



Literature Review on the Welfare Implications of the Use of β -Adrenoreceptor Agonists

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WHAT THEY ARE

Certain β -adrenoreceptor agonists (β -agonists) are labeled for use as feed additives in food-producing animals in the United States to improve feed efficiency, increase growth rate, alter adipose accretion, and increase muscle mass.¹ In addition, β -agonists have been used to address medical conditions in humans and animals (e.g., β_1 -agonists [‘cardio-selective’] for acute heart failure, β_2 -agonists for chronic obstructive pulmonary disease). β -agonists mimic the binding effects of the catecholamines norepinephrine and epinephrine at specific types of β receptors. Norepinephrine is known to enhance arousal^{2,3} and some believe that, because β -agonists mimic this catecholamine, they have the potential to stimulate aggression.⁴ The action of β -agonists varies by species depending on which type of β receptors predominate^{5,6} (e.g., pig adipocytes contain nearly 80% β_1 receptors⁶) as well as on the pharmacokinetics and pharmacodynamics of the β -agonist in that species.

Ractopamine hydrochloride and zilpaterol hydrochloride are the only β -agonists labeled for use as feed additives for cattle in the United States. Ractopamine hydrochloride is also labeled for use as a feed additive for turkeys and swine in the United States. Food and Drug Administration approval of these drugs signifies the drugs have been determined to be safe and efficacious when used according to label directions. FDA regulations prohibit extralabel use of medicated feeds.

The β -agonist class of compounds includes numerous agents with widely varying pharmacologic effects and potency. There are other β -agonists that are not labeled for use in food-producing animals as feed additives and, therefore, cannot be used commercially. β -agonists that have been used experimentally to address various medical conditions in animals and humans, but that are not labeled for use as feed additives, include cimaterol, R-salbutamol and clenbuterol.

β -agonists labeled for use as feed additives are typically fed to livestock in the final weeks before slaughter to increase growth and leanness. The FDA-approved dosage range of ractopamine hydrochloride fed to swine (heavier than 150 lbs for the last 45 to 90 lbs of weight gain before slaughter) is 4.5 to 9 grams per ton of complete feed⁷ (approximately 5 to 10 mg/kg of diet or a concentration of 5 to 10 ppm). The FDA-approved dosage of ractopamine hydrochloride for cattle is 10 to 30 ppm in cattle feed (90% DM) to provide a range from 70 to 430mg/head/day during the final 28 to 42 days of the finishing period.⁸ The labeled concentration of ractopamine hydrochloride in turkey diets is 4.6 to 11.8 grams per ton of feed (5 to 13 ppm) for the last 7 to 14 days before slaughter.⁹ The labeled dosage of zilpaterol hydrochloride in cattle diets is 7.5 ppm (90% DM) to provide 60 to 90 mg/head/day during the final 20 to 40 days of the finishing period, followed by a minimum 3-day withdrawal.¹⁰ Although there are no β -agonists labeled as feed additives for use in horses, sheep or fish, there have been studies on the effects of the additives in each of these species (horses,^{11,12} sheep,^{13,14,15,16,17} rainbow trout,¹⁸ and

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channel catfish¹⁹). In addition ractopamine hydrochloride has been used illegally in performance race horses.²⁰

PRODUCTION BENEFITS

Swine—Feeding ractopamine hydrochloride to swine at the labeled dosage increases average daily gain (0.20 kg/day or 0.19 kg/day improvement over controls at 5 ppm and 10 ppm, respectively); improves feed efficiency (gain to feed ratio [G/F] 0.03 or 0.04 improvement over controls at 5 ppm and 10 ppm respectively); and increases carcass lean (0.89% or 0.98% at 5 ppm and 10 ppm respectively).⁷

Cattle—Feeding ractopamine hydrochloride to cattle at the labeled dosage increases average daily gain (0.5lb/day improvement over controls at 400 mg) and improves feed efficiency (G/F 0.018 improvement over controls and feed to gain ratio [F/G] 1.31 improvement over controls at 400 mg).⁸ Feeding zilpaterol hydrochloride to cattle at the labeled dosage increases average daily gain (0.72lb/day improvement over controls at 7.5 ppm); improves feed efficiency (F/G ratio 1.88 improvement over controls at 7.5 ppm); and increases carcass lean (0.72% at 7.5 ppm).¹⁰

Turkeys—Feeding ractopamine hydrochloride to turkeys at the labeled dosage increases average daily gain (Toms: 0.12, 0.016, 0.017 kg/day improvement over controls at 5 ppm, 9 ppm and 13 ppm respectively for 14 days. Hens: 0.015, 0.019, 0.021 kg/day improvement over controls 5 ppm, 9 ppm and 13 ppm respectively for 7 days; 0.011, 0.017, 0.023 kg/day improvement over controls at 5 ppm, 9 ppm and 13 ppm respectively for 14 days) and improves feed efficiency (Toms: G/F 0.02, 0.036, 0.034 improvement over controls at 5 ppm, 9 ppm and 13 ppm respectively for 14 days. Hens: G/F 0.035, 0.042, 0.049 improvement over controls at 5 ppm, 9 ppm and 13 ppm respectively for 7 days; G/F 0.026, 0.041, 0.057 improvement over controls at 5 ppm, 9 ppm and 13 ppm respectively for 14 days).⁹

WELFARE CONCERNS

Swine—In some studies, approved dosages of ractopamine hydrochloride in conjunction with rough handling have been linked to increased incidence of non-ambulatory, non-injured pigs.²¹ Non-ambulatory, non-injured (NANI) pigs can be defined as pigs that, in the absence of obvious injury, trauma, or disease, refuse to walk during any one of the respective stages of the marketing channel from loading at the farm to stunning at the plant.²² In response to an increase in non-ambulatory pigs in slaughter plants subsequent to the approval of ractopamine hydrochloride (Paylean^{®a}) the FDA approved the following label change in June 2002: *“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.”*¹⁰

The NANI pig condition is a multi-factorial phenomenon, and its occurrence is not exclusive to the use of beta agonists. Predisposing factors include handling and overall management (people), pig (genetics), environment, facility design, transportation, and the processing plant.^{22,23,24,25,26,27,28} National statistics for the incidence of NANI pigs are not available; however, these pigs are a concern for the pork industry because of economic and welfare costs.^{25,26} One group of authors, based on several field studies, estimated that >50% of all pigs identified as non-ambulatory at the plant are NANI and anticipated that ~0.3 to 0.4% of all pigs delivered to the plant will develop the syndrome.²² A more recent survey of commercial field trials conducted from 2003 to 2007 showed that the average proportion of NANI pigs at the plant was 0.37 percent.²⁷ A 2012 publication approximates the proportion of NANI pigs in the United States to be 0.34%.²⁸ According to the USDA Livestock Slaughter Annual Summary 113,257,000 hogs were slaughtered in 2012,²⁹ which would put the estimated number of NANI pigs for that year at approximately 385,074.

^a Paylean is a registered trademark of Eli Lilly and Company

Physiologic Indicators: Aggressive handling on its own typically results in increased body temperatures, increased concentrations of serum lactate and decreased blood pH.^{30,31} Pigs fed ractopamine hydrochloride that experienced aggressive handling have increased body temperature (20 ppm),³¹ increased concentrations of serum lactate (10 ppm³² and 20 ppm³¹) and decreased blood pH (20 ppm)³¹ compared with pigs that do not receive ractopamine hydrochloride and experience aggressive handling, indicating that ractopamine hydrochloride-fed pigs are more susceptible to handling-related stress. Results of one study suggest that the heart rates of pigs fed ractopamine hydrochloride at 10 ppm for 4 weeks leading up to slaughter increase above those of control pigs in response to an unfamiliar handler, as well as during transport.³³ One study found that pigs fed 5 and 7.5 ppm of ractopamine hydrochloride for 28 days were not different than controls with regard to rectal temperature, blood pH or blood cortisol.³⁴ The catecholaminergic system is one of the first neurochemical systems to react during the fight-or-flight response^{2,3} and one study found that pigs fed ractopamine hydrochloride had increased circulating concentrations of catecholamines in their blood.³³

Recently, researchers have begun evaluating ractopamine hydrochloride's effects on gene expression of serotonin and dopamine receptors in pigs. Although ractopamine has no direct effect on serotonergic gene expression, it did affect expression of genes associated with the dopamine D1 receptor, especially in gilts, and its effect may be associated with the increased aggressiveness seen in ractopamine-fed gilts in the corresponding behavioral study,^{4,45} though the mechanisms remain poorly understood.

Studies evaluating joint lesions of pigs fed ractopamine hydrochloride at 20 ppm³⁵ found no significant difference between control and treatment groups with regard to frequency of pigs with lesions. A study evaluating lesions on the feet of pigs found more hoof lesions on both fore- and hind limbs of pigs fed ractopamine hydrochloride using a step-up protocol at slaughter than on the feet of pigs that were not fed ractopamine hydrochloride.³⁶

Results of studies looking at relationships between ractopamine hydrochloride and incidence of lameness and hoof lesions have been inconsistent and contradictory.

When other β -agonists have been evaluated experimentally, one study found that R-salbutamol use in finishing pigs had no effect on heart rates in response to an unfamiliar handler or during transport.³⁷ R-salbutamol did increase circulating blood catecholamine concentrations in pigs under acute stress in one study³⁸ and had no effect in another.³⁸

Experimental studies evaluating joint lesions of pigs fed cimaterol (0.00, 0.25, 0.50, or 1.00 mg/kg)³⁹ found no significant difference between control and treatment groups with regard to frequency of pigs with lesions. Some have found that the frequency of lesions found at slaughter on the feet of pigs fed cimaterol (0.25, 0.50, or 1.00 mg/kg^{40,41} from 55 to 104 kg live weight⁴¹) were not different between control and treatment groups,⁴⁰ while another found an increased incidence of hoof lesions in the treated pigs (1 mg/kg from 64.5 to 103.7 kg live weight).⁴⁰ Several researchers have found that lameness scores are not affected by feeding cimaterol (0.25, 0.50, or 1.00 mg/kg [55 to 104 kg live weight⁴¹ at 28 days and day of slaughter, 64.5 to 103.7 kg live weight day of slaughter⁴², or 61 to 105 kg live weight at 42 days and day of slaughter⁴¹]). A study evaluating lesions on the feet of pigs fed R-salbutamol found that pigs fed R-salbutamol (1 to 5 mg/kg for 21 to 28 days) had more hoof lesions at slaughter than control pigs and that higher doses of R-salbutamol tended to produce more severe lesions.⁴²

Behavioral Indicators: Results of studies indicate that pigs fed ractopamine hydrochloride for 4 weeks leading up to slaughter (10 ppm³³; step-up diet⁴) have higher activity levels. Studies have also indicated that gilts fed ractopamine hydrochloride in a step-up protocol are more likely to exhibit aggressive behaviors toward other pigs,⁴ and toward handlers.⁴³ In contrast to these results, others have not found abnormal or aggressive behavior in pigs fed ractopamine hydrochloride consistently at 10 ppm,^{44,45} 15

ppm⁴⁶ or 20 ppm.⁴⁶ One of the studies⁴³ evaluated behaviors after pigs had been fed ractopamine hydrochloride for 5 to 6 weeks, which is longer than the typical duration of use.

Other experimental studies with β -agonists that are not labeled for use as feed additives have been evaluated, one study using R-salbutamol in finishing pigs indicated no effect on activity levels,²⁴ while another found greater immobility (standing still for longer than 2 seconds without head movement).³⁸ Pigs fed R-salbutamol did not show an increase in aggressive behaviors.²³

Ruminants—Most available data on β -agonist use in ruminants relates to growth performance and carcass characteristics. Published information related to the physiologic or behavioral impacts of β -agonists in ruminants is scarce, and anecdotal information^b indicates that research in this area is needed.

Physiologic Indicators: Research found that the use of zilpaterol hydrochloride increased the surface body temperature of sheep affected by heat stress.¹⁴ While most published studies do not include specific death loss data, one study found an increased mortality rate when zilpaterol hydrochloride was fed to feedlot steers at 8.3 mg/kg as compared to steers not fed zilpaterol.⁴⁶ This finding was recently corroborated by others who found, “the cumulative risk and incidence rate of death was 75 to 90% greater in animals administered the [β -agonists] compared to contemporaneous controls”⁴⁷ and that “During the exposure period, 40 to 50% of deaths among groups administered the [β -agonists] were attributed to administration of the drug.”⁴⁷

Behavioral Indicators: At a dose of 200 mg/steer/day of ractopamine hydrochloride cattle entered the restraining chute at a greater speed than untreated animals, however this was not considered problematic.⁴⁸

Tyson Fresh Meats suspended the purchase of cattle treated with zilpaterol hydrochloride until completion of a pending independent investigation of recent instances of difficulty walking and inability to move in some of their cattle.⁴⁹ Shortly after Tyson’s announcement, Merck Animal Health announced it would temporarily suspend sales of its product, Zilmax^{®c} (zilpaterol hydrochloride).⁵⁰ Moving forward, Merck Animal Health has indicated that it will control purchasing of Zilmax[®], requiring feedyards to be certified in some manner to use the product. Additionally, Merck Animal Health has communicated that they are conducting research to further investigate reports of cattle having difficulty walking.

Turkeys— Limited data are available for ractopamine hydrochloride use in turkeys. A literature search did not reveal data on the impacts of ractopamine hydrochloride on physiologic variables or behavior in turkeys, however, the Freedom of Information Summary on Topmax^{®d} indicates the use of ractopamine hydrochloride in tom turkeys during periods of excessive heat (i.e., internal barn temperatures above 29.5°C [85°F] for multiple days) can result in increased mortality.⁹

Other Species—Data were not found on the impacts of β -agonists on the physiology or behavior of fish. In horses zilpaterol hydrochloride resulted in the rapid onset of adverse effects including muscle tremors, profuse sweating and tachycardia.¹¹

AROUND THE WORLD

Recently the Codex Alimentarius Commission adopted maximum residue limits (MRLs) for ractopamine hydrochloride in beef and pork as recommended by the Joint Expert Committee on Food Additives

^b Cattle Industry Summer Conference, Beta-Agonists: Perceptions vs. Reality, Hyatt Regency Hotel, Denver CO. August 7, 2013

^c Zilmax[®] is a registered trademark of Merck Animal Health, Summit, N.J., USA

^d Topmax[®] is a registered trademark of Eli Lilly and Company

(JECFA).⁵¹ The Codex Alimentarius Commission was created by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to develop food standards, guidelines and related texts with their purpose being to: 1) protect the health of consumers, 2) ensure fair practices in the food trade, and 3) promote coordination of all food standards work undertaken by international governmental and nongovernmental organizations.⁵² Regulatory authorities in numerous countries, including but not limited to Japan, Mexico, Canada, and the United States, have determined that meat from animals fed ractopamine hydrochloride is safe for human consumption and allow its use.⁵³ β -agonists are prohibited as a dietary additive for food animals by all member countries of the European Union, plus Guadeloupe, Iceland, Martinique, Monaco, Norway, and Switzerland (which follow EU requirements), and China and Russia (only prohibited for turkeys).⁵⁴

SUMMARY

Swine—The use of ractopamine hydrochloride in swine at labeled dosages increases average daily gain, improves feed efficiency and increases carcass lean, however, use of the additive has been associated with an increased number of non-ambulatory pigs (due to fatigue and/or injury) during the marketing process (i.e., loading, transport, slaughter).⁷ The NANI pig condition is a multi-factorial phenomenon, with several predisposing factors. NANI pigs at slaughter may exhibit signs of extreme stress including high concentrations of lactate in their blood, lower blood pH, blotchy skin, open-mouthed breathing, vocalizations, and muscle tremors, and may refuse to walk. Feeding β -agonists may exacerbate these signs of stress²⁶ as the indicated dosages combined with rough handling result in lower blood pH (20 ppm)³⁰, increased blood cortisol (20 ppm)³⁰, increased rectal temperature (20 ppm)³⁰ and increased blood lactate (10 ppm³¹ and 20 ppm³⁰). Handling of swine during transport and through the slaughter facility should be made as stress-free as possible, especially for swine that have received β -agonists as a feed additive.

Cattle—The use of ractopamine hydrochloride in cattle at labeled dosages increases average daily gain, and improves feed efficiency,⁸ while zilpaterol hydrochloride in cattle at the labeled dosages increases average daily gain, improves feed efficiency and increases carcass lean (i.e., alters adipose accretion and increases muscle mass).¹⁰ While death is a rare event in feedlot cattle, recent research indicates that mortality is increased in response to administration of FDA-approved β -agonists. Additional research investigating welfare of cattle is needed to determine whether feeding of β -agonists is one factor contributing to difficulty walking and an inability to move exhibited by some cattle at processing facilities. The phenomenon may be multifactorial with possible predisposing factors including the size of the animal, genetics, management, length of haul, β -agonist dosage and/or use, and heat stress.

Turkeys—Feeding ractopamine hydrochloride to turkeys at the labeled dosage increases average daily gain and improves feed efficiency. However, the use of ractopamine hydrochloride in tom turkeys during periods of excessive heat can result in increased mortality.⁹ Internal barn temperatures should be monitored closely when ractopamine hydrochloride is used.

Other Species—More research is needed on other species before any conclusions about the impacts of feeding β -agonists on the welfare of those animals can be drawn.

Drugs that are not labeled for use as feed additives in a particular species do not have safe use guidelines and should not be used to promote meat production or improve performance.

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