



A Holstein heifer will never grow horns thanks to gene-editing. Regulators have now found serious mistakes caused by the editing process. Alison Van Eenennaam, UC Davis

Biotechnology / CRISPR

Gene-edited cattle have a major screwup in their DNA

Bid for barnyard revolution is set back after regulators find celebrity “hornless” bovines contaminated by bacterial genes.

by **Antonio Regalado** Aug 29, 2019

They were the poster animals for the gene-editing revolution, appearing in [story](#) after [story](#). By adding just a few letters of DNA to the genomes of dairy cattle, a US startup company had devised a way to make sure the animals never grew troublesome horns.

To Recombinetics—the St. Paul, Minnesota gene-editing company that made the hornless cattle—the animals were messengers of a new era of better, faster, molecular farming. [“This same outcome could be achieved by breeding in](#)

[the farmyard,”](#) declared the company's then-CEO [Tammy Lee Stanoch in 2017](#). [“This is precision breeding.”](#)

Except it wasn't.

Food and Drug Administration scientists who had a closer look at the genome sequence of one of the edited animals, a bull named Buri, [have discovered](#) its genome contains a stretch of bacterial DNA including a gene conferring antibiotic resistance.

The “unintended” addition of DNA from a different species occurred during the gene-editing process itself, the government says. It went undetected by the company even as it touted the animals as 100% bovine and assailed the FDA for saying the animals needed to be regulated at all.

“It was not something expected, and we didn’t look for it” says Tad Sontesgard, CEO of Acceligen, a subsidiary of Recombinetics that owns the animals. He says a more complete check “should have been done.”

The blunder is a setback for Recombinetics, whose pioneering prototypes of gene-edited animals include heat-resistant cattle as well as pigs that never hit puberty. It’s also a strike against efforts to make such gene editing a routine practice in animal reproduction. All along, Recombinetics had noisily objected to oversight by the FDA, which categorizes gene-edited animals as new drugs that need extensive testing and approval. It even [lobbied the Trump Administration](#) to wrest oversight away from the health agency, saying it was holding back a barnyard revolution.

But gene editing isn’t yet as predictable or reliable as promoters say. Instead, the procedure, meant to make pinpoint changes to DNA, can introduce significant unexpected changes without anyone noticing. “As genome-editing technology evolves, so does our understanding of the unintended alterations it produces,” wrote the FDA scientists, led by Alexis Norris and Heather Lombardi, in [a paper they released in July](#). They think gene-editing errors “are under reported” and a “blind spot” for scientists.

The risk of haphazard engineering isn’t just to barnyard animals. Genome-editing treatments to cure rare diseases are being tested on people and it is possible that patients will end up with unplanned genetic mutations. Unintended consequences are a particular concern in connection with attempts to modify human

children before birth with gene editing—as occurred [for the first time in China last year](#).

Independent scientists still haven’t had a chance to confirm whether the Chinese children—twin girls—also have unintended mistakes in their DNA. This year the World Health Organization [said](#) any further attempts to make gene-edited people would be “irresponsible” in part because of technical uncertainty.

Celebrity bovines

To make its hornless cows, Recombinetics started with skin cells from Holstein dairy bulls. That’s where the bacterial genes came in: to convey DNA instructions to the cell, the company, in work carried out in 2013, employed plasmids—a type of circular mini-chromosome present in bacteria.

The plasmids (meant to persist only temporarily) carried DNA instructions both for the genetic editing tool (known as TALENs) and the “no horns” genetic change, found in other breeds, and which involves swapping out about 200 genetic letters. Later, edited skin cells were used in a cloning procedure to generate two new animals, named Buri and Spotigy. These were copies of the original bulls, but they didn’t grow horns.

The hornless cattle, born in 2015, soon became gene-editing celebrities. While Spotigy was killed to analyze his tissues, Buri lived long enough to sire about 17 offspring, which are split between facilities at the University of California, Davis, and a farm in Australia. One hornless daughter cow posed for the cover of [Wired](#) in April.

“We know exactly where the gene should go, and we put it in its exact location,” Recombinetics executives [told Bloomberg](#) in 2017. “We have all the scientific data that proves that there are no off-target effects.”

Eat the animals

In part because it disagreed with regulations, the company never pursued formal approval for the hornless cattle in the US. However, its collaborator at the University of California, Davis, veterinary scientist Alison Van Eenennaam, opened a file on the animals with the FDA last year, she says, to trade information with the agency.

According to Sontesgard, Van Eenennaam then chose to test the FDA's thinking by asking whether some of the surplus gene-edited animals taking up space at the Davis facility could go to a slaughterhouse, where they'd be made into steaks and hamburger.

Sontesgard calls the bid to win a "food exemption" an attempt to assess the FDA's views. "Alison was curious whether the animals would be approved as food. I said 'Okay, you can take a shot,'" says Sontesgard. "If they'd said okay, that would have been a nice outcome, and if they said no, they would have to come up with a logical reasoning. I just didn't want them to go to waste because there's really nothing wrong with them."

Sontesgard thinks the animals are "safe to eat with or without the plasmid."

Van Eenennaam had financial factors in mind. It costs 60 cents a pound to incinerate experimental animals, which weigh about a ton, which she considers a large expense for her university program. Better to sell them as hamburger.

By March, though, an FDA bioinformatician running tests on the bulls' genomes had stumbled on the presence of the plasmid—it had somehow integrated into Buri's genome. Agency officials that month arranged a conference call break the bad news, Van Eenennaam says. The animals contained bacterial genes and were GMOs, by any definition.

"We were surprised, but when you get new information, you proceed ahead," says Van

Eenennaam. "That is what science does." She says that half Buri's offspring would be expected to have also inherited the bacteria genes.

It could seem hard to explain why the company and UC Davis failed to see the bacterial genes, which ended up right next to their 'no-horns' edit in the animals' genomes. However, to study DNA, researchers first have to decide which bits to isolate or check for—in effect, they're often looking in the lamplight, a process that introduces assumptions and biases, according to the FDA scientists.

It's not clear if the bacterial DNA poses a larger risk. It's unlikely to affect the cow or a person who eats it; instead, the concern is that the antibiotic resistance gene could be taken up by any of the billions of bacteria present in a cow's gut or body. John Heritage, a retired microbiologist from Leeds University, says he doesn't see a large chance of the gene jumping further but says its presence in a cow could create unpredictable opportunities for it to spread.

The discovery that some of the hornless animals have unwanted DNA from another species has sealed their fate. No one is going to win regulatory approval for them now. Already, regulators in Brazil [rejected a revised petition](#) by Recombinetics connected to the animals, Sontesgard confirmed.

"It's novel DNA, so right there that throws it into the whole GMO debate," says Van Eenennaam. "It doesn't worry me from a food safety perspective, but regulatory—well, you wouldn't even try. It's not a product that would move forward."

Van Eenennaam says since the FDA discovery, UC Davis has incinerated three of the five males who were living at its farms. The animal who posed for the cover of Wired is pregnant and will be spared for the time being.