[Protect Farm Animals]

THE HUMANE SOCIETY OF THE UNITED STATES

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An HSUS Report: Welfare Issues with the Use of Hormones and Antibiotics in Animal Agriculture

Introduction

The use of hormones and antibiotics is common in animal agriculture. While there has been a long history of discussion of the human health and environmental implications of the use of these pharmaceuticals in the United States, they can also have significant animal welfare impacts, some of which have not been fully addressed. Research on animal health and behavior effects would help to develop a more comprehensive understanding of the potential side effects in animal populations.

a) Hormones

Steroid hormones have been approved for use in food-producing beef cattle and sheep in the United States since the 1950s.[1] The purpose of hormone drugs is to increase the animals' productivity and the efficiency by which they convert the feed they eat into meat or milk. Implants are typically placed under the skin on the back side of the animal's ear, where the pellets dissolve slowly and do not require removal. The ears of the treated animals are removed at slaughter and do not enter the human food chain.[2]

In the United States, there are five hormones that are administered to cattle via small solid ear implants and one hormone that is used as a feed additive for feedlot heifers (see Table 1). In addition, recombinant bovine growth hormone (rBGH) is administered to dairy cows by injection to promote milk production.[3] In the United States, about two-thirds of all cattle and about 90% of cattle finished in feedlots are thought to be given growth promoting hormones.[4] In the dairy industry, recent statistics indicate that 42.7% of large-scale producers in the United States use rBGH, and the drug is administered to 17.2% of all cows.[5]

b) Beta-agonists

Although hormone use is technically not permitted in pig or poultry production,[6] beta-agonists (a class of hormone-like compounds) are routinely fed to cattle and swine. Like hormones, beta-agonists are used for growth promotion. They increase the rate and efficiency of weight gain, as well as the leanness and yield of meat. There are currently two FDA-approved beta-agonists used for beef cattle, which are given as a feed additive (typically in feedlot operations): ractopamine hydrochloride and zilpaterol hydrochloride.[7] Turkey[8] and pigs in the finishing stages of growth may also be fed ractopamine hydrochloride.[9] Beta-agonists have only been commercially available for cattle since 2004,[10] and in 2013 one of the two approved products was suspended from sale in the United States by its producer, due to animal welfare concerns,[11] as discussed below.

c) Antibiotics

Antibiotics are commonly used in food-producing animals for disease treatment, control, and prevention, as well as for growth promotion or increased feed efficiency to promote weight gain.[12] In 2012, more than 32 million pounds of antibiotics were sold for farm use.[13] Antibiotics are administered directly into feed or drinking water, for example, for cattle, poultry, pigs, and other food-producing animals. The U.S. Food and

Drug Administration (FDA), which regulates antibiotic use in humans and animals, has introduced a voluntary plan for animal pharmaceutical companies to phase out the use of certain antibiotics that are considered medically important for people in order to avoid the development of drug resistant bacteria.[14]

Regulatory history

The use of hormones in animal agriculture has a troubling past. The first hormone approved for farmed animal use in the United States was diethylstilbestrol (DES), which was authorized in oral form for growth promotion in cattle in 1954, followed by implant use for cattle and sheep in 1956.[15] Use of DES spread rapidly and, at its peak use, approximately 80-95% of all cattle were administered the hormone in some form. However, concerns over carcinogenic properties plagued DES throughout the period of its approved use until 1979, when the FDA banned all use of DES in cattle and sheep following the discovery of a form of cancer in the daughters of human mothers who had DES administered to prevent miscarriages.[16]

The hormones and beta-agonists currently approved for use in cattle and swine in the United States are listed in the table below.

Table 1. Hormone and beta-agonist drugs approved for use in animal production in the United States[17,18,19]

Type	Name	Delivery mode	Species	Year approved
naturally-occurring	17 beta-estradiol	Ear implant	Beef cattle	1956
naturally-occurring	testosterone	Ear implant	Beef cattle	1958
naturally-occurring	progesterone	Ear implant	Beef cattle	1956
synthetic	trenbolone acetate (TBA)	Ear implant	Beef cattle	1987
synthetic	zeranol	Ear implant	Beef cattle and sheep	1969
synthetic	melengestrol acetate	Feed additive	Beef cattle	1968
synthetic[20]	ractopamine	Feed additive	Beef cattle, swine and turkeys[21]	2003[22]
synthetic[23]	zilpaterol	Feed additive	Beef cattle	2006[24]
synthetic[25]	recombinant bovine growth hormone (rBGH)	Injection	Dairy cattle	1993[26]

In contrast to the United States, the European Union has banned the use of growth-promoting hormones due to consumer health and safety concerns. The European Union issued a series of Directives in the 1980s that placed restrictions on the use of substances having thyrostatic, oestrogenic, androgenic, or gestagenic action, first restricting their administration to therapeutic purposes in 1981,[27] then restricting the movement of animals administered such substances between member states, as well as the import of such animals from non-European Union countries in 1988.[28] In 1996[29] and 2003, the European Union amended its regulations, but maintained the ban, and included beta-agonists.[30]

The Scientific Committee on Veterinary Measures Relating to Public Health's 1999 report to the European Commission presented a scientific assessment of the effects of hormone-treated meat on human health, identifying several areas of concern. These included potential neurobiological, developmental, reproductive, and immunological effects, as well as potential immunotoxicity, genotoxicity, and carcinogenicity. 17 beta-estradiol in particular was recognized as having carcinogenic properties due to its tumor-initiating and tumor-promoting effects, while prepubescent children were identified as the group most at risk. As the findings did not yield a quantitative estimate of risk, no acceptable threshold levels have been established for hormone use.[31]

rBGH was first permitted in the United States in 1993 when the FDA approved Posilac, manufactured by the Monsanto Company.[32] However, numerous other countries, including EU member states, Canada, Japan, Australia, and New Zealand have prohibited the use of rBGH for dairy cows.[33] The ban in Europe was based on animal health and welfare concerns (discussed below), but historically, uncertainty regarding potential

human health risks and agricultural policy considerations were also at issue.[34] Although not administered to cows in the European Union, dairy products from rBGH-treated cows may still be imported and sold there.[35]

The welfare of cattle and sheep treated with growth hormones

The effects of hormone use on animal welfare have been most widely studied in connection with rBGH use in dairy cows. One of the most recognized side effects of rBGH is mastitis, or inflammation of the mammary gland. Monsanto's own studies, conducted for the purpose of obtaining FDA approval, found that use of Posilac increased risk for clinical mastitis.[36]

Subsequent studies suggest that an increase in mastitis may not be due to rBGH treatment *per se*, but rather to the increase in productivity caused by rBGH, the same as would be expected when genetic selection leads to greater milk production.[37] Regardless of its cause, clinical mastitis is a serious animal welfare issue, and can be fatal in severe cases. It is one of the leading causes of cow mortality.[38] Mastitis has other significant implications for animal welfare, as it is known to cause pain in the udder,[39] as well as fever and depression.[40]

Despite widespread recognition of the increased risk for the disease, the FDA did not address the animal welfare implications of mastitis in its decision to approve rBGH use. It focussed instead on the human health risk posed by the possible increased use of antibiotics to treat the mastitis,[41] while stating that its approval "…does not mean that there are no risks of adverse effects to the treated animal."[42]

rBGH has also been associated with clinical lameness and skeletal disorders in dairy cows. These diseases were most prominently documented through a post approval monitoring program (PAMP) carried out by Monsanto and published in 1996. The PAMP revealed an increased prevalence of many musculoskeletal disorders in rBGH-treated cows compared to the control group, with the number of multi-parous cows (those who have given birth more than once) having foot disorders at a rate 2.2 times higher than control cows, and with the number of days affected 2.1 times higher for rBGH-treated animals than in the control group.[43]

Another animal welfare implication of rBGH used in dairy cows is irritation at the injection site. Pooled results from three clinical trials showed that administration of 500 mg of rBGH every 14 days during lactation resulted in numerous animals having visible swelling at the injection site and/or other complications (e.g., draining, lesion, hematoma, etc.).[44,45]

Additional health issues that have been observed in dairy cattle administered rBGH include: lower pregnancy rate, indicating failure to conceive; increased frequency of multiple births; lower body condition score at the end of the lactation period; and digestive disorders such as bloating, indigestion, and diarrhea. As an indication of overall impact on animal welfare, higher culling (selection for removal and slaughter or euthanasia) rates have been observed for cows treated with rBGH.[46] There is also evidence that cows treated with rBGH are more prone to heat stress under high environmental temperatures.[47]

In contrast to the effects of rBGH on dairy cows, little is known about the effects of hormones on the welfare of cattle used in meat production. However, evidence suggests that hormone usage can have adverse effects on cattle under certain climactic conditions. A 2005 study found that in temperatures nearing 30º C (86º F), estrogen implants in cattle limit heat loss, increasing heat stress and the potential for death from heat episodes.[48] Additionally, 2013 research into the use of zeranol implants in lambs linked it with incidence of vaginal and rectal prolapse and overall mortality, both of which increased linearly with higher dosages used in the study.[49]

The welfare of cattle and swine treated with beta-agonists

The beta-agonists ractopamine hydrochloride (sold as Optaflexx by Elanco) and zilpaterol hydrochloride (sold as Zilmax by Intervet, a subsidiary of Merck & Co.) are FDA approved drugs used to promote weight gain and growth of lean muscle in cattle. They are mixed into feed during the final 20 to 42 days prior to slaughter.[50,51] However, beta-agonists provide no health benefits to the cattle themselves[52] and their use has concerning implications for animal welfare.[53]

In 2013, cattle expert Dr. Temple Grandin noted that "[w]hen beta-agonists first came on the market, I observed some strange new problems in fed cattle when they arrived at the packing plant. Brahman crosses, Holsteins, and many other types of cattle had occasional lots where on hot summer days cattle arrived that were stiff and sore footed. A few animals went down and had severe heat stress symptoms."[54] Issues with Zilmax came to a head at a meeting of the National Cattlemen's Beef Association (NCBA) in August 2013. During the meeting Lily Edwards-Calloway from JBS, a major U.S. meat processor, showed a video of lame, stiff-gaited cattle. She explained that at least 20% of the cattle arriving at two JBS plants during hot summer weather were "tender-footed," and more difficult to move out of holding pens.[55,56] At the same time, Tyson Foods Inc. informed its suppliers that it would stop buying cattle fed Zilmax effective September 6, 2013, due to concerns that Zilmax may have been a factor in cattle showing up at slaughter plants unable to walk or move.[57,58] Immediately following this, Merck announced that it was confident that problems witnessed by Tyson were not caused by Zilmax.[59] Five days later, Merck offered to conduct audits for packers and processors to determine potential causes of mobility problems in cattle.[60] However, by the following week, Merck announced that it was temporarily suspending sales of Zilmax in the United States and Canada while it conducted its audits and studies.[61,62] Merck's plan to conduct studies on Zilmax were stalled as cattle producers refused to participate, instead switching to the older drug ractopamine.[63,64]

Subsequent studies have confirmed the welfare implications of zilpaterol. Researchers in 2014 found that death rates in cattle consistently increased across datasets in response to the administration of zilpaterol. However, the use of ractopamine was equally problematic. The cumulative risk of mortality was 75-90% greater when cattle were given either beta-agonist, and these results could not be explained by other co-variables in the study. The study emphasized that while cattle death is an uncommon event in feedlots, administration of FDA-approved beta-agonists substantially increases death incidence.[65]

A separate 2014 study investigating the behavioral effects of zilpaterol administered to cattle (in combination with an implant of trenbolone acetate and estradiol) found significant effects on the behavior of the animals, including more pushing and lateral lying (lying on the side of the body) among the treated cattle. The study authors noted that the meaning of the increase in lateral lying was unclear, but that in observations of cattle undergoing castration it appeared to be associated with pain.[66]

Throughout this period, Merck has maintained that Zilmax "is safe when used according to the product label and in conjunction with sound animal husbandry practices."[67] In support of this, Merck cites its own studies conducted in support of FDA approval,[68] including studies examining carcass cutability and consumer palatability, and undisclosed data.[69]

Ractopamine is used not only in cattle production but may also be used in the finishing rations of swine, where it is sold under the trade name Paylean.[70] However, feeding ractopamine to pigs causes disturbing animal welfare side effects. Within a couple of years of it receiving approval in 1999, questions of its safety began to arise, as the FDA received numerous reports of sick and dying pigs.[71,72] At the request of the FDA, Elanco added a warning label to the product.[73]

Between 2000 and 2003 Purdue University conducted a series of research trials to determine, among other things, optimal doses of Paylean for growth efficiency.[74] Although part of the purpose of the studies was to assess the economic benefits of Paylean, researchers also found behavioural and physiological problems.[75] Studies showed that pigs finished with Paylean had elevated heart rates and catecholamine concentrations (indicators of stress), and showed less willingness to walk when fed the drug.[76,77,78] The Purdue studies also found that pigs finished with Paylean initially became more active and then more difficult to handle, and showed heightened reactions in response to transportation.[79]

Researchers further determined that the pigs' reluctance to move may put them more at risk from rough handling during loading and unloading, as there was a marked increase in the number of pats, slaps, and pushes stockpersons used,[80] impairing the welfare of the pigs.[81] These concerns were restated in a 2015 University of Illinois study, which corroborated that ractopamine affected metabolic and physiological responses of pigs, and that pigs subjected to aggressive handling showed increased open-mouthed breathing and skin discoloration.[82] Continued studies with increasing focus on animal welfare have determined that

pigs also showed greater susceptibility to fearfulness, as indicated by increased heart rates and immobility,[83] abnormal behavior,[84] increased impulsive aggression,[85,86,87] and a greater frequency of hoof lesions.[88]

Antibiotic resistance – consequence for animal health and welfare

In addition to the routine use of hormones in commercial animal agriculture, the administration of antibiotics is also of concern. Antibiotics are administered to farm animals for three primary reasons: therapeutically to treat disease, prophylactically to prevent expected disease, and routinely as a growth promoting drug.[89] The therapeutic use of antibiotics to improve the health of sick animals is important to their welfare. The use of antibiotics as growth promotors and prophylactically, however, are contentious practices, because feeding low doses for extended periods of time can lead to antibiotic resistant bacteria.[90]

Table 2. Subtherapeutic antibiotic use in farm animals[91]

Animal type	Antibiotic use	Delivery mode
Swine	prophylaxis or growth promotion	feed
Feedlot cattle	prophylaxis or growth promotion	feed or water
Veal and dairy calves	prophylaxis or growth promotion[92]	milk or milk replacer
Dairy cows	prophylaxis	intramammary infusion
Broiler chickens	prophylaxis or growth promotion	feed or water
Turkeys	prophylaxis or growth promotion	feed or water
Hatching eggs	prophylaxis	dipping or injection

Much has been written about the potential human health threat resulting from antibiotic-resistant bacteria.* However, antibiotics are also used to treat sick non-human animals, whose health can also be threatened by antibiotic resistance.[93] A number of different contagious bacterial diseases cause illness and suffering in animals raised for food.[94,95] Respiratory and enteric diseases are among the most common in pigs and cattle, and, as previously discussed, mastitis is common in cows used for milk production.[96] Because these diseases are contagious they can be more readily spread when animals are kept in large groups and crowded together, as researchers found with bovine respiratory disease in feedlots.[97]

Some antibiotics are already no longer recommended as first-line choices for treating animal diseases because of bacterial resistance. Emergence of penicillin or tetracycline resistance in *Pasteurellamultocida* and *Mannheimiahaemolytica,* which cause pneumonia in calves, has rendered these antibiotics less effective under intensive rearing conditions for veal production.[98,99] Similarly, resistance to drugs previously used to control swine dysentery (a serious enteric infection in growing pigs caused by *Brachyspirahyodysenteria*), such as tylosin and lincomycin, is now widespread. However, resistance to pleuromutilins, another drug used to control these infections, has also been reported, increasing the difficulty of controlling swine dysentery.[100,101]

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become common among pigs, and is also appearing among other animals used in food production.[102] Reports of MRSA in milk from dairy cows, sometimes in association with mastitis, are increasing.[103,104,105,106] MRSA isolated from dairy cows has generally been resistant to penicillins as well as tetracyclines and sometimes to other antibiotics as well.[107,108]

Given the potential human and animal health concerns, the widespread use of antibiotics for growth promotion has been restricted in the European Union since 2006.[109] The experience in Denmark is instructive, as the use of antibiotics for growth promotion was banned there even earlier, in 2000. Without

* For more information, see "An HSUS Report: Human Health Implications of Non-Therapeutic Antibiotic Use in Animal Agriculture" at www.humanesociety.org/assets/pdfs/farm/HSUS-Human-Health-Report-on-Antibiotics-in-Animal-Agriculture.pdf.

antibiotics, Denmark initially had difficulty weaning piglets in the conventional way, because of problems with infection and diarrhea,[†] and piglet mortality increased following the ban. However, pig farmers were able to bring the mortality rate back down by implementing improved animal husbandry practices, including weaning piglets at a later age, improving nutrition, and increasing space per animal.[110] Overall swine mortality rates have been shown to be similar before and after the ban.[111] As with pigs, mortality did not increase in Danish broiler flocks after the ban on growth promoting antibiotics.[112]

The situation in Denmark is evidence that improved animal husbandry practices, resulting in better animal health, can reduce the need for antibiotics. In the United States, producers report that additional management practices such as providing bedding for newborn calves, and allowing greater access to the outdoors and more space per animal are good preventative measures.[113] Certainly, it is preferable to prevent disease by making sanitary and animal welfare improvements, rather than by using drugs as a crutch for poor management.

The use of both hormones and antibiotics are not permitted in organic agriculture.[114] Organic producers are required to provide outdoor access, shade, shelter, fresh air, clean water, and direct sunlight, better ensuring that animals can express their natural behavior.[115] While organic products produced in the United States cannot be derived from any animal treated with antibiotics,[116] organic producers are also not permitted to withhold antibiotics from an animal needing treatment in order to preserve the animal's organic status.[117] However, it has been speculated that the economic impact of the loss of organic status of an animal could incentivize some farmers to delay antimicrobial treatment when it is needed, which could prolong any suffering of sick animals.[118] It is not known if, or how often, this practice occurs on organic farms.

Conclusions

The push to engineer ever increasing levels of productivity in animal agriculture has serious welfare consequences for animals. While hormones and hormone-like drugs must be tested for consumer safety in the United States, comparative monitoring for animal welfare effects has not been emphasized. Research is beginning to reveal concerning side effects and unintended outcomes for the use of these drugs, even when approved and regulated.

The use of antibiotics in agriculture must be more carefully scrutinized, for both human and animal health reasons. It is unlikely that any new antibiotic classes will be developed in the area of veterinary medicine, with research focusing instead on human health. However, this may be an incentive towards better animal welfare, both through encouraging greater care to prevent disease in the first place, and in limiting the use of antibiotics to more judicious treatment of infectious diseases.[119]

There is a growing demand for animal products raised without antibiotics and hormones. Many major food companies are enacting policies to eliminate or reduce the use of one or both in their supply chains, including Panera Bread,[120] Chipotle,[121] Starbucks,[122] and McDonalds.[123] The sale of organic food continues to grow.[124] In 2015, California became the first state in the Nation to prohibit the use of low doses of antibiotics to enhance growth or prevent disease in healthy animals.[125] Reliance on growth promoting pharmaceuticals may decrease in the years ahead, and such a development would be a promising outcome for the welfare of farmed animals.

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[†]For more information on the welfare issues associated with early weaning of piglets, see "An HSUS Report: The Welfare of Piglets in the Pig Industry" at www.humanesociety.org/assets/pdfs/farm/welfare_piglets.pdf.

[2] U.S. Food and Drug Administration. 2015. Steroid hormone implants used for growth in food-producing animals. www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055436.htm. Accessed December 16, 2015.
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