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Theodore F. Shults

Kimberly Brewer

Jake Machin

Eric Hamelback

Thomas Tobin

University of Kentucky, ttobin@uky.edu

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RATIONAL REASONING *on* RACTOPAMINE

Kentucky regulators reach appropriate responses to inconsequential trace-level environmental substance identifications

By Theodore F. Shults, JD, MS; Kimberly Brewer, DVM, MSc; Jake Machin, BSc; Eric Hamelback; and Thomas Tobin, MVB, MRCVS



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Kentucky Downs, located just north of the Kentucky-Tennessee border, runs a five-day, high-end European-style race meet each September. The purses are attractive, so the meet brings in horses and horsemen from around North America, and the actual amount of time that any individual horse spends at the facility is minimal.

So, to have three horses test positive for small urinary traces of ractopamine during the September 2016 meet was unusual. One horse finished third in the fourth race on September 10, another won the following race that same day, and then five days later, the final horse finished second in the fourth race. All of these identifications were in urine, all were identified in the certificates of analysis as being ractopamine, and all were among the lowest ractopamine concentrations reported anywhere up to that time.

The first and most obvious factor was the “cluster” nature of these ractopamine identifications with the three horses shipping in and essentially simul-

taneously presenting similar low-concentration urinary ractopamine identifications. Three commonalities were identified: 1) each horse spent time in the test barn, with the first two most likely there at the same time; 2) each spent a small amount of time on the Kentucky Downs grounds; and 3) all previous and subsequent runners from the two affected trainers’ operations tested negative for ractopamine, further focusing attention on the location commonality of these identifications.

The horsemen involved immediately underwent the usual racing commission-directed post-positive barn search and came up clean. The next suggestion to the horsemen was standard: they should check their horse feed. Indeed, all foodstuffs and supplements in their training operations were tested; the tests were performed by the Kentucky Horse Racing Commission (KHRC). Ractopamine is a widely used pig and cattle feed additive that directs an animal’s metabolism to increase muscle fibers and thereby reduce fat. While many previous ractopamine cases have been traced to inadvertent low-level

contamination in horse feed, the feed and other supplements from the trainers' barns tested clean, directing attention back to the Kentucky Downs location commonalities of these events.

Our understanding is that the horse feed/supplement testing suggestions came from the KHRC, and it also seems that either the commission or Kentucky Downs (or both) initiated a significant upgrading to the track's test barn facilities. The test barn facility at Kentucky Downs only serves in that function for two weeks out of the year; what it functions as during the other 50 weeks of the year and the specifics of the annual transformation process from regular barn to test barn remain unclear. What is clear, however, is that shortly after the positive reports occurred, a significant upgrading of the test barn at Kentucky Downs commenced.

The next step in evaluating these identifications was initiated by one of the trainers to define precisely what the actual substance present in these urine samples was. According to the certificates of analysis, the substance was ractopamine, a problematic identification. If the urine samples contained unchanged ractopamine, as the certificate stated, this would be good evidence that the ractopamine in these samples had not passed through the horse but had directly contaminated the urine during or post-collection. The fact that two horses from two different stables passed through the same test barn on the same afternoon, within a matter of minutes of each other, and tested positive for a not-uncommon environmental substance meant that collection contamination was a possibility that had to be excluded.

The exclusion process is straightforward: you perform an analytical test with an appropriate control step. When ractopamine passes through a horse, the substance becomes chemically modified/metabolized in the horse's body before it gets into the urine. The horse modifies ractopamine by chemically linking it to a highly water-soluble sugar molecule, so what is found in the urine when the drug has passed through the horse is not ractopamine but rather a highly water-soluble glucuronidated metabolite of ractopamine.

Racing chemists figured this out 40-plus years ago, and the standard urinalysis technique is to treat the urine enzymatically to release the actual ractopamine for the chemist to detect. This is the standard procedure, and the chemist usually (historically) reports that the urine sample contains ractopamine, when in fact the urine most often contains the expected and chemically quite different glucuronide metabolites of ractopamine.

The next step, therefore, was to repeat the drug test correctly and determine which substance—ractopamine itself or the more commonly found ractopamine metabolite—was actually present in these urine samples. When performed correctly, the analysis showed that urine samples contained not ractopamine, as stated on the certificates of analysis, but rather the glucuronide metabolites of ractopamine. This finding ruled out during or post-collection contamination of these samples, placing the most likely source of the ractopamine somewhere in the overall Kentucky Downs environment to which these horses had access, a pretty open question.

Furthermore, as a matter of interest, for the trainer with two ractopamine identifications in one week at Kentucky Downs, these were his first significant drug infractions in a 41-year training career, again pointing to the unusual circumstances associated with this cluster of ractopamine identifications.

The next events in this matter were regulatory. At the stewards' hearing in late January 2018, more than one year after the ractopamine positives were first reported, the trainer with two infractions was suspended for three months, professionally a quite significant penalty. The trainer announced his decision to appeal, and given his longstanding and unblemished regulatory record, there seems to have been significant support for the sentiment that these ractopamine identifications were (1) of no regulatory significance, (2) completely outside the control of the trainer, and (3) of unknown environmental origin. Those sentiments were clearly articulated by the trainer and his professional colleagues.

Within days of the trainer's announcement to appeal the ruling, the stewards rescinded their penalties and also presumably their rulings in the matter. It appears that the combination of these various circumstances and the lack of any sentiment that the trainers were in any way at fault led to further discussions between the KHRC and the testing laboratory.

The discussions led to a reevaluation of the positives by the testing laboratory, where the laboratory director noted in a communication dated February 19, 2018, that "*although it was previously my opinion as expressed to the KHRC staff that the issuance of the Reports of Finding for ractopamine in these cases was appropriate, I have since revised my opinion and now believe that absent evidence of the presence of the parent drug, these findings do not constitute rule violations.*"

Next, the racing commission's executive director, communicating this regulatory reevaluation of the chemical findings to the chief state steward, noted that "*absent evidence of the presence of the parent drug in the sample, there is insufficient evidence to support a violation of the applicable Kentucky medication regulations.*"

The take-home messages from this sequence of events are numerous and—we are happy to note—all ultimately favorable for racing regulation in Kentucky.

1. The simplest message is that ractopamine can show up in unexpected locations and circumstances, most commonly as a feed contaminant, but in this case the specific source of these ractopamine identifications remains unknown.
2. The time and location commonalities are consistent with the horses in question being exposed to a specific inadvertent environmental source, one not in any way associated with the trainers involved.
3. The concentrations were low and apparently transient, so there was, as a practical matter, no possibility of a pharmacological effect.
4. The ractopamine identified in the urine samples was the pharmacologically inactive metabolite, and there was no evidence for actual ractopamine itself in any of these horses.
5. The longtime clean regulatory history of the trainers involved in this matter is also fully consistent with innocent inadvertent environmental exposure as the source of these technically interesting but forensically insignificant urinary identifications.
6. The KHRC approached these identifications cautiously and entirely correctly, assisting the trainers in evaluating their feedstuffs and supplements as a possible source.
7. It appears that the KHRC or Kentucky Downs was careful to promptly upgrade the test barn facilities at the track to reduce any possibility of inadvertent during or post-collection contamination of post-race samples.
8. Most important, the KHRC carefully reviewed the regulatory and forensic significance of the ractopamine metabolite findings and concluded that "*absent evidence of the presence of the parent drug in the sample, there is insufficient evidence to support a violation of the applicable Kentucky medication regulations.*"

This is a significant step forward in the increasingly important matter of the appropriate regulatory handling of pharmacologically insignificant trace-level detections of urinary metabolites of dietary and environmental substances. **HJ**