Clarifying ionophores: NRDC muddies science by suggesting all animal antibiotics lead to resistance crisis

In early November, a physician with the Natural Resources Defense Council advocacy group wrote a well-meaning essay in *Food Safety News*: “What Subway Serves for Lunch Can Help Save Lives”. Predictably, David Wallinga called for a ban on antibiotic use in food animals:

> The invention of antibiotics has been a miracle of modern medicine — providing quick and effective treatment for infections that once often meant death. For a slew of reasons, physicians still depend on the same classes of antibiotics developed decades ago. But when we overuse them, they stop working. It’s the rampant overuse of antibiotics in both agriculture and human medicine that has created the global crisis we now face.
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> Fortunately, we know how to slow down the resistance crisis: Stop overusing antibiotics. Specifically, use these precious medicines only when people and animals are sick. With the vast majority of antibiotics used in livestock, reigning in overuse in that sector is critical to reducing our overall use of antibiotics and reducing the spread of drug-resistant bacteria.

The op-ed followed s string of recent announcements by major restaurant chains of plans to roll back their use of antibiotics. Subway claims that it will eventually use only meat from animals that have never been given antibiotics. Anne Burkholder, a rancher/feedlot operator who spoke up in response to Subway’s announcement, pointed out that in her operation 7.8 percent of the cattle were treated with antibiotics for disease.

“In my mind, Subway’s announcement states that *a bullet is their treatment of choice for sick food animals* ,” wrote Burkholder. She noted that her treated animals are held on the farm until it was sure that no antibiotics were present in their meat when they went to slaughter — which was still not enough to meet the standards demanded by many activists.

Clearly, if we get to a point where no antibiotics can be given to cattle, those 7.8 percent would not be marketable, and would therefore represent a substantial loss of food.

“If Subway does not want the meat from an animal that required antibiotic treatment for illness at any time during its lifetime, then I have two choices: leave the sick animal to suffer until it likely dies, or shoot it with a bullet and end its life immediately,” she noted. Obviously, as long as some other market besides Subway accepts meat from animals that have been treated with antibiotics, those animals are not wasted food.

To further confuse the issues, science writer Tara Smith of the *Washington Post* directly referenced the blog by the feedlot operator, claiming "Farmers who are responding to Subway's news suggesting that compliance means additional animals will die are either uninformed or intentionally misleading consumers."

Science of antibiotics

The anti-antibiotic frenzy overlooks the fact that not all chemicals that are "antibiotics" work the same way or are used the same way. Farmers and ranchers rely on one important class of chemicals, called "ionophores" to prevent their animals from needing treatment for disease. At the same time, ionophores induce faster growth and greater feed efficiency with the overall effect that the animal reaches maturity with about 10% less feed that would otherwise be required.

Ionophores are a win-win for everyone: the animal is not as likely to get sick and it uses less feed and water. Most importantly, ionophores do not cause bacteria to develop resistance to ionophores or to any other antibiotic. Best of all, ionophores cannot be used in human medicine, because they are lethal to humans!

It should be clear that allowing the cattle and dairy industries to continue to use ionophores would promote the goal of reducing the development of antibiotic resistance while reducing the need to use therapeutic antibiotics in cattle.

Let's look a little deeper into what ionophores are, how they work, and why we should use them.

Ionophores do not contribute to antibiotic drug resistance

The defining paper on the use of ionophores in livestock feed is a 2003 paper by James Russell and Adam Houlihan, then professors with the USDA's Agricultural Research Service at Cornell University. They concluded that "use of ionophores in animal feed is not likely to have a significant impact on the transfer of antibiotic resistance from animals to man."

There appears to have been little original work on ionophores subsequent to that paper and no contesting of the position that ionophores are not therapeutic agents in veterinary medicine or human medicine, and do not contribute to the development of antibiotic resistance. The American College of Veterinary Internal Medicine Consensus Statement agrees, stating: "The Committee strongly supports a recommendation that all antimicrobials intended for use in animals (excluding ionophores) should be available only by prescription by a veterinarian…"

In a PLoS One article earlier this year, USDA investigators wrote, "It should be noted that one-third of the antimicrobials utilized in food animal production (ionophores) do not have any equivalent drugs used for human therapeutic purposes."

A few groups still want ionophores removed from animal feed

In spite of an apparent universal scientific consensus that ionophores do not contribute to the development of bacterial resistance to either ionophores themselves or to any other class of drug, a few activist groups are demanding that ionophores not be incorporated into cattle and poultry feed simply because ionophores are technically “antibiotics”. Activist campaigns in part led the EU in 2006 to ban monensin, an ionophore antibiotic widely used in ruminant animal feeds, from cattle feed; the use of monensin for control of ketosis in dairy cattle is allowed, and monensin and salinomycin are still used in poultry feed in the EU.

Suggesting unintended consequences of good but unscientific intentions, several articles have also appeared in agricultural publications suggesting that the elimination of ionophores from animal feed has led to a significant increase in the use of prescription human-medicine relevant drugs in food animals.

Antibiotic resistance and ionophores

Many antibacterial agents (antibiotics) act against one specific chemical process in the bacterium. Antibiotic resistance arises because the bacteria can undergo a spontaneous genetic mutation (which happens frequently in nature) that will alter how a particular required chemical process is carried out. When that happens to a process that is targeted by an antibiotic, the antibiotic is no longer effective. Because ionophores do not target a specific process, the bacteria cannot mutate to avoid the action of the ionophore.

Many bacteria are resistant to ionophores because there are specific chemicals on the surface of those bacteria that prevent the ionophore from attaching to the surface of the bacteria. Many ionophore-resistant bacteria are found in the rumen of cattle, even if those cattle have not been exposed to ionophores. The ruminal contents of cattle have been extensively studied by both commercial and academic research groups around the world for at least 50 years. Our scientific knowledge about cattle nutrition far exceeds our knowledge about nutrition of any other mammal, including ourselves. There has never been any evidence reported that continued high levels of ionophore administration has had any permanent or long-lasting effect on the bacterial population in the rumen. When the ionophore is removed, ruminal bacterial populations return to their unperturbed state.

Ionophores are toxic to the point of lethality in many species, notably humans and horses. In cattle, ionophore molecules are absorbed through the epithelial cells of the small intestine, after which they move into the blood stream. Toxicity is avoided because the ionophores are rapidly removed from the blood stream by the liver, which then excretes about 35% of them unaltered back into the intestine via bile secretions; the liver breaks down the other 65% into inactive compounds that are also secreted in bile.

As a consequence of the extensive use of ionophores in cattle feed, and the fact that ionophores are not completely decomposed by cattle and are thus excreted in manure, ionophores are found in airborne dust samples collected near cattle feedlots. There appears to be no data on the half-life of ionophores in thesoil or in airborne particulate matter. The effects of ionophores have apparently not been studied inspecies beyond food and companion animals, probably because there have never been reports of wild lifebeing found inexplicably dead near large cattle operations.

Ionophores in cancer research

In the past few years, ionophores have attracted the interest of cancer research labs, due to the unique toxicity of ionophores. However, this use of ionophores would not be impacted by antibiotic resistance, nor would it contribute to antibiotic resistance.

The use of antibiotics as growth promoters in Europe ceased some 15 years ago, yet the data on the effect on human health has been mixed, with the debate still ongoing. In Denmark, total antibiotics used in pork production declined, while therapeutic use of antibiotics in pigs increased. Some reports suggest that since 1997 there has been an increase in observed cases of antibiotic resistant bacteria in humans in Denmark. It is not possible to know to what extent any increase in antibiotic resistance has been due to use of drugs in humans, and what, if any, was due to the lack of suppression of some bacteria in pigs and chickens. The only conclusion that can be objectively drawn from the European experience is that there is no compelling data to suggest that the policy of not using antibiotics as growth promoters has had a positive or negative effect on human health over the last 15 years.

In some countries, the use of ionophores has been restricted, but there does not appear to be any usable data regarding the outcome of those restrictions. Most tellingly, the European Centre for Disease Prevention and Control, in its factsheet for the general public, stated in answer to the question "Does the use of antibiotics in food-producing animals contribute to the problem [of antibiotic resistance]": "…the major cause of antibiotic resistance in humans remains the use of antibiotics in human medicine".

The European experience and the biological evidence both suggest that David Wallinga's opinion piece is unduly alarmist and is based on some false assumptions.

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