

AMERICA'S SECRET ANIMAL DRUG PROBLEM

HOW LACK OF TRANSPARENCY IS ENDANGERING
HUMAN HEALTH AND ANIMAL WELFARE



CENTER FOR
FOOD SAFETY

FULL REPORT
SEPTEMBER 2015

ABOUT CENTER FOR FOOD SAFETY

CENTER FOR FOOD SAFETY (CFS) is a non-profit public interest and environmental advocacy membership organization established in 1997 for the purpose of challenging harmful food production technologies and promoting sustainable alternatives. CFS combines multiple tools and strategies in pursuing its goals, including litigation and legal petitions for rulemaking, legal support for various sustainable agriculture and food safety constituencies, as well as public education, grassroots organizing and media outreach.

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Authors: Cristina Stella, Cameron Harsh

Copy Editors: Abigail Seiler, Lauren Skillen

Legal Consultant: Paige Tomaselli

Science Review: Margaret Mellon, PhD

Design: Hummingbird Design Studio



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INTRODUCTION

The animal agriculture industry uses over 450 animal drugs, drug combinations, and other feed additives to promote animal growth and to suppress the negative effects that heavily-concentrated confinement has on farm animals.



TODAY, MANY AMERICANS recognize that most animals raised for food in the United States are not roaming freely on iconic pasture. Instead food animal production has shifted dramatically in the past several decades toward large factory-style facilities that raise thousands of animals. By some estimates, 99.9 percent of chicken and 78 percent of beef consumed in the United States come from animal factories¹—production systems in which animals are industrially bred for rapid growth and high output and are tightly cramped, caged, and sometimes even chained or tethered.² Extreme growth rates and unsanitary, overcrowded conditions are now commonplace in large industrial animal factories, or Concentrated Animal Feeding Operations (CAFOs).

What many Americans may not realize, however, is that to keep pace with the increasing growth and concentration of livestock raised in animal factories,³ the animal agriculture industry uses over 450⁴ animal drugs, drug combinations, and other feed additives to promote growth of the animals and to suppress the negative effects that heavily-concentrated confinement has on farm animals. Thus, food animal producers regularly use these drugs for reasons that have nothing to do with medical necessity or animal health.

The U.S. Food and Drug Administration (FDA or the Agency) is primarily responsible for approving and regulating these drugs. FDA is required by federal law to ensure an animal drug is safe for both humans and animals before approving its sale, and to take a drug off the market if it is later found to be unsafe. Yet, Center for Food Safety (CFS) has found that there are serious questions about the safety of many drugs on the market today. CFS's research demonstrates that some drugs on the market pose significant threats to human, animal, and environmental health and are therefore unsafe. For other drugs, there is alarmingly little information, and certainly too little to justify FDA's determination that such drugs are safe. In either case, FDA and industry are not at all transparent about the information they have.

Consumers and businesses have begun to recognize the risks associated with overuse of animal drugs in animal factories and are slowly taking action. Concern for the connection between routine reliance on antibiotics in industrial animal production and the rise of antibiotic-resistant infections in humans has prompted the public to demand critical changes. Large restaurant chains such as Chipotle, Panera, and most recently McDonald's have made public commitments to reduce or eliminate nontherapeutic uses (i.e., uses other than disease treatment) of antibiotics through their meat and poultry suppliers. In the case of McDonald's, public concern and negotiations with environmental and consumer organizations helped spur the company to establish a policy to phase out the use of medically important antibiotics that are used for growth promotion among its poultry suppliers.⁵

Drug manufacturers have also withdrawn products in response to public pressure or bad press. When a drug called Zilmax was linked to cattle becoming too sick to walk or stand on their own, the media caught wind of the story and publicized the inhumane treatment of the animals. Most egregious, the feet of roughly a dozen of the cattle that arrived for slaughter had almost completely fallen off. The media attention led the manufacturer, Merck Inc., to temporarily withdraw the product for further study.

Market-based actions such as these can be important drivers of change, but must be accompanied by regulatory reform. Without corresponding government action, the industry can easily continue to rely on routine and excessive use of animal drugs. Merck's withdrawal of Zilmax, for example, lasted roughly one year before the company submitted New Animal Drug Approvals to FDA for other formulations of the drug.⁶ Additionally, McDonald's new policy extends only to poultry despite the significant amount of antibiotics administered to pigs and cattle at nontherapeutic levels. The policy also allows the continued use of antibiotics in poultry for purposes of "disease prevention" (i.e., regularly treating healthy birds with drugs in order to keep them from getting sick.).

Regulatory action by FDA is critical to institutionalizing these changes such that the pendulum cannot swing back. In addition, if market pressures successfully

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FDA is required by federal law to ensure animal drugs are safe for both humans and the animals for which they are intended before approving their sale, and to take drugs off the market that are later found to be unsafe. Yet, Center for Food Safety (CFS) has found that some drugs on the market today may pose significant threats to human, animal, and environmental health and are therefore unsafe.

reduce or eliminate the ubiquitous use of antibiotics for growth promotion, some drug manufacturers have already indicated they intend to ramp up marketing and sales of non-antibiotic growth-promoting drugs to fill the gap. Drugs with significant adverse impacts on human health or animal welfare, such as ractopamine or zilpaterol, may become even more prevalent in industrial animal production.

FDA has authority to reevaluate the safety of approved animal drugs. Rather than use that authority, FDA has effectively placed the burden on the public to conduct investigations and present the Agency with new data about the uses and effects of animal drugs. Assuming this burden, CFS has petitioned FDA several times to evaluate or withdraw approvals for antibiotic, arsenical, and beta-agonist animal drugs. In 2014, CFS successfully forced FDA to withdraw approval for all but three arsenicals used in animal agriculture, after suing the Agency for failing to respond to CFS’s petition calling for withdrawal. Even with this significant victory, there are many drugs still on the market that FDA should reevaluate and ultimately withdraw. Until FDA thoroughly assesses the safety of animal drugs, and withdraws those found to be unsafe, the well-being of food animals, consumers, and the environment will continue to be put at risk by an industry that thrives on keeping the government and the public in the dark.

This report summarizes the current safety information on animal drugs that urgently demand reexamination by FDA. The drugs approved by FDA and regularly administered to livestock in the United States are organized into the broader categories of:

- | | | |
|---------------|------------------|---------------|
| Beta-agonists | Steroid Hormones | Antioxidants |
| Antibiotics | Arsenicals | Coccidiostats |

For each drug type, this report provides an overview of the most up-to-date information available, including their use in agriculture, their impacts on animal health, human health, and the environment, as well as comparisons between United States and international regulations. Antibiotics, an animal drug class under increasing scrutiny, are given particular attention through a detailed case study. Finally, the report provides recommendations for action to reduce the numerous harmful effects of these animal drugs.

FEDERAL REGULATION OF ANIMAL DRUGS



REGULATORY OVERSIGHT of animal drugs in the United States is complex, and involves the Centers for Disease Control and Prevention (CDC), the Center for Veterinary Medicine (CVM) within FDA, the Food Safety and Inspection Service (FSIS) within the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA).⁷ Among these, FDA serves as the primary regulatory agency because it must pre-approve animal drugs before they can be commercialized, and because it regulates their use and distribution afterward.

Through the Federal Food, Drug, and Cosmetic Act (FFDCA), Congress tasked FDA with the mission of promoting and protecting public health “**by promptly and efficiently reviewing clinical research** and taking appropriate action on the marketing of regulated products [food, drugs, devices, and cosmetics] in a timely manner,” and ensuring that regulated products “are safe, wholesome, sanitary, and properly labeled.”⁸ The primary purpose of the FFDCA is protecting human health and safety, and FDA’s authority includes reviewing products used on animals.⁹ The

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Typically, FDA does not determine the absolute safety of a drug, but whether the benefits that the drug produces outweigh the costs of its restricted use. In the case of animal drugs, that cost is the risk of harm presented to humans and animals.

statute adopts a precautionary approach to the safety of regulated products, and requires FDA to protect humans and animals from substances that **may** be harmful to health.¹⁰ Based on these mandates, FDA cannot carry out its mission with regard to animal drugs without adequate scientific information about the effects of these drugs.

The FFDCA governs the use of all new animal drugs.¹¹ The statute defines a “new animal drug” as “any drug intended for use for animals other than man, including any drug intended for use in animal feed”¹² In order for animal factories to purchase and use animal drugs, the drug manufacturers must submit a New Animal Drug Application (NADA) to FDA for approval.¹³ The application must contain certain specific information, including:

- Full reports of investigations showing whether or not the drug is safe and effective for use;
- A full list of the articles used as components of such drug;
- A full statement of the composition of such drug;
- A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
- Samples of the drug, its components, animal feed that will contain the drug, edible portions or products (before or after slaughter) of animals to which the drug (directly or in or on animal feed) is intended to be administered;
- Samples of the labeling proposed to be used for such drug, or in case such drug is intended for use in animal feed, proposed labeling appropriate for such use, and samples of the labeling for the drug to be manufactured, packed, or distributed by the applicant;
- A description of practicable methods for determining the quantity, if any, of such drug in or on food, and any substance formed in or on food, because of its use; and
- The proposed tolerance or withdrawal period or other use restrictions for the drug, if required to assure that the proposed use of such drug will be safe.¹⁴

After a manufacturer submits an application, FDA, in turn, must evaluate the safety of the animal drug for both animals and humans before granting approval. In doing so, FDA must consider, among other relevant factors, (1) the probable consumption of the drug and of any substance formed in or on food because of the use of the drug, and (2) the cumulative effect the drug has on humans or animals, taking into account any chemically or pharmacologically related substance.¹⁵ Typically, FDA does not determine the absolute safety of a drug, but whether the benefits that the drug produces outweigh the costs of its restricted use.¹⁶ In the case of animal drugs, that cost is the risk of harm presented to humans and animals.

Once FDA approves an animal drug, it issues regulations governing its lawful use, labeling, distribution, and conditions of use.¹⁷ FDA can also establish tolerance levels for animal drug residues if it finds there is a “reasonable probability” that the drug presents a risk to public health.¹⁸ As long as the drug is used in compliance with FDA regulations for conditions of use and does not exceed FDA’s tolerance levels, it is considered safe.¹⁹

Under the FFDCA, FDA also collects sales data from sponsors of drugs with antimicrobial active ingredients. The sponsor of an antimicrobial drug must submit an annual report to FDA on the amount of each microbial active ingredient in the drug that is sold or distributed for use in food-producing animals. The report must be broken down by month and must specify the amount of each antimicrobial active ingredient by container size, strength, and dosage form; by quantities distributed domestically and quantities exported; and by dosage form, including, for each such dosage form, a listing of the target animals, indications, and production classes that are specified on the approved label of the product.²⁰ Aside from this mandate, FDA does not currently collect data on feed additive usage.

FDA’s involvement in the oversight of approved animal drugs is generally minimal unless or until questions arise about a drug’s safety. The Agency does not routinely monitor emerging data on approved drugs but relies on others to bring the data to its attention.

FDA may suspend or withdraw approval for drugs on its own.²¹ However, FDA rarely uses this authority. As a rare example, in 2000, FDA proposed the withdrawal

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THE PRECAUTIONARY PRINCIPLE

The “precautionary principle” or “precautionary approach” emerged as a concept in Europe in the 1970s as a framework for managing environmental risks. It has since been recognized at the



international level by the United Nations and employed beyond the environmental field. Acknowledging that innovations and new technologies may come with unforeseen consequences, the principle requires governments and non-governmental organizations (NGOs) to proceed with caution in implementing them. When concerns arise that serious or irreversible damage may occur as result, measures to prevent this damage should be taken despite a lack of certainty or consensus.¹ An important component of this approach to risk management is that the proponent(s) of a new activity, technology, etc. bears the burden of demonstrating that its benefits outweigh any costs.²

¹ Commission of the European Communities. *Communication from the Commission on the precautionary principles*, Brussels: Commission of the European Communities (February 2, 2002), available at: http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf.

² J. Adler. *The Problems with Precaution: A Principle without Principle*, *The American* (May 25, 2011), available at: <http://www.aei.org/publication/the-problems-with-precaution-a-principle-without-principle/>.

Agricultural use of antibiotics has contributed significantly to the development of resistance among the microorganisms that the drugs are designed to target, because exposing organisms to sub lethal concentrations of antibiotics drives the selection of resistant genes. In the United States, an estimated 60-80 percent of national antibiotic usage—amounting to approximately 20-26 million pounds—is fed to food animals for nontherapeutic uses.



of Bayer's product Baytril due to new evidence that the main drug ingredient, enrofloxacin, was not shown to be safe.²² Most drugs withdrawn by FDA proposals in the past decade have been at the request of the manufacturers because the product is no longer manufactured: Pfizer's request to withdraw approval for lincomycin and buquinolate in broiler chickens in 2010,²³ Truow Nutrition's withdrawal of tylosin phosphate and other drugs in 2011,²⁴ Novartis' request to withdraw tiamulin for swine in 2012,²⁵ and Zoetis's request to withdraw chlortetracycline, sulfathiazole, and penicillin in 2014, were all submitted on the basis of the products' discontinuation by the companies.²⁶ For issues of safety, however, the Agency relies heavily on private citizens and organizations, like CFS, to petition the Agency to withdraw approval for a drug.

Regardless of who requests review of a drug's safety, FDA has a mandatory duty to withdraw approval of an animal drug when it finds the drug to be unsafe.²⁷ The FFDCFA provides that FDA **must** withdraw approval for an animal drug if:

- A} "[E]xperience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved or the condition of use authorized under [the FFDCFA];"²⁸
- B} New evidence, tests, or methods developed since approval of the application show that the drug is not safe for use "under the conditions of use upon the basis of which the application was approved . . . ;"²⁹ or
- C} New information, combined with the evidence available at the time the application was approved show a "lack of substantial evidence that such drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."³⁰

If FDA finds that a drug presents an "imminent hazard to the health of man or animals," it may suspend approval of the drug immediately.³¹

In practice, FDA conducts a two-fold inquiry to determine whether to withdraw approval for an animal drug. First, it determines whether there is a reasonable basis from which "serious questions" about the safety of the new animal drug may be inferred from new scientific evidence. Second, it determines whether, in light of the new data, the use of the new animal drug under the approved conditions is still considered to be safe.³² "Serious questions" about the safety of a new animal drug

can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect.³³

Before withdrawing approval for an animal drug, FDA must afford the manufacturer notice and a hearing. During withdrawal proceedings, CVM has the “initial burden of producing new evidence that raises serious questions about the ultimate safety” of the drug.³⁴ The scope of “new evidence” is not limited to data developed after a drug is approved, but includes the re evaluation or novel application of pre-existing data.³⁵ When FDA meets this threshold the burden shifts to the manufacturer to demonstrate the safety and efficacy of the drug.³⁶ The cancellation process affords the company several layers of appeal. If companies choose to contest a cancellation, the process can take years (e.g. the contested withdrawal of Baytril for use in poultry took 5 years) or decades and consume substantial agency resources. Because of this, FDA has prioritized encouraging companies to voluntarily withdraw drugs from the market over official, enforceable cancellations.

FDA can reverse its decision to suspend or withdraw approval for a drug and reinstate approval at any time. This is left entirely in FDA’s hands; the FFDCFA provides that this can occur “[w]hensoever the Secretary finds that the facts so require.”³⁷

FDA’s decisions to approve animal drugs or keep animal drugs on the market must be based on sufficient evidence of the drug’s safety. Applications for new animal drugs must include full reports of investigations demonstrating the drug is safe and effective for use. Yet, our research shows that in many cases there are few substantial studies available that investigated the effects of drugs on the market on animal, human, and environmental health. In other cases, studies of these effects are or have become available but the drugs have remained on the market despite the harms that the evidence shows. The regulatory process both assumes that approval was given based on solid data, and understands that new information will emerge after a drug is on the market. When new data is suggestive of harmful effects, the Agency has authority to review and amend the drug’s approval.

Overall, it is extremely difficult to know what information FDA actually possesses about these drugs. Center for Food Safety’s FOIA requests have been largely ignored. Industry is even more secretive about what evidence exists, especially when such evidence shows negative effects. As a result, and contrary to the clear mandates of federal law, the burden of proving that these harmful drugs are unsafe falls on the public.

There was increased interest in coccidiostat residues in food after a number of contamination incidents were reported in the 1990s, with particular attention paid to their high presence in egg yolks. A significant amount of lasalocid, for example, is transferred to the egg when fed to laying hens, and the European Food Safety Authority determined that lasalocid in eggs could reach concentrations 63.6 times of that contained in the feed.

THE PUBLIC'S (LACK OF) INFORMATION ON ANIMAL DRUGS

At least twelve of the specific drugs discussed in this report are prohibited for use as animal drugs in other countries, and the EU has issued a ban on the use of all antibiotics for growth promotion. For six of the drugs, FDA has established residue tolerance levels significantly higher than the international standards.



GIVEN FDA'S MANDATE of promoting and protecting public health "by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner," and ensuring that regulated products "are safe, wholesome, sanitary, and properly labeled,"³⁸ most people assume that FDA actually has and considers the results of clinical research when making regulatory decisions about animal drugs. This may not be the case.

While FDA oversees the approval and regulation of drugs used for food animal production, it is extremely difficult to know what information the Agency has regarding their use and safety. CFS's review of available literature and data has found few comprehensive, scientific studies investigating the potential impacts of approved drugs on the environment, non-target organisms, and human health. Much of the publicly-available research has focused on the efficacy of the drugs, e.g., determining the dosages, rates, or mixtures that produce the largest animals with the least amount of feed and time required. In addition, qualitative, farm-level

data on the frequency and amount of drugs administered to food animals is currently unavailable because no entity collects quantitative usage data. Producers also often use drugs in combination to achieve multiple desired effects,³⁹ and data on the interactions of these compounds in the environment is extremely limited. Understanding these interactions is critical for a full assessment of the impacts and risk associated with the use of these drugs.

Rather than use its statutory authority to gather and review data, FDA places the burden on the public to show that drugs are unsafe. Based on CFS’s review of publicly-available studies, the following sections detail what information we have and what information we lack about the impacts of six major categories of animal drugs on animal health, human health, and the environment.

I. BETA-AGONISTS

Beta-agonists are widely used in U.S. meat production due to their efficacy in increasing animal growth by inhibiting fat, increasing protein synthesis, and reducing protein breakdown in muscle.⁴⁰ Producers feed beta-agonists to animals during the “finishing” stage of growth—the final period of weight gain before slaughter—to encourage a last-minute increase in muscle mass and overall carcass weight of the animals. Manufacturers’ names for these drugs reflect their effects: ractopamine is marketed as “Paylean” for swine, “Optaflexx” and “Heifermax” for cattle, and “Topmax” for turkeys; zilpaterol is marketed as “Zilmax.”

Available research shows that beta-agonists have negative impacts on meat quality, animal well-being, and the environment. In animals they induce increased heartbeat, relaxation of blood vessels and muscle, and contraction of cardiac tissue. Residues in meat may also harm human health. Beta-agonists are excreted through manure, degrading water quality and threatening drinking water sources. In fact, beta-agonists are banned or restricted in many other countries.

FDA regulations require that animal drug labels clearly list all possible negative side effects, but in recent years drug companies have successfully weakened the language on beta-agonist labels. For example, the label for Paylean previously stated that pigs treated with Paylean were at an “increased risk for exhibiting the downer pig syndrome.”⁴¹ Now, the label simply states that the drug “may increase the number of injured and/or fatigued pigs during marketing.”⁴² **Since FDA has to approve the labels proposed by drug manufacturers,⁴³ federal regulators are complicit in downplaying the negative impacts of beta-agonists.**

CFS submitted requests for information about zilpaterol and ractopamine to FDA under the Freedom of Information Act in January and February 2013, respectively. After FDA failed to adequately respond to the requests, CFS sued to force the Agency

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Most independent studies of beta-agonists evaluate what the proper dosage is for livestock in order to obtain the desired feed efficiency, weight gain, and meat leanness. These studies rarely, if ever, investigate potential adverse effects of the drugs on animal behavior, human health, animal welfare, non-target species, or the environment.

to release its records. The litigation is ongoing. CFS also sued FDA in November 2014 for failure to comply with the National Environmental Policy Act when approving eighteen new animal drug applications for ractopamine and ractopamine-based combination drugs.

FDA's unwillingness to provide the requested information illustrates the lack of transparency that is typical from the Agency with regard to animal drugs. Whether this is because FDA hopes to withhold the information that would cast doubt on its approval of these drugs or because the Agency never collected the requested information is unknown. What is known is that without access to these records, the public remains in the dark.

The full risks that ractopamine and zilpaterol pose to consumers and the environment remain at least partly unknown because no one has conducted an adequate, rigorous assessment. Most independent studies of beta-agonists evaluate what the proper dosage is for livestock in order to obtain the desired feed efficiency, weight gain, and meat leanness.⁴⁴ These studies rarely, if ever, investigate potential adverse effects of the drugs on animal behavior, human health, animal welfare, non-target species, or the environment. Thus, existing scientific studies are inadequate and insufficient to provide a full understanding of their effects.

The Reason for their Use:

FDA has approved the use of ractopamine and zilpaterol as a feed additive during the “finishing process” to increase weight gain, improve feed efficiency, and increase carcass leanness.⁴⁵ FDA approved continuous use of ractopamine for a specified period right up until slaughter.⁴⁶ Zilpaterol, on the other hand, requires a short three-day withdrawal period for cattle. Manufacturers of the drug estimate that ractopamine use allows producers to increase their profits by as much as \$2 per head.⁴⁷ For pigs, studies have demonstrated that ractopamine produces 10 percent more meat on average compared to animals not receiving the drug. Similarly, zilpaterol, causes cattle to gain weight 4 percent more efficiently, adding 20-30 pounds on average in those last weeks before slaughter.⁴⁸ This same amount of growth without the drug would require 200 pounds of feed. However, these profit and production increases are not without significant detrimental impacts.

How They Affect Animals:

Multiple studies have shown that ractopamine contributes to increased numbers of “downer” animals, a common term for animals that cannot walk or stand on their own due to illness or injury, such as broken appendages, severed tendons or ligaments, nerve paralysis, fractured vertebral columns, or metabolic conditions.⁴⁹ Zilpaterol, in comparison, has been understudied, but recent events discussed later in this section highlight the risk of “downer” conditions among cattle fed zilpaterol. The connection between beta-agonists and “downer” animals suggests



significant adverse impacts on the health and welfare of food animals, although there are no studies elucidating how the drugs lead to the syndrome.

RACTOPAMINE: FDA approved the use of ractopamine for pigs in 1999, for cattle in 2003, and for turkeys in 2008. The use of ractopamine is pervasive in U.S. animal agriculture, administered to an estimated 60 to 80 percent of U.S. pigs.⁵⁰ FDA’s own records show that ractopamine has resulted in more reports of sickened or dead pigs than any other livestock drug.^{51,52} [Yet since FDA approval, there have been a number of studies on potential animal and human health risks though few are publically accessible.]

Existing studies show that ractopamine mimics stress hormones, increasing heart rate and relaxing blood vessels,⁵³ and is linked to significant health problems and behavioral changes in animals, such as cardiovascular stress, muscular skeletal tremors, increased aggression, hyperactivity, acute toxicity, and genotoxicity.⁵⁴ As discussed above, ractopamine also increases the number of “downer” or lame animals, and is associated with broken limbs, a complete inability to walk, and death.⁵⁵ Highly-stressed animals exhibit behavioral problems and have difficulty socializing with other animals, resulting in more hierarchical issues and fights within a flock or herd. Some reports indicate animals on ractopamine become so aggressive and hyperactive that they must be medicated to calm them down for shipping to slaughter.⁵⁶ “Downer” pigs also have increased cortisol levels, which may result from experiencing stress caused by illness, trauma, or environmental changes.⁵⁷ Research has demonstrated that among pigs in stressful conditions, those fed Paylean had elevated cortisol levels, leading to increased blood glucose concentrations.⁵⁸ According to one study by the biotech industry and university researchers that evaluated the effects of ractopamine on pigs, “[t]he occurrence of downer pigs may

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In under an hour after ingestion [of zilpaterol] the horses developed skeletal muscle tremors and increased heart rates, and exhibited restlessness and profuse sweating. Despite discontinuing the drug, the increased heart rates and muscle tremors took 2 weeks and 1 week to fully resolve, respectively.

be amplified by the industry trend of producing a more heavily muscled, lean genotype pig.”⁵⁹ These studies show that ractopamine warrants further and more comprehensive scientific study.

ZILPATEROL: FDA first approved the use of zilpaterol for cattle in 2006 and heifers in 2008. Since 2008 FDA has also approved various combinations for cattle and heifers.⁶⁰

Zilpaterol is commonly marketed for food animals by Merck & Co. Inc. under the name Zilmax. Prior to Zilmax’s approval, the number of beef cattle euthanized before slaughter—due to “downer” illnesses that prohibited their inclusion in the food supply—averaged 670 per year. In the first two years following the drug’s introduction the number rose dramatically, and currently ranges from 1,600 to 2,300.⁶¹

There are fewer studies on zilpaterol than ractopamine, but the available data on health effects are alarming. Scientists at North Dakota State University, for example, fed three healthy horses 0.17mg/kg zilpaterol via feed with the intent of studying how the animals processed and excreted the drug. In under an hour after ingestion, the horses developed skeletal muscle tremors and increased heart rates, and exhibited restlessness and profuse sweating.⁶² Despite discontinuing the drug, the increased heart rates and muscle tremors took 2 weeks and 1 week to fully resolve, respectively. The horses also showed symptoms of muscle and kidney damage.⁶³ Producers around the United States have also noted increased hoof loss and animal death associated with Zilmax. Merck’s own reports indicate that Zilmax-fed cattle suffer from stomach ulcers, brain lesions, blindness, lethargy, bloody noses, respiratory problems, and heart failure.⁶⁴

Zilmax generated media controversy in 2013 when a slaughterhouse in Washington State owned by Tyson Foods received over a dozen “downer” heifers and steers. These cattle, all of which had been “finished” on feed containing Zilmax, were unable to walk and all had lost their hooves.⁶⁵ With little scientific data guaranteeing the drug’s safety, large meat processing companies such as Tyson Foods and Cargill publicly announced in 2013 that they would no longer accept Zilmax-fed cattle due to the horrific and inhumane physical condition of the animals.⁶⁶ Cargill and Tyson Foods plan to refuse Zilmax-fed cattle until Merck can sufficiently prove its safety. This alone should have prompted FDA to seriously consider withdrawing approval of the drug on the basis of its effects on animal health.

How They May Affect Human Health:

Ractopamine residues are widely present in our food supply: a recent Consumers Union study tested approximately 240 pork products for ractopamine, and found residual amounts of the drug in about one-fifth of the samples tested.⁶⁷ Despite the likelihood of consumer exposure to drug residues in foods, little is currently



Ractopamine (and zilpaterol) enter the environment mainly through livestock manure. Manure storage and disposal by CAFOs is known to contaminate groundwater, streams, rivers, and other surface waters—providing a pathway for beta-agonists to enter aquatic environments.

known about how they affect humans. Studies have recognized that “there is a possibility that adulteration of feed with ractopamine could result in residues in animal tissues and lead to human poisoning.”⁶⁸ For example, the Sichuan Pork Trade Chamber of Commerce in China estimates that between 1998 and 2010, 1,700 people were poisoned from eating pigs fed Paylean.⁶⁹ Yet, USDA does not have a strong testing or certification program in place for ractopamine.⁷⁰ USDA’s Food Safety and Inspection Service (FSIS) has done little sampling. For example, in 2010, **USDA did not perform a single test** on 22 billion pounds of pork, and only tested 712 samples from 26 billion pounds of beef.⁷¹

Despite this known risk, industry-sponsored studies almost exclusively test ractopamine on mice, rats, monkeys, and dogs. In mice, ractopamine caused dose-dependent decreases in testicular weights in males and increases in heart weights in both sexes. Studies of rhesus monkeys found that ractopamine caused elevated heart rates that persisted for 16 hours after dosing. Another study exposed monkeys to different levels of ractopamine by inhalation and found that increased heart rates persisted for two weeks after treatment was stopped in all subjects.⁷² Only **one** human study has been conducted thus far. Even though the study had a very small sample size of only 6 men, one was removed from the study when he experienced an abnormally rapid heart rate after dosing.⁷³ More studies with adequate sample sizes are warranted.

How They Affect the Environment:

Ractopamine (and zilpaterol) enter the environment mainly through livestock manure. Animals excrete approximately 95 percent of ingested ractopamine in the first three days after consumption.⁷⁴ In a typical CAFO system, the manure is pumped into open-air lagoons or disposed of without treatment via land application

or in-ground injection. Manure storage and disposal by CAFOs is known to contaminate groundwater, streams, rivers, and other surface waters—providing a pathway for beta-agonists to enter aquatic environments. Elanco, the manufacturer of Optaflexx, Paylean, and Topmax, acknowledges that ractopamine may leach “into the soil and groundwater from confinement areas . . . and runoff from land fertilized with manure from treated animals,” and that this will potentially alter the chemical composition of those waterways. Despite this, the company has conducted no field studies of the drug’s impacts on waterways. A 2010 study of veterinary pharmaceuticals in groundwater near livestock operations detected ractopamine in water samples downstream from swine facilities.⁷⁵

Elanco has also stated that ractopamine is moderately toxic to plants and slightly toxic to aquatic invertebrates. When FDA adverse drug reports for ractopamine are cross referenced with habitat data from the U.S. Fish and Wildlife Service, at least 98 species of threatened and endangered aquatic invertebrates and plants have critical habitat in areas where ractopamine is used.⁷⁶ However, FDA has yet to provide an assessment of the degree to which ractopamine’s approval and use may affect endangered and threatened species or their habitats. FDA has also not conducted an environmental analysis, as required under the National Environmental Policy Act (NEPA) before approving ractopamine for use in animal factories.

CODEX & INTERNATIONAL STANDARDS

FDA’s standards for animal drugs generally are laxer than those adopted by The Codex Alimentarius Commission (Codex), the international food safety authority established by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) in the early 1960s. Codex develops international food standards, guidelines and codes of practice designed to facilitate safety and quality in international food trade. One aspect of the Codex standards is the determination of Maximum Residue Levels (MRLs) for residues of veterinary drugs in food, based on the available science and input from independent bodies. Codex standards are not mandatory, but a way for countries to access information for determining national standards and tolerance levels. The EU and other countries have elected to set stricter tolerance levels than the Codex standards in some cases. In contrast, the United States, and specifically FDA, commonly set tolerance levels that are significantly higher than those recommended by Codex. This is despite FDA’s own regulations that require the Agency to review Codex food standards.¹

Additionally, other countries and health authorities have restricted or banned drugs that are approved by FDA and regularly administered to food animals in the United States. For example, the European Union (EU) banned most antimicrobials for use as growth promoters in agriculture in the 1990s due to the risk of increased antimicrobial resistance undermining the efficacy of important human medicines. Despite this, FDA continues to allow their use for growth promotion in the United States. The European Union has likewise banned beta-agonists, like Ractopamine, used as growth promoters.

¹ 21 C.F.R. § 130.6(a).

CFS and other groups sued the Agency in November 2014 for failing to do so before approving eighteen ractopamine based animal drugs. The litigation is ongoing.

In addition to the high prevalence of the drug itself in animal wastes, manure from animals fed ractopamine ultimately has higher nutrient levels. Studies in 2001 and 2009 concluded that nitrogen and phosphorus levels in pig manure were reduced in correlation to increased ractopamine in the pigs' diets, but the trials were extremely short-term: only 5 days and 15 days, respectively.⁷⁷ Ractopamine is approved in feeds for the last 28–42 days for cattle and the last 45–90 pounds of gain for pigs,⁷⁸ which, based on growth performance studies, would take roughly 22–45 days.⁷⁹ A 2013 study by university veterinarians in Brazil conducted over 28 days found that after the second week of the trial, nitrogen and phosphorus levels in manure exceeded the levels prior to adding ractopamine. Pigs also ingested greater amounts of water after the second week, leading to an increase in the water content of the manure.⁸⁰ Over the entire four weeks, the sulfur content of the manure consistently increased.⁸¹ The use of ractopamine over the allowed period of use, therefore, may increase nutrient loading associated with agricultural wastes. Nutrient loading from large operations frequently leads to runoff entering waterways and overloading surface waters, which is a major contributor to declines in water quality. Nutrient runoff from manure application causes algal blooms and threatens aquatic life.

International Restrictions:

Europe, China and other countries in the world have strict standards or bans on ractopamine and similar drugs. Despite these stringent restrictions, in 2012 the United Nations international food standards body, Codex Alimentarius Commission, adopted a less restrictive maximum residue limit (MRL) for ractopamine.⁸² These tolerance levels are insufficient to protect human and animal health, and less protective than an outright ban—and even so they are still more stringent than current U.S. standards.

Summary

The available data on beta-agonists like ractopamine and zilpaterol warrant immediate action. The analysis of publically available studies strongly suggests that the drugs adversely affect animal health to an alarming degree. The high rate of downer, over-stressed, and physically impaired animals raises serious questions about the continued use of these growth-promoting agents on animal health. Ractopamine's animal health impacts also raise significant concern for consumers, especially considering the detection of ractopamine residues in pork products and cases of ractopamine poisonings in China. FDA has seemingly ignored this information by failing to take any action to restrict the use of these drugs. It has also failed to respond to CFS's requests for any data the Agency gathered during the drug approval process but has not made public.

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Studies of steroid hormones in animal agriculture to date have largely focused on performance measures and achieving the greatest growth-promotion results, while studies investigating the environmental fate and/or human health impacts of agricultural hormones are limited.



STERIOD HORMONES

FDA has approved a number of steroid hormone drugs for use in beef cattle and sheep since the 1950s. Their purpose in livestock production is to increase animal growth rates, the efficiency by which the animals convert the feed they eat into meat, and the leanness of their meat.⁸³ Growth hormones, while varied, generally affect how nutrients are processed in the body by facilitating protein synthesis—and thus muscle/meat development—at the expense of fat deposition.⁸⁴

In November 2013, CFS and the Animal Legal Defense Fund submitted a joint request for information about trenbolone acetate to FDA and EPA under the Freedom of Information Act. EPA did not fully respond to the request until June 2014. To date, FDA has entirely failed to respond to the request or release any records.

There are six hormones currently approved for use in cattle and sheep, the naturally-occurring hormones: estradiol, testosterone, and progesterone,⁸⁵ and synthetics designed to mimic each: zeranol, trenbolone acetate, and melengestrol acetate, respectively.⁸⁶ Hormones can be estrogens (estradiol/zeranol), which affect female characteristics; androgens (testosterone/trenbolone acetate), which affect male characteristics; or progestogens (progesterone/melengestrol acetate), which are precursors to estrogens and androgens.⁸⁷ Estrogens are the most widely used in animal agriculture, and the other hormones are typically used in combination with estrogen.⁸⁸

These drugs are commonly formulated as pellets and implanted under the skin behind the ear where they slowly dissolve, releasing the hormones over time. The

exception is melengestrol acetate, which is added to feed.⁸⁹ FDA has established a zero-day withdrawal period for the additive, meaning animals do not have to be taken off the drugs before slaughter.⁹⁰

The Reason for their Use:

Hormones are used in animal agriculture primarily for increased growth rate and feed efficiency. Natural hormones help produce more muscle and protein and deposit less fat, making for better meat. In some cases, industrial practices interfere with natural hormone production and provide drugs to compensate. For example, male cattle are commonly castrated at a young age, inhibiting the natural production of androgenic hormones that help produce more muscle and protein and deposit less fat.⁹¹ Administering hormones also enables producers to have more control over their animals. Hormone production in female cattle is naturally low prior to sexual maturity; providing an external source of hormones promotes higher growth rates earlier in life. When females do reach sexual maturity but are not going to be bred, providing progestogens like melengestrol acetate (MGA) in feed shuts down their reproductive cycle (by signaling the female's non-sexually receptive phase⁹²), freeing up resources that are then diverted to muscle growth.⁹³ MGA is "an effective suppressant of cyclic heat in heifers," and has been shown to induce a 7 to 10 percent improvement in growth.⁹⁴

Studies of steroid hormones in animal agriculture to date have largely focused on performance measures and achieving the greatest growth-promotion results, while studies investigating the environmental fate and/or human health impacts of agricultural hormones are limited. The meat industry and FDA regularly defend the drugs with claims that the residues consumed through animal tissue are dramatically lower than the levels produced naturally in the human body, and therefore are inconsequential.⁹⁵ However, **new data question this claim.**

How They Affect People:

The American Public Health Association acknowledges that "[t]here is clear evidence that hormones originating outside the body can interfere with our own hormone function."⁹⁶ Few studies on the effects of low doses of exogenous estrogenic hormones on human health exist and even fewer on the role of progesterone and testosterone. In 2002, the European Union Scientific Committee on Veterinary Measures reviewed scientific data and concluded that exogenous growth-promoting hormones pose health risks to consumers, confirming in particular that estradiol has mutagenic and genotoxic effects.⁹⁷ For the other five drugs, the panel concluded that **limited quantitative data inhibited complete assessment**, but that risks to consumers have been identified in qualitative terms.⁹⁸

Meat from cattle not treated with hormones has an average estradiol concentration of 4.3 nanograms (ng)/500 grams (g), compared to 20 ng/500 g in meat from

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Further evidence suggests that females exposed to elevated levels of estradiol in utero have an increased risk of breast cancer as adults. Zeranone in particular has been strongly linked to breast cancer.

treated cattle.⁹⁹ Despite this almost five-fold increase, the meat industry and FDA argue that residue levels in food are low compared to levels naturally produced in the human body and therefore have no effect on consumers. However, increasing evidence suggests that any dose of external hormones may have significant effect on humans. Some studies have shown that children and fetuses are especially sensitive to steroids and even a small variation may account for significant phenotypic effects. A 2007 study found that sperm concentration of male children was inversely related to the mother's self-reported beef consumption during pregnancy—the more beef consumed, the lower the sperm concentration.¹⁰⁰ Observed low-dose effects of estradiol in children are consistent with results from animal studies, and researchers have concluded that “there is no lower threshold for estrogenic action: any dose may have an effect.”¹⁰¹ The industry's defense of low residues in food also fails to account for all possible environmental routes of exposure to the hormones used in livestock production, such as drinking water.

For women, elevated estradiol levels can lead to isolated breast development in girls before the age of 8 with no other clinical signs of sexual maturation.¹⁰² Exposure to one of zeranone's metabolites, zearalenone, is thought to trigger “central precocious puberty” in young girls, meaning it causes the brain to release the hormones responsible for puberty before 8 years old.¹⁰³ In another study, the presence of serum levels of zearalenone in Hungarian girls was associated with early breast development and mastopathy,¹⁰⁴ a painful breast disorder that can later turn into cancer.¹⁰⁵ Research indicates that estradiol and the synthetic zeranone are up to 5 and 6 orders of magnitude more potent estrogens than Bisphenol-A—a chemical linked to breast cancer¹⁰⁶—and researchers observed significant changes in human breast cancer MCF7 cells at low concentrations of estradiol and zeranone.¹⁰⁷ Further evidence suggests that females exposed to elevated levels of estradiol in utero have an increased risk of breast cancer as adults.¹⁰⁸ Zeranone in particular has been strongly linked to breast cancer.¹⁰⁹

Data from animal exposure studies and women prenatally exposed to high levels of diethylstilbestrol (DES),¹¹⁰ an estrogenic hormone previously approved by FDA, demonstrate the carcinogenic effects of synthetic estrogen.¹¹¹ Different tissues have different sensitivities towards estrogen, such that it is difficult to establish specific threshold doses.¹¹² Furthermore, a study of estradiol-induced sex reversal in turtle embryos led researchers to conclude that, if the threshold for estrogen is already exceeded by natural levels in a person's body, no threshold dose exists for external estrogens.¹¹³ In other words, any exposure could trigger physiological effects.

Experience with steroids used by athletes suggests that non-estrogenic steroids used in food animal production may cause human health problems. Trenbolone, for instance, is an illicit drug abused by athletes due to its effectiveness as an anabolic steroid, and many of its metabolites have anabolic activity several times above that of natural testosterone. It therefore has a higher affinity for and effect on the testos-

terone receptor than naturally-produced testosterone. For this reason, human exposure is a significant concern and further research is needed to justify its use. In addition, trenbolone can cross the placenta during late pregnancy,¹¹⁴ posing particular risk to fetuses. A 2010 ChemWatch data sheet warns that trenbolone “[m]ay damage fertility or the unborn child.”¹¹⁵ One study on melengestrol acetate showed that it caused delayed menstruation in normal-ovulating women and induced withdrawal (non-menstrual) bleeding in women of reproductive age with absent or irregular menstrual cycles.¹¹⁶



Researchers took the results one step further, stating that this new knowledge of how the chemicals behave in the environment makes the current regulatory and risk-assessment paradigms inadequate.

How They Affect the Environment:

Since the 1970s researchers have shown that synthetic hormones are excreted by food animals and subsequently contaminate local watersheds. A 2004 study measured estrogenic and androgenic activity in waterways near CAFOs in Nebraska. The researchers determined that the detected androgenic activity decreased with distance from feedlot sites, suggesting that the hormones originated in the feedlots. They also found that the estrogenic activity measured would be sufficient to produce significant effect on target cells.¹¹⁷ These findings were reinforced by a 2007 study that found hormones in surface waters around CAFOs.¹¹⁸

Studies of steroid residues in manure found that the drugs do not break down during storage in either liquid or dried manures and therefore are still present when the manure is applied to fields as fertilizers. While the levels of hormones detected in the manure decreases rapidly after application, researchers caution that the portion of the drug that was transported off-site via runoff instead of breaking down is unknown.¹¹⁹

There is also growing evidence that steroid hormones in the environment may never actually disappear entirely. A 2013 study by researchers at multiple U.S. universities found that while synthetic hormones such as trenbolone are broken down by exposure to light, the metabolites have “strong structural similarity to parent steroids” and “retain enough biological activity to elicit observable changes to endocrine function at trace concentrations.”¹²⁰ In fact, the hormones transform in daylight in such a way as to avoid detection, then readily transform back at nighttime.¹²¹ Researchers concluded that the transformation of steroid hormones in the environment does not necessarily reduce their toxicity.¹²² The researchers took the results one step further, stating that **this new knowledge of how the chemicals behave in the environment makes the current regulatory and risk-assessment paradigms inadequate.**¹²³

Hormones that have contaminated waterways have altered the reproductive habits of aquatic species, including decreasing the fertility of female fish.



Scientists have expressed concern with the effects of endocrine-disrupting agricultural hormones on both aquatic and land animals since the 1970s. Exposure to exogenous natural and synthetic hormones can directly affect the gonads, reproductive fitness, and sexual differentiation in a number of species.¹²⁴ Studies in rabbits have demonstrated that all three synthetic hormones can pass through the placental wall, posing a risk to the fetus.¹²⁵ Hormones that have contaminated waterways have altered the reproductive habits of aquatic

species, including decreasing the fertility of female fish.¹²⁶ Existing literature is limited and has focused primarily on estrogens. **Information on the impact of androgens and progestogens in the environment is even scarcer.**

The endocrine-disrupting effects on fish of the hormones estradiol/zeranol in the environment are well documented.¹²⁷ Available data demonstrates that estradiol can negatively impact sexual differentiation, gamete development, maturation, and spawning in a broad range of fish species.¹²⁸ Zeranol, a non-steroidal synthetic derivative of a fungal estrogen,¹²⁹ is not as commonly used in feedlots in large quantities since estradiol is a higher potency growth promoter, but it has been found in low concentrations in sewage discharges.¹³⁰ Exposures to both low and high doses of zeranol have caused a variety of reproductive irregularities in rats.¹³¹

Testosterone/trenbolone acetate (TBA) is metabolized into 17 β - and 17 α -trenbolone both of which have been present in detectable concentrations in feedlot effluent.¹³² In castrated male rats, researchers found that while TBA stimulated the growth of androgen-dependent tissues, it did not behave exactly like its natural counterpart, testosterone. Specifically, trenbolone had relatively little impact on prostate growth. **This difference suggests that researchers will be unlikely to predict exactly how trenbolone affects wildlife and individual species.**¹³³ Both metabolites bind with high affinity to androgen receptors in mammals and fish, and can cause masculinization and decreased fertility in concentrations comparable to those detected in effluent discharges from feedlots.¹³⁴

A 2010 ChemWatch data sheet warns that trenbolone is “toxic to aquatic life with long lasting effects.”¹³⁵ Studies of fathead minnows downstream from Nebraska feedlots demonstrate that males exposed to waterborne androgens had reduced testis size and smaller skull size, signs that their bodies were producing less of their own testosterone and were thus feminized. Female minnows in the same area became masculinized, developing bumps on their heads that should only appear on reproductively available males.¹³⁶

How They Affect Animals

There are few studies on the effects of synthetic hormones on food animals, as opposed to the wildlife and aquatic species that are affected by exposure from their environment. Most studies to date have been carried out on steers and focused on growth performance and feed conversion efficiency.¹³⁷ Some of these performance-oriented studies reported negative side effects of the use of estrogens in steers such as feminization and increased frequency of steer-buller syndrome,¹³⁸ a behavioral problem characterized by aggressive mounting of other steers.¹³⁹

Two studies have evaluated progesterone/melengestrol acetate in cattle. One study found that twelve percent of MGA fed to cattle is unabsorbed and excreted in feces. Hence, the hormone has been found in waterways downstream from cattle feeding operations.¹⁴⁰ Researchers calculated that if 30 percent of heifers for beef production are fed 0.5 mg MGA daily for 120 days, an additional 10 kg of MGA will enter the environment via manure.

A study of feedlot cattle in Canada determined that heifers fed MGA were 3.2 times more likely to be diagnosed with acute interstitial pneumonia that led to emergency slaughter.¹⁴¹ The authors concluded that, “the most cost-effective method of reducing the incidence of [pneumonia]-related emergency slaughter in feedlot heifers may be to eliminate MGA from the diet.”¹⁴² Melengestrol acetate is also fed to certain animals confined in zoos to control reproduction. A 2002 study of 212 captive felines of various species found that MGA contraceptive treatment increased the risk of some diseases and impaired fertility.¹⁴³

International Restrictions:

In 1988, concerns about the potential health risks of drug residues led the EU to ban the importation of meat of hormone-treated animals.^{144,145} The United States and Canada, which produce such meat, have vigorously fought the ban through both punitive tariffs on various imports from Europe and appeals to the World Trade Organization. **The EU has expressed hope that new research will provide additional scientific ground to rebut these challenges to its ban.**¹⁴⁶

Guidelines from FDA and the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization of the United Nations and World Health Organization suggest that the maximum acceptable daily intake of natural sex steroids is equal to 1 percent of the normal daily production rate of the same hormone in pre-pubertal children.¹⁴⁷ For estradiol, however, the concentrations in pre-pubertal children were previously highly overestimated in early measurements. Studies have suggested that the production rate used by FDA/JECFA to determine intake levels might be significantly higher than actual rates.¹⁴⁸ **Without further study, it is impossible to know whether and at what levels these synthetic drugs are safe.**

In 1988, concerns about the potential health risks of drug residues led the EU to ban the importation of meat of hormone-treated animals. The United States and Canada, which produce such meat, have vigorously fought the ban through both punitive tariffs on various imports from Europe and appeals to the World Trade Organization.

Medical and public health organizations have expressed concerns that external exposure to hormones has adverse impacts on the human reproductive system, in particular fetuses and adolescent females.

Summary

There is sufficient evidence in the studies and data CFS has compiled to suggest that significant adverse human health effects have arisen as a result of administering steroid hormones to food animals. The FDA and industry claims that residue levels in animal products do not exceed natural production levels in the human body and therefore pose no harm to consumers, but these claims are unfounded. Medical and public health organizations have expressed concerns that external exposure to hormones has adverse impacts on the human reproductive system, in particular fetuses and adolescent females. Recent evidence of the ability hormones have to not only enter the environment from agricultural uses, but persist for longer than previously thought, also means that food products are likely not the only route of human exposure to these animal drug residues. While FDA has resisted making any data it possesses accessible to the public, there is sufficient evidence currently available to raise serious questions about the use of steroid hormones. Under FFDCA, FDA can issue an order withdrawing approval of any animal drug if new evidence not contained in the application shows that the drug is not safe for use under the conditions of its approval.¹⁴⁹ In the case of hormones, there is sufficient data to compel the Agency to act.

ANTIOXIDANT FEED ADDITIVES

Ethoxyquin is a synthetic antioxidant currently used for multiple agricultural purposes. Although technically not an animal “drug”—it has no therapeutic or animal growth and productivity uses—ethoxyquin is an animal feed additive that raises similar concerns as the other drugs outlined in this report. Marketed under the trade names Santoquin, Santoflex, and Quinol, it was developed as a pesticide by Monsanto in the 1950s. The most common use is to inhibit scald (browning) in pears during post-harvest processing and transport, but it can be also used as a color preservative for spices, a stabilizer, and in rubber to prevent cracking due to oxidation. Ethoxyquin was approved as an animal feed additive in 1976,¹⁵⁰ used to stabilize fat soluble vitamins—such as A and E—to maintain the quality of feed. Ethoxyquin’s use continues to expand: in 2013, a manufacturer petitioned FDA to approve its use in vitamin D formulations in animal feed.¹⁵¹

The Reason for Its Use

Unlike drugs approved for use in animal production, ethoxyquin has no growth-promotion or disease prevention qualities. Its primary purpose as a feed additive is to stave off rot. Under current regulations, ethoxyquin is only permitted for use in animal feed as “a chemical preservative for retarding oxidation of carotene, xanthophylls, and vitamins A and E in animal feed and fish food” and “as an aid in preventing the development of organic peroxides in canned pet food.”¹⁵² In other words, it helps prevent the fats in livestock feed and pet foods from becoming rancid, essentially allowing products to have longer shelf lives by inhibiting natural



decay processes. Some poultry farms add ethoxyquin to drinking water to enhance the yellow color of egg yolk.¹⁵³

How It Affects People

Ethoxyquin residues are of concern in consumer products, and the World Health Organization established an acceptable daily intake for humans of 0.06 mg/kg.¹⁵⁴ The EPA acknowledges that ethoxyquin has not been tested for its carcinogenicity.¹⁵⁵ While tolerances have been set for the parent compound and products generally do not exceed the tolerances, the metabolites are not regulated.¹⁵⁶ The main metabolite of ethoxyquin (ethoxyquin dimer, or EQDM) has an unknown toxicity profile and a much longer half-life than ethoxyquin.¹⁵⁷ Studies have shown that EQDM concentrations increase as ethoxyquin concentrations decrease in animal tissue when feed containing ethoxyquin is withdrawn, accounting for up to 99% of ethoxyquin and its metabolites.¹⁵⁸ EQDM was also identified in commercially-farmed fish species, including salmon, suggesting that it accumulates in many fish species.¹⁵⁹ Most of these studies were conducted on fish fed ethoxyquin, and **there is little literature examining its effects in animal feed for mammalian species.**

FDA has long acknowledged the “deleterious and poisonous” effects of ethoxyquin. FDA’s correspondence in response to Monsanto’s petition for approval—both internally and with concerned public individuals—demonstrates that ethoxyquin was well-recognized as harmful and poisonous. Ethoxyquin can cause significant damage at dosage rates higher than those approved by FDA. For example, rats fed ethoxyquin at a rate of 0.1 percent displayed clear evidence of injury to vital organs, and a rate of 0.2 percent inhibited growth.¹⁶⁰ Other researchers found that

Ethoxyquin was approved as an animal feed additive in 1976, used to stabilize fat soluble vitamins—such as A and E—to maintain the quality of feed. FDA’s correspondence in response to Monsanto’s petition for approval—both internally and with concerned public individuals—demonstrates that ethoxyquin was well-recognized as harmful and poisonous.

Ethoxyquin is excreted by mammals in the urine and feces, thus entering the environment. Despite this, there is no indication that FDA has considered ethoxyquin's impacts on the environment.

ethoxyquin in rat diets increased the incidence and number of tumors.¹⁶¹ While the carcinogenicity and mutagenicity of ethoxyquin itself have not been sufficiently studied, ethoxyquin has been shown to enhance the activity of other hazardous compounds.¹⁶² In 1990, FDA nominated ethoxyquin for carcinogenicity testing, reasoning that its toxicological effects were unknown and it appeared “to have a modifying effect on other chemicals (hepatocarcinogens and bladder carcinogens).”¹⁶³ Despite its expressed concern about the safety of ethoxyquin, to date it has failed to take meaningful action to reevaluate or restrict the use of the additives.

How It Affects Animals

There are several reported cases of adverse effects and toxicity relating to uses of ethoxyquin. In 1997, its toxicity to dogs led FDA to request that pet food manufacturers voluntarily reduce the quantity of ethoxyquin in their products.¹⁶⁴ This followed numerous reports to FDA from concerned pet owners regarding ethoxyquin's noticeable and alarming effects in dogs.¹⁶⁵ Multiple studies found that ethoxyquin caused liver, kidney and intestinal damage, abdominal tenderness, and discolored urine in dogs.¹⁶⁶ Studies of rats demonstrated growth-inhibiting effects of consuming ethoxyquin, as well as kidney damage, including lesions and increased organ weight.¹⁶⁷ Increased kidney weights were observed at a dose rate of 75 mg/kg/day. A reproduction study in rats found decreased litter size and birth weights.¹⁶⁸ These studies suggest ethoxyquin's toxicity may vary among mammals, and existing toxicity studies may not be sufficient.

How It Affects the Environment

Beyond ethoxyquin's effects on the species consuming the feed, ethoxyquin can also affect the environment. Ethoxyquin is excreted by mammals in the urine and feces, thus entering the environment. Despite this, **there is no indication that FDA has considered ethoxyquin's impacts on the environment.** In fact, documents that CFS has obtained from the Environmental Protection Agency (EPA) through a Freedom of Information Act (FOIA) request reveal that because environmental exposure was not anticipated with regard to ethoxyquin's use for pear scald, it was not studied.

However, the assumption of no environmental exposure does not extend to the use of ethoxyquin in animal feed. Environmental exposure can result from its use in animal feed from accidental feed spillage and, as mentioned above, through manure excretions. Ethoxyquin is also commonly used in fish feed formulations as an antioxidant, **yet its effects on the marine environment are unknown.** These pathways must be assessed before ethoxyquin can be considered safe.

International Restrictions

The European Union banned the use of ethoxyquin as a pesticide in 2009 due to



concerns of its toxicity. However, the EU has continued to approve its use as an animal feed additive for ruminants and poultry up to 150 mg/kg, and has not established Maximum Residue Levels (MRLs) for animal products.¹⁶⁹ Codex has also failed to establish an MRL for its use.

ANTIBIOTICS: AN ANIMAL DRUG CASE STUDY

In recent years, there has been growing concern over the use of antibiotics in animal agriculture. In 2014, the World Health Organization announced that the world is nearing a “post-antibiotic era” in which the available drugs are no longer effective against common infections.¹⁷⁰ At risk is the fundamental viability of essential antibiotic drugs used in human medicine. Without these oft taken-for-granted tools, common infections can become life threatening.

Antibiotics¹⁷¹ are used in food animal production for three different purposes: treating disease (therapy), preventing infections (prophylaxis), or promoting growth and feed efficiency.¹⁷² Disease prevention and growth promotion both involve giving drugs to healthy animals and are considered nontherapeutic uses. Antibiotics are part of a broader class of antimicrobials, which are compounds that kill or prevent the growth of microorganisms. Other antimicrobials include antivirals, antifungals, and antiprotozoals. Antibiotics are administered to poultry, swine, and cattle. They are used to a more limited extent in aquaculture, on crops, and on fruit trees.¹⁷³

Farmers began using antibiotics for nontherapeutic purposes after World War II when they were faced with a lack of quality feed. Experiments demonstrated that

Agricultural use of antibiotics has contributed significantly to the development of resistance among the microorganisms that the drugs are designed to target, because exposing organisms to sub lethal concentrations of antibiotics drives the selection of resistant genes. In the United States, an estimated 60-80 percent of national antibiotic usage—amounting to approximately 20-26 million pounds—is fed to food animals for nontherapeutic uses.

As early as the 1960s, scientists recognized that the same antimicrobial-resistant bacteria were found in both food animals and humans. Starting in the 1970s, countries in Europe began to ban the use of antibiotics as growth promoters.

low levels of antibiotics added to feed caused animals to grow faster.¹⁷⁴ Since then, their nontherapeutic use has skyrocketed. In the United States, an estimated 60 to 80 percent of national antibiotic usage¹⁷⁵—amounting to approximately 20 to 26 million pounds¹⁷⁶—is fed to food animals for nontherapeutic uses. Roughly 300 milligrams of antibiotics are now used to produce every kilogram of meat and eggs in the United States.¹⁷⁷ Although use of antibiotics for growth promotion is regulated by FDA, there currently “is no U.S. data collection system regarding the specific types and amounts of antibiotics that are used for this purpose.”¹⁷⁸

Animals absorb roughly only 25 percent of the antibiotics they consume, excreting the vast majority in their waste.¹⁷⁹ For example, tests indicate that an animal’s urine and feces can contain 67 percent of tylosin phosphate consumed and 75 to 85 percent of tetracycline.¹⁸⁰ Field information on the fate and transport of antibiotics is still limited, but low amounts are present in some soil and water environments.¹⁸¹ In addition, the metabolites of antibiotic compounds can become bioactive and transform back to the parent compound after excretion.¹⁸² For example, the antibiotic sulfamethazine is inactivated in the liver by sugars. Once excreted, microbes in the environment degrade the sugars, allowing the compounds to return to their bioactive forms.¹⁸³

Studies of the toxic effects of veterinary antibiotics on aquatic species have found acute and chronic toxicity effects of nine commonly used antibiotics on freshwater crustaceans. Of the drugs studied, bacitracin was found to be the most toxic.¹⁸⁴

Studies are limited, however, and few have investigated the fate and overall impacts of antibiotics in the food web. In addition, few studies have specifically investigated the impacts of the metabolites of common antibiotics as they break-down.¹⁸⁵

Agricultural Antibiotics in the Environment: Reservoirs of Resistance

Agricultural use of antibiotics has contributed significantly to the development of resistance among the micro-organisms that the drugs are designed to target. Exposing organisms to sub-lethal concentrations of antimicrobial agents drives the selection of resistant genes.¹⁸⁶ Many of the antibiotics used in animals are also used in humans. As early as the 1960s, scientists recognized that the same antimicrobial-resistant bacteria were found in both food animals and humans. Starting in the 1970s, countries in Europe began to ban the use of antibiotics as growth promoters.¹⁸⁷ In the United States, an FDA Task Force convened in 1970 concluded that animals receiving antimicrobial treatment may serve as reservoirs of drug-resistant pathogens that posed a risk to humans. FDA proposed to withdraw approval for nontherapeutic use of penicillin and tetracyclines in 1977 due to their importance as human medicines, but Congress forced the Agency to continue studying the issue before taking action. **To date, FDA has not taken any enforceable action to rein in nontherapeutic uses of any antibiotic** (see Sidebar). In contrast, the EU

continued to move forward with banning specific antimicrobials in animal feed, officially banning bacitracin zinc, spiramycin, tylosin, and virginiamycin in 1999.¹⁸⁸

For bacteria in particular, resistance to drugs can spread with great efficiency due to how and how rapidly the organisms reproduce and transfer genetic characteristics.¹⁸⁹ As early as the 1980s, 97 percent of *Escherichia Coli* (*E. coli*) in swine waste in Japan had developed resistance to at least one of the following: ampicillin, furatrizine, chloramphenicol, kanamycin, streptomycin, sulfonamides, or tetracycline.¹⁹⁰ A 2000 study found that 71 percent of another common gut bacterium, *Enterococcus faecalis*, in swine manure was resistant to tetracycline.¹⁹¹ In a 2004 study, more than half of the isolates taken from poultry farms in the eastern United States contained

WHITE HOUSE TASK FORCE ON ANTIBIOTICS

In September 2014, President Obama announced an Executive Order (EO) and strategic plan to address the problem of antibiotic-resistant bacteria. The President framed the issue as one of national security. The President established an interagency task force, co-chaired by the Departments of Health and Human Services, Agriculture, and Defense, and charged it with developing a 5-year national strategy for combatting antibiotic resistance. The EO coincided with the release of a report on combatting antibiotic resistance by the President's Council of Advisors on Science and Technology (PCAST). Both the Order and the PCAST report minimized the role of drug use in animal agriculture in the development of antibiotic resistant organisms, and instead placed major



emphasis on improving the capacity for diagnosing resistant infections in patients. Dealing with the human healthcare component of the emerging crisis is a critical aspect, but failing to adequately address the misuse of antibiotics in animals produced for food ignores an important root of the issue. The Order called for the national strategy to address improved surveillance of agricultural use of antibiotics, but provides little concrete measures to hold the industry accountable.

In March 2015, the National Action Plan on Combatting Antibiotic-Resistant Bacteria was released. Instead of taking the needed steps to address antibiotics overuse in animal factories, the President's Action Plan relies exclusively on implementing FDA's Guidance 213 for eliminating the use of antibiotics for growth promotion. This guidance, however, is voluntary, and leaves wiggle room for producers to comply and still continue to administer antibiotics at nontherapeutic dosage levels. The guidance still allows producers to administer antibiotics for disease prevention. CFS and others have consistently called for USDA and FDA to collect data on the amount of antibiotics used in animal agriculture. However, while the Action Plan mentions the need for collecting data on agricultural use of antibiotics, it only requests data on sales and the prevalence of antibiotic-resistant isolates on retail meat. Supply and end-point data will not present the full picture of antibiotic use. Information on how producers are using antibiotics in their animals, at what rates, and for how long is critical in a successful strategy to combat the threat of antibiotic-resistance.

Livestock manure from large feedlots using nontherapeutic doses of antibiotics can introduce resistant bacteria into local waterways, and wastewater from intensive farming facilities in particular “is probably a major source of pathogenic and antibiotic-resistant organisms and antibiotic-resistance genes that are released into the environment.”

E. faecalis bacteria resistant to lincomaside, macrolide, and tetracycline classes of antimicrobials, and nearly one-third contained *E. faecium* bacteria resistant to fluoroquinolones and penicillins.¹⁹² A study of three large-scale pig farms in China in 2013 found that all manure samples contained pathogens with genes conferring resistance to aminoglycosides, tetracyclines, sulfonamide, and florfenicol.¹⁹³

The National Antimicrobial Resistance Monitoring System (NARMS) was established in 1996 as a collaborative effort among the Centers for Disease Control and Prevention (CDC), FDA, and USDA, as well as state and local health departments. NARMS is a national surveillance system to track antibiotic resistance among bacteria commonly transmitted through food. The most current NARMS data available for isolates on retail meat is from 2012.¹⁹⁴ The 2012 data found that the percentage of antibiotic resistant *Campylobacter coli* isolates in retail chicken meat increased from 2010 to 2012 for many classes, including quinolones and macrolides. The percentage of *C. coli* isolates from retail chicken that were resistant to 3 or more antibiotic classes increased from 2011 to 2012, despite a previous downward trend from 2005 to 2011. The NARMS data also shows that 40 percent of *Salmonella* isolates on ground turkey were resistant to 3 or more antibiotic classes, and 24 percent of isolates on chicken were resistant to 5 or more classes. The percentage of multi-drug resistant *E. coli* also increased in ground turkey and ground beef from 2011 to 2012.¹⁹⁵

A 2003 study found that between 4 and 32 percent of bacteria in swine manure were resistant to tylosin.¹⁹⁶ Evidence that tylosin-resistant bacteria contributed to cross-resistance to erythromycin, an important human medicine, led the EU to ban its use in agriculture in 1999. Similarly in 1999, the EU withdrew approval for the use of virginiamycin for growth promotion in animal agriculture. Virginiamycin is part of a class of antibiotics, called streptogramins, considered to be “last resort therapeutic agents” to treat germs that have developed resistance to other antimicrobial agents.¹⁹⁷

E. coli, due to its natural occurrence in animal guts and the ease with which it acquires antibiotic resistance, is often used as an indicator organism for resistance monitoring.¹⁹⁸ From 2002–2008, 53 percent of *E. coli* isolated from retail meat and poultry displayed resistance to tetracycline,¹⁹⁹ and chicken and turkey in particular are the greatest source of human exposure to antibiotic-resistant *E. coli*.²⁰⁰ Studies have demonstrated compelling evidence that increased exposure to antibiotic-resistant *E. coli* via retail meat consumption is increasing drug-resistant urinary tract infections (UTIs), especially among women, and has even generated a new term: foodborne urinary tract infection (FUTI).^{201,202}

Livestock manure from large feedlots using nontherapeutic doses of antibiotics can introduce resistant bacteria into local waterways, and wastewater from intensive farming facilities in particular “is probably a major source of pathogenic and

antibiotic-resistant organisms and antibiotic-resistance genes that are released into the environment.”²⁰³ The proportion of macrolide and tetracycline-resistant bacteria was significantly higher downstream from concentrated swine feeding operations than upstream.²⁰⁴ Tetracycline resistance was determined in soils sampled from land near nine swine farms in China.²⁰⁵

Veterinarians and other people who handle livestock are at a particularly high risk of exposure to clinically important, drug-resistant organisms. A 2004 study comparing



LOOPHOLES IN FDA VOLUNTARY GUIDANCE #213

In December 2014, Pew Charitable Trusts released an extensive analysis of veterinary drug labels within the context of FDA Guidance #213. Guidance #213 requests that drug manufacturers voluntarily withdraw their approvals for the growth-promoting and feed efficiency uses of their antimicrobial products. Removing language that provides information on administering for growth-promotion or feed efficiency from drug labels means the drugs cannot be sold for those purposes. The Agency believes that this will stem the administration of antimicrobials to food animals for extended durations, limiting their use only to the treatment and prevention of disease. Critics, however, doubt that companies will easily give up a large portion of their sales and Pew’s analysis demonstrates they may not have to even if they follow FDA’s guidance.

Guidance #213 continues to erroneously consider disease prevention to be a therapeutic use of antimicrobials along with disease treatment. Companies can continue to sell many antimicrobial drugs under existing approvals for prevention. Pew’s investigation of the 287 antibiotic products currently marketed for use in food animals affected by the guidance revealed that many have label indications for both growth promotion and disease prevention and the lines between “growth promotion” and “disease prevention” uses can be blurry. The researchers found that for 83 antibiotics, companies have approvals for both growth promotion and disease prevention and the dose levels for growth promotion and disease prevention overlap. This means that, if manufacturers voluntarily remove growth promotion indications from labels, over a quarter (29 percent) of antibiotics could still be administered prophylactically at the same doses previously used by producers to promote growth. Further, Pew found that 66 of these 83 products had no duration limits, meaning they can be administered throughout the life of the animals. An additional 26 product labels contain language stating the drugs “maintain weight gain” in the presence of an ambiguous illness, such as “respiratory disease.”¹ This language is allowed under Guidance 213 and the products are not viewed as used for growth promotion, despite the intention of the companies that they would be so used. The end result has been no reduction in overall antibiotic use in feed or water—and therefore no public health benefits.

¹ Pew Charitable Trusts. *Gaps in FDA’s Antibiotics Policy*, Issue Brief (November 30, 2014), available at: <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/11/gaps-in-fdas-antibiotics-policy>.

113 pig farmers to 113 comparable, non-farming individuals found a higher prevalence of various antimicrobial-resistant bacteria in the pig farmers.²⁰⁶ Another study in 2013 found that, while the levels of *Staphylococcus aureus* and the resistant strain MRSA (methicillin-resistant *Staphylococcus aureus*) were similar among workers on both industrial livestock operations and antibiotic-free livestock operations, a significantly higher percentage of the industrial workers carried strains of multi-drug resistant *Staph* (MDRSA). In addition, only the industrial workers carried strains of MRSA and MDRSA specifically associated with veterinary drugs administered in livestock, such as tetracycline-resistant strains (as opposed to those associated with human medicines).²⁰⁷

VETERINARY CONFLICT OF INTEREST

Recognizing that certain drugs should require producers to receive approval from a licensed veterinarian in order to administer them to their animals—similar to requiring a physician's prescription in order to access certain human medicines—FDA established the Veterinary Feed Directive (VFD). Producers must have a written order from a vet in order to purchase medicated feeds that include any of the drugs regulated under the VFD. The order is submitted to a licensed feed mill, which, similar to a pharmacy, will manufacture a feed batch for the producer in the quantity and dose requested. Beginning in 2016, all feed containing medically-important antibiotics will require VFDs.



However, no regulation currently exists that would prevent or restrict a veterinarian from owning their own animals and/or feed mill. This presents a significant conflict of interest and potential loophole in the FDA's regulatory efforts. For example, if a licensed veterinarian also owns a licensed medicated feed mill, they stand to profit by diagnosing a flock or herd and prescribing their own medicated feed blend. If that person also owns their own animals the conflict of interest is even more

apparent and the routine use of antibiotics at nontherapeutic levels could continue unabated. The FDA publishes a list of all medicated feed mills in the United States. A superficial review of that list by CFS in 2015 revealed that the ownership of many mills is difficult to determine. However, licensed veterinarians undeniably own at least a few mills. In addition, vertically integrated animal producers often own their animals and feed mills, and employ veterinarians on staff. Employing vets also blurs the line between business and animal health decision-making.

CFS and others have expressed concerns with veterinarians having an economic interest in animal production. In response, FDA has stated that "[t]he requirement for the veterinarian issuing the VFD to comply with all State practice requirements includes compliance with standards of ethical conduct."¹ The existence of a standard of conduct is not sufficient guarantee that abuses will be prevented, and FDA should take measures to ensure that veterinarians with financial interest in feed manufacturing are subject to proper regulation.

¹ 80 Fed. Reg 31703, 31735 (Jun 3, 2015).

Livestock producers have expressed opposition to a ban on nontherapeutic use of antibiotics in the United States, citing cost burdens associated with not using them. A study by the National Research Council assessed the costs of such a ban and concluded that, “producers who practice good management would not be as greatly affected by a ban as producers who do not. This raises the interesting possibility that a ban on [non]therapeutic drug use would actually result in an economic incentive to improve animal care and could result in a more efficient industry in the long term.”²⁰⁸ However, there is also substantial concern that the ban would result in an increase in non-antimicrobial drugs with growth-promoting properties. Many of the drugs outlined in this report, such as beta-agonists and arsenicals, are administered primarily for weight gain and improved growth rates and do not have antibiotic properties. It is imperative that when a ban is implemented, producers are encouraged to practice humane management and accept natural growth rates rather than pursue alternative growth-promoting agents as compensation.

Despite the detection of multiple coccidiostat residues in retail foods, few scientific studies have investigated the potential health affects for consumers.

COCCIDIOSTATS

Coccidiostats are a class of antiparasitic drugs designed to prevent coccidiosis, an intestinal infection caused by a single-celled parasite (coccidia) that affects pigs, poultry, cattle, sheep, and rabbits.²⁰⁹ Once established, coccidiosis can lead to intestinal lesions, diarrhea, poor weight gain, poor feed conversion, and in some cases, death.²¹⁰ Commonly administered coccidiostats include **clopidol**, **amprolium**, **nicarbazin**, **monensin**, **ethopabate**, **zoalene**, and **lasalocid**.

The Reason for their Use

Coccidia are a class of microscopic, spore-forming parasites, and are especially prevalent in warm, humid conditions and among intensively farmed livestock. It is excreted in the feces of infected animals and passes to other animals when feces is ingested. According to Merck & Co., Inc., clinical (pathogenic) coccidiosis “is most prevalent under conditions of poor nutrition, poor sanitation, or overcrowding, or after the stresses of weaning, shipping, sudden changes of feed, or severe weather.”²¹¹ Many of these are common—and unnecessary—realities for animals raised in confinement.

The disease is most commonly found in intensively-farmed chicken. Infected chickens have stunted growth and increased susceptibility to other epidemic diseases. Because the disease is difficult to control once present in an intensively-raised flock, it is financially more viable to administer coccidiostats prophylactically (preventatively) as feed additives throughout the entire life of chickens than to treat the disease therapeutically as it emerges.²¹² **FDA has approved the use of numerous coccidiostats, despite an incredible lack of available scientific data on the fate and impacts of their use.** Nicarbazin has been in use since the 1950s and was the first coccidiostat to have broad spectrum activity.

In addition, the overuse of these antimicrobials throughout the life of a poultry flock happens as a result of the overcrowded and unsanitary conditions of industrial poultry farms, which makes it unfeasible to treat birds only when illnesses arise.



The causes of coccidia outbreaks—the poor conditions that are prevalent on factory farms—make it painfully clear that its presence could be managed without animal drugs if animals were raised in living conditions that prevent regular contact with animal waste and promote strong immune systems.

How They Affect People

Existing scientific literature analyzing the environmental and human health impacts of coccidiostats is extremely limited. There was increased interest in coccidiostat residues in food after a number of contamination reports in the 1990s, especially with two drugs in particular: nicarbazin and lasalocid.²¹³ These drugs are concerning because they are present in egg yolks that humans consume. A significant amount of lasalocid fed to laying hens is transferred to the egg, and even following a withdrawal period eggs still have levels of lasalocid above detectable limits. For example, feed containing 0.1–5 mg/kg lasalocid results in concentrations in eggs ranging from 6 to 300 parts per billion (ppb), mostly in the yolk. In the body, lasalocid is distributed primarily to the liver; in chickens, the precursors to yolk development are formed in the liver before being transported to the egg.²¹⁴ The European Food Safety Authority (EFSA) determined that lasalocid in eggs could reach concentrations 63.6 times of that contained in the feed. EFSA also determined that nicarbazin in feed led to the concentration of low levels of two of its metabolites, dinitrocarbanilide and 2-hydroxy-4,6-dimethylpyrimidine, in eggs.²¹⁵ In addition, a 2014 study found clopidol residues in egg yolk, egg white and whole egg in 10 percent of commercial samples, ranging between 10 and 443 ppb.²¹⁶

Despite the detection of multiple coccidiostat residues in retail foods, **few scientific studies have investigated the potential health affects for consumers.** The exception is for zoalene (or dinitolmide), which FDA considers hazardous enough to prohibit as a feed additive for laying hens. However, it is still approved for broilers.²¹⁷ Exposure to dinitolmide can cause methemoglobinemia, a blood disorder that inhibits the ability of red blood cells to release oxygen to tissues.²¹⁸ At mild to moderate levels, this can cause fatigue, dizziness, headache, rapid heart rate, and rapid or impaired breathing.²¹⁹ At severe levels, it can cause coma, convulsions, cardiac dysrhythmias, acidosis, and death.²²⁰ Zoalene can also induce liver changes in animals (dogs and rats), such as increased liver weight and fatty tissue content.²²¹ Poultry attendants have experienced skin irritation from direct contact, and chronic exposure can cause severe dermatitis.²²² It also becomes unstable when exposed to prolonged heat and has caused at least one fatal factory explosion.²²³

How They Affect the Environment

As with human health studies, there is a lack of sufficient research into the fate and impact of coccidiostats in the environment. What we do know is alarming. A survey of multiple veterinary drugs in the 1970s found clopidol in fish had bioaccumulated to concentrations over 5 times higher than in the surrounding aquatic ecosystem.²²⁴ In addition, a study of 545 farms across nine provinces in China found higher instances of drug-resistant coccidian in areas in which coccidiostats were more frequently administered.²²⁵ **These few studies suggest that coccidiostats are entering and impacting the environment from their use as animal drugs.** Without adequate scientific studies, there is little information on which FDA could have based their approval.

Summary

It is troubling to consider that, despite substantial evidence that residues of the drugs persist both in the environment near farms and in animal products at retail, research investigating the effects of the drugs on human health and the environment is lacking. There are a variety of parasites in the coccidia subclass, many of which can infect a wide range of animals, including dogs, cats, and humans. The higher instance of drug-resistant coccidia as a result of their frequent use therefore poses a threat to non-livestock species of animals. In addition, the overuse of these antimicrobials throughout the life of a poultry flock happens as a result of the overcrowded and unsanitary conditions of industrial poultry farms, which makes it unfeasible to treat birds only when illnesses arise. Coccidiostats, as a group of approved animal drugs, not only call into question FDA's approval of drugs about which we know so little but also the Agency's allowance of administering drugs continuously to prevent diseases from emerging in otherwise healthy animals.

The causes of coccidia outbreaks—the poor conditions that are prevalent on factory farms—make it painfully clear that its presence could be managed without animal drugs if animals were raised in living conditions that prevent regular contact with animal waste.

Arsenicals are generally added to feed for chicken, turkey, and swine. Until recently, their use was pervasive: an estimated 70 percent of chickens in the United States were fed arsenic-containing compounds in 2002.



ARSENICALS

Arsenic is a heavy metal and a naturally-occurring element. It is most commonly found in nature in compounds with oxygen, sulfur, or chlorine, which are called inorganic arsenic compounds. In plants and animals, arsenic combines with carbon or hydrogen, forming what is called organic arsenic compounds.

Arsenic was first approved for use in animal feed in the United States in the 1940s.²²⁶ Arsenic-based compounds, or arsenicals, are approved for therapeutic and nontherapeutic uses—such as growth promotion, improved feed efficiency, and desirable pigmentation—in food animals throughout their lifetimes, up until 5 days before slaughter. Arsenicals are generally added to feed for chicken, turkey, and swine. Until recently, their use was pervasive: an estimated 70 percent of chickens in the United States were fed arsenic-containing compounds in 2002.²²⁷ While four arsenicals were at one time approved by FDA—roxarsone, arsanilic acid, nitarosone, and carbarsone—currently, only nitarosone is approved for use in animal feed (see Sidebar). FDA has committed to withdrawing approval for this last arsenical by the end of 2015.

If FDA follows through on its commitment to withdraw approval for nitarosone, no arsenic-based additives will be on the market by 2016. However, the effects of past uses of these drugs can still present problems because arsenic does not degrade in the environment. Further, the long-time use of these drugs demonstrates that FDA is not quick to act to protect public health, even in the face of serious risks.

The Reason for their Use

Arsenic-containing feed additives are given to livestock for production and therapeutic reasons. Arsenicals promote weight gain and improve feed efficiency, allowing producers to grow bigger chickens, turkeys, and pigs with less feed. As growth stimulators, arsenicals are used by chicken producers for both broilers to increase the meaty parts of the chicken and for layers to increase egg production. They also affect pigmentation, giving meat a “healthier” color thought to be more aesthetically pleasing for consumers.²²⁸

Arsenicals are also used therapeutically as antimicrobials, to inhibit the growth of microorganisms. Prior to FDA withdrawing approval for the drug, roxarsone was the most frequently used organic arsenic compound in animal agriculture. It was added to feed for broiler chickens to help control coccidiosis,²²⁹ an intestinal parasite that can spread through flocks by contact with manure. Nitarsone—the arsenical that remained on the market after FDA withdrew approval for roxarsone—is primarily used to control a debilitating infection in turkeys called blackhead disease. It is also given to chickens to accelerate growth and treat coccidiosis.²³⁰ The Center for a Livable Future at John Hopkins University estimates that roughly 249,000 pounds of nitarsone were sold for use in animal feed in 2012.²³¹

Arsanilic acid is fed to pigs for the same nontherapeutic reasons as other arsenicals are fed to poultry: to increase weight gain, improve feed efficiency, and create aesthetically-pleasing pigmentation. However, a study published in the *Journal of Animal Science* found that pigs fed different levels of arsanilic acid in feed demonstrated no significant difference in weight gain, feed efficiency, or carcass quality compared to the control group fed no arsanilic acid. However, **all** pigs fed diets including arsanilic acid retained arsenic in their tissues that corresponded to the level in the feed (e.g., those with highest amount in their diet had highest residue levels in their tissues).²³²

How They Affect Animals

There is limited scientific data on the health effects of arsenical feed additives on animals produced for food, as most studies address consumer health impacts. Plus, broilers’ lives are so short that there is simply not enough time for cancer to develop. However, researchers at Auburn University found that chickens fed diets containing roxarsone had significantly higher percentage of leg abnormalities than those not fed roxarsone.²³³ Interestingly, that same study found no significant difference in feed efficiency among the various diet formulations despite improved feed efficiency being one of the industry’s justifications for its use.²³⁴ There is also evidence that arsenic poisoning in cattle causes gastrointestinal distress and agitation.²³⁵

Arsenicals promote weight gain and improve feed efficiency, allowing producers to grow bigger chickens, turkeys, and pigs with less feed. As growth stimulators, arsenicals are used by chicken producers for both broilers to increase the meaty parts of the chicken and for layers to increase egg production.

PLAYING CHICKEN: AVOIDING ARSENIC IN YOUR MEAT



Nearly ten years ago, the Institute for Agriculture and Trade Policy (IATP) issued a landmark study, "Playing Chicken: Avoiding Arsenic in Your Meat."¹ IATP tested U.S. supermarket and fast food chicken and found that the majority of it contained arsenic residues. These findings led CFS and IATP to petition FDA in 2009 calling for the removal of arsenic from all animal feed based on the risk to human health.

The Agency never responded to the petition. In the meantime, in 2011, FDA concluded its own test of poultry confirming what the IATP study and the petition both suggested: arsenic is in fact present in the edible parts of chicken. This spurred Pfizer, now Zoetis, to temporarily remove the then most popular arsenical—roxarsone—from the market. However, FDA failed to take the next logical steps and ban all the arsenic-based animal feeds. Despite evidence that the U.S. public was being exposed

to a carcinogen and this exposure was, according to FDA, "completely avoidable," FDA still refused to ban arsenic-based feed additives.

In 2013, CFS sued FDA for its failure to respond to its 2009 petition. Weeks after CFS filed the lawsuit another group, the Center for a Livable Future, confirmed FDA's findings and published a major study² documenting arsenic residues in chicken breast sold to American consumers. The evidence could not be clearer. In 2013, the drug companies themselves asked FDA to withdraw approval of 98 out of 101 arsenic-based feed additives.

FDA left nitarosone on the market on the grounds that it is the only known treatment of blackhead disease in turkeys.³ However, although there is ample data on other arsenical drugs, there is only limited data available on the genotoxic and carcinogenic effects of nitarosone and no data on developmental and reproductive effects.⁴ Thus FDA insisted on continuing use of the only arsenical about which there is little to no information and data. In the litigation over the 2009 petition, FDA promised to study nitarosone in the first quarter of 2014. In April 2015, FDA announced that it received a letter of commitment from nitarosone's manufacturer, Zoetis Animal Health, that the company will suspend sale of the drug and formally request that the FDA withdraw the approval for the drug by the end of 2015. While this is a positive result, the company could reverse its commitment at any time.

¹ D. Wallinga. *Playing Chicken: Avoiding Arsenic in Your Meat*, Minneapolis, MN: Institute for Agriculture and Trade Policy (April 2006).

² K.E. Nachman, et al. *Roxarsone, Inorganic Arsenic, and Other Arsenic Species in Chicken: A U.S.-Based Market Basket Sample*, 121(7) *Environmental Health Perspectives*, 818 (July 2013).

³ A. Nguyen. *Three Arsenic-Based Drugs Withdrawn from Market*, *Wolters Kluwer Law & Health* (October 1, 2013), available at: <http://health.wolterskluwer-erlb.com/2013/10/three-arsenic-based-animal-drugs-withdrawn-from-market/>.

⁴ European Food Safety Authority. *Opinion of the Scientific Panel on Additives and Products or Substances used in Animal Feed on a request from the Commission related to the preliminary assessment of the safety of Nitarosone (4-nitrophenylarsonic acid), as a feed additive in accordance with Regulation (EC) N° 178/2002 and Regulation (EC) N° 1831/2003, article 15*, 121 *EFSA Journal*, 1 (October 28, 2004), available at: <http://www.efsa.europa.eu/en/efsajournal/doc/121.pdf>.

How They Affect People

Humans are exposed to arsenic from a variety of sources, including water, dust, fumes, and diet. For adults not exposed to arsenicals in the workplace, ingestion in food is the main route of exposure.²³⁶ A study of government data on arsenic levels in chickens from 1994–2000 found that concentrations in young chickens and adult chickens ranged from 0.33–0.43 parts per million (ppm) and 0.10–0.16 ppm, respectively.²³⁷ Tests of packaged raw chicken, fast-food chain chicken sandwiches, and chicken nuggets conducted in 2004–05 revealed detectable levels of arsenic in a majority of supermarket chicken and all fast-food chicken sampled. In contrast, chicken from birds for which there was a claim of “no arsenic given” contained either no or undetectable amounts of arsenic. This suggests that the use of arsenic in feed directly leads to arsenic residues in chicken meat.²³⁸ Tests conducted by FDA in 2011 confirmed these findings, concluding that levels of inorganic arsenic in chicken livers were significantly higher for chickens treated with roxarsone than untreated chickens.²³⁹

Arsenic is found in both inorganic and organic forms. Inorganic arsenicals are classified as human carcinogens. However, recent studies have found considerable variation in toxicity among all arsenicals; certain organic forms may be as or more toxic than inorganic forms.²⁴⁰ In addition, recent research has shown that organic arsenic can convert to inorganic arsenic during digestion.²⁴¹ Environmental bacteria as well as microflora in human and chicken digestive systems can convert organic arsenic into various inorganic forms, such as arsenate (As(V)) and arsenite (As(III)).²⁴² Studies of Canadian food samples found that 65 percent of arsenic in poultry meat is inorganic.²⁴³

Both human and animal studies have confirmed that inorganic arsenic compounds are readily absorbed from the gastrointestinal tracts of humans.²⁴⁴ Despite increased evidence of the risks associated with arsenic exposure and the voluntary withdrawal of organic arsenical pesticide products due to concerns of negative health impacts, the average American’s cumulative exposure to arsenic has greatly increased since FDA first approved arsenicals in animal feed. While EPA has taken steps to reduce public exposure to arsenic in drinking water²⁴⁵ and organic arsenical pesticides,²⁴⁶ there is abundant evidence that Americans are exposed to dramatically higher levels of arsenic today than when arsenical feed additives were first approved in the 1940s.²⁴⁷

Arsenic is not poisonous to everyone to the same degree: children, infants, and fetuses are the most vulnerable.²⁴⁸ Studies of in utero exposure to arsenic indicate that the compounds can alter susceptibility of endocrine and reproductive organs. In all humans, long-term exposure has been associated with hyper-pigmented skin, skin nodules, vessel disease, and a heightened risk of high blood pressure, heart disease, and diabetes.²⁴⁹ Chronic arsenic exposure in the range of 0.01–0.04 mg per kilogram of body weight per day (mg/kg/day) has been associated with: skin cancer,²⁵⁰ respiratory cancers,²⁵¹ bladder cancer,²⁵² increased mortality from hyper-

Humans are exposed to arsenic from a variety of sources, including water, dust, fumes, and diet. For adults not exposed to arsenicals in the workplace, ingestion in food is the main route of exposure. Arsenic is not poisonous to everyone to the same degree: children, infants, and fetuses are the most vulnerable. The average American’s cumulative exposure to arsenic has greatly increased since FDA first approved arsenicals in animal feed.

Despite evidence that the U.S. public was being exposed to a carcinogen and this exposure was, according to FDA, “completely avoidable,” FDA still refused to ban arsenic-based feed additives.

tensive heart disease, nephritis and nephrosis, prostate cancer,²⁵³ late fetal mortality, neonatal mortality, post-natal mortality,²⁵⁴ and cytogenetic damage.²⁵⁵

A number of studies have demonstrated that exposure to even extremely low concentrations of arsenite, an inorganic arsenic compound, stimulates angiogenesis, which is associated with vascular disease and tumor development.²⁵⁶ **Effects on mammalian tissues have not been sufficiently evaluated.** One study did expose cells from human vascular and lung tissue to roxarsone. As with arsenite, exposure to Roxarsone induced an increase in angiogenesis, a condition that underlies many deadly and debilitating conditions including cancer, skin diseases, age-related blindness, diabetic ulcers, cardiovascular disease, stroke, and many others.²⁵⁷ However, not only was the link to angiogenesis more potent for roxarsone than for arsenite, but roxarsone acted via a mechanism that is distinct from and independent of the one induced by arsenite. In other words, roxarsone could potentially promote angiogenesis and subsequent tumor growth via two distinct and independent processes—via conversion to As(III) in the body and via its own direct mechanism.²⁵⁸ It is doubly dangerous. While few studies have investigated nitarosone, which currently remains on the market, it can also be converted to arsenite when metabolized by the body.

How They Affect the Environment

Approximately three-quarters of the arsenic-containing compounds fed to animals pass unchanged into animal waste. Because arsenic is an element, it **neither degrades nor disappears. Disposal methods, therefore, only redistribute arsenic in different forms.** Waste from animal agriculture is disposed in several different ways. Around 90 percent is applied to nearby fields and cropland as fertilizer, and poultry litter fertilizers are also marketed for commercial use on crops, residences, and golf courses.²⁵⁹ Various estimates have placed the amount of arsenic-based compounds and their degradation products dispersed to the environment at 0.5 to 2.6 million pounds annually.²⁶⁰ Long-term studies of fields treated with poultry litter from chickens fed roxarsone found very little arsenic accumulated in the agricultural surface soils. The arsenic is instead dispersed to the environment through leaching and runoff into waterways.²⁶¹ It is estimated that 70 to 90 percent of arsenic in poultry waste becomes water soluble, and studies have shown elevated arsenic levels in river sediments near poultry farms.²⁶²

Arsenicals enter local watersheds from agricultural runoff, and adverse effects of arsenicals on aquatic organisms have been reported at concentrations of 19–48 micrograms(μg)/liter in surrounding water, 120 mg/kg in diets, and 1.3–5 mg/kg in tissues.²⁶³ The ability of marine phytoplankton to accumulate concentrations of inorganic arsenicals that are then transferred in the food chain has been well documented.²⁶⁴ Animal studies have demonstrated that arsenic acts as a developmental toxin in hamsters, mice, rats, and rabbits, leading to malformation, growth retardation, and death.²⁶⁵ As one example, exposure to arsenic during embryo development in



Although it has ultimately been a success, the years-long battle that consumer advocates have waged against FDA demonstrates how much effort is required on behalf of the public to force FDA to keep these harmful drugs out of our food supply.

Killifish leads to poor muscle development.²⁶⁶

International Restrictions

Arsenic has never been approved for use in animal feed in the European Union, and is listed in the European Commission's (EC) regulation on "undesirable contaminants in animal feed."²⁶⁷ The regulation defines "undesirable substance" as any substance "which presents a potential danger to animal or human health or to the environment." The EC allows for a maximum limit of 2 ppm of arsenic in feed materials, with a few limited exceptions.²⁶⁸

With respect to nitarstone, the European Food Safety Authority concluded that the absence of toxicological data prevents it from establishing of an acceptable daily intake (ADI), and the European Union has not approved its use.²⁶⁹

Summary

Luckily, if FDA keeps its commitment to withdraw approval for nitarstone, then arsenicals will no longer be on the market by 2016. This is a huge success for consumers and public health. However, the long-term and widespread use of arsenic in animal factories serves as a cautionary tale. Because arsenic persists in the environment, the effects of the previous decades of use in animal factories will continue to be felt, and American consumers will still be exposed to arsenic. And, although it has ultimately been a success, the years-long battle that consumer advocates have waged against FDA demonstrates how much effort is required on behalf of the public to force FDA to keep these harmful drugs out of our food supply. FDA could have, and should have, taken action on arsenicals far sooner.

RECOMMENDATIONS: WHAT FDA, STATES, AND CONSUMERS CAN DO

Despite sufficient evidence that these drugs have negative effects on human health, the environment, and/or animal health, FDA has failed to use its authority under FFDCa and take appropriate action.



THIS REPORT EXAMINED six classes of chemicals approved for use in animals raised for food in the United States. All of the drugs outlined in this report have a commonality: substantial data is available to raise serious questions about their continued use. Despite sufficient evidence that these drugs have negative effects on human health, the environment, and/or animal health, FDA has failed to use its authority under FFDCa and take appropriate action.

At least twelve of the specific drugs discussed in this report are prohibited for use as animal drugs in other countries, and the EU has issued a ban on the use of all antibiotics for growth promotion. For six of the drugs, FDA has established residue tolerance levels significantly higher than the international standards set by Codex (see Appendix A). The public interest community has consistently attempted to persuade the Agency to act and either review, suspend, or withdraw certain drug approvals. Over the past several years CFS has filed requests under the Freedom of Information Act for all information FDA has on ractopamine, zilpaterol, trenbolone,

ethoxyquin, and arsenicals. To date, the requests have been largely unfulfilled; CFS is currently litigating against FDA to bring its delay on several requests to an end.

Nevertheless, CFS conducted a thorough analysis of available research and literature, outlined in this report, and determined that the information casts substantial doubt on the safety of approved animal drugs. FDA should take this data into account in a timely and forthright manner. Ideally, the Agency should facilitate an open exchange of information on important drugs but at a minimum it must respond to formal requests for information.

Based on the available data, CFS recommends the following:

FDA Should Increase Transparency

Though FDA is charged with regulating animal drugs to ensure they are safe for humans and animals, it has informally placed the burden on the public to uncover and bring to the Agency's attention new data questioning the finding of safety on which original approvals were based. **But the public cannot effectively serve as a watchdog without knowing what information the Agency has or needs to update its evaluations of the safety of animal drugs.** Most alarmingly, the Agency even fails to respond to FOIA requests from the public that would at least shed some light on its current state of knowledge.

To address the secret drugs problem in American agriculture, FDA should make scientific data on the health and safety of animal drugs within its possession publicly available. It should publish the data on its website as it currently does for Adverse Drug Events, and as FSIS does for the National Residue Program. In addition, FDA should respond adequately and meaningfully to requests for information under FOIA.

FDA Should Conduct Systematic Re-Reviews of Drug Safety, with the Burden on Industry To Prove Safety

FDA has authority to review the safety of animal drugs that are already on the market. In practice, however, the Agency places the burden on the public to present it with new information in the form of citizen petitions. It can take years for members of the public to compile enough data to complete a petition, and the Agency often takes years to respond to such petitions—if it responds at all. This process allows unsafe drugs and unsafe food to stay on the market long after the science suggesting a problem has surfaced.

To address this, FDA should use its existing authority under the FFDCA to conduct regular, systematic reviews of the safety of animal drugs to ensure that they are still safe to be marketed. To bolster FDA's duty to do so, the FFDCA should be amended to provide for specific re-review procedures, such as those providing EPA with a duty to periodically reevaluate the safety of pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act.

To address the secret drug problem in American agriculture, FDA should make scientific data on the health and safety of animal drugs within its possession publicly available.

Due to consumer demands and attention, large restaurant chains have made public commitments to reduce or eliminate nontherapeutic uses of antibiotics through their meat and poultry suppliers, and drug manufacturers have withdrawn products.

Where Safety Data are Compelling, FDA Should Take Prompt Action.

FDA has authority to immediately suspend approval for any drug that presents an imminent hazard to the health of humans or animals. Under the FFDCA, FDA has a duty to withdraw approval for drugs that are shown to be unsafe. In two of the cases above—beta-agonists and steroid hormones—the available information is suggestive of adverse effects and raises serious questions about the safety of these drugs on the market. FDA should immediately evaluate these data and consider initiating procedures to withdraw approval for these drugs.

FDA Should Collaborate with USDA to Develop Collection of Producer-Level Drug Usage Data

FDA collects data on antibiotics sales but not on use in agriculture. It has already indicated that it intends to, in collaboration with CDC and USDA, identify strategies for collecting producer-level data for antimicrobials.²⁷⁰ The Agency should engage seriously in this collaboration and expand their efforts to include collecting usage data for all animal drugs. Producer-level usage data is an important component in identifying the types of drugs producers administer and for what purpose, duration, and dose level.

FDA authority under FFDCA to collect usage data from antimicrobial drug sponsors should be expanded to include collecting usage data for all animal drugs and from producers raising animals for food. Volume and sales figures from drug manufacturers alone are only half of the picture. While antimicrobials have gained particular notoriety due to their likely role in the rise in drug-resistant infections among humans, they are not the only group of animal drugs that may pose a threat to humans, animals, or the environment.

States and Localities Can Regulate in the Absence of Federal Action

Although the FFDCA authorizes FDA to act, states, counties, and cities do not have to wait for FDA to protect the health of their citizens. The FFDCA leaves room for states to regulate in the absence of effective federal legislation. For example, six states—California, Maryland, Minnesota, New York, Pennsylvania, and Vermont—have proposed legislation that would regulate the nontherapeutic use of antibiotics in livestock. Maryland succeeded in passing legislation that banned antimicrobial arsenical drugs in chicken feed before FDA took action. And, cities and counties across the country have passed resolutions supporting state and national bans on nontherapeutic uses of antibiotics in livestock production.

Consumers Should Continue to Pressure

Due to consumer demands and attention, large restaurant chains have made public commitments to reduce or eliminate nontherapeutic uses of antibiotics through their meat and poultry suppliers, and drug manufacturers have withdrawn products. While regulatory reform is critical to any long-term solution, market-based actions



The growth of animal factories in the past few decades, propped up by the use of approved animal drugs, stems from an unsustainable approach towards food production, non-human animals, and the environment.

can be an important driver of change. History has shown us that consumers do have power when it comes to what is in their food supply. Consumer campaigns that call upon food retailers and drug manufacturers to reduce the use and production, respectively, of harmful animal drugs can be an effective tool to curb the harmful proliferation of animal drugs until FDA takes appropriate regulatory action.

IMPLICATIONS OF THE REPORT

The growth of animal factories in the past few decades, propped up by the use of approved animal drugs, stems from an unsustainable approach towards food production, non-human animals, and the environment. This report outlined the many human, animal, and environmental harms of many drugs currently approved for use in animals raised for food. The “benefits” these drugs provide to producers and industry—namely, more profitable growth rates and greater survivability in unsanitary conditions—are only considered beneficial within the industrial system that prioritizes processing as many animals as possible as quickly and efficiently as possible. Over-reliance on drugs and additives is part of larger, systemic failures in animal agriculture, of which addressing inadequacies in the regulatory mechanism is only a piece.

A wide range of drugs are administered to animals produced for food with little information provided to the public, including the scientific data provided as proof of their safety or data on their actual use by producers. Given the serious questions raised in this report on a number of animal drugs currently on the market, it is clear that the current regulatory regime is failing to protect both consumers and animals. As the market today is dominated by factory-raised animal products, the continued use of animal drugs without periodically reviewing the evidentiary base for their approvals cannot be allowed.

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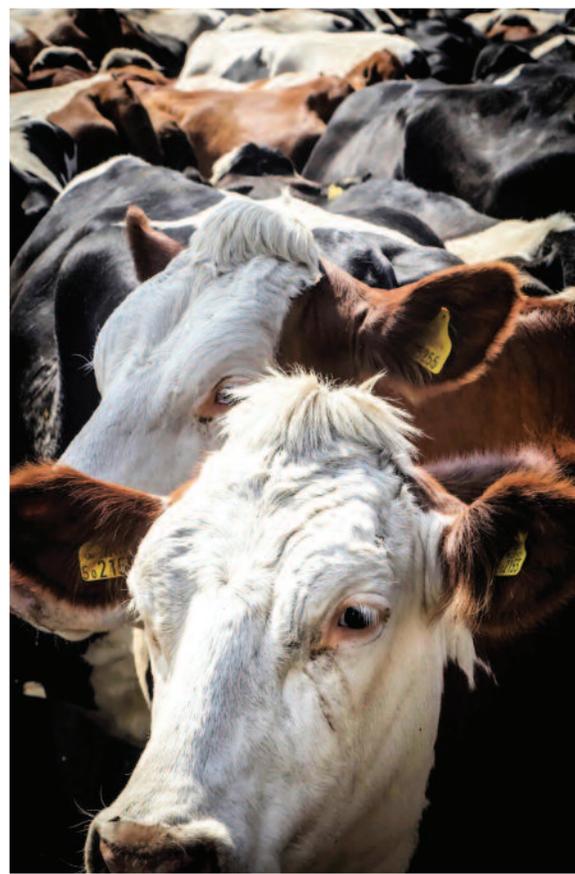
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TABLE 1: BETA-AGONIST TOLERANCE LEVELS - US AND CODEX			*ppb= parts per billion
		FDA TOLERANCE LEVELS²⁷¹	CODEX TOLERANCE LEVELS
Ractopamine	Acceptable Daily Intake (human)	1.25 ppb* of body weight per day	0-1 ppb of body weight per day
	Cattle Muscle	30 ppb	10 ppb
	Cattle Liver	90 ppb	40 ppb
	Pig Muscle	50 ppb	10 ppb
	Pig Liver	150 ppb	40 ppb
	Turkey Muscle	100 ppb	None established
	Turkey Liver	450 ppb	None established
Zilpaterol	Acceptable Daily Intake (human)	0.083 ppb	None established
	Cattle Liver	12 ppb	

TABLE 2: STEROID HORMONE TOLERANCE LEVELS—US AND CODEX			
HORMONE		FDA TOLERANCE LEVELS²⁷²	CODEX TOLERANCE LEVELS²⁷³
Trenbolone acetate	Acceptable Daily Intake (human)	0.4 ppb	0.2 ppb
	Cattle Muscle	unnecessary	2 ppb
	Cattle Liver	unnecessary	10 ppb
Estradiol	Acceptable Daily Intake (human)	—	0.5 ppb
	Cattle Muscle	0.12 ppb	unnecessary
	Cattle Liver	0.24 ppb	unnecessary
	Cattle Kidney	0.36 ppb	unnecessary
	Cattle Fat	0.48 ppb	unnecessary
Testosterone	Acceptable Daily Intake (human)	—	2 ppb
	Cattle Muscle	0.64 ppb	unnecessary
	Cattle Liver	1.3 ppb	unnecessary
	Cattle Kidney	1.9 ppb	unnecessary
	Cattle Fat	2.6 ppb	unnecessary
Progesterone	Acceptable Daily Intake (human)	—	30 ppb
	Cattle Muscle	5 ppb	unnecessary
	Cattle Liver	15 ppb	unnecessary
	Cattle Kidney	30 ppb	unnecessary
	Cattle Fat	30 ppb	unnecessary
Melengestrol acetate	Acceptable Daily Intake (human)	—	0.3 ppb
	Cattle Muscle	—	1 ppb
	Cattle Liver	—	5 ppb
	Cattle Kidney	—	2 ppb
	Cattle Fat	25 ppb	8 ppb
Zeranol	Acceptable Daily Intake (human)	1.25 ppb	0.5 ppb
	Cattle Muscle	Unnecessary	2 ppb
	Cattle Liver	Unnecessary	10 ppb
	Sheep	20 ppb	—

TABLE 3: ETHOXYQUIN MAXIMUM RESIDUE LIMITS—US AND CODEX			
		FDA TOLERANCE LEVELS²⁷⁴	CODEX TOLERANCE LEVELS
	Fat (excl. Poultry)	5 ppm	—
	Muscle	0.5 ppm	—
	Fat (Poultry)	3 ppm	—
	Liver	3 ppm	—
	Eggs	0.5 ppm	—
	Milk	0 ppm	—

TABLE 4: COCCIDIOSTAT TOLERANCE LEVELS—US AND CODEX			
*ppb= parts per billion			
		FDA TOLERANCE LEVELS	CODEX TOLERANCE LEVELS²⁷⁵
Nicarbazin	Acceptable Daily Intake (human)		
	Broiler Muscle	4000 ppb	200 ppb
	Broiler Liver	4000 ppb	200 ppb
	Broiler Kidney	4000 ppb	200 ppb
	Broiler Fat	4000 ppb	200 ppb
	Eggs	100 ppb	
	Milk	5 ppb	
Amprolium	Chicken & Turkey Liver	1000 ppb	None established
	Chicken & Turkey Kidney	1000 ppb	None established
	Chicken & Turkey Muscle	500 ppb	None established
	Egg Yolk	8000 ppb	None established
	Cattle Fat	2000 ppb	None established
	Cattle Muscle, Liver, & Kidney	500 ppb	None established
Clopidol	Chicken & Turkey Liver	15000 ppb	None established
	Chicken & Turkey Muscle	5000 ppb	None established
	Chicken & Turkey Kidney	15000 ppb	None established
	Cattle, Sheep & Goat Kidney	3000 ppb	None established
	Cattle, Sheep & Goat Liver	1500 ppb	None established
	Cattle, Sheep & Goat Muscle	200 ppb	None established
	Swine (all tissues)	200 ppb	None established
	Milk	20 ppb	None established
Ethopabate	Chicken Liver	1500 ppb	None established
	Chicken Kidney	1500 ppb	None established
	Chicken Muscle	500 ppb	None established
Lasolocid	Acceptable Daily Intake (human)	10 ppb	None established
	Cattle Liver	700 ppb	None established
	Chicken Fat	1200 ppb	None established
	Chicken Liver	400 ppb	None established
	Turkey Liver	400 ppb	None established
	Turkey Fat	400 ppb	None established
	Rabbit Liver	700 ppb	None established
	Sheep Liver	1000 ppb	None established
Monensin	Acceptable Daily Intake (human)	12.5 ppb	None established
	Cattle Liver	100 ppb	100 ppb
	Cattle Muscle	50 ppb	10 ppb
	Cattle Kidney	50 ppb	10 ppb
	Cattle Fat	50 ppb	100 ppb
	Milk	Not required	2 ppb
	Chicken Liver	Not required	10 ppb
	Chicken Muscle	Not required	10 ppb
	Chicken Kidney	Not required	10 ppb
	Chicken Fat	Not required	100 ppb
	Turkey Liver	Not required	10 ppb
	Turkey Muscle	Not required	10 ppb
	Turkey Kidney	Not required	10 ppb
	Turkey Fat	Not required	100 ppb
Zoalene/Dinitolmide	Chicken Liver & Kidney	6000 ppb	None established
	Chicken Muscle	3000 ppb	None established
	Chicken Fat	2000 ppb	None established
	Turkey Muscle & Liver	3000 ppb	None established



**CENTER FOR
FOOD SAFETY**

NATIONAL HEADQUARTERS

660 Pennsylvania Avenue S.E., Suite 302
Washington, D.C. 20003
T: 202-547-9359 | F: 202-547-9429

CALIFORNIA OFFICE

303 Sacramento Street, 2nd Floor
San Francisco, CA 94111
T: 415-826-2770 | F: 415-826-0507

PACIFIC NORTHWEST OFFICE

917 S.W. Oak Street, Suite 300
Portland, OR 97205
T: 971-271-7372 | F: 971-271-7374

HAWAI`I OFFICE

1132 Bishop Street, Suite 2107
Honolulu, HI 96813
T: 808-681-7688 | F: 808-203-5725

email: office@centerforfoodsafety.org

www.centerforfoodsafety.org