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# Beta agonists in livestock feed: Status, health concerns, and international trade

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**ABSTRACT:** Since the U.S. Food and Drug Administration approved ractopamine hydrochloride and zilpaterol hydrochloride in animal feeds, usage of those compounds has been a topic of worldwide debate. Ractopamine and zilpaterol are  $\beta$ -adrenergic agonists used as veterinary drugs to increase weight gain in certain animals raised for food. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established maximum residue limits for ractopamine, which were adopted by the Codex Alimentarius Commission (Codex). No maximum residue limits for zilpaterol have been adopted by JECFA, and new

reports of animal mobility issues confront the use of this feed additive. However, many countries disagree with the Codex standards and are restricting or banning meat products containing  $\beta$  agonists. The bans by major importers of U.S. meat products have prompted some to advocate that the United States use the World Trade Organization dispute settlement body. This paper looks at the developments to provide a fuller accounting of what the issues may mean to U.S. firms selling meat products containing residues of  $\beta$  agonists.

**Key words:** beta agonists, Codex Alimentarius Commission, livestock, ractopamine, World Trade Organization, zilpaterol

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## INTRODUCTION

Ractopamine and zilpaterol hydrochloride were approved by the U.S. Food and Drug Administration (FDA) in 2000 and 2006, respectively (FDA, 2000, 2006). Since that time, these 2 classes of veterinary drugs have been used in selected food animals to not only enhance muscle growth and limit the amount of fat in meat products (Mersmann, 2002) but also to improve feed efficiency and carcass weight gain (Rathmann et al., 2009, 2012). Ractopamine and zilpaterol are  $\beta$ -adrenergic agonists ( $\beta$  agonists) that are sold as feed additives for food animals in the United States. Ractopamine used in livestock has been reported in more than 20 countries (FAO, 2012) while zilpaterol has been used by livestock producers in only 5 countries (Canadian Food Inspection Agency, 2009, 2010; FDA, 2006; Merck, 2009).

Beta agonists are administered to livestock to stimulate skeletal muscle growth (Beermann, 2002) without increasing natural hormone levels (Radunz, 2011). They are organic molecules that activate protein synthesis and decrease protein degradation on a cellular level (Gonzalez et al., 2007; Mersmann, 1998). Beta agonists as feed additives need to be used according to specific dosing regimens, which generally limit their use to a few weeks immediately before slaughter (FDA, 2006). For cattle and swine, 3 main feed additive products exist. The first is Optaflexx, which contains the active ingredient ractopamine hydrochloride and is used for cattle (Boler et al., 2012). The second is Paylean, which contains the active ingredient ractopamine hydrochloride and is used for swine (Apple et al., 2007; Patience et al., 2007). The third is Zilmax, which contains the active ingredient zilpaterol hydrochloride and is used for cattle (Delmore et al., 2010).

Although the FDA's approval processes are thorough, some people are concerned about the possibility that  $\beta$  agonists pose health risks to humans. Human health concerns based on the lack of sufficient information have led some countries to restrict or ban meat

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imports with traces of ractopamine (Bories et al., 2009). These bans adversely affect U.S. meat exports (Bottemiller, 2013a). This paper reviews the decisions of international authorities on establishing maximum residue limits for ractopamine, bans that are interfering with U.S. exports, and changes in usage in the United States and what may be important if the issue was to go to the World Trade Organization (WTO) dispute settlement body.

## INTERNATIONAL STANDARDS FOR VETERINARY DRUGS

Many national authorities look to the United Nations' Food and Agriculture Organization (FAO), the World Health Organization (WHO), and their combined Joint FAO/WHO Expert Committee on Food Additives (JECFA) for guidance. Since its first meeting in 1956, the JECFA has worked as an international scientific expert committee focusing on the "evaluation of contaminants, naturally occurring toxicants, and residues of veterinary drugs in food" (FAO, 2013a). Working in conjunction with the JECFA, the Codex Alimentarius Commission (Codex) "develops harmonized international food standards, guidelines and codes of practice to protect the health of... consumers and ensure fair practices of the food trade" (Codex Alimentarius Commission, 2012). For the European Union, the European Food Safety Authority (EFSA) conducts safety evaluations of veterinary drug residues that may be permitted in food.

### *Joint FAO/WHO Expert Committee on Food Additives*

The JECFA is a well-respected scientific authority that evaluates contaminants and residues of veterinary drugs in food and provides safety assessments of chemicals in food (WHO, 2013b). The JECFA's assessments are used by the Codex Alimentarius Commission to establish international standards. The Codex standards enumerate guidance for nations to use in developing national legislative provisions to provide consumers safe and wholesome food products (FAO, 2010a). The FAO and WHO have complementary functions in selecting experts to serve on the JECFA (WHO, 2013a).

The history of ractopamine evaluation by the JECFA dates back to 1993 when the JECFA attempted to establish an acceptable daily intake (ADI) for ractopamine residues in food (WHO, 1993). The JECFA was unable to determine an ADI in 1993 because the data available were inadequate. In 2004, the JECFA established an ADI for ractopamine and presented recommendations to the Codex Committee on Residues of Veterinary Drugs in Foods for maximum residue limits (MRL) in cattle and pig tissues (WHO, 2004a). The Codex Alimentarius

Commission and JECFA defined ractopamine as "a synthetic substance that is used as a veterinary drug in animal feed to promote muscle growth in approved food animal species, namely pigs and cattle and, to a limited extent, heavy turkeys" (FAO, 2012).

Reviewing new data available in 2010, the JECFA looked again at ractopamine in pig lung, heart, and intestinal tissues taking into account studies and data provided by the People's Republic of China (FAO, 2010b). Because pig organs are often consumed as part of a traditional Chinese diet, a major concern in the 2010 reassessment centered on the residue levels present in the organs. The JECFA considered the submitted studies from China and concluded that the recommended ractopamine MRL for muscle (150 µg/kg), liver (150 µg/kg), kidneys (200 µg/kg), and fat (150 µg/kg) were still below the upper bound of the ADI (FAO, 2006, 2010b). The data on organ tissues from the heart, lung, stomach, and intestine were inconclusive so more studies were recommended (FAO, 2010b).

In 2012, the JECFA established an ADI for zilpaterol hydrochloride (FAO, 2013b). However, the JECFA concluded that there were inadequate data to establish MRL for zilpaterol (FAO, 2013b). The JECFA listed 3 needs for data: 1) results from studies investigating marker residue in liver and kidney, 2) results from studies determining marker residue to total residue ratio in liver and kidney, and 3) results from depletion studies to enable the derivation of MRL compatible with the ADI (FAO, 2013b).

### *Codex Alimentarius Commission, 35th Session, 2012*

The Codex Alimentarius Commission discussed ractopamine in a number of sessions without adopting the MRL recommended by the JECFA (Codex Alimentarius Commission, 2012). In 2012, however, the Codex Alimentarius Commission adopted MRL for ractopamine in cattle and pig tissues (Codex Alimentarius Commission, 2012). The process of adopting the Codex MRL occurred through a series of secret ballot votes and resulted in a 69 to 67 majority in favor of adopting the MRL (Codex Alimentarius Commission, 2012).

While the United States was pleased with the majority vote adoption of MRL, the European Union, Norway, China, and 8 other members of the Codex Alimentarius Commission expressed their concerns (Codex Alimentarius Commission, 2012). Several countries in opposition felt that possible risks to human health existed. Another objection by some opponents was the fact that decisions on international standards should require a consensus rather than majority vote (Codex Alimentarius Commission, 2012). Specifically,

the delegation from Norway noted that “the draft MRL had been pushed forward when many members had asked for a consensus-based decision and the MRL had been adopted despite a clear lack of consensus” (Codex Alimentarius Commission, 2012). The United States noted that the adoption of the standard should be “a rare exception to the general principle of consensus” (Codex Alimentarius Commission, 2012). The lack of consensus on ractopamine MRL raises a question about the meaning of the Codex standards under the WTO Agreement on the Application of Sanitary and Phytosanitary Measures.

### *European Food Safety Authority*

In 1996, 3 yr after the first JECFA evaluation of ractopamine but well before ractopamine came to market as a livestock growth promoter, the European Union imposed a general ban on the use of  $\beta$ -agonists with farm animals (EU Council Directive, 1996). In response to the JECFA’s 2006 reconfirmation of ADI and MRL for ractopamine and because the EU had not conducted any studies on ractopamine before adding it to the list of banned veterinary drugs, a panel of the EFSA conducted a safety evaluation of ractopamine in 2009 (Bories et al., 2009). While the examination did not introduce any new research, the EFSA panel took into account all available information about ractopamine, including studies on pigs, cattle, laboratory animals, dogs, monkeys, and humans (Bories et al., 2009).

Since the data from studies of ractopamine in laboratory animals gave a large range of results, the EFSA panel found that human data were of primary concern. Both the EFSA panel and the JECFA assessed consumer safety for the development of an ADI and MRL for ractopamine by examining the results of 1 human study (Bories et al., 2009). The study looked at indices of cardiovascular function and safety to increasing doses of ractopamine (WHO, 2004b). Researchers gave 6 healthy male volunteers placebo and ractopamine beginning at 5 mg and increasing the dose to 40 mg over the course of 5 doses (WHO, 2004b). Data on 14 cardiovascular variables were obtained (WHO, 2004b). While no serious adverse effects were reported, heart rates were elevated with the 3 higher doses.

While the human study proved sufficient for the JECFA in determining an ADI and MRL for ractopamine use in livestock, the EFSA panel expressed concern about methods used in the experiment. In particular, the EFSA report found that 6 subjects did not provide a sufficient sample size for the responses to ractopamine to be statistically significant (Bories et al., 2009). Moreover, 1 man was withdrawn from the study due to adverse cardiac effects (WHO, 2004b, p. 148). In conclusion, the EFSA report found that a number of “weak-

nesses and uncertainties” limited meaningful conclusions from the study (Bories et al., 2009). Therefore, the EFSA panel decided that no MRL could be established because no conclusion could be rendered on the safety of ractopamine residues in meat products consumed by humans (Bories et al., 2009). In the absence of a conclusion that the consumption of ractopamine residues by humans was safe, the detailed scientific investigation did not provide support to overturn the earlier decision by the European Communities banning ractopamine.

### **UNITED STATES EXPORTS AND PRODUCTION ISSUES**

United States beef and pork exports have become very important to the economic well-being of the country’s animal production industry (Lively, 2013). Although the United States is a net importer of beef, it ranks fourth in world beef exports (USDA, 2013c) and is ranked first in world pork exports (USDA, 2014c). In 2012 beef exports (1,113,569 t) accounted for 9.48% of total U.S. production with a net value of US\$5.114 billion (USDA, 2014a). During the same time frame, pork exports (2,440,327 t) accounted for approximately 20% of U.S. production (USDA, 2014b) with a net value of \$6.322 billion (USMEF, 2014). Over the past 10 yr, beef consumption, animal inventories, and the number of animals slaughtered in the United States have decreased (USDA, 2013a). United States firms have sought to export greater amounts of meat products, and exports to countries including China, Russia, Taiwan, and South Korea are seen as critical to maintaining sales outlets for beef and pork products (Stuart, 2013). The industry also adopted the practice of using  $\beta$  agonist feed additives. In 2012, more than 70% of the cattle in the United States purportedly were being fed Zilmax or Optaflexx (Cargill, 2013).

The restrictions and bans on meat products with traces of ractopamine in countries importing beef and pork are seen as adversely affecting the viability of the United States’ meat industry (Lively, 2013). An estimated 160 countries, including the European Union, currently ban or restrict the use of ractopamine, while 26 countries have approved the use of ractopamine for animals producing at least 1 kind of meat product (Gillam, 2012).

### *United States Exports*

Significant pork and beef exports from the United States to China, Russia, South Korea, and Taiwan are needed to maintain the current production and marketing infrastructure of the U.S. meat industry. United States’ pork exports to China are valued at \$886 million (Center for Food Safety, 2013a). If both domestic usage and exports of pork products are considered, approxi-



mately 3.8 kg from each U.S. barrow and gilt slaughtered are exported (Stuart, 2013). China's "zero tolerance" policy for ractopamine residues in meat imports has existed since 2009 (People's Republic of China Embassy in Australia, 2009). Hence, the U.S. Food Safety and Inspection Service advises exporters to work closely with Chinese meat importers to ensure that they meet proper testing requirements (USDA, 2013b).

United States beef exports to Russia totaled 80,408 t in 2012, making Russia the sixth leading export market for U.S. beef (USMEF, 2012). In early 2013, however, Russia imposed a ban on imports of U.S. meat products containing ractopamine (Bottemiller, 2013b). The consequences of this ban to the U.S. meat industry may be the loss of \$500 million in sales per year (Center for Food Safety, 2013a).

Two other major players in the U.S. meat export market include Taiwan and South Korea. Although Taiwan had banned meat products containing ractopamine residues, in 2012 it passed a bill to lift the ban (Hsu, 2012). Taiwan currently allows meat so long as the residues are less than the established legal limit (Anonymous, 2013c). However, there is a movement in Taiwan to require meats to be labeled (Yang et al., 2013). South Korea made a decision in 2013 to suspend some U.S. beef imports because of traces of zilpaterol in the meat (Anonymous, 2013d).

In response to ractopamine bans, Canada has implemented a "ractopamine-free pork certification program" to meet demands by importing countries for ractopamine-free meat products (Canadian Food Inspection Agency, 2013). In November 2013, the USDA introduced a certification program that would allow labels for meat products from animals "Never Fed Beta Agonists" (USDA, 2013d). These certification programs would facilitate the marketing of meat products to countries with restrictions on ractopamine residues, but abandoning the use of  $\beta$  agonists will increase costs for U.S. producers (Lively, 2013).

### ***Changes in the United States***

Some companies in the United States are moving away from the use of  $\beta$  agonists as feed additives. In early 2013, Smithfield Foods Inc., the largest pork producer in the United States, announced "it would be 50% ractopamine-free by June 1" (Bottemiller, 2013b). This was followed by Shuanghui International Holdings Ltd., China's largest meat producer, purchasing Smithfield Foods for \$4.7 billion (Curran, 2013). In August 2013, Merck, the manufacturer of Zilmax, withdrew the drug from the U.S. and Canadian markets after the FDA received a small number of reports of lameness or lying down of Zilmax-fed cattle (Anonymous, 2013b). A possible explanation is that some animals fed zilpaterol experience muscle fatigue

(Grandin, 2013). Concerns about animal mobility led to announcements from major packers that they would stop accepting Zilmax-fed beef (Anonymous, 2013a; Cargill, 2013; Gee, 2013; Huffstutter and Baertlein, 2013; Tyson Foods, Inc., 2014). Furthermore, a recent study conducted by Loneragan et al. (2014) concluded that although the incidence of death in feedlot cattle is low, the addition of  $\beta$  agonists to feedlot diets increased the cumulative risk and incidence of death.

A number of restaurant and supermarket chains have decided to stop buying meat products from animals fed  $\beta$  agonists. Most notably, Chipotle restaurants and Whole Foods Market, Inc. source their meat products from producers who do not use  $\beta$  agonists (Bottemiller, 2012). In addition, special interest groups are raising issues about the image of U.S. beef (Consumers Union, 2013). It has been documented for both ractopamine (Boler et al., 2012; Scramlin et al., 2010; Woerner et al., 2011) and zilpaterol (Avendaño-Reyes et al., 2006; Garmyn et al., 2010; Scramlin et al., 2010) that beef from cattle fed  $\beta$  agonists is less tender (Consumers Union, 2013). However, Scramlin et al. (2010) and Boler et al. (2012) both reported that the decreased tenderness associated with ractopamine could be overcome with postmortem aging for 14 and 28 d, respectively. The Animal Legal Defense Fund and Center for Food Safety filed lawsuits in October 2013 in the Federal District Court of Northern California seeking information under the Freedom of Information Act "related to the psychological, physiological, and behavioral effects" of the animal drug ractopamine and zilpaterol (Center for Food Safety, 2013b). Future publicity about the use of  $\beta$  agonists in meat production could lead more consumers to purchase products with a "never fed  $\beta$  agonists" label.

### ***World Trade Organization Dispute Settlement and Possible Consequences***

Given the adoption of Codex MRL for ractopamine, the United States may decide to address bans of meat products with ractopamine residues below the Codex MRL through the WTO dispute settlement mechanism. The United States could make a request to the WTO dispute settlement body that the bans on ractopamine are contrary to the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS). The SPS references the FAO/WHO Codex Alimentarius as the relevant standard-setting organization for food additives and veterinary drugs (WTO, 1993). After a request and consultations, the WTO dispute settlement body could appoint a panel to consider the dispute.

While WTO panels traditionally have deferred to Codex standards (Ni, 2013), Article 11 of the SPS agreement allows a WTO panel to seek advice from experts it

chooses and to establish a technical experts group (WTO, 1993). With the JECFA and EFSA interpreting the same data but reaching different conclusions, the possibility exists for a WTO panel to appoint a technical experts group that would make a new evaluation on the safety of ractopamine residues in meat products. When a WTO appellate body considered the hormones dispute in the late 1990s between the United States and the European Communities, the WTO panel consulted individually with experts for advice (WTO, 2008). Moreover, it was found that experts who were directly involved in a JECFA risk assessment should not review a subsequent risk assessment that questioned the validity of the JECFA work (WTO, 2008). A WTO technical experts group needs to independently and impartially assess scientific findings to reach its conclusions (Ni, 2013).

Countries with ractopamine bans may argue that the adoption of the MRL by the Codex Alimentarius Commission was not by consensus as is recommended by Article 12 of the SPS agreement (WTO, 1993). This argument is unlikely to garner support. Earlier WTO panels have upheld Codex standards that were not adopted by consensus (Ni, 2013). The European Communities may argue that the risk assessment undertaken by the EFSA in support of EU Council Directive 96/22/EC (EU Council Directive, 1996) satisfies Article 5 of the SPS agreement. This fact could be addressed by the appointment of a technical experts group that would reach its own independent conclusions.

## CONCLUSION

Many U.S. livestock producers have embraced the use of ractopamine and zilpaterol due to the economic benefits associated with faster weight gains of animals fed these veterinary drugs. Extensive safety testing occurred under the review of the FDA for both of these drugs. For ractopamine, the JECFA also adopted MRL for meat products, and these were accepted by the Codex Alimentarius Commission. Conversely, the EFSA concluded that the scant data on the safety of ractopamine residues to humans meant it was not appropriate to develop MRL for ractopamine. The established MRL by Codex for ractopamine means that bans of meat products by foreign countries may not be justified under international law. For zilpaterol, no international MRL have been established so bans on meat products containing this drug are reasonable.

Nonetheless, the action by Codex does not answer the question of whether foreign countries are violating international law by banning meat products with ractopamine residues. Divergences in opinions among scientists occur as shown by the timing and conclusions by the FDA, JECFA, and EFSA panels. Acceptable daily

intakes and MRL use safety factors in establishing their limits. A group of experts interprets data to reach a scientific conclusion of what MRL is required to keep people safe. The Codex MRL for ractopamine are one of these interpretations, but given the data, a WTO dispute panel would be free to make its own conclusions. The Codex MRL are important but not beyond reproach.

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