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TRACE-LEVEL IDENTIFICATIONS ARE NOT POSITIVES

THE SCIENTIFICALLY CORRECT AND PUBLIC RELATIONS-APPROPRIATE APPROACH TO MEDICATION REGULATION

By Clara Fenger, DVM, PhD, DACVIM; Peter Sacopulos; and Thomas Tobin, MVB, MRCVS

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ensational headlines sell advertising for media outlets. In horse racing, the words “drug positives” are a prime example and may help generate attention for websites, blogs and print media, but they also can create a public relations dilemma for the industry. Time and again, irrelevant trace levels of substances found in racehorses are reported as drug positives, making headlines that lead lay readers to shake their collective heads: “if only horse racing could eliminate the endemic problem with drugs.”

The facts are sharply different and would not sell a single newspaper or generate any online clicks. The problem is that horse racing has the most highly advanced and sensitive drug testing on earth. Period. Horse racing boasts the longest established drug testing program on this planet, with drug testing in horses beginning more than a century ago. Racehorse drug testing has always been at the leading edge of testing technologies, and improvements are constantly being undertaken.

Since Dancer’s Image won the 1968 Kentucky Derby and then was disqualified for a trace-level positive of (then-impermissible) phenylbutazone, the sensitivity of equine testing has increased one-billion-fold, and there has never been another Kentucky Derby positive. This marked improvement in the sensitivity of drug testing in horse racing has not come without a price. An inevitable side effect of this one-billion-fold increase in testing sensitivity is the identification of irrelevant, trace levels of the almost 1,000 foreign substances classified by the Association of Racing Commissioners International (ARCI).

ARCI UNIFORM CLASSIFICATION GUIDELINES FOR FOREIGN SUBSTANCES

The ARCI has recognized nearly 1,000 substances that may be identified in a horse’s post-race test and classified them according to their potential to influence the horse’s performance, including the appropriateness of their use in the horse. The classifications are shown in Table 1. A key point implied but not expressly stated in the guidelines is that these foreign substances have been classified according to their potential effects on the horse *when they are present in the horse in sufficient amount to exert an effect during the race*. In other words, size matters. The size of the dose and the size of the blood level determines the effect, just as much or more than the identity of the drug.

THERAPEUTIC MEDICATIONS AS FOREIGN SUBSTANCES

Racehorses, as living, breathing animals, share the same organ systems and physiologic processes as humans. They fall ill; they become injured; they require intervention with modern medicine and therapeutic medications. The rigors of athletic endeavor require that every medical issue be addressed in the athlete, and horses are no exception. The obligation to treat every malady in a horse, no matter how minor, is even higher than in humans, simply because we hold great responsibility as their caretakers. They rely on us for everything.

To this end and in pursuit of uniform medication regulations, legitimate therapeutic medications that are appropriate for use in the athlete in training

TABLE 1. ARCI UNIFORM CLASSIFICATION GUIDELINES FOR FOREIGN SUBSTANCES

Class 1	Stimulant and depressant drugs that have the highest potential to affect performance and have no generally accepted medical use in the horse
Class 2	Drugs with a high potential to affect performance but with less potential than drugs in Class 1; drugs generally not accepted as therapeutic agents in racing horses and with a high potential for abuse
Class 3	Drugs that may or may not have generally accepted medical use in the racing horse, but the pharmacology suggests less potential to affect performance than drugs in Class 2
Class 4	Therapeutic medications that would be expected to have less potential to affect performance than Class 3
Class 5	Therapeutic medications that have very localized actions only, such as anti-ulcer drugs and certain anti-allergic drugs, for which thresholds have been established



THE OHIO RIVER RUNS NOT FAR FROM CHURCHILL DOWNS IN LOUISVILLE, KENTUCKY, AND IS USED FOR THE CITY’S DRINKING WATER; LIKE MOST OTHER RIVERS IN POPULATED AREAS OF THE UNITED STATES, IT CONTAINS A VARIETY OF PHARMACEUTICALS AND RECREATIONAL SUBSTANCES.



WINTERCRESS, SOMETIMES CALLED YELLOW ROCKET, MIGHT LOOK PRETTY AND MAKE FOR NICE PHOTOGRAPHS, BUT IT HAS ALSO BEEN LINKED TO POSITIVE TESTS FOR AMINOREX.

but that should not be present *at pharmacologically effective concentrations* on race day have been identified with a specific threshold concentration set in blood or urine and practical withdrawal time guidelines developed to enable compliance with these thresholds. In lay terms, the approach was to identify an appropriate timeframe for withdrawal and determine a blood or urinary concentration at that withdrawal point below which any identification is, by definition, an event of no regulatory significance. As a rule, these thresholds are well below any possibility of a pharmacological effect.

DIETARY SUBSTANCES AS FOREIGN SUBSTANCES

This threshold approach is now well established for therapeutic medications in North American racing, and a broadly similar system is in place in Europe. The thresholds are far from perfect, but the concept is sound. The next hurdle to overcome in the regulation of foreign substances in horse racing remains somewhat problematic.

Hay, oats and water all include substances foreign to the horse. Hay is, by its very nature, contaminated with weeds. Soil is routinely amended with fertilizers and animal manure, and any number of possible foreign substances may be directly applied to the plants. One such example is acetanilide, a common broadleaf herbicide used in corn and soybean production; it is also listed as a Class 4, Penalty Class B foreign substance in the ARCI guidelines.

In addition to inadvertent contaminants, horse feeds also contain innumerable additives, mostly for the purpose of balancing the feed to contain all nutrients that the horse may require. Common feed additives for food animal production, such as ractopamine, may carry over in infinitesimal quantities in a feed mill from a ruminant feed batch to a horse feed batch, spurring a positive test.

Even water fails to be foreign substance-free. The tap water in nearly every major metropolitan area contains measurable levels of pharmaceuticals and recreational substances. Louisville, Kentucky, home of Churchill Downs, draws

its drinking water from the Ohio River, which contains as many as 56 different pharmaceuticals in measurable concentrations at any given time. Clearly, foreign substances are present, albeit at relatively low concentrations, in all biological systems, including horses, at all times.

This problem of casual contact with foreign substances is not lost on regulatory agencies. Both the International Federation of Horseracing Authorities (IFHA) and ARCI have begun to address the matter of feed contaminants and environmental substances. The IFHA has published what it terms “residue limits” for nine substances—caffeine, theophylline, theobromine, atropine, scopolamine, morphine, hordenine, bufotenine and dimethyltryptamine—that inadvertently show up at trace levels in post-race urine. ARCI similarly has produced a list of screening limits for endogenous and feed-contaminant foreign substances that may show up at trace levels in blood or urine. Long story short, the basic concept of cut-offs or screening limits well below any possible pharmacological effect on the horse also has been internationally accepted for dietary substances and feed contaminants and environmental substances.

Of course, there are many more than nine dietary substances that may inadvertently find their way into the feed or hay of a horse. A recent case of aminorex, possibly from the wintercress (*Barbarea vulgaris*) plant family, is a classic example.

Aminorex was an amphetamine-related substance that was prescribed for weight loss in the 1950s and rapidly lost its appeal for human use because of untoward side effects such as high blood pressure. It has not been available as a commercial pharmaceutical for decades. Nonetheless, aminorex began to show up as positive tests in horse racing, first in 2004, then in increasing numbers to a peak in 2009. Investigation determined that these identifications were in connection with the use of levamisole for the treatment of equine protozoal myeloencephalitis (EPM). Levamisole is available over the counter as a dewormer for ruminants but gained popularity for its immune-modulating benefits for treatment of EPM in the 2000s. Levamisole is metabolized into several components, one of which is aminorex. The aminorex produced in this



COMMON COUGH AND COLD MEDICINES, SUCH AS NYQUIL, CAN BE TRANSFERRED FROM A GROOM OR TRAINER TO A HORSE, BUT IN SUCH CASES THE CONCENTRATIONS ARE FAR TOO LOW TO HAVE A PHARMACOLOGICAL EFFECT.

manner is in irrelevant amounts, unable to exert its stimulant effect but present nonetheless, and it turned out to be responsible for the rash of aminorex positives between 2004 and 2009.

The story of aminorex does not end with levamisole. In 2017 there were seven aminorex identifications in the United States, all among horsemen who were adamant that their horses had not received levamisole. At the same time, a cluster of aminorex positives appeared in non-racing horses in the United Kingdom. The testing laboratory LGC-Fordham launched an investigation that led them down an unexpected path. They identified aminorex as a component of members of the wintercress plant family, a ubiquitous weed that infests hay fields the world over with a vengeance. The weed is not palatable, but some horses will eat it. A possible environmental source of aminorex is currently under investigation.

ENVIRONMENTAL SUBSTANCES AS FOREIGN SUBSTANCES

The third area of concern is environmental transfer of human prescription medications and recreational substances showing up as trace-level environmental substances in post-race samples. In the United States, a highly significant environmental substance detected in post-race urine is benzoylecgonine (BZE), the major urinary metabolite of cocaine. Cocaine at trace levels is widely distributed in the United States, readily found on dollar bills. Keep in mind that money is perhaps the most frequently exchanged human artifact. This wide distribution is further complicated by the fact that BZE is very efficiently concentrated in equine urine, up to 2,500 fold, making it a highly effective biomarker of inadvertent exposure to trace amounts of environmental cocaine.

Cocaine is, in fact, so widely distributed in the United States that the urinary BZE cut-offs for airline pilots are 150 ng/ml screening and 100 ng/ml

confirmation. Below these urinary cut-offs, a BZE identification is of no regulatory significance and is not considered to in any way influence the ability of a pilot to fly an airplane. Consistent with these scientific and regulatory realities, a number of U.S. racing jurisdictions—Illinois, Ohio, Louisiana, Minnesota, Oklahoma, Pennsylvania and Washington—have adopted similar urinary cut-offs for BZE of between 50 ng/ml and 150 ng/ml.

Another human recreational substance of concern is methamphetamine, which shows up sporadically worldwide as trace amounts in equine samples. A recent example of inadvertent environmental exposure to methamphetamine involved a Michigan trainer racing Quarter Horses near Toronto, Ontario, Canada. Shortly prior to shipping north, the trainer purchased a large used horse trailer, loaded three of her four horses on this trailer and vanned them to Canada. The three horses shipped in the newly purchased trailer tested positive in Canada for traces of methamphetamine, while the fourth horse shipped in a different trailer tested clean. The Ontario authorities reviewed this matter and swabbed the newly purchased trailer, which tested positive for methamphetamine. The Ontario stewards fined and suspended the trainer.

The trainer appealed the ruling, and on appeal the Ontario Racing Commission set aside the stewards' penalties and accepted the trainer's position that the traces of methamphetamine identified in the three horses were both pharmacologically irrelevant and of inadvertent environmental origin. In other words, the commission fully accepted the concept that methamphetamine may be present in a concentration well below any chance of an effect on the horse as a result of environmental transfer. Additionally, the commission's ruling on this matter noted that with environmental substances the need was "to set limits high enough to cut off the environmental noise and low enough to stop performance enhancement"—words defining the scientifically correct application of the threshold concept to environmental substances. Based on the Ontario data, we proposed an interim urinary cut-off for methamphetamine of

at least 15 ng/ml in urine. This has since been adopted by the Oklahoma Horse Racing Commission.

A more recent sequence of trace-level environmental identifications occurred in Kentucky, where the first of a sequence of urinary dextrophan identifications was traced to the use of the over-the-counter product NyQuil by the groom of the horse in question. As might be expected, the dextrophan concentrations were in the 15 parts per billion range and completely unlikely to be associated with a pharmacological effect. This lack of any possible pharmacological effect apparently led the Kentucky Horse Racing Commission to decide that “further prosecution of these cases is not necessary,” and the cases were dismissed “in the interests of fairness to the trainers and owners involved,” effectively setting a urinary cut-off for dextrophan of at least 15 ng/ml in urine. Based on our review of the concentrations identified in these three Kentucky dextrophan identifications, we have suggested an interim 25 ng/ml urinary environmental substance cut-off for dextrophan in equine urine.

A second important take-home message from the Kentucky dextrophan identifications is that these identifications appeared to be primarily cold season/winter identifications. This seasonal pattern is consistent with the fact that NyQuil is a medication for upper respiratory conditions, and inadvertent equine exposure events would therefore be more likely to occur during the winter months. This suggestion is supported by the seasonal pattern of dextrophan concentrations in the South Platte River downstream from Denver, Colorado, where the amounts of dextrophan found are five-fold higher in the winter months than during the summer months. This finding suggests marked seasonal differences in the rate of use of NyQuil and similar medications and parallel seasonal variations in the probability of an inadvertent environmental exposure to NyQuil, as apparently occurred in Kentucky.

ZERO TOLERANCE AS PART OF THE ABSOLUTE INSURER RULE

The principle of defined thresholds for therapeutic medications and dietary and environmental substances is now recognized and applied worldwide in racing regulation. This brings us to the next step in racing regulation, which is to remove the word “positive” from analytical reports. In current usage, a positive means “a chemical identification that is evidence of a deliberate attempt to improperly influence the outcome of a race.” However, such findings are rare, an estimated one in 6,700 samples tested in horse racing. Usually what the chemist identifies is nothing more than a trace-level overage of a therapeutic medication or a trace-level identification of a dietary or environmental substance, totaling about one in 400 of all samples tested. These trace-level overages are most commonly due to horse-to-horse variability in the metabolic handling of substances, are not associated with any possibility of a performance effect and are effectively background noise picked up by a highly sensitive modern piece of laboratory equipment. These trace findings called “positives” in post-race samples have had a chilling effect on every trainer and owner. When the call comes in from the racing commission shortly after a race, the heart of every

trainer now skips a beat. The absolute insurer rule immediately kicks in, and the trainer is held responsible, in most jurisdictions, regardless of the acts of third parties, including, apparently, Acts of God.

The first step is a hearing, scheduled and conducted before the track stewards or judges. Because of the absolute insurer rule, in most cases, the result of this first stage is adverse to the licensee. If the trainer chooses to appeal the decision, an administrative complaint is filed and an administrative law judge appointed. The administrative process then proceeds to a hearing on the merits before the administrative law judge. In most cases, the findings of the administrative law judge are similarly adverse to the licensee because the trainer is still the absolute insurer of the horse. Most administrative law judges’ findings of fact, conclusions of law and penalties are subsequently reviewed by the state’s racing commission, concluding the administrative process. The next step is an appeal in the form of a petition for judicial review to a state trial court. At each step along the way, the trainer/licensee remains the absolute insurer of the horse.

The absolute insurer rule, also known as the trainer responsibility rule, states that a trainer is responsible for any prohibited substances found in the horse. Depending on the jurisdiction, this rule may provide a presumption of responsibility on a trainer or an irrebuttable presumption. The key difference is that an irrebuttable presumption precludes the trainer from presenting exculpatory evidence.

Where trainers may rebut the presumption of guilt, there is still the presumption that trainers are responsible for the positive test results. However, the trainer is afforded an opportunity to rebut the presumption by presenting evidence, in the form of testimony or documentation, that demonstrates a lack of responsibility of the trainer. In presumption states, the burden of persuasion, that being by a preponderance of the evidence, rests with the trainer. This is often difficult and nearly always an uphill battle involving considerable expense.

Trace-level identifications and zero tolerance become not only problematic but arguably unconstitutional in states having an irrebuttable presumption that a trainer is responsible for positive results. Many states, including Louisiana, Florida, Maryland, New Jersey and Texas, have promulgated rules that make a positive finding irrebuttable.

It has long been argued that the absolute insurer rule that incorporates an irrebuttable presumption deprives horsemen of due process rights. For decades, that argument was not persuasive. However, in a recent case before Judge Thomas Wingate of the Franklin County Circuit Court in Frankfort, Kentucky, the court held that:

“Trainers must be able to present evidence to rebut their liability in an instance of a violation. To disallow a trainer to safeguard its license, a trainer must receive due process to be heard on the propriety of his action to challenge liability for a dosing violation.”

Judge Wingate’s decision is both refreshing and forward-thinking, especially given the ever-increasing sensitivity of equine testing and the advancing position that therapeutic medications, dietary substances and environmental substances are all foreign substances at ever-increasing miniscule trace levels.

CONCLUSION

It does not require a scientist to realize that zero tolerance of foreign substances is neither achievable nor desirable in the regulation of horse racing. None of us nor our equine athletes are ever foreign substance-free. With contaminants in the food, water and even the air surrounding us, we are bombarded constantly by foreign substances. As testing technology becomes ever more sensitive, the line between meaningful and irrelevant levels of medications has become blurred. The *size of the dose matters*, and it is more important than ever to understand at what point a level has meaning in relation to the racing contest. In order to move the integrity of racing forward, we need to move away from regulations that make it easier to penalize horsemen with minimal investigation and toward fairness and integrity for all participants. **HJ**