms, and (g) physiological responses to handling in market weight pigs. The majority of the studies reviewed fed RAC at doses of 5, 7.5, 10, or 20 mg/kg for feeding durations of 21 to 42 d. Currently, the 2 most common RAC feeding programs in North America are 5 and 7.5 mg/kg for 21 to 35 d prior to the barn close-out (Kutzler et al., 2011; Hinson et al., 2012), with 5.6 mg/kg being the average dose fed by the U.S. swine industry in 2014 (Agri Stats, 2015).

### *Effects of Ractopamine on Mortality*

Although no experiments have been designed to specifically evaluate RAC effects on swine mortality, Table 6 provides a review of 11 controlled, commercial studies involving over 15,000 pigs and shows minimal differences in pig mortality when fed at 0, 5, or 7.5 mg/kg RAC. It is important to note that U.S. wean-to-finish mortality was reported to be 9.3% in 2011 by the Agri Stats database, which represents approximately 40 M market pigs (Bilbrey, 2012), and that the studies in Table 6 only tracked mortality for the last 18 to 28 d

**Table 6.** Effects of ractopamine (RAC) dose on the mortality of market weight pigs during the feeding period

Study	Pigs, #	Duration, d	RAC dose		
			0 mg/kg	5 mg/kg	7.5 mg/kg
Parks et al., 2007	1671	24.5	1.79	2.15	2.16
Hinson et al., 2012 <sup>1</sup>	1635	21	1.20	0.62	0.82
Hinson et al., 2012	1708	21	0.96	0.43	0.29
Pompeu et al., 2013	1102	27	0.18	—	0.36
Ritter, unpublished data	694	18	1.15	0.86	—
Tavárez et al., 2012	261	28	0.77	—	0.00
Gerlemann et al., 2013 <sup>2</sup>	1744	26	0.17	—	0.26
Gerlemann et al., 2014	1740	28	0.46	—	0.34
Christianson et al., 2014 <sup>2</sup>	2471	23	0.12	—	0.49
Pelger, unpublished data <sup>2</sup>	742	27	0.00	0.53	0.54
Ritter et al., 2011	1476	24	0.41	0.61	0.41
Total Pigs Evaluated	15,244	24.1 <sup>3</sup>	5191	2602	7451
<i>Weighted Average Mortality for 0 vs 5 mg/kg<sup>4</sup>, %</i>			1.08	0.92	—
<i>Weighted Average Mortality for 0 vs 7.5 mg/kg<sup>4</sup>, %</i>			0.54	—	0.56

<sup>1</sup>Includes a 7.5 mg/kg treatment, a 5 to 7.5 mg/kg step-up program, and a 5 to 10 mg/kg step-up program.

<sup>2</sup>Includes both a 7.5 mg/kg treatment and a 5 to 10 mg/kg step-up program.

<sup>3</sup>Weighted average duration of feeding.

<sup>4</sup>Weighted average treatment mortality was calculated using only studies where direct comparisons were available, with each study weighted by sample size.

prior to market when RAC was fed. Furthermore, the mortality data in Table 6 were not divided into cause of death due to: 1) limited overall differences between control and RAC treatments; and 2) the subjective nature of diagnosing cause of death. The causes of death reported in these studies were related to general health issues commonly found in market weight pigs such as hemorrhagic bowel, respiratory issues, and gastric ulcers. Overall, the studies presented in Table 6 demonstrate that feeding 5 and 7.5 mg/kg of RAC to market weight pigs has minimal effects on mortality during the last 18 to 28 d prior to market.

### *Effects of Ractopamine on Lameness and Injuries*

As mentioned previously, RAC may contribute to an increased number of fatigued and injured pigs during unloading (Swan et al., 2007) and injured pigs during the final drive at the packing plant (Gillis et al., 2007), especially when aggressive handling methods are implemented. Poletto et al. (2009) reported that pigs fed a 5 to 10 mg/kg RAC step-up diet had more total hoof lesions compared to control pigs (Table 7). It is important to note that hoof lesions were not evaluated in the RAC heavy weight clinical safety studies (FDA, 2006; Gillis et al., 2007; Swan et al., 2007), so it is possible that hoof lesions may have contributed to the higher injured pig rates observed at the packing

**Table 7.** Effects of ractopamine (RAC) dose on lameness of market weight pigs

Authors	RAC doses	Duration, d	Pigs, #	Treatments	Measurements	Results
Campos et al., 2012	0 and 5 mg/kg	34	112	Fed 4 different available phosphorous (AP) concentrations (0.109%, 0.209%, 0.309%, and 0.409%).	Bone strength, calcium, phosphorus, and ash concentrations of metatarsals.	No effect of RAC on parameters evaluated, and no interaction with phosphorus level. Authors recommend feeding 0.33% AP to RAC and control pigs.
Poletto et al., 2009	0 mg/kg and RAC step-up (5 to 10 mg/kg)	31	32	Treatments: diet (RAC vs. control), gender (barrows vs. gilts), and social rank (dominant vs. subordinate).	Number of splits, cracks-erosions, and bruises on the front and rear hooves.	Average of 2.1 more total lesions across all hooves with RAC. One RAC pig required treatment for lameness vs. 2 control pigs.
Pardo et al., 2004	0 and 10 mg/kg	28	120	Different combinations of RAC, phytase (0 vs. 500 FTU/kg), and inorganic P (0.45 vs. 0.65%) were fed.	Metacarpal bone ash, force, and stress.	RAC did not compromise bone traits. However, bone traits improved when inorganic P was increased 0.2%
Lutz and Stahly, 2003	0 and 20 mg/kg	35	120	Fed 6 different available phosphorous (AP) concentrations (0.08%, 0.13%, 0.18%, 0.23%, 0.28%, and 0.33%) and kept the Ca:AP ratio constant at 2.5:1.	Ham-loin bone weight and mineral content of the fifth vertebrae and femur.	RAC reduced bone weights and bone mineral content. Authors recommend increasing AP in RAC diets by 0.02 to 0.03%.
He et al., 1993	0 and 20 mg/kg	43	48	Treatments evaluated included diet (RAC vs. control), gender (gilt vs. barrow), and crude protein (17 vs. 20%).	The incidence and severity of osteochondrosis, as measured by bone accretion rates, joint-cartilage soundness and uronic acid concentrations.	RAC did not affect bone accretion rates, the incidence or severity of joint-cartilage soundness, or uronic acid concentrations.

plant for RAC fed pigs. Additional research is necessary to understand the effects of RAC on hoof lesions and the effect hoof lesions have on the incidence of injured pigs at the packing plant.

Another factor that could affect lameness and injuries in RAC fed pigs is bone strength/density. He et al. (1993) reported that feeding RAC at 0 or 20 mg/kg to pigs for 43 d did not adversely affect the incidence and severity of osteochondrosis (Table 7). However, carcass dissection studies have shown that RAC increases total carcass lean muscle weights while decreasing total carcass fat and bone weights in market weight pigs (Bark et al., 1992; Crome et al., 1996). It is important to note that phosphorus is needed to support both muscle and bone growth. On this basis, Lutz and Stahly (2003) hypothesized that RAC fed pigs may require additional dietary phosphorous to maximize muscle accretion rates and to minimize potential reductions in bone mass. Therefore, a number of studies have been conducted to determine the phosphorus requirements for RAC fed pigs.

The effects of RAC on bone strength are summarized in Table 7. Lutz and Stahly (2003) evaluated 6 different phosphorous concentrations in control vs. RAC fed pigs and reported that feeding 20 mg/kg of

RAC for 35 d reduced bone weights and bone mineral content. These authors recommended that RAC diets should be supplemented with additional available phosphorus to maintain the same bone mineral content as control pigs. Contrary to these results, Campos et al. (2012) fed 4 different levels of available phosphorus to control and RAC pigs, and concluded that feeding RAC at 5 mg/kg for 34 d did not affect bone strength or the percentage of bone phosphorus, calcium, or ash. Pardo et al. (2004) evaluated the effects of phytase and inorganic phosphate in pigs fed 0 or 10 mg/kg of RAC for 28 d and reported that RAC did not adversely affect bone traits compared to control pigs. However, these authors did report that bone traits were improved when inorganic phosphate was increased in RAC diets.

Overall, the findings presented above and in Table 7 demonstrate that (1) feeding 20 mg/kg of RAC may decrease bone mass and strength, but there are minimal effects of RAC on bone traits at low doses (5 to 10 mg/kg) and (2) RAC effects on bone mass and strength can be managed by increasing dietary phosphorous concentrations. Additional research is warranted to determine RAC effects on hoof lesions and the incidence of injured pigs at the packing plant.



### Effects of Ractopamine on Pig Behavior in Pens

A review of 6 studies that evaluated RAC on market weight pig home and lairage pen behavior is provided in Table 8. Two of the 6 studies reported that RAC fed pigs were more alert and active in their home pen than were control pigs (Marchant-Forde et al., 2003; Poletto et al., 2010a). Marchant-Forde et al. (2003) found that pigs fed 10 mg/kg RAC spent more time performing active behaviors (walking, rooting, manipulating pen mates and pen components, and belly-nosing) and were more alert in the home pen. The RAC fed pigs also took longer to lie down after being disturbed compared to control pigs during wk

1 and 2, but not wk 3 and 4 (Marchant-Forde et al., 2003). Likewise, Poletto et al. (2010a) used a 2 × 2 × 2 factorial arrangement of the following treatments: (1) RAC for 28 d (control vs. RAC 5 to 10 mg/kg step-up); (2) gender (barrows vs. gilts); and (3) social rank (dominant vs. subordinate) to determine behavioral effects. These authors reported that RAC fed pigs spent more time active (defined as being alert, bar biting, sham chewing and feeding behaviors, walking, nosing or rooting, chain chewing, non-agonistic interactions, drinking, and feeding) and alert in their home pens than control pigs. Treatment differences for activity level and alertness in the home pen were mainly

**Table 8.** Effects of ractopamine (RAC) dose on home pen and lairage pen behavior of market weight pigs

Authors	RAC dose	Duration, d	Pigs, #	Measurements	Results
Athayde et al., 2013	0, 5, and 10 mg/kg	28	340	Behavior scan sampling in the home pen was conducted (6 times per d, 3 d per wk) on: calm behaviors (lying, standing, and sitting); moving behaviors (nosing, biting, walking, exploring, running, playing, and mounting); and feeding behaviors (eating feed and drinking water).	RAC had no effect on behavior when the 13 behaviors were grouped and summarized as calm, moving, or feeding behaviors. Relative to controls, 5 mg/kg RAC increased nosing by 1.11% and drinking by 0.48%, and reduced playing by 0.20%, while RAC 10 mg/kg increased standing by 0.54%.
Rocha et al., 2013	0 and 7.5 mg/kg	28	1488	Behavior scan sampling was conducted (every 2 min during the first h of lairage) on: lying, sitting, and standing behaviors.	RAC did not affect the % of pigs standing, sitting, or lying in the lairage pen at the packing plant.
Poletto et al., 2010a	0 mg/kg and RAC step-up (5 to 10 mg/kg)	28	32	Behavior scan sampling was conducted on subordinate and dominant pigs in the home pen (every 10 min for 24 h on d 2, 5, 8, 12, 15, 19, 22, and 26 of RAC feeding) on: activity (alert, walking, nosing or rooting, bar biting, sham chewing, chain chewing), non-agonistic interactions (drinking, feeding), inactivity, and posture (standing, lying, sitting).	RAC increased % sitting (1.5%) and decreased % lying (2.3%), but did not affect % standing. RAC pigs spent 3.9% more time being active via increases in alertness (2.2%), bar biting (0.2%), sham chewing (0.7%), and feeding behaviors (0.9%). Differences in activity were statistically significant only on d 12, 15, 19, and 26.
Benjamin et al., 2006	0 and 10 mg/kg	28	288	Willingness to approach a novel handler sitting in the home pen after a disturbance was measured by latency approach time for 5 out of 6 pigs to contact and touch the handler on d 7 and 28 of RAC feeding.	Feeding RAC at 10 mg/kg did not affect willingness to approach a handler after a disturbance.
Marchant-Forde et al., 2003	0 and 10 mg/kg	28	72	Behavior scan sampling in the home pen was conducted (every 5 min for 22 h, one time per wk) on: inactivity vs. activity (walking, rooting, manipulating pen mates/pen components, and belly nosing), alertness, chewing, agonistic interactions, drinking, feeding, and posture (lying, standing, and sitting). Pigs were also subjected to weekly disturbance tests, and latency to lie down after disturbance was recorded.	Over the 4 wk feeding period, RAC pigs spent more time active (3.5%), feeding (0.8%), lying sternally (5.8%), and less time lying laterally (7.3%) than controls. RAC fed pigs spent 5.6% more time active and 1.9% more time alert during wk 1 and 2. Differences were not significant on wk 3 and 4. RAC pigs took on average 297 s more to lie down after disturbance during wk 1 and 2.
Schaefer et al., 1992	0, 10, 15, and 20 mg/kg	38.5	86	Behavior scan sampling was conducted in the home pen (every 5 min for 4 h) on: investigating/walking, drinking, feeding, sleeping (individually and in groups), nosing (nose to nose contact and nose to body contact), agonistic, and sexual behaviors.	Relative to controls, 20 mg/kg RAC pigs spent 8.3% less time walking and investigating, and 10 mg/kg RAC pigs spent 0.9% less time engaged in nose to nose contact. RAC groups (10, 15, and 20 mg/kg) spent 15% more time sleeping than controls in the 30 min following a meal. No abnormal, stereotyped, or agonistic behaviors were observed in pigs fed 10, 15, or 20 mg/kg of RAC.

observed toward the end of the study when the RAC step-up treatment dose was increased to 10 mg/kg.

In contrast to the studies above, 4 studies have reported minimal RAC effects on market weight pig behavior. Schaefer et al. (1992) reported that pigs fed 20 mg/kg spent less time walking and investigating their pen compared to pigs fed 10 mg/kg RAC or control pigs. In addition, these authors reported no RAC effect on abnormal, stereotypic, or agonistic behaviors. Similarly, Athayde et al. (2013) reported no effect of 5 or 10 mg/kg RAC on calm (lying, sitting, or standing), moving, or feeding behaviors. In response to a novel handler entering pig home pens, Benjamin et al. (2006) reported no difference in latency to approach handlers for market weight pigs fed 0 or 10 mg/kg RAC. Furthermore, Rocha et al. (2013) reported no difference in standing, sitting, or lying behaviors during lairage for pigs fed either 0 or 7.5 mg/kg of RAC.

Overall, the studies presented above and in Table 8 show that the effects of RAC on home pen and lairage pen behavior are inconsistent in the literature. Two studies reported that RAC fed pigs were more active and alert, while 4 other studies reported that RAC did not affect general pig behavior. Additional behavioral research is warranted to (1) better understand the effects of RAC dose and duration on general pig behaviors and (2) understand if more active and alert behaviors translate to changes in stress physiology.

### ***Effects of Ractopamine on Agonistic Behavior***

Table 9 summarizes 6 studies that investigated RAC effects on agonistic behavior in market weight pigs. Agonist behaviors measured in these studies included aggressive behaviors displayed among pigs in home and lairage pens, and the number of skin/carcass lesions at the packing plant. Poletto et al. (2010a; 2010b) utilized a  $2 \times 2 \times 2$  factorial arrangement of RAC (0 vs. 5 to 10 mg/kg step-up), gender (barrows vs. gilts), and social ranking (dominant vs. subordinate) to evaluate agonistic behaviors of market weight pigs toward pen mates (Poletto et al., 2010a) and unfamiliar pigs (Poletto et al., 2010b) on the same group of 64 pigs. Poletto et al. (2010a) reported that the total number of agonistic social interactions in the home pen was not affected by RAC or gender. However, there were RAC  $\times$  gender interactions for the percent change in average number of bites, pursuits, and total actions per agonistic interaction relative to baseline values. These authors inferred that RAC increased aggressive gilt behavior, but not barrows. The study by Poletto et al. (2010b) evaluated the effects of RAC on the aggressive encounters between gender and social rank of unfamiliar pigs using a resident-intruder (R-I) test for 300 s. Latency to

first attack was not affected by RAC, however, there were RAC  $\times$  gender  $\times$  social rank interactions for the cumulative frequency of attacks by resident pigs at 30, 90, 180, and 300 s of the R-I test. During the first 30 s of all the R-I tests, RAC dominant and RAC subordinate gilts had higher cumulative attack rates than the other treatment combinations. From these results, the authors inferred that gilts are more agonistic when fed RAC, and that the underlying mechanisms may relate to the dopaminergic and serotonergic systems in the brain that are associated with aggression regulation (Poletto et al., 2010b; Poletto et al., 2011). It is interesting to note that in one of the companion papers to the Poletto et al. (2010a; 2010b) studies, the increased levels of aggression reported for RAC fed gilts in these studies did not translate to: (1) negative effects on growth performance traits (RAC improved ADG by 16%); (2) increased number of therapeutic treatments for lameness (1 RAC and 2 control); or (3) increased morbidity/mortality (all 32 test pigs completed the study) during the 28 d feeding period (Poletto et al., 2009).

Minimal effects of RAC on aggression and skin/carcass lesions have been reported by Rocha et al. (2013), who utilized a  $2 \times 2 \times 2$  factorial arrangement of treatments to evaluate the effects of genetic line (2 crossbreeds with either 25 vs. 50% Piétran genetics), castration method (immunocastrates vs. surgical), and RAC (0 vs. 7.5 mg/kg) on agonistic behaviors during lairage. These authors reported that fighting bouts were shorter among RAC fed pigs vs. controls, and a more than two-fold greater number of fights were observed in the 25% Piétran pigs vs. 50% Piétran pigs. There was a RAC  $\times$  castration method interaction for the number of fights that occurred, where RAC increased the number of fights within immunocastrates, but not in surgical castrates. However, the effects of RAC on fighting may have been minor as this did not result in greater carcass damage scores at the plant. The results of Rocha et al. (2013) align with a previous study that reported no effects of RAC on skin/carcass lesions (Athayde et al., 2013). Lastly, other studies designed to measure the impact of RAC on general behaviors reported minimal RAC effects on agonistic behaviors (Schaefer et al., 1992; Marchant-Forde et al., 2003).

Overall, RAC effects on agonistic market weight pig behaviors are inconsistent in studies reported in the literature and listed in Table 9. This may be attributed to differences in study methodology and degree of mixing unfamiliar pigs. Additional studies involving a larger number of market weight pigs under typical U.S. commercial conditions are needed to understand (1) RAC effects on aggression in the home pen and during mixing of unfamiliar pigs during transport and lairage at the packing plant and (2) the interactive

**Table 9.** Effects of ractopamine (RAC) on agonistic behavior in market weight pigs

Authors	RAC dose	Duration, d	Pigs, #	Methodology	Results
Rocha et al., 2013	0 and 7.5 mg/kg	28	1488	Continuous observation of agonistic behaviors during the first hour of lairage was conducted on the number and duration of fights (a sequence of 2 or more pigs biting, head knocking, pushing, and shoving lasting greater than 3 s). Skin damage and bruising were evaluated using a 5-point photographic scale) in the cooler the d of slaughter.	RAC fed immune-castrates had 4 more fights than non-RAC immune-castrates, and 10 more fights than RAC fed surgical castrates ( $P < 0.05$ ). RAC pigs fought for shorter durations (5 s; $P = 0.05$ ) than control pigs. RAC had no effect on overall skin damage score.
Athayde et al., 2013	0, 5, and 10 mg/kg	28	90	The number of skin and carcass lesions were evaluated on the shoulder, loin, and ham of pigs before loading, after unloading, during lairage, and 24 h after slaughter.	RAC and gender had no effects on the total number of skin or carcass lesions.
Poletto et al., 2010a	0 mg/kg and RAC step-up (5 mg/kg for 14 d, then 10 mg/kg for 14 d)	28	32	Continuous observation was conducted in the home pen (for 3 h periods, once per wk for 5 wk) on the number of agonistic social interactions (Offensive behaviors: bites, head knocks, pursuit, threats; Defensive behaviors: freeze, avoidance or flight) and constituent actions displayed by 2 pigs.	The average number of agonistic interactions increased (55%) in RAC fed gilts and decreased (approximately 26%) in all other RAC $\times$ Gender treatments. RAC fed gilts increased bites (96%) and pursuits (335%) per agonistic interaction vs. baseline, while decreased bites (34%) and pursuits (46%) occurred in the other RAC $\times$ Gender treatments ( $P < 0.001$ ). Head knocks per agonistic interaction increased for RAC fed barrows (14%) and CON gilts (21%) vs. baseline, and decreased head knocks (20%) occurred in the other RAC $\times$ Gender treatments ( $P < 0.05$ ). The total number of agonistic social interactions was not affected by RAC.
Poletto et al., 2010b	0 mg/kg and RAC step-up (5 mg/kg for 14 d, then 10 mg/kg for 14 d)	28	32	Dominant and subordinate pigs from each pen were subjected to six 300 s resident-intruder (R-I) tests on d -6, -5, 9, 10, 23, and 24 of the feeding trial. The latency to the first attack (physical bite or a sequence of bites) and number of attacks over the 300 s tests by resident and intruder pigs were recorded.	RAC did not affect the latency to first attack. There was a significant RAC $\times$ gender $\times$ social rank interaction for the increased likelihood of resident dominant control gilts initiating bites compared to subordinate control (272%) and subordinate RAC fed gilts (276%), but not different from dominant RAC fed gilts. At 30 s of the R-I tests, increased cumulative resident pig attacks occurred by the RAC dominant gilts (38%) and RAC subordinate gilts (42%) vs. the average frequency (11%) of the other treatments. At 300 s, higher cumulative attacks occurred by control dominant gilts (92%), RAC dominant barrows (79%), and RAC subordinate gilts (79%) compared to control subordinate gilts (46%) and barrows (54%), and RAC subordinate barrows (46%). Within RAC, the odds of biting increased for dominant resident pigs (gilts = 228%; barrows = 185%), and subordinate barrows were 58% more likely to initiate bites than subordinate RAC fed gilts.
Marchant-Forde et al., 2003	0 and 10 mg/kg	28	72	Behavior scan sampling in the home pen was conducted (every 5 min for 22 h, one time per wk) on agonistic interactions. Pigs were also subjected to weekly disturbance tests, and latency to lie down after disturbance was recorded.	RAC had no effects on agonistic behaviors.
Schaefer et al., 1992	0, 15, and 20 mg/kg	25–36	86	Behavior scan sampling in the home pen was conducted on Lacombe bred gilts and barrows every 5 min (between 0800 and 1200 h) for the frequency of the following for agonistic behaviors: parallel pressing. Reverse parallel pressing, head-to-head knocks, head-to-body knocks, biting, and replacing another pig.	RAC and gender had no effects on agonistic behaviors.

effects of RAC with other management factors (e.g., genetics, group size, mixing/regrouping, social rank, etc.). Special care should be taken in future studies to evaluate the effects of RAC on the animal's agonistic behaviors using standardized and validated metrics and combining this information with the animal's stress physiology and key performance metrics such as lameness, morbidity, mortality, and carcass damage.

### ***Effects of Ractopamine on Ease of Handling***

Six studies have evaluated RAC effects on market weight pig handling characteristics (Table 10). These studies evaluated handling ease in the pig handling models described before. In 4 of the 6 studies, investigators reported that pigs fed RAC at doses of 7.5 to 20 mg/kg were more difficult to handle than control pigs as measured by longer times to complete the handling course (Marchant-Forde et al., 2003; Miller, unpublished data), shorter distances voluntarily moved (Miller, unpublished data; Puls et al., 2015), more handling interventions/inputs applied by the handler (Marchant-Forde et al., 2003; Miller, unpublished data; Rocha et al., 2013), and higher ease of handling scores (Puls et al., 2015). Conversely, 2 studies reported that RAC did not affect handling time or handling inputs when fed at doses of 5 to 10 mg/kg (Benjamin et al., 2006; Peterson et al., 2015).

Overall, pigs fed RAC may be more difficult to handle. Generally speaking, the majority of studies reporting that RAC fed pigs were more difficult to handle involved higher doses of RAC (7.5, 10, and 20 mg/kg) compared to the 2014 industry average dose of 5.6 mg/kg (Agri Stats, 2015). Additional research is necessary to (1) determine the effects of feeding 5 mg/kg of RAC on handling characteristics and (2) understand why pigs fed high doses of RAC are more difficult to handle.

### ***Effects of Ractopamine on Fatigued Pig Symptoms***

As previously mentioned, fatigued pigs refuse to walk or keep up with the group at the packing plant and display physical indicators of acute stress that may include open mouth breathing, skin discoloration, muscle tremors, and/or abnormal vocalizations (Ivers et al., 2002; Ritter et al., 2009a; Johnson et al., 2010). The studies presented in Table 11 evaluated RAC effects on the incidence of physical indicators of acute stress (open-mouth breathing, skin discoloration, and muscle tremors) and fatigued pigs in response to gentle or aggressive handling procedures. A total of 4 studies have evaluated the RAC effects on physical indicators of acute stress (Table 11), and the results are inconsistent. Peterson et al. (2015) and Ivers (unpublished data; Study #1) reported that increasing RAC dose resulted in

higher percentages of open-mouth breathing (Ivers, unpublished data; Study #1) and skin discoloration (Ivers, unpublished data; Peterson et al., 2015). Meanwhile, the 2 other studies reported that RAC did not affect physical indicators of acute stress at 10 mg/kg (Puls et al., 2015) or 20 mg/kg RAC (Miller, unpublished data).

Furthermore, 5 studies have utilized handling models to evaluate the effects of RAC on the fatigued pig incidence, which were defined as pigs unable to walk, pigs that refused to move with encouragement, pigs too exhausted to return to their home pen, and/or pigs with a rectal temperatures  $> 40.6^{\circ}\text{C}$  immediately post-handling (Table 11). As previously mentioned, the studies by Miller (unpublished data) and Ivers (unpublished data, Study #1) evaluated the effects of 20 mg/kg of RAC and handling methods and reported that the effects of RAC dose on fatigued pigs is dependent on handling methods. More recently, Noel et al. (2016) found that barrows fed 10 vs. 0 mg/kg RAC reached subjective exhaustion earlier and covered less distance in a circular track when continuously handled during a performance test. Peterson et al. (2015) reported that feeding RAC at 7.5 mg/kg resulted in a higher rate of non-ambulatory pigs than 0 and 5 mg/kg of RAC. Conversely, Puls et al. (2015) fed 0 or 10 mg/kg RAC and subjected all of the pigs to aggressive handling and found no effects of RAC on non-ambulatory pigs. It is interesting to note that the Peterson et al. (2015) and Puls et al. (2015) studies were conducted by the same researchers using the same handling model, but the effects of RAC on non-ambulatory pigs varied across studies. The most notable difference between the 2 studies was the genetic lines of pigs and the time of year. Although breed differences in the hypothalamic-pituitary-adrenal (HPA) axis activation and stress behavioral reactivity have been demonstrated in pigs (Desautels et al., 1997), it is currently unknown if RAC  $\times$  genotype interactions exist for non-ambulatory pigs. This concept, however, is supported by anecdotal field data (Anderson et al., 2002).

Overall, the findings presented above and in Table 11 demonstrate that (1) the effects of RAC on physical indicators of acute stress are inconsistent in the literature and (2) the effects of RAC on fatigued pigs are dependent on RAC dose and handling methods. Additional research is necessary to determine relationships between physical indicators of stress and physiological measurements.

### ***Effects of Ractopamine on Physiological Responses***

Several studies have evaluated the effects of RAC dose (5, 7.5, 10, 20, and 40 mg/kg) on market weight pig physiological responses before, during, and after handling. The most common measures used across studies include heart rate, epinephrine, norepinephrine, cortisol,

**Table 10.** Effects of ractopamine (RAC) on handling characteristics of market weight pigs

Authors	RAC dose	Duration, d	Pigs, #	Methodology	Results
Peterson et al., 2015	0, 5, and 7.5 mg/kg	28	216	The time to complete handling procedures was evaluated when pigs were moved individually through a handling course (total distance 50 m) with 1 of 3 handling intensity treatments: gentle, moderate, or aggressive handling. Pigs were then loaded on a trailer and transported for 1 h. Afterward, pigs were subjected to a final handling procedure, which consisted of moving pigs through the same handling course, but for a distance of 100 m and all pigs were moved at their own pace using gentle handling.	RAC did not affect the time to complete the initial or final handling procedures.
Puls et al., 2015	0 and 10 mg/kg	28	141	Pigs were subjected to handling and transport procedures to evaluate the distance pigs moved voluntarily, ease of handling scores (1 = very easy to 5 = very difficult), and the number of handler inputs (push or bump with a sorting board) needed. Pigs were moved 50 m through a handling course with 8 shocks from an electric prod (defined as aggressive handling), transported 30 min with 0.46 m <sup>2</sup> /pig, unloaded, and moved 100 m through the same original handling course with gentle handling applied.	RAC pigs voluntarily moved 7 m less than control pigs following handling, loading, and 30 min transportation (85.3 vs. 92.0 m for 0 and 10 mg/kg RAC, respectively). There was no difference in ease of handling during pre-transport handling, but there was a tendency ( $P = 0.06$ ) for RAC fed pigs to be more difficult to handle during post-transport handling than controls (1.9 vs. 2.4, respectively). RAC pigs did not require more handler inputs during either pre- or post-transport handling.
Rocha et al., 2013 <sup>1</sup>	0 and 7.5 mg/kg	28	1488	Handler inputs (vocal sound, physical contact, and rattle noise), pig behaviors (slip/fall, overlap, 180° turn, back up, backward, underlap, vocalize, balk, and squeeze), and loading time were measured to assess RAC levels, castration method (immunocastration vs. surgical) and genetic type (A vs. B). Behavior during loading was recorded from the alley to the barn door and from the barn door to the trailer door.	RAC did not affect loading behavior. However, RAC fed pigs required more physical handling interventions during movement in the alley from their home pen to the trailer than control pigs (8.45 vs. 6.83 handling interventions, respectively).
Benjamin et al., 2006	0 and 10 mg/kg	28	288	The number of handler interventions to maintain pig movement and the time needed to complete a handling course were measured as pigs were moved individually through an obstacle course on d 7 and 28.	The number of handler interventions and handling time was not different between RAC treatments.
Marchant-Forde et al., 2003	0 and 10 mg/kg	28	72	Handling characteristics were evaluated during weekly movements from the home pen to the weigh scale. The characteristics evaluated included the number of pigs that voluntarily exited the home pen, latency to exit the home pen, duration and handler inputs needed to get pigs into the weigh scale, duration and handler inputs needed for pigs to exit the scale, and duration to return to the home pen.	RAC pigs were more difficult to handle, with 51% fewer RAC pigs exiting the home pen voluntarily (approximately 1.5 pigs on average). RAC pigs also took 136% longer to remove from the home pen (approximately 10 s), 83% longer to move from the home pen and into a weigh scale (approximately 5 s), and needed 52% more handler inputs (2 to 3 more pats, slaps, and pushes) than control pigs.
Miller, unpublished data <sup>2</sup>	0 and 20 mg/kg	31	160	Handling intensity (aggressive vs. gentle) and RAC level were evaluated by measuring the number of handler inputs, laps completed, and handling duration. Pigs were moved individually for 8 laps (approximately 200 m) through a handling course with 0 shocks (gentle handling) or 32 shocks (aggressive handling) from an electric prod.	Within the aggressive handling groups, RAC pigs required more pushes (2.98 vs. 1.64 pushes per pig, respectively), experienced more applications of an electric prod (35.6 vs. 33.0 prods, respectively), moved a shorter distance (7.6 vs. 7.9 laps, respectively), and took longer to complete the handling course (265.1 vs. 251.9 s, respectively) compared to control pigs. In the gentle handling groups, RAC pigs took longer to complete the handling course (411.8 vs. 374.6 s, respectively) than control pigs.

<sup>1</sup>There was a significant RAC × genotype method interaction for handler interventions ( $P < 0.05$ ).<sup>2</sup>There was a significant RAC × handling method interaction ( $P < 0.05$ ).

**Table 11.** Effects of ractopamine (RAC) on the physical indicators of acute stress<sup>1</sup> and incidence of fatigued pigs<sup>2</sup>

Authors	RAC dose	Duration, d	Pigs, #	Methodology	Results
Noel et al., 2016	0 or 10 mg/kg	32	34	Barrows were individually walked around a circular track (30.67 m perimeter) at an average speed of 0.79 m/s until subjectively exhausted (defined as a barrow stopping forward movement 5 times and/or refused to continue forward movement after 20 s of encouragement by handlers during a single stop). Time and distance to exhaustion were recorded for each barrow and average speed was calculated based on laps per min.	There was no difference in the average speed in which barrows moved around the track. Ractopamine fed barrows reached subjective exhaustion earlier (282.40 vs. 395.57 s, respectively) and covered less distance compared to control barrows (372.53 vs. 563.76 m, respectively).
Peterson et al., 2015	0, 5, or 7.5 mg/kg	28	216	The incidence of physical indicators of stress <sup>1</sup> and fatigued pigs <sup>2</sup> were assessed when pigs were moved individually through a 50 m handling course with 1 of 3 handling intensity treatments: gentle, moderate, or aggressive. Pigs were then loaded on a trailer, transported for 1 h, and then subjected to a final handling procedure consisting of moving pigs through the same handling course for 100 m with gentle handling.	Pigs fed 7.5 mg/kg RAC had an increased percentage of skin discoloration compared to 5 mg/kg (30.6% vs. 15.3%, respectively), but were similar to control pigs (18.1%). Across the handling intensity treatments, the overall incidence of skin discoloration and open-mouth breathing was greater after the handling intensity treatments were applied and after the final handling procedure. Pigs fed 7.5 mg/kg RAC had a greater incidence of fatigued pigs compared to 5 mg/kg and control pigs (9.7% vs. 2.8% vs. 0%, respectively).
Puls et al., 2015	0 or 10 mg/kg	28	141	Physical indicators of stress <sup>1</sup> and the incidence of fatigued pigs <sup>2</sup> were assessed after pigs were moved 50 m through a handling course with 8 shocks from an electric prod (defined as aggressive handling), transported 30 min with 0.46 m <sup>2</sup> /pig, unloaded, and moved 100 m through the same original handling course with gentle handling applied.	During the handling and transport procedures, RAC did not affect the incidence of physical indicators of stress. The incidence of fatigued pigs was similar between the control and RAC fed pigs (2.8 vs. 1.4%, respectively).
Ivers, unpublished data, Study #1	5 or 20 mg/kg	31	144	The incidence of physical indicators of stress <sup>1</sup> and fatigued pigs <sup>2</sup> were evaluated when pigs were subjected to gentle or aggressive handling while moving through a handling course (approximately 293 m) with crowding in a narrow aisle at the end of the course. Aggressive handling consisted of using an electric prod as the primary driving tool to move pigs. Gentle handling consisted of using a plastic tube as the primary tool (no electric prod) to move pigs through the same course.	The proportion of pigs exhibiting physical indicators of stress during or after handling was numerically higher for aggressive vs. gentle handling and for 20 vs. 5 mg/kg RAC fed pigs <sup>3</sup> . See Table 2 for treatment means and P-values for fatigued pigs <sup>2</sup> .
Miller, unpublished data	0 or 20 mg/kg	31	160	Handling intensity (aggressive vs. gentle) and RAC level were evaluated by assessing the incidence of clinical indicators of stress <sup>1</sup> and fatigued pigs <sup>2</sup> . Pigs were moved individually for 8 laps (approximately 200 m) through a handling course with 0 shocks (gentle handling) or 32 shocks (aggressive handling) from an electric prod.	RAC did not affect the incidence of open-mouth breathing or skin discoloration before or after handling. RAC × handling method interactions existed for post-handling vocalizations and fatigued pigs. See Table 2 for treatment means and P-values for fatigued pigs <sup>2</sup> .

<sup>1</sup>Physical indicators of acute stress are defined as presence/absence of open-mouth breathing, skin discoloration, muscle tremors, vocalizations.

<sup>2</sup>Fatigued pigs are defined as pigs unable to walk, pigs that refused to move with encouragement, pigs too exhausted to return to their home pen, and/or pigs with a rectal temperatures > 40.6°C immediately post-handling.

<sup>3</sup>Data on the physical signs of stress were not statistically analyzed.

body temperature, blood pH, blood lactate, and creatine kinase. Studies evaluating these common measures are summarized in Tables 12 through 19 and will be discussed below. These factors are often evaluated to determine an animal's ability to cope with stress; however, interpretation of these responses can be difficult due to the interconnection between physiological systems, role of environmental and inherent factors, variability across individual responses and adaptation mechanisms, and temporal influences (Mormède et al., 2007).

**Heart Rate.** Ractopamine effects on market weight pig heart rates has been evaluated in 4 studies (Table 12), but it is worth mentioning that 1 of these studies only reported raw treatment means (Ivers, unpublished data, Study #1). Catalano et al. (2012) reported no difference in baseline resting heart rates at the end of the feeding period among pigs fed 0, 10, 20, or 40 mg/kg RAC. Meanwhile, the RAC effects on heart rate during marketing events (presence of unfamiliar human, handling, loading, transport, and unloading) are conflicting in the literature. Marchant-Forde et al. (2003) reported that the heart rate of pigs fed 10 mg/kg of RAC was higher (+8 bpm) than control pigs when handlers entered the home pen and during min 6 to 14 of transport in an 18-min journey to the packing plant. However, the authors reported no differences in heart rates during loading, unloading or transport (averaged over the 18-min journey). Likewise, James et al. (2013) reported no difference in heart rates immediately post-handling in market weight pigs fed 0 or 20 mg/kg RAC subjected to gentle and aggressive handling.

Overall, the studies listed in Table 12 demonstrate that RAC has minimal effects on resting baseline heart rates and the effects of 10 and 20 mg/kg RAC on heart rates during marketing events (handler entering the pen, loading, transport, and unloading) are inconsistent in the literature. When RAC fed pigs had higher heart rates, the magnitude of increase was 8 to 12 bpm

(Marchant Forde et al., 2003; Ivers, unpublished data, Study #1). More studies involving larger numbers of market weight pigs are warranted to understand the impact of approved doses of RAC on heart rates before, during, and after handling/transport.

**Catecholamines.** Epinephrine (EPI) and norepinephrine (NOREPI) are catecholamine hormones released by the adrenal medulla during challenging events to produce the “fight or flight response” that increases the animal's heart rate, vasoconstriction, bronchodilation, and the availability of glucose and fatty acids thereby providing a rapid source of energy for the animal to cope with the challenge (Voet et al., 1999; Nelson and Cox, 2000). More specifically, EPI activates glycogen phosphorylase, which converts glycogen to glucose in liver and skeletal muscle. In skeletal muscle, glucose is then converted to lactate and ATP via anaerobic glycolysis (Voet et al., 1999; Nelson and Cox, 2000). Therefore, during exercise and challenging events, catecholamine concentrations have important implications for glycogen depletion and metabolic acidosis, both of which may contribute to the onset of muscle fatigue and the fatigued pig syndrome (Ritter et al., 2009a).

Several studies have evaluated the effects of RAC on EPI and NOREPI concentrations in market weight pigs before handling, immediately after handling/transportation, and at exsanguination. The results from these studies are reported in Tables 13 (EPI) and 14 (NOREPI). Four studies evaluated the effects of RAC on resting baseline values for EPI and NOREPI. Marchant-Forde et al. (2003) reported that pigs fed 10 mg/kg of RAC for 28 d had two-fold higher plasma EPI and NOREPI than controls. However, this conflicts with the findings of 3 other studies that reported that RAC had no effects on baseline plasma EPI and NOREPI when fed at 5, 7.5, or 10 mg/kg for 28 d (Poletto et al., 2010a; Peterson et al., 2015; Puls et al., 2015). Two of these studies measured EPI and NOREPI immediately after handling and trans-

**Table 12.** Effects of ractopamine (RAC) dose on the heart rate of market weight pigs measured in beats per minute

Sampling time	Authors	Pigs, #	Duration, d	RAC dose				
				0 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg
Baseline	Catalano et al., 2012	32	35	119.0	–	116.0	110.0	120.0
Baseline	Ivers, unpublished data, Study #1 <sup>x</sup>	48	31	–	131.5	–	134.3	–
Handler enters home pen	Marchant-Forde et al., 2003	72	28	136.4 <sup>a</sup>	–	144.6 <sup>b</sup>	–	–
Post-Handling	James et al., 2013 (Study #1)	46	28	205	–	–	203	–
Post-Handling	Ivers, unpublished data, Study #1 <sup>x</sup>	46	31	–	178.7	–	191.0	–
0.5 h Post-Handling	Ivers, unpublished data, Study #1 <sup>x</sup>	46	31	–	146.5	–	165.9	–
Loading	Marchant-Forde et al., 2003	32	28	NS <sup>1</sup>	–	NS	–	–
Transport	Marchant-Forde et al., 2003	32	28	NS	–	NS	–	–
Unloading	Marchant-Forde et al., 2003	32	28	NS	–	NS	–	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>x</sup>Data were not statistically analyzed, so only raw treatment means are reported.

<sup>1</sup>NS: LS means were not reported by the authors, but treatments did not differ ( $P > 0.10$ ).

**Table 13.** Effects of ractopamine (RAC) dose on epinephrine concentrations of market weight pigs

Sampling time	Samples evaluated	Units of measure	Authors	Pigs, #	Duration, d	RAC dose			
						0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg
Baseline	Plasma	pg/mL	Peterson et al., 2015	216	28	206.0	165.1	209.2	–
Baseline	Plasma	pg/mL	Puls et al., 2015	144	28	45.6	–	–	48.8
Baseline	Plasma	pg/mL	Marchant-Forde et al., 2003	72	28	101.5 <sup>a</sup>	–	–	253.0 <sup>b</sup>
Baseline	Plasma	pg/mL	Poletto et al., 2010a <sup>1</sup>	32	28	71.5	–	78.7	–
Post-handling/Transportation	Plasma	pg/mL	Peterson et al., 2015	216	28	889 <sup>a</sup>	1109 <sup>ab</sup>	1275 <sup>b</sup>	–
Post-handling/Transportation	Plasma	pg/mL	Puls et al., 2015	144	28	468.1 <sup>a</sup>	–	–	728.3 <sup>b</sup>
Exsanguination	Urine	Log <sub>10</sub>	Rocha et al., 2013	239	28	1.14	–	1.18	–
Exsanguination	Brain–amygdala	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	1.61	–	1.28	–
Exsanguination	Brain–frontal cortex	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	0.52	–	0.60	–
Exsanguination	Brain–raphe nuclei	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	2.89	–	2.66	–
Exsanguination	Brain– hypothalamus	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	15.43	–	17.04	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>1</sup>Pigs were fed a RAC step-up diet (5 mg/kg for 14 d followed by 10 mg/kg for 17 d), thus the average dose fed was 7.5 mg/kg.

**Table 14.** Effects of ractopamine (RAC) dose on norepinephrine concentrations of market weight pigs

Sampling time	Samples evaluated	Units of measure	Authors	Pigs, #	Duration, d	RAC dose			
						0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg
Baseline	Plasma	pg/mL	Peterson et al., 2015	216	28	903.6	984.3	980.9	–
Baseline	Plasma	pg/mL	Puls et al., 2015	144	28	291.9	–	–	275.5
Baseline	Plasma	pg/mL	Marchant-Forde et al., 2003	72	28	480 <sup>a</sup>	–	–	991 <sup>b</sup>
Baseline	Plasma	pg/mL	Poletto et al., 2010a <sup>1</sup>	32	28	357.1	–	423.1	–
Post-handling/Transportation	Plasma	pg/mL	Peterson et al., 2015	216	28	3987	4167	3951	–
Post-handling/Transportation	Plasma	pg/mL	Puls et al., 2015	144	28	887.2	–	–	1053.4
Exsanguination	Urine	Log <sub>10</sub>	Rocha et al., 2013 <sup>2</sup>	239	28	1.31	–	1.31	–
Exsanguination	Brain- amygdala	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	35.46	–	33.94	–
Exsanguination	Brain–frontal cortex	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	16.91	–	18.22	–
Exsanguination	Brain–raphe nuclei	µg/mg	Poletto et al., 2010b <sup>1,3</sup>	32	31	43.31	–	45.54	–
Exsanguination	Brain– hypothalamus	µg/mg	Poletto et al., 2010b <sup>1</sup>	32	31	124.21	–	141.34	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>1</sup>Pigs were fed a RAC step-up diet (5 mg/kg for 14 d followed by 10 mg/kg for 17 d), thus the average dose fed was 7.5 mg/kg.

<sup>2</sup>There was a trend for a RAC × castration method interaction ( $P < 0.10$ ).

<sup>3</sup>There was a significant RAC × social rank interaction ( $P < 0.05$ ).

port. Ractopamine did not affect post-handling/transport NOREPI in either study (Peterson et al., 2015; Puls et al., 2015). However, RAC increased EPI immediately post-handling/transport when fed at 7.5 (Peterson et al., 2015) and 10 mg/kg (Puls et al., 2015), but not when fed at the lowest approved dose of 5 mg/kg (Peterson et al., 2015). Furthermore, 2 studies measured catecholamine concentrations at exsanguination. Poletto et al. (2010a,b) reported no effects of a 5 mg/kg to 10 mg/kg RAC step-up on exsanguination brain amygdala, frontal cortex, raphe nuclei, or hypothalamus. Likewise, Rocha et al. (2013) reported that 7.5 mg/kg of RAC had no adverse effects on urinary EPI or NOREPI concentrations at exsanguination.

Collectively, the studies presented in Tables 13 and 14 demonstrate that (1) RAC has minimal effects on baseline plasma catecholamine values, (2) RAC may increase post-handling plasma epinephrine in pigs fed

doses of RAC greater than 5 mg/kg, which is the most common dose currently used in industry (Agri Stats, 2015), and (3) RAC had no effects on epinephrine or norepinephrine concentrations at exsanguination.

**Cortisol.** Another measure associated with the animal physiological response to an acute challenge is a glucocorticoid called cortisol. When the HPA axis is activated, corticotropin-releasing hormone and adrenocorticotrophic hormone are synthesized and released from the hypothalamus and pituitary gland respectively, which results in the secretion of cortisol from the adrenal cortex (Mormède et al., 2007). Cortisol affects numerous physiological processes including cardiovascular output and blood flow to the brain (potentiated with catecholamines), mobilization of energy stores, HPA regulation, pro- and anti-inflammatory effects on the immune system, and the suppression



of non-essential activities such as feeding, digestion, growth, and reproduction (Sorrells and Sapolsky, 2007; Sorrells et al., 2009).

The RAC effects on cortisol concentrations during baseline, post-handling, post-transport, and exsanguination are summarized in Table 15. These studies indicate that RAC had no effect on baseline cortisol values at 5 and 7.5 mg/kg (Peterson et al., 2015), 10 mg/kg (Marchant-Forde et al., 2003), or 20 mg/kg (James et al., 2013; Study #1) for feeding durations of 28 d. Likewise, 3 studies reported no effects of feeding 5 mg/kg (Athayde et al., 2013), 7.5 mg/kg (Rocha et al., 2013), or 10 mg/kg (Marchant-Forde et al., 2003; Athayde et al., 2013) on either plasma or urinary cortisol values measured at post-transportation or exsanguination. The effects of RAC on post-handling cortisol values are inconsistent in the literature. Two studies reported that RAC increased post-handling plasma or whole blood cortisol values at doses of 5 mg/kg (Puls et al., 2013; data not shown as means were not reported by authors) and 20 mg/kg (James et al. (2013), study #1), but not at doses of 5 mg/kg (Peterson et al., 2015), 7.5 mg/kg (Puls et al., 2013; Peterson et al., 2015) or 20 mg/kg (James et al. (2013), study #2). It is interesting to note that James et al. (2013) reported a RAC × handling intensity interaction for post-handling cortisol concentrations in study #1 (but not in study #2), where feeding 20 mg/kg of RAC increased cortisol concentrations in aggressively handled pigs, but not in pigs subjected to gentle handling.

Overall, the studies in Table 15 demonstrate that (1) RAC had no effect on baseline cortisol concentrations, (2) RAC had minimal effects on post-transportation and exsanguination cortisol values, and (3) the effects of RAC on post-handling cortisol values are inconsistent in the literature and the variation in cortisol concentrations may be due to methodology differences in study design.

**Body Temperature.** It is well documented that swine transport mortality increases as ambient temperature increases (Haley et al., 2008; Sutherland et al., 2009; Correa et al., 2013). Resting market weight pig rectal temperature is approximately 39°C (Table 16), but heat stress related deaths have been reported to occur in pigs as rectal temperatures approach 43°C (Marple et al., 1974). Therefore, it is important to know if handling methods and management factors increase rectal temperature as this may have direct implications for transport mortality. Nine studies evaluated the effects of RAC on body temperature before and after handling (Table 16). Several of these studies report that feeding RAC at 5 mg/kg (Puls et al., 2013; Peterson et al., 2015), 7.5 mg/kg (Puls et al., 2013; Peterson et al., 2015), 10 mg/kg (Puls et al., 2015), and 20 mg/kg (Miller, unpublished data; James et al., 2013) did not affect baseline rectal temperature values. Feeding RAC at 5 or 7.5 mg/kg had no effects on post-handling rectal temperatures (Puls et al., 2013; Peterson et al., 2015) or GI tract temperature from loading at the farm to stunning (Rocha et al., 2013). However, feeding 10 (Gillis et al., 2007) or 20 mg/kg (Miller, unpublished data; James et al., 2013) of RAC increased post-handling rectal temperature (Table 16). It is important to note that the 2 studies reporting significant effects of 20 mg/kg of RAC on post-handling rectal temperature had RAC × handling interactions demonstrating that feeding 20 mg/kg of RAC increased rectal temperature in aggressively handled pigs, but not in gentle handled pigs (Miller, unpublished data; James et al., 2013). Furthermore, 3 studies evaluated the effects of RAC on rectal temperature measured at 0.5 (Miller, unpublished data; Ivers, unpublished data– Study #1), 1 (James et al., 2013) or 2 h post-handling (Miller, unpublished data; Ivers, unpublished data– Study #1). Of these studies, only James et al. (2013) reported that RAC increased rectal temperature in the resting period (0.5 to 2 h) after pigs were handled.

**Table 15.** Effects of ractopamine (RAC) dose on cortisol concentrations in market weight pigs

Sampling time	Samples evaluated	Units of measure	Authors	Pigs, #	Duration, d	RAC dose				
						0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg	20 mg/kg
Baseline	Plasma	ng/mL	Peterson et al., 2015	216	28	33.4	33.0	30.9	–	–
Baseline	Whole blood	ng/mL	James et al., 2013 (Study #1)	128	28	13.9	–	–	–	14.6
Baseline	Plasma	ng/mL	Marchant-Forde et al., 2003	72	28	45.5	–	–	40.9	–
Post-handling	Plasma	ng/mL	Peterson et al., 2015	216	28	42.8	51.4	51.2	–	–
Post-handling	Whole blood	ng/mL	James et al., 2013 (Study #1) <sup>1</sup>	128	28	44.2 <sup>a</sup>	–	–	–	50.7 <sup>b</sup>
Post-handling	Whole blood	ng/mL	James et al., 2013 (Study #2)	128	28	39.5	–	–	–	43.1
1 h Post-handling	Whole blood	ng/mL	James et al., 2013 (Study #2)	128	28	40.1	–	–	–	46.6
Post-transport	Plasma	ng/mL	Marchant-Forde et al., 2003 <sup>2</sup>	72	28	64.6	–	–	71.5	–
Exsanguination	Plasma	ng/mL	Athayde et al., 2013	90	28	63.5	80.2	–	76.6	–
Exsanguination	Urine	Log <sub>10</sub>	Rocha et al., 2013	239	28	1.52	–	1.52	–	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>1</sup>Indicates a RAC × handling intensity (gentle vs. aggressive) interaction ( $P < 0.05$ ).

<sup>2</sup>Sample was collected during exsanguination and reported as post-transport Cortisol.

**Table 16.** Effects of ractopamine (RAC) dose on body temperature of market weight pigs measured in °C

Sampling time	Temperature evaluated	Authors	Pigs, #	Duration, d	RAC dose				
					0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg	20 mg/kg
Baseline	Rectal	Peterson et al., 2015	216	28	38.74	38.73	38.76	–	–
Baseline	Rectal	Puls et al., 2015	144	28	38.33	–	–	38.38	–
Baseline	Rectal	Puls et al., 2013	180	21	NS <sup>1</sup>	NS	NS	–	–
Baseline	Rectal	James et al., 2013 (Study #1)	128	28	39.18	–	–	–	39.24
Baseline	Rectal	Miller, unpublished data	160	31	39.02	–	–	–	39.03
Baseline	Rectal	Ivers, unpublished data (Study #1) <sup>x</sup>	72	31	–	39.33	–	–	39.32
Post-handling	Rectal	Peterson et al., 2015	216	28	38.85	38.98	39.05	–	–
Post-handling	Rectal	Puls et al., 2015	143	28	38.88	–	–	39.00	–
Post-handling	Rectal	Puls et al., 2013	180	21	NS	NS	NS	–	–
Post-handling	Rectal	James et al., 2013 (Study #1) <sup>2,3</sup>	128	28	40.48	–	–	–	40.66
Post-handling	Rectal	James et al., 2013 (Study #2) <sup>4</sup>	128	28	40.60 <sup>a</sup>	–	–	–	40.90 <sup>b</sup>
Post-handling	Rectal	Miller, unpublished data <sup>5</sup>	160	31	39.77 <sup>a</sup>	–	–	–	39.98 <sup>b</sup>
Post-handling	Rectal	Ivers, unpublished data (Study #1) <sup>x</sup>	72	31	–	41.16	–	–	41.19
0.5 h Post-handling	Rectal	Miller, unpublished data	160	31	39.47	–	–	–	39.57
0.5 h Post-handling	Rectal	Ivers, unpublished data (Study #1) <sup>x</sup>	72	31	–	40.53	–	–	40.71
1 h Post-handling	Rectal	James et al., 2013 (Study #2) <sup>6</sup>	128	28	39.76 <sup>a</sup>	–	–	–	40.06 <sup>b</sup>
2 h Post-handling	Rectal	Miller, unpublished data <sup>7</sup>	160	31	39.12	–	–	–	39.14
2 h Post-handling	Rectal	Ivers, unpublished data (Study #1) <sup>x</sup>	72	31	–	39.27	–	–	39.29
Handling to Stunner	Rectal	Gillis et al., 2007 <sup>8</sup>	284	35	38.71	38.79	–	38.82	–
Loading to Stunning	GI Tract	Rocha et al., 2013	135	28	NS	–	NS	–	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>x</sup>Data were not statistically analyzed, so only raw treatment means are reported.

<sup>1</sup>NS: LS means were not reported by the authors, but treatments did not differ ( $P > 0.10$ ).

<sup>2</sup>There was a trend ( $P < 0.10$ ) for the main effect of RAC.

<sup>3</sup>Indicates a RAC x handling method interaction for post-handling change from baseline ( $P < 0.06$ ).

<sup>4</sup>Indicates a RAC x L-carnitine interaction ( $P < 0.05$ ).

<sup>5</sup>Indicates a RAC x handling method interaction ( $P < 0.05$ ).

<sup>6</sup>There was a trend for RAC x L-carnitine interaction ( $P < 0.10$ ).

<sup>7</sup>Indicates a RAC x live weight interaction ( $P < 0.05$ ).

<sup>8</sup>10 mg/kg RAC tended ( $P < 0.10$ ) to have higher rectal temperatures than 0 mg/kg.

Collectively, the studies summarized above and in Table 16 demonstrate that (1) RAC had no effect on baseline rectal temperature values, (2) post-handling rectal temperatures may be affected by RAC in a dose dependent manner, (3) there were no effects of RAC on post-handling rectal temperature when fed at 5 or 7.5 mg/kg, but trends for higher rectal temperatures were observed for pigs fed 10 and 20 mg/kg of RAC, and (4) the effects of 20 mg/kg RAC on post-handling rectal temperature depends on handling methods and are most pronounced during aggressive handling conditions.

**Blood Lactate and pH.** It is well documented that fatigued pigs are in a metabolic state of acidosis (Anderson et al., 2002; Ivers et al., 2002). During the launch of RAC, there were anecdotal concerns about RAC and non-ambulatory pigs. These concerns led to several studies investigating the effects of RAC on blood pH (Table 17) and lactate (Table 18) values to determine if RAC fed pigs are more susceptible to developing metabolic acidosis and fatigue.

These studies demonstrated that RAC had no effect on baseline blood lactate values at doses of 5 or

7.5 mg/kg (Puls et al., 2013; Peterson et al., 2015), but RAC increased baseline blood lactate values by approximately 1 mmol/L when fed at 10 or 20 mg/kg (Miller, unpublished data; James et al., 2013; Puls et al., 2015). Interestingly, RAC had minimal effects on baseline blood pH values regardless of RAC dose (ranging from 5 to 20 mg/kg), suggesting that the animals are able to buffer out the additional lactate and H<sup>+</sup> allowing them to maintain physiological pH values.

A total of 8 studies have measured the effects of RAC on blood lactate and/or pH values immediately after pigs were subjected to different handling intensity procedures (Tables 17 and 18). These studies demonstrate that RAC had no effects on post-handling blood lactate or pH values when fed at 5 or 7.5 mg/kg (Puls et al., 2013; Peterson et al., 2015). Ractopamine also had no effects on blood lactate and pH values measured at stunning/exsanguination when fed at 5 mg/kg (Gillis et al., 2007; Athayde et al., 2013) and 7.5 mg/kg (Rocha et al., 2013). However, feeding 10 mg/kg of RAC produced conflicting results for blood lactate values measured immediately post-handling (Puls et al., 2015; Noel et al., 2016) and at stunning/

**Table 17.** Effects of ractopamine (RAC) dose on whole blood pH of market weight pigs

Sampling time	Authors	Pigs, #	Duration, d	RAC dose				
				0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg	20 mg/kg
Baseline	Peterson et al., 2015	216	28	7.38 <sup>a</sup>	7.36 <sup>ab</sup>	7.35 <sup>b</sup>	–	–
Baseline	Puls et al., 2015	144	28	7.38	–	–	7.37	–
Baseline	Puls et al., 2013	180	21	NS <sup>1</sup>	NS	NS	–	–
Baseline	James et al., 2013 (Study #1)	128	28	7.40	–	–	–	7.40
Baseline	Dorton et al., 2006 (phase 3 and 4)	18	4	7.39	–	–	–	7.37
Baseline	Dorton et al., 2006 (phase 5 and 6)	18	4	7.42	–	–	–	7.38
Baseline	Miller, unpublished data <sup>2</sup>	160	31	7.37	–	–	–	7.35
Baseline	Ivers, unpublished data (Study #1) <sup>3</sup>	72	31	–	7.37	–	–	7.39
Baseline	Ivers, unpublished data (Study #2) <sup>x</sup>	56	24	7.41	–	–	–	7.41
Post-handling	Peterson et al., 2015	216	28	7.27	7.26	7.26	–	–
Post-handling	Puls et al., 2015	144	28	7.30	–	–	7.29	–
Post-handling	Puls et al., 2013	180	21	NS	NS	NS	–	–
Post-handling	James et al., 2013 (Study #1) <sup>4</sup>	128	28	7.31 <sup>a</sup>	–	–	–	7.23 <sup>b</sup>
Post-handling	James et al., 2013 (Study #2)	128	28	7.28 <sup>a</sup>	–	–	–	7.24 <sup>b</sup>
Post-handling	Miller, unpublished data <sup>4,5</sup>	160	31	7.19 <sup>a</sup>	–	–	–	7.15 <sup>b</sup>
Post-handling	Ivers, unpublished data (Study #1)	72	31	–	7.22	–	–	7.19
1 h Post-handling	James et al., 2013 (Study #2)	128	28	7.40	–	–	–	7.40
2 h Post-handling	Miller, unpublished data	160	31	7.40 <sup>a</sup>	–	–	–	7.38 <sup>b</sup>
2 h Post-handling	Ivers, unpublished data (Study #1)	72	31	–	7.36	–	–	7.38
Handling to Stunner	Gillis et al., 2007	284	35	7.40	7.41	–	7.41	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>x</sup>Data were not statistically analyzed, so only raw treatment means are reported.

<sup>1</sup>NS: LS means were not reported by the authors, but treatments did not differ ( $P > 0.10$ ).

<sup>2</sup>There was a trend ( $P < 0.10$ ) for the main effects of RAC.

<sup>3</sup>20 mg/kg RAC tended ( $P < 0.10$ ) to have higher blood pH values than 5 mg/kg RAC.

<sup>4</sup>Indicates a RAC  $\times$  handling method interaction ( $P < 0.05$ ).

<sup>5</sup>Indicates a RAC  $\times$  live weight interaction ( $P < 0.05$ ).

**Table 18.** Effects of ractopamine (RAC) dose on blood lactate concentrations of market weight pigs measured in mmol/L

Sampling time	Samples evaluated	Authors	Pigs, #	Duration, d	RAC dose				
					0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg	20 mg/kg
Baseline	Plasma	Noel et al., 2016	34	32	3.58	–	–	4.38	–
Baseline	Whole blood	Peterson et al., 2015 <sup>1</sup>	216	28	2.63	2.97	3.42	–	–
Baseline	Whole blood	Puls et al., 2015	144	28	2.58 <sup>a</sup>	–	–	3.62 <sup>b</sup>	–
Baseline	Whole blood	Puls et al., 2013	180	21	NS <sup>2</sup>	NS	NS	–	–
Baseline	Whole blood	James et al., 2013 (Study #1)	128	28	2.19 <sup>a</sup>	–	–	–	2.92 <sup>b</sup>
Baseline	Whole blood	Miller, unpublished data	160	31	2.94 <sup>a</sup>	–	–	–	4.43 <sup>b</sup>
Baseline	Serum	Ivers, unpublished data (Study #1)	72	31	–	4.23	–	–	3.87
Post-handling	Plasma	Noel et al., 2016	34	32	8.99	–	–	10.05	–
Post-handling	Whole blood	Peterson et al., 2015	216	28	10.47	11.52	11.97	–	–
Post-handling	Whole blood	Puls et al., 2015 <sup>3</sup>	144	28	10.35	–	–	12.10	–
Post-handling	Whole blood	Puls et al., 2013	180	21	NS	NS	NS	–	–
Post-handling	Whole blood	James et al., 2013 (Study #1)	128	28	12.1 <sup>a</sup>	–	–	–	15.2 <sup>b</sup>
Post-handling	Whole blood	James et al., 2013 (Study #2)	128	28	11.3 <sup>a</sup>	–	–	–	13.4 <sup>b</sup>
Post-handling	Whole blood	Miller, unpublished data	160	31	11.1	–	–	–	12.2
Post-handling	Serum	Ivers, unpublished data (Study #1)	72	31	–	9.90 <sup>a</sup>	–	–	13.8 <sup>b</sup>
1 h Post-handling	Whole blood	James et al., 2013 (Study #2) <sup>4</sup>	128	28	6.32	–	–	–	7.44
2 h Post-handling	Whole blood	Miller, unpublished data	160	31	3.08 <sup>a</sup>	–	–	–	5.03 <sup>b</sup>
2 h Post-handling	Serum	Ivers, unpublished data (Study #1)	72	31	–	4.43	–	–	4.61
Handling to Stunner	Whole blood	Gillis et al., 2007 <sup>3</sup>	284	35	2.63	2.75	–	3.01	–
Exsanguination	Plasma	Athayde et al., 2013	90	28	40.3	40.8	–	39.8	–
Exsanguination	Plasma	Rocha et al., 2013	238	28	22.6	–	23.5	–	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>1</sup>There was a trend ( $P < 0.10$ ) for the main effects of RAC.

<sup>2</sup>NS: LS means were not reported by the authors, but treatments did not differ ( $P > 0.10$ ).

<sup>3</sup>10 mg/kg of RAC tended ( $P < 0.10$ ) to have higher blood lactate values than 0 mg/kg.

<sup>4</sup>Indicates a trend for a RAC  $\times$  handling method interaction ( $P < 0.10$ ).

exsanguination (Gillis et al., 2007; Athayde et al., 2013). Interestingly, Miller (unpublished data) and James et al. (2013; Study #1 and 2) reported that pigs fed 20 mg/kg of RAC may have lower blood pH and/or higher blood lactate values after handling, especially if the pigs are subjected to aggressive handling.

Overall, the studies presented in Tables 17 and 18 demonstrate that (1) RAC affects baseline blood lactate values in a dose dependent manner, but has minimal effects on baseline blood pH values, (2) feeding RAC at 5 and 7.5 mg/kg had minimal effects on baseline and post-handling blood pH and lactate values, and (3) pigs fed 20 mg/kg of RAC may experience larger post-handling changes in blood pH and blood lactate values, especially if aggressive handling procedures are utilized.

**Creatine Kinase.** Creatine kinase is an enzyme found in heart and skeletal muscle that catalyzes the following reaction: phosphocreatine + ADP  $\leftrightarrow$  creatine + ATP. This reaction is important for intracellular energy transport and muscle contraction (Saks et al., 1978; Crozatier et al., 2002; Baird et al., 2012). Since creatine kinase is found in heart and skeletal muscle, its presence in blood serves as an indicator of physical activity and muscle damage (Broom and Johnson, 1993; Knowles and Warriss, 2000; Baird et al., 2012).

A total of 5 studies have evaluated the effects of RAC on serum creatine kinase values in market weight pigs (Table 19). Although there are limited data for the effects of RAC dose, it appears that RAC increases baseline, post-handling, and exsanguination serum creatine kinase values. The biological significance of these findings is not fully understood. Athayde et al. (2013) recently hypothesized that serum creatine kinase values may be increased in RAC fed pigs due to increased muscle mass or due to RAC fed pigs being more susceptible to muscle fatigue and physical stress. There are 2 studies that support the

hypothesis that RAC fed pigs have higher creatine kinase values due to increased muscle mass: (1) Miller (unpublished data) reported that RAC increased resting baseline creatine kinase values before any stressors were applied; and (2) Rocha et al. (2013) reported that the effects of RAC on creatine kinase values were more pronounced in high lean genotypes (50% Piétrain genetics).

Collectively, the studies above and in Table 19 demonstrate that there is large animal to animal variability in creatine kinase values and there is a lack of pre- vs. post-handling creatine kinase data by RAC dose, especially at the currently approved doses of 5 to 10 mg/kg. Further research is warranted to (1) investigate if the increased creatine kinase values observed in RAC fed pigs is a function of increased muscle mass, physical stress (e.g., crushing injuries or wedging) and/or fatigue, and (2) to determine what biological significance increased creatine kinase values may have on the welfare of RAC fed pigs.

## DISCUSSION

Currently, the most common dose of RAC fed in the U.S. swine industry is 5 mg/kg (Agri Stats, 2015). The literature reviewed in the previous text evaluated the RAC effect on market weight pigs' functioning, behavior, and physical response to challenges at doses ranging from 5 to 20 mg/kg. Results of these studies suggest that in market weight pigs: (1) RAC has minimal effect on mortality, lameness, and home pen behavior; (2) RAC fed pigs demonstrated inconsistent prevalence and intensity of aggressive behaviors; (3) RAC fed pigs may be more difficult to handle at doses above 5 mg/kg; and (4) RAC fed pigs may have increased stress responsiveness and higher rates of non-ambulatory pigs to aggressive handling when 20 mg/kg of RAC is fed. It is currently unknown why RAC fed pigs may have increased physi-

**Table 19.** Effects of ractopamine (RAC) dose on serum creatine kinase concentrations of market weight pigs

Sampling time	Units of measure	Authors	Pigs, #	Duration, d	RAC dose				
					0 mg/kg	5 mg/kg	7.5 mg/kg	10 mg/kg	20 mg/kg
Baseline	IU/L	Miller, unpublished data <sup>1</sup>	160	31	1,711 <sup>a</sup>	–	–	–	2,834 <sup>b</sup>
Baseline	IU/L	Ivers, unpublished data (Study #1)	72	31	–	1,590 <sup>a</sup>	–	–	2,103 <sup>b</sup>
Post-handling	IU/L	Miller, unpublished data <sup>2</sup>	160	31	4,811	–	–	–	7,961
Post-handling	IU/L	Ivers, unpublished data (Study #1)	72	31	–	2,409 <sup>a</sup>	–	–	3,019 <sup>b</sup>
2 h Post-handling	IU/L	Miller, unpublished data	160	31	2,988 <sup>a</sup>	–	–	–	5,806 <sup>b</sup>
2 h Post-handling	IU/L	Ivers, unpublished data (Study #1)	72	31	–	3,801	–	–	4,451
Handling to Stunner	IU/L	Gillis et al., 2007 <sup>3</sup>	284	35	6,891	7,467	–	11,527	–
Exsanguination	U/L	Athayde et al., 2013	90	28	5,811 <sup>a</sup>	12,436 <sup>b</sup>	–	10,707 <sup>b</sup>	–
Exsanguination	Log <sub>10</sub>	Rocha et al., 2013 <sup>4</sup>	238	28	3.65 <sup>a</sup>	–	3.76 <sup>b</sup>	–	–

<sup>a,b</sup>Means with different superscripts differ ( $P < 0.05$ ).

<sup>1</sup>Indicates a trend ( $P < 0.10$ ) for a RAC  $\times$  live weight interaction.

<sup>2</sup>Indicates a significant ( $P < 0.05$ ) RAC  $\times$  live weight  $\times$  handling method interaction.

<sup>3</sup>10 mg/kg of RAC tended ( $P < 0.10$ ) to have higher creatine kinase values than 0 and 5 mg/kg.

<sup>4</sup>Indicates a RAC  $\times$  genotype interaction ( $P < 0.05$ ).

ological responses to aggressive handling compared to control pigs. Two hypotheses that may explain these findings are: (a) increased carcass muscling and/or (b) increased catecholamine concentrations, both of which may be affected by RAC in a dose dependent manner.

### ***Effect of Increased Carcass Muscling on Muscle Fatigue***

As mentioned previously, RAC increases carcass muscling and muscle hypertrophy (Mersmann, 1998; Moody et al., 2000) by increasing the percentage of Type IIB glycolytic muscle fibers at the expense of Type IIA oxidative fibers (Aalhus et al., 1992; Depreux et al., 2002; Gunawan et al., 2007). Increasing the percentage of Type IIB muscle fibers has important implications for stress responses during handling and transportation as Type IIB muscle fibers are recruited and utilized for short periods of high-intensity exercise. These muscle fibers have fast contraction speed and generate the most force. Furthermore, Type IIB fibers rely on anaerobic/glycolytic metabolism to produce ATP by converting muscle glycogen to lactate and hydrogen ions, and thus, Type IIB fibers are easily fatigued (Karp, 2001). As Type IIB muscle fibers start becoming fatigued, creatine kinase can be used to produce ATP (from phosphocreatine and ADP) for a short period of time. However, prolonged ATP production from creatine kinase can cause a build-up of inorganic phosphate in muscle, which contributes to the onset of muscle fatigue (Dahlstedt et al., 2000; Westerblad et al., 2002). Therefore, pigs with increased carcass muscling and a higher proportion of Type IIB glycolytic muscle fibers may be more susceptible to developing metabolic acidosis and fatigue during handling and transportation, especially in response to aggressive handling. This hypothesis is supported by the recent work of Noel et al. (2016) who reported that market weight pigs fed 10 mg/kg of RAC walked at the same pace as control pigs, but took less time and distance to become subjectively exhausted. These authors reported that RAC increased the cross-sectional area of muscle fibers, but reduced the overall oxidative capacity of four key muscles involved in walking, which may have contributed to RAC fed pigs having earlier onset of muscle fatigue.

### ***Effect of Increased Catecholamines on Behavior and Metabolic Responses to Handling***

Three studies have reported that feeding doses of RAC at 7.5 or 10 mg/kg for 28 d to market weight pigs may increase epinephrine and norepinephrine concentrations (Tables 13 and 14), which are catecholamines involved in the “fight or flight” response. Epinephrine, norepinephrine, and RAC have similar chemical

structures and are considered  $\beta$ -agonists because they bind and activate  $\beta$ -adrenergic receptors (Mersmann, 1998). Epinephrine has equal binding affinity for the  $\beta_1$  and  $\beta_2$  receptor subtypes, while norepinephrine has a higher binding affinity for  $\beta_1$ . Meanwhile, RAC binds to both the  $\beta_1$  and  $\beta_2$  receptors, but the binding affinity depends on the RAC isomer present (RR vs. RS vs. SR vs. SS; Mills, 2002). Since epinephrine, norepinephrine, and RAC bind to  $\beta_1$  and  $\beta_2$  receptor subtypes, Marchant-Forde et al. (2003) hypothesized that as the  $\beta$ -adrenergic receptors become desensitized and/or downregulated to RAC, production of norepinephrine and epinephrine in pigs may be increased to compete with RAC for the remaining  $\beta$ -adrenergic receptors. Although this hypothesis has not been tested, it provides a plausible explanation for why RAC fed pigs may have higher plasma catecholamine concentrations. Increased plasma epinephrine concentrations may explain why RAC fed pigs have been reported to express more active and alert behaviors (Marchant-Forde et al., 2003; Poletto et al., 2010a) and larger physiological responses to aggressive handling (increased rectal temperature and blood lactate, and decreased blood pH) than control pigs (Miller, unpublished data; Swan et al., 2007; James et al., 2013). Additional research is necessary to understand: (1) the effects of RAC dose and  $\beta$ -adrenergic receptor downregulation on plasma catecholamine concentrations; and (2) how increased plasma catecholamine concentrations impact the metabolic responses of market weight pigs to gentle and aggressive handling.

### ***Key Learnings since the Launch of Paylean***

As previously mentioned, increased rates of non-ambulatory pigs were observed at U.S. packing plants after the Paylean launch (FDA, 2002). Shortly thereafter, the National Pork Board and Elanco Animal Health sponsored numerous research projects to identify management strategies that reduce dead and non-ambulatory pigs at the packing plant. These research studies were recently reviewed by Ritter et al. (2009a) and Johnson et al. (2013), which concluded that: (1) approximately 0.7% of all market weight pigs die or become non-ambulatory at the packing plant; (2) these transport losses cost the U.S. swine industry approximately \$46 million in 2006; (3) the vast majority of transport losses (dead and non-ambulatory pigs) at U.S. packing plants are fatigued pigs that are in a metabolic state of acidosis; and (4) transport losses are a multi-factorial problem that involve people, pig, facility design, management, transportation, packing plant, and environmental factors.

It is now well established that transport losses are impacted by the HAL-1843 gene, aggressive handling

with electric prods, group size during loading, facility design, crowding pigs during transport, and extreme weather conditions (Ritter et al., 2012; Johnson et al., 2013). Furthermore, transport losses can be managed by implementing training programs, developing databases for transport losses, improving facility designs, better preparing pigs for transport, and by minimizing stress throughout the marketing process (Ritter et al., 2009b; Hill, 2009; Ritter et al., 2012). For example, Iowa Select Farms was able to reduce their rate of dead and non-ambulatory pigs at the packing plant by 50% over a 3-yr period by focusing on training, monitoring loads, analyzing/interpreting data, and conducting field research (Hill, 2009; Johnson et al., 2010). Moreover, the U.S. incidence of dead pigs at the packing plant has decreased by approximately 0.1% since the commercial launch of Paylean in the summer of 2000 (Fig. 3; FSIS, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016).

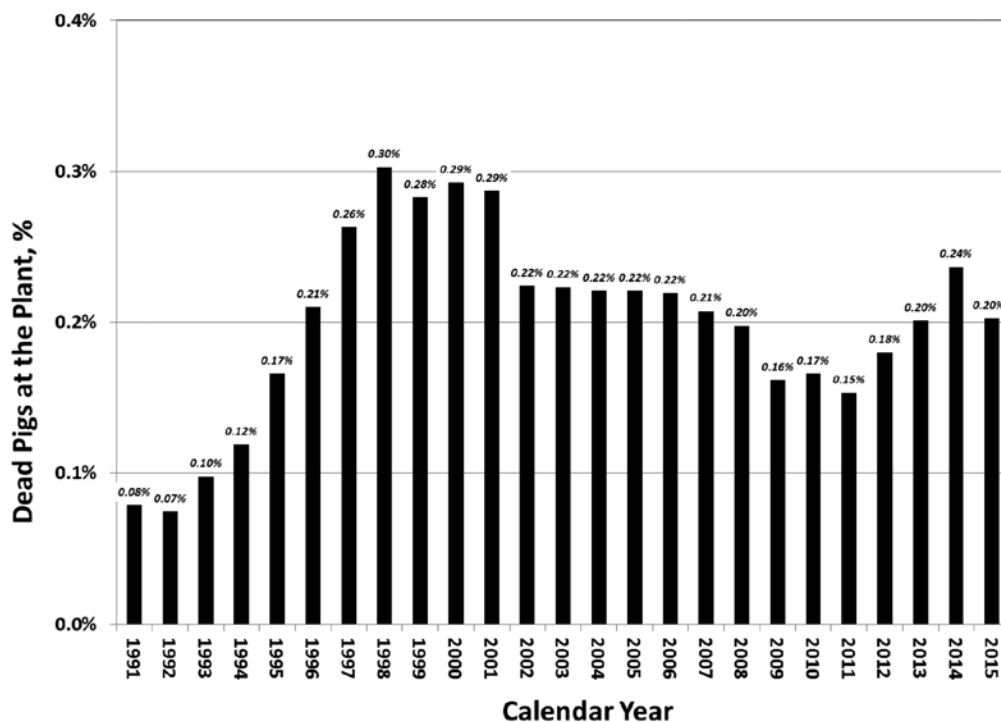
### Implications

The evidence presented in the current review demonstrates that RAC fed pigs may be more difficult to handle at doses above 5 mg/kg and physiological responses and rates of non-ambulatory pigs may increase when RAC fed pigs are subjected to aggressive handling, especially at the 20 mg/kg dose. Low stress handling and transportation practices should be implemented to safeguard

pig welfare and minimize market weight pig transport losses through: (1) continued training programs such as National Pork Board's Pork Quality Assurance and Transport Quality Assurance Programs and the Canadian Livestock Transporter Certification Program; (2) loading and unloading evaluations that provide feedback and recommendations for continuous improvement; (3) data analytics on transport losses to identify and manage risk factors; and (4) research to continue providing science-supported management strategies that reduce transport losses under commercial conditions.

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**Figure 3.** Percentage of dead pigs at USDA inspected plants by calendar year from 1991 to 2015 (FSIS, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016).

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