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Zilpaterol and Ractopamine: Reaching Consensus on Trace-Level Transfers to Racehorses

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Zilpaterol + Ractopamine:

Reaching Consensus on Trace-Level Transfers to Racehorses

DENIS BLAKE

Worldwide clusters show trace-level positives typically result from contaminated feed

By Jacob Machin, MS; Kimberly Brewer, DVM, MSc; Clara K. Fenger, DVM, PhD, DACVIM; Sarah White-Springer, PhD; Abelardo Morales-Briceno, DVM; and Thomas Tobin, PhD, MRCVS, DABT

Trace-level positive tests in racehorses

that result from inadvertent environmental exposure beyond the control of the trainer are becoming a recurrent theme in horse racing. Substances are categorized and assigned a penalty class by the Association of Racing Commissioners International (ARCI) according to their effect on the horse if present at pharmacological levels, but the actual effect of the substances on the horse at the level in which they are found is often ignored. In most cases, penalties are assessed solely based on the ARCI classification, without mitigation resulting from the recognition that trace levels from environmental contaminants are unlikely to have a meaningful effect on the horse. With the ever-increasing sensitivity of drug testing technology, guidelines should be developed and adopted to guide regulators in how to identify environmental contamination as a mitigating circumstance to avoid inappropriate penalties for circumstances beyond the control of the trainer.

In this article, we review the investigation of trace amounts of β-2 adrenergic agonists, a drug class that poses a significant risk to the integrity of horse racing whether intentionally used or through the inadvertent contamination of feed. Clenbuterol is the most recognizable of the β-2 adrenergic agonists, but others include albuterol, ractopamine and zilpaterol. This drug class can, on the one hand, include valuable therapeutic agents and, on the other hand, provide a potential performance edge in sprint races and even endanger the life of the animal when intentionally used.

This drug class also has a repartitioning effect, increasing lean mass and decreasing fat mass. This effect is responsible for the approval by the Food and Drug Administration (FDA) of zilpaterol (Zilmax) and ractopamine (Paylean) for use in food-producing animals for the purpose of improving carcass quality by increasing the lean meat. Within skeletal muscle specifically, β-2 adrenergic agonist administration increases Type 2x muscle fibers, large fibers responsible for explosive power that use sugar for energy, at the expense of Type 2a fibers, which require oxygen and burn fat. This results in impaired aerobic capacity during exercise, which actually negatively impacts racehorse performance when distances exceed short sprints.

Zilpaterol and ractopamine are typically added to finishing feed during the milling process, which means they are intended to be fed for the last three to six weeks before slaughter. Zilpaterol and ractopamine are not approved for any purpose in horses, but both may show up in trace levels in horse feed that is manufactured in the same facility in which cattle, pig or poultry feed is milled. These identifications occur because, in horses, zilpaterol and ractopamine are well absorbed orally and excreted unchanged in urine with a long terminal half-life. When these inadvertent transfers occur, they usually occur as clusters of low-concentration identifications, which helps considerably in determining the source of these identifications, although in some cases, a specific source can be elusive.

In equine drug testing we define a cluster as at least three identifications in horses of the same substance in the same general location and timeframe, usually from three or more trainers. This definition is based on the unlikelihood of multiple unrelated trainers simultaneously deciding to use the same inappropriate substance in their racehorses. The reviewed zilpaterol and ractopamine identifications mostly meet this definition in that the clusters involved relatively large numbers of unrelated horses/trainers at specific locations and within specific timeframes. A further consideration is that the concentrations of the substance involved in such clusters are likely to be completely ineffective, a further indication of the random and non-trainer-associated origins of the identifications in question—in this case, pharmacologically insignificant trace-level identifications of zilpaterol.

Zilpaterol

TABLE 1: FEEDSTUFF-RELATED CLUSTERS OF EQUINE ZILPATEROL

Year	Country	Horses	Detection	Control Authority	Lab	Horse Feed	Penalty
2013, March/April	United States (California)	48	Post-race	California Horse Racing Board	UC Davis	1 U.S. brand	No trainer penalties
2013, July	Hong Kong	16 (80-plus?)	Post-race	Hong Kong Jockey Club	HKRC Lab	2 U.S. brands	
2019, March	Mauritius	24	Out-of-competition	Mauritius Turf Club	QuantiLab	South African	
2020	France	18	Post-race	France Galop, Le Trot	LCH France	Irish	

Table 1. Feedstuff-related clusters of zilpaterol identifications, 2013 through 2021, dates of events, jurisdiction, number of cases reported, pattern of testing, authority, laboratory, source of feed and penalties. In Hong Kong, 16 horses were initially identified, but there were suggestions that at least 80 more horses had been exposed. In related 2020 events, 18 horses were withdrawn from racing in England and France because of exposure to horse feed containing zilpaterol.

Since 2013, these events have occurred a number of times in horse racing worldwide. The first well-characterized zilpaterol identification cluster took place in March/April 2013 in California, where molasses containing zilpaterol was inadvertently added to horse feed. Zilpaterol began to show up in racehorses about two weeks after their first exposure to the affected feed, consistent with the delayed urinary excretion of zilpaterol. A total of about 48 horses were reported positive for zilpaterol before the feed source was identified. The California racing authorities also recognized that the horsemen involved were innocent. The horses were disqualified, but no regulatory action was taken against the affected horsemen.

Shortly thereafter, in July 2013, a similar zilpaterol identification cluster unfolded in Hong Kong, where 16 horses were reported as testing positive for zilpaterol. The source was again traced to feed, which had been provided by the Hong Kong Jockey Club itself. Although 16 horses were identified, possibly 80 or so more horses may have been exposed. It turned out that the Hong Kong feed was imported from the same source as the earlier California identifications, with the later Hong Kong identifications reflecting transpacific shipping time.

The next cluster of zilpaterol identifications was in March 2019, when the Mauritius Turf Club reported zilpaterol in out-of-competition tests on 24 horses from seven stables. The stewards considered that these zilpaterol identifications were due to feed contamination, so no action was taken against the affected trainers. In a later communication, dated November 25, 2019, the Mauritius Turf Club authorities reported that the most likely source of these zilpaterol identifications was feed originating in South Africa.

Shortly before the Mauritius Turf Club released its report, concerns about possible zilpaterol detections in racehorses in South Africa were communicated, although to our knowledge no formal positive identifications were called. On November 8, 2019, the South African *Sporting Post* noted that the National Horseracing Authority (NHA) in South Africa released a statement noting that "in some racehorse specimens emanating countrywide, traces of a substance … may be indicative of zilpaterol," thereby reporting the possible presence of zilpaterol in South African racing samples. This communication created concern among South African trainers, who did not know what the NHA expected them to do besides contacting their feed merchants, which was likely part of the reason for the NHA communication. These zilpaterol concerns in South African racing are fully consistent with approval of zilpaterol for use in cattle feed in South Africa and the ease with which zilpaterol can transfer in microgram amounts from cattle feed to horse feed and therefore to post-race urine samples.

The next cluster of zilpaterol identifications occurred in fall 2020 in France, involving approximately 12 France Galop Thoroughbred horses, four Le Trot Standardbred horses and two horses from trainers' yards, to date 18 total samples, all reported by the Laboratoire des Courses Hippiques (LCH). The first samples reported positive were collected around August 30, with the zilpaterol identifications reported by LCH starting September 29. The samples contained microgram amounts of zilpaterol inadvertently incorporated into some horse feed products, with the estimated daily intake per horse being minimal, in the order of 15 micrograms per horse per day. This 2020 French zilpaterol cluster is unusual in that positives were reported only in France by LCH testing, even though the feeds in question also were given to horses racing in England and Ireland. This cluster is therefore forensically similar to the 2019 Mauritius cluster in that the feed failed to draw attention in the jurisdiction where it originated until horses were tested in a jurisdiction with more sensitive testing methods.

Related fallout from these French events included 11 horses trained by Aiden O'Brien and his sons Joseph and Donnacha being withdrawn from the Prix de l'Arc de Triomphe in October 2020 and a trainer in England scratching seven runners, all because of exposure to zilpaterol-contaminated feed.

Reviewing these 2020 zilpaterol cluster events, the International Federation of Horseracing Authorities (IFHA) and the European Horseracing Scientific Liaison Committee have recommended that horse racing jurisdictions should offer elective testing for zilpaterol where contaminated feed is suspected to have been fed. This elective testing should be performed in the country in which the horse holds an entry, and no regulatory action should be taken against any screening findings for zilpaterol when it can be demonstrated that the horse was likely fed contaminated feed. A further recommendation was that the IFHA racing jurisdictions and their analytical laboratories should work together to harmonize the reporting limits for zilpaterol and other key substances that are prohibited at all times.

In these zilpaterol clusters, it is important to note that to our knowledge no significant regulatory actions were taken against any of the horsemen involved. In the 2013 Hong Kong cases, triggered by post-race identifications in horses trained by Ricky Yui, the Hong Kong Jockey Club stewards conceded the zilpaterol finding was due to the "feed product imported by the Club at the request of the trainers, including Mr. Yui, being contaminated." Yui was therefore not penalized because the stewards considered that Yui and the other Hong Kong trainers involved were innocent of any wrongdoing, although the zilpaterol-positive horses were taken down.

A further consideration is that the concentrations of zilpaterol involved in these identifications are considered to be without pharmacological or forensic significance, and at times, the amounts detected were defined simply by the sensitivity of the testing laboratory in question, as in the 2019 Mauritius and 2020 French clusters. In the Mauritius matter, the Mauritius Turf Club reported on March 22, 2019, that "after due consideration, the Racing Stewards found, beyond reasonable doubt, that the above horses had been tested positive for 'zilpaterol' as a result of feed contamination. Accordingly, no action was taken against any one of the above trainers." Similarly, as reported by *BloodHorse* on March 27, 2013, "the California Horse Racing Board, citing feed contamination, has dismissed all 48 positive tests for zilpaterol."

To address this problem, the British Equestrian Federation (BEF), which regulates show horses, instituted "a 14-day moratorium over positive doping tests." During this moratorium, any horse returning a positive result for zilpaterol was not to be subjected to any regulatory action under the BEF anti-doping rules, provided the positive is consistent with feed contaminated with zilpaterol. The moratorium also could "be extended depending upon updating information relating to the contamination." Additionally, the British Equestrian Trade Association indicated that there were "no health or welfare issues in a horse consuming feed containing the level of zilpaterol found."

As this report was being drafted, the National Horseracing Authority in South Africa elected to get into the zilpaterol cluster business, calling 10 positives on eight trainers in the KwaZulu-Natal province. Seven of these trainers retained counsel, and one trainer with two positives pleaded not guilty. Despite the extensive worldwide precedents set forth in this article, this trainer was found guilty by the NHA and issued a warning. The downside for this trainer is that he now has a Class 1 forbidden substance violation on his record, despite being, to our knowledge, no less guilty of such a violation than any of the other 100-plus trainers worldwide with similar trace-level zilpaterol positives.

The first well-characterized zilpaterol identification cluster took place in March/April 2013 in California, where molasses containing zilpaterol was inadvertently added to horse feed.

Ractopamine

TABLE 2: FEEDSTUFF-ASSOCIATED RACTOPAMINE IDENTIFICATIONS

Year	Country	Horses	Detection	Control Authority	Lab	Horse Feed	Penalty
2013	Canada (Ontario)	5	Post-race	CPMA	Maxxam	1 Canadian brand	Cleared
2014	Canada (Ontario)	5	Post-race	CPMA	Maxxam	1 Canadian brand	Cleared
2016	United States (Iowa)	2	Post-race	Iowa	Industrial	1 U.S. brand	Cleared
2016	United States (Minnesota)	4	Post-race	Minnesota	Industrial	1 U.S. brand	Cleared
2017	United States (Kentucky)	3	Post-race	Kentucky	Industrial	Unknown	Cleared*

**Positive horses were disqualified, except in the Kentucky identifications*

The ractopamine cluster identifications comprise smaller numbers of horses than the zilpaterol cases. This is likely related to the manner in which the feed contamination took place. In most of the zilpaterol contaminations, the offending feed additive was a zilpaterol-molasses mixture that was added to the horse feed. In the case of the ractopamine contaminations, a cattle or swine feed was improperly mixed in the feed mill prior to the mixture manufactured for horses. This likely resulted in lower amounts of ractopamine in the horse feed than in the case of zilpaterol. It is notable that in one of the clusters, the 2017 Kentucky ractopamine positives, a common feed source could not be identified. However, based on the levels and the cluster circumstances of the positive tests, the horses were not disqualified.

Atypical Findings Policy

The federation that regulates international horse shows addressed the issue of inadvertent contamination in a different way. On November 23, 2020, the Federation Equestre Internationale (FEI) proposed a new analytical findings category, the atypical findings (ATF) policy. This category was created to address the ever-increasing inadvertent transfer of substances from the environment, resulting in trace identifications in competition animals. We note that the zilpaterol and ractopamine identifications meet each of the ATF policy criteria presented by the FEI. The policy states that when reviewing a potentially adverse analytical finding for consideration as an ATF, the FEI will take a number of factors into account, all of which are met by the zilpaterol and ractopamine identifications reviewed in this article.

The ATF policy criteria include a requirement that there be identifications of the same prohibited substance arising from other samples taken at the relevant event, a criterion readily met by the described clusters. The second criterion is that there be ATFs arising from the same prohibited substance from other samples taken in previous events held at the same venue or in the same region, a second criterion also met. The third criterion is that samples taken from feed or bedding at the relevant event test positive for the substance in question; this criterion also has been met by almost all of these zilpaterol and ractopamine identifications. The ATF policy also addresses whether or not the level found in the analytical samples is likely to have any effect on the performance of the animal. In particular, it specified zilpaterol as a prohibited substance that would be treated as an ATF as of January 1, 2021.

β-2 Agonists

Zilpaterol and ractopamine and the common therapeutic substances clenbuterol and albuterol are only four of at least 20 readily obtainable β-2 agonists, with innumerable unnamed β-2 agonists that can be theoretically synthesized, obtained and used. The threat to the integrity of racing lies not with these four β-2 agonists that are readily identifiable and even FDA approved for use in horses but with the unauthorized use of those alternative drugs.

The zilpaterol and ractopamine story is reassuring in that some jurisdictions are actually following the science and not penalizing trainers for circumstances beyond their control. Rational thresholds and thorough investigation of adverse analytical findings should continue to be encouraged, and horse racing should follow the lead of the FEI to establish an ATF policy, thus turning away from the irrational penalties that often accompany inadvertent environmental exposure. The integrity of racing could be better served if our attention were diverted from finding FDA-approved and accepted therapeutics and contaminants of hay and feed at ever lower levels and directed at finding substances that might actually be used nefariously, such as the other 20 or so β-2 agonists. **HJ**