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Trace-level detections of methamphetamine in racing horses – a review and forensic analysis

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Summary: Methamphetamine is a central stimulant and an approved human therapeutic medication which is also clandestinely synthesized and marketed worldwide as a recreational substance. Users of clandestinely synthesized methamphetamine may handle and use methamphetamine in far greater amounts than medically approved dosages. Given that mucous membrane exposure of a horse to 10 milligrams of methamphetamine has produced jugular blood plasma/serum methamphetamine concentrations of 88,400 picogram/ml, inadvertent transfer of picogram/ml amounts of methamphetamine from recreational users to racing horses is a well understood process. Evaluating such picogram/ml methamphetamine identifications, the first factor to consider is that methamphetamine presents as two chemically distinct mirror image enantiomers, d-methamphetamine and l-methamphetamine. d-Methamphetamine is the more pharmacologically active enantiomer, marketed in the United States (US) as Desoxyn®, a US Drug Enforcement Administration (DEA) Schedule II prescription medication. l-Methamphetamine is pharmacologically less active and is marketed in the US in several Over-The-Counter (OTC) nasal decongestant inhalers. Forensically correct evaluation of picogram/ml jugular blood/plasma/serum methamphetamine identifications in racing horses requires quantitative evaluation of the blood, urinary and hair concentrations of each methamphetamine enantiomer, as well as the presence or absence of the expected amphetamine metabolite. Evaluation of the regulatory significance of a jugular blood/plasma/serum concentration of methamphetamine must also take into account the fact that following oral exposure to methamphetamine jugular blood concentrations will be much higher than systemic blood concentrations, given that the jugular vein is the direct venous connection between the local high mucous membrane concentration of methamphetamine and the systemic circulation of the horse. Based on published scientific data, mucous membrane exposure of a horse to 100 micrograms of methamphetamine, a very conservative 1/1,500 of a possibly pharmacologically effective equine dose may give rise to jugular blood/plasma/serum concentrations of methamphetamine of 884 picograms/ml, a conservative guideline value for evaluating the pharmacological and forensic significance of jugular blood/plasma/serum concentrations of methamphetamine.

Keywords: trace-level detection, racing horse, methamphetamine, forensic, analysis

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Introduction

Methamphetamine (R,S)-N-methyl-1-phenylpropan-2-amine, formula, $C_{10}H_{15}N$, molar mass 149.237 g·mol− (Figure 1) is an amphetamine related substance at times detected in post-race blood and urine samples from racing horses[1]. The methamphetamine concentrations involved in these equine blood/plasma/serum or urinary identifications are usually picogram/ml concentrations and unlikely to be pharmacologically significant. Such relatively low concentration blood/plasma/serum/urinary identifications are consistent with their being the result of inadvertent exposure of the horse to trace amounts of environmental methamphetamine from recreational methamphetamine users in contact with the horse, either directly or indirectly.

The first published scientific report detailing a case of random and indirect exposure of horses to environmental methamphetamine is that presented by *Brewer* et al. 2016[1], who reported on an October 2014 sequence of events in which horses were transported to a race meet in Ontario in a newly purchased methamphetamine contaminated horse trailer that had apparently previously been used as an illicit methamphetamine synthesis laboratory. Three horses transported in this trailer tested post-race *"positive"* for picogram/ml urinary concentrations of methamphetamine, while a fourth horse transported in another trailer tested negative. The urinary methamphetamine concentration in these horses ranged from 56 picograms/ml to 340 picograms/ml. Reviewing these identifications the Ontario Racing Commission (ORC) noted

"the very low levels of methamphetamine identified in these horse urines, levels in the opinion of the ORC with no possible impact on the performance health and safety of horses and levels consistent with inadvertent environmental contamination". The ORC also noted the need *"to set limits high enough to cut-off the environmental noise and low enough to stop performance enhancement."* Reporting these regulatory events in the scientific literature, Brewer et al 2016 wrote that *"an interim regulatory cut-off of 15 ng/mL for methamphetamine in post-race urine is proposed"*.

Consistent with these Ontario Racing Commission rulings, the year 2016 saw a sequence of six urinary methamphetamine identifications at Lone Star Park in Grand Prairie, Texas, the first reported on April 17th, rapidly followed by two more identifications on April 23rd, and 24th. The next identifications in this sequence were two identifications on May 13th, in one of which May 13th horses the urinary methamphetamine concentration was reported at 460 picograms/ml, in the same general range as the 2014 methamphetamine identifications in Ontario. The sixth and to our knowledge last horse in this sequence tested methamphetamine "positive" on July 4th, 2016. All of these six horses tested blood/plasma/serum negative for methamphetamine, leading the Texas Racing Commission (TRC) regulatory authority to consider these identifications as not being trainer related [1]. Among the factors considered by the TRC were the low concentrations of methamphetamine identified in the urine samples in question, the fact that the corresponding blood/plasma/serum samples were negative for a detectable concentration of methamphetamine, the fact that methamphetamine is recognized as a substance of human use and addiction and potentially can be found in a horse due to its close association with humans as an inadvertent contaminant. Additionally, no evidence was found indicating that the drug was intentionally or inadvertently administered by any of the trainers in question or their employees. Given these circumstances the Texas Racing Commission ruled that the presence of methamphetamine in the samples was sufficient cause to disqualify the horses in the races in question but that the mitigating circumstances warranted no further penalty for either the Owners or Trainers.

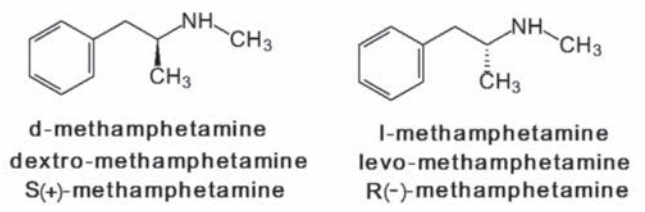

Fig. 1 Methamphetamine (N-methyl-1-phenylpropan-2-amine) exists as two mirror image enantiomers, d-methamphetamine and l-methamphetamine. d-Methamphetamine, the more pharmacologically active enantiomer, is a US DEA Schedule II controlled substance available in the US as the prescription medication Desoxyn®. l-Methamphetamine is less pharmacologically active and available in the US as a number of Over-The Counter (OTC) preparations such as Vicks Vapoinhaler® and NeilMed Sinu Inhaler®. | *Methamphetamin (N-Methyl-1-phenylpropan-2-amin) existiert als zwei spiegelbildliche Enantiomere, d-Methamphetamin und l-Methamphetamin. d-Methamphetamin, das pharmakologisch aktivere Enantiomer, ist eine kontrollierte Substanz der US-amerikanischen DEA Schedule II, die in den USA als verschreibungspflichtiges Medikament Desoxyn® erhältlich ist. l-Methamphetamin ist pharmakologisch weniger aktiv und in den USA als eine Reihe rezeptfreier Präparate (OTC) wie Vicks Vapoinhaler® und NeilMed Sinu Inhaler® erhältlich.*

These inadvertent methamphetamine transfer events are consistent with a similar sequence of events that occurred at Canterbury Park in Minnesota [3]. Two methamphetamine "positives" were reported in different horses for the same trainer, one horse in 2014 and a second in 2017. This second methamphetamine "positive" was for the pharmacologically insignificant concentration of 126 picograms/ml of blood/serum/plasma, a violation of the then-in-place Minnesota Racing Commission's "zero tolerance" policy. Other Canterbury trainers have also had horses test methamphetamine positive in 2015 and 2017 respectively, consistent with the number of US racing methamphetamine *"positives"* presented in Figure 2.

With regard to how these Canterbury Park inadvertent environmental transfer events may have occurred, one prominent regulatory veterinarian was cited in the *Lyden* Fox News report as saying that *"I think it is probably an incidental transfer from a human substance abuser likely through contact with the human hands to the horse's mucous membranes"* [3]. Consistent with this suggested mechanism of methamphetamine contamination of a racing horse, shortly after the Canterbury Park 2014 methamphetamine identification, the local Shakopee Minnesota police arrested two members of the Canterbury Park starting gate crew, both of whom were found to be in possession of methamphetamine, and the Fox 9 investigators also reported that they *"discovered at least five other horse handlers at Canterbury busted for drugs during this period"* [3]. Review of the history of methamphetamine detections in US Racing shows that while these identifications are sporadic (Figure 2), they are also ongoing [4]. This ongoing pattern of

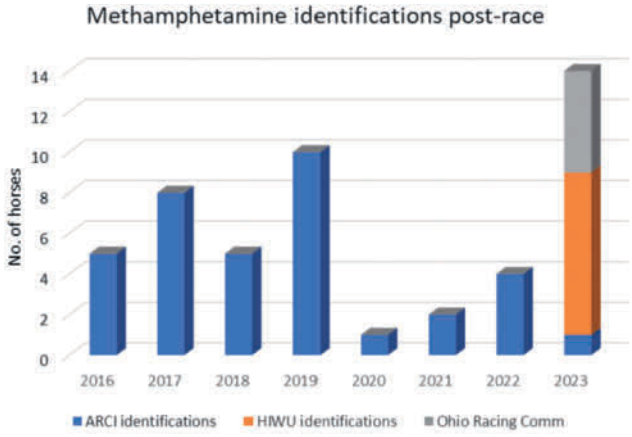

Fig. 2 Methamphetamine identifications reported in US racing, 2016 to October 2023, as per the Association of Racing Commissioners International (ARCI). Methamphetamine identifications reported since May 22nd, 2023, as per the Horse Racing Integrity and Welfare Unit (HIWU) are represented by the orange section under 2023 and detailed in Table 1. Ohio State Racing Commission identifications are identified by the gray section under 2023. | *Gemeldete Methamphetamin-Identifizierungen im US-Rennsport von 2016 bis Oktober 2023, gemäß der Association of Racing Commissioners International (ARCI). Methamphetamin-Identifizierungen, die seit dem 22. Mai 2023 von der Horse Racing Integrity and Welfare Unit (HIWU) gemeldet wurden, sind im orangefarbenen Abschnitt unter 2023 dargestellt und in Tabelle 1 aufgeführt. Identifizierungen der Ohio State Racing Commission sind im grauen Abschnitt unter 2023 gekennzeichnet.*

methamphetamine identifications is consistent with the associated horsemen being unaware of the source(s) of these identifications and therefore not being in a position to proactively prevent these identifications.

The likelihood of these methamphetamine identifications being associated with recreational use of methamphetamine by individuals working with or around these horses is supported by the number of racetrack workers identified as being linked to methamphetamine use in the Association of Racing Commissioners International (ARCI) methamphetamine records [4]. As shown in Figure 3, recording of the number of racetrack workers per year in the ARCI records with methamphetamine charges commenced in 2016 and increased in numbers to the high forties in 2019, the same year in which the number of equine methamphetamine identifications peaked prior to 2022, and after which year both the number of equine methamphetamine identifications and the number of racetrack workers with methamphetamine charges declined. These post-2019 declining numbers for equine methamphetamine identifications and racetrack workers with methamphetamine charges are presumably based on both increased industry awareness of human methamphetamine use and its potential to give rise to inadvertent transfer of trace level amounts of environmental methamphetamine to racing horses.

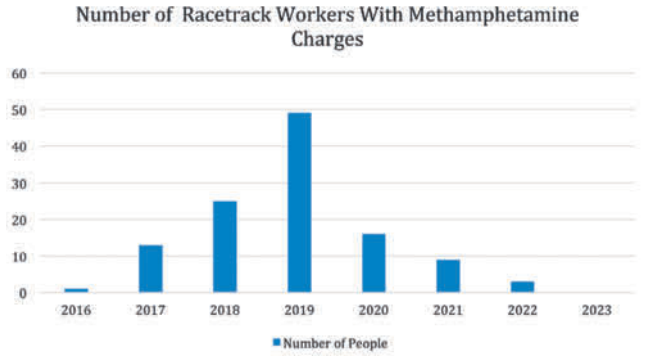

Fig. 3 Number of racetrack workers per year recorded as having methamphetamine related charges per year in Association of Racing Commissioners International (ARCI) methamphetamine records.[4] | *Anzahl der Rennstreckenarbeiter pro Jahr, bei denen in den Methamphetamin-Aufzeichnungen der Association of Racing Commissioners International (ARCI) pro Jahr Anklagen im Zusammenhang mit Methamphetamin gemeldet wurden.* [4]

Other evidence of methamphetamine being a substance of environmental concern in horse racing comes from data developed by the West Virginia Racing Commission who in or about 2017 swabbed the ship-in stalls at the Charles Town Racetrack based on concerns that the stalls might be contaminated with Naproxen and therefore causing environmental Naproxen identifications. A total of 21 ship-in stalls were swabbed yielding identifications of no fewer than 25 substances of regulatory concern, 5 being identifications of human recreational substances. Among the human recreational substances, cocaine/BenZoylEcgonine (BZE) led the list with 10 total identifications, with 1 identification of methamphetamine and 2 identifications of amphetamine, the expected human urinary metabolite of methamphetamine, as set forth in Figure 4 [5] .

Consistent with the ongoing pattern of these identifications, there has been increasing regulatory understanding of the circumstances driving these identifications and starting in about 2020 there has been an increasing tendency for regulatory authorities to identify mitigating circumstances, namely random environmental exposure, as factors in rulings on these low concentration methamphetamine identifications, and where appropriate to evaluate and treat these identifications as random and pharmacologically insignificant events occurring largely outside of the control of the horsepersons involved.

Regulation of methamphetamine under the horseracing integrity and safety authorit (HISA) and the horseracing integrity and welfare unit (HIWU)

More recently, however, since May 22nd, 2023, when medication regulation in Thoroughbred horse racing in most US states came under the control of the *Horseracing Integrity and Safety Authority* (HISA) [6] and its enforcement arm, the Horseracing Integrity and Welfare Unit (HIWU), there has been a significant increase in the frequency with which methamphetamine identifications/"positives" are being called, as set forth in Figure 2 and Tables 1 and 2. As detailed in Table 1, between May 23rd and October 7th, 2023, there have been a total of eight reported identifications of methamphetamine, starting with three identifications involving the same trainer at Prairie Meadows, Iowa. The penalties involved in these

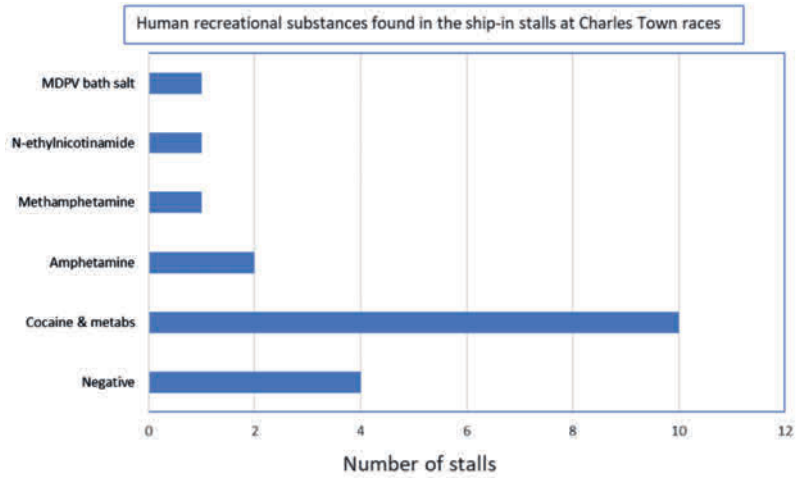

Fig. 4 Listing of the human recreational substances identified in equine ship-in stalls at the Charles Town racecourse, where 79% of the stalls were found to contain substances of regulatory interest. MDPV is 3,4-methylenedioxypyrovalerone; N-ethylnicotinamide is a metabolite of the stimulant nikethamide; cocaine & metabolites include benzoylecgonine. | *Auflistung der Substanzen für den menschlichen Freizeitgebrauch, die in Pferdeställen auf der Pferderennbahn Charles Town identifiziert wurden, wo festgestellt wurde, dass 79% der Pferdeboxen Substanzen von regulatorischem Interesse enthielten. MDPV ist 3,4-Methylendioxypyrovaleron; N-Ethylnicotinamid ist ein Metabolit des Stimulans Nikethamid; zu Kokain und seinen Metaboliten gehört Benzoylecgonin.*

Table 1 HIWU reported methamphetamine identifications in US Thoroughbred racing, May 22nd-December 15th, 2023, showing date of the race, name of the trainer, name of the horse, claimed violation, substance in question, racetrack, testing matrix, claimed concentration, and where available, resultant regulatory action and trainer response, if any. DQ = DisQualification; Meth = methamphetamine; Presence = Presence of a banned substance and/or its metabolites or markers; PS = Provisional Suspension; PS-lifted = Provisional Suspension lifted based on ADMC Program Rule submissions to FTC & case stayed pending the FTC's approval of the new Rules. | *HIWU gemeldete Methamphetamin-Identifizierungen bei Vollblutrennen in den USA, 22. Mai, 15. Dezember 2023, mit Angabe des Datums des Rennens, des Namens des Trainers, des Namens des Pferdes, des behaupteten Verstoßes, der fraglichen Substanz, der Rennstrecke, der Testmatrix und der angeblichen Konzentration und, sofern verfügbar, daraus resultierende behördliche Maßnahmen und Reaktion des Trainers, falls vorhanden. DQ = DisQualifikation; Meth = Methamphetamin; Presence = Vorhandensein einer verbotenen Substanz und/oder ihrer Metaboliten oder Marker; PS = Vorläufige Aussetzung; PS-aufgehoben = Die vorläufige Aussetzung wurde auf der Grundlage der Einreichungen der ADMC-Programmregeln bei der FTC aufgehoben und der Fall wurde bis zur Genehmigung der neuen Regeln durch die FTC ausgesetzt.*

Date	Trainer	Horse	Offense	Substance	Location	Concentration	Subsequent activity	Penalty	Trainer plea
6/19/2023	Dick Clark	Colonel Klink	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Prairie Meadows, Altoona Iowa	n/a	Raced 3 times after that (7/3, 7/9, 7/22)	Provisional suspension 7/20/23, then 18-month suspension, DQ, Fine $12,500	Admission of EAD violation and acceptance of consequences
6/19/2023	Dick Clark	My Heart's On Fire	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Prairie Meadows, Altoona Iowa	n/a	Won maiden special weight	18-month suspension, DQ, fine $12,500	Admission of EAD violation and acceptance of consequences
7/22/2023	Dick Clark	Kissed a Cadet	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Prairie Meadows, Altoona Iowa	n/a	1st maiden special weight	18-month suspension, DQ, fine $12,500	Admission of ECM violation and acceptance of consequences
7/30/2023	Hector Palma	Baladi	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Del Mar, California	n/a	Claiming	n/a	n/a
5/29/2023	John Pimental	Golovkin	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Monmouth, New Jersey	n/a	Last in claiming race, claim voided	n/a	n/a
7/7/2023	Ramon Rechy	Night Livin	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Horseshoe, Indianapolis	n/a	Won claiming race	n/a	n/a
7/20/2023	Randy Preston	Fly Home	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Belterra Park, Ohio	824 pg/ml blood d-Methamphetamine	1st maiden claiming	n/a	n/a
10/7/2023	Jimmy Corrigan	Stay Lost	Presence of a banned substance and/or its metabolites or markers	Methamphetamine	Belterra Park, Ohio	143 pg/ml plasma serum	n/a	n/a	n/a

HISA/HIWU Iowa methamphetamine identifications are also considerably more severe than those utilized prior to the new HISA/HIWU regulation, for example 18-month suspensions and a US$12,500.00 fine in each of the three Iowa identifications presented in Table 1, sharply differ from pre-HISA/HIWU regulatory approaches to trace level methamphetamine identifications.

Commercially available d- and l-methamphetamine products

Methamphetamine, Figure 1, is a member of the amphetamine group of sympathomimetic amines. Chemically, methamphetamine exists as two mirror image enantiomers, d- and l-methamphetamine [7]. d-Methamphetamine is the more pharmacologically active enantiomer, being a potent central nervous system stimulant, producing euphoria, increased energy and alertness and improved self-esteem in humans. In the US, d-methamphetamine is a DEA Schedule II stimulant under the Controlled Substances Act, with just one legal methamphetamine product, the human prescription medication Desoxyn® approved in the US for use in obesity and Attention Deficit Hyperactivity Disorder (ADHD) [8]. The l-isomer, l-methamphetamine is considered to be less pharmacologically active, acting primarily as a sympathomimetic vasoconstrictor and is available in a number of OTC nasal decongestant inhalers in the US [9]. Additionally, methamphetamine is also synthesized in clandestine laboratories and available and used worldwide as a recreational substance, including in the United States [10]. The enantiomer ratios in these clandestinely synthesized products are uncertain and depend on the starting materials and synthetic methodologies used by the clandestine laboratories in question. Synthesis from ephedrine or pseudoephedrine results in a relatively pure d-methamphetamine, whereas the alternative synthesis from phenyl-2-propanone results in a racemic mixture of d- and l-methamphetamine [11].

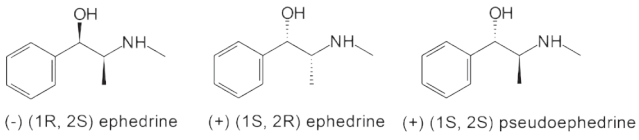

Fig. 5 Ephedrine stereoisomers that are used as methamphetamine precursors. (-)1R, 2S-ephedrine (left) is marketed as pharmaceutical grade ephedrine; (+)1S, 2R-ephedrine (middle) constitutes its mirror image as would be found in racemic ephedrine. A different ephedrine stereoisomer, (+)1S, 2S-pseudoephedrine (right), is the active component of decongestants. | *Ephedrin-Stereoisomere, die als Methamphetamin-Vorläufer verwendet werden. (-)1R,2S-Ephedrin (links) wird als Ephedrin in pharmazeutischer Qualität vermarktet; (+)1S, 2R-Ephedrin (Mitte) stellt sein Spiegelbild dar, wie es im razemischen Ephedrin zu finden wäre. Ein anderes Ephedrin-Stereoisomer, (+)1S,2S-Pseudoephedrin (rechts), ist der aktive Bestandteil von abschwellenden Mitteln.*

The pharmacological and regulatory differences between these d- and l- enantiomers of methamphetamine have been recognized in US racing where d-methamphetamine is an Association of Racing Commissioners International Drug Class 1, Penalty class A substance [12]. with the notation that "*recommended Penalty B if testing can prove the presence of only levo-methamphetamine in the sample*", reflecting the lesser pharmacological efficacy and Over The Counter availability of l-methamphetamine. However, review of the HISA banned substances list [13] shows that HISA does not specifically distinguish between d- and l-methamphetamine. Under the heading "*SUBSTANCE*" HISA lists just "*Methamphetamine*" noting that its "*ACTION*" is "*Stimulant*" and under "*COMMERCIAL/DEVELOPMENTAL NAME(S) where available*" listing "Desoxyn DEA Schedule II". The absence of l-methamphetamine and its various OTC commercial products from the HISA banned substances list is somewhat unusual.

More recently, on or about October 23rd, 2023, HIWU created a subcategory for human-abuse drugs including cocaine, methamphetamine, MDMA (3,4-methylenedioxy-methamphetamine) and THC (delta-9-tetrahydrocannabinol) [14]. Under this new rule, public disclosure of a "positive" test will not result in a suspension until a second test (if this second

Table 2 Methamphetamine identifications in Harness Racing reported by the Ohio Department of Agriculture Analytical Toxicology Laboratory during 2022–2023 showing where available the date of the race, name of the trainer, name of the horse, breed, location, lab, testing matrix, and claimed concentration. | *Vom Ohio Department of Agriculture Analytical Toxicology Laboratory im Zeitraum 2022–2023 gemeldete Methamphetamin-Identifizierungen bei Trabrennen mit Angabe des Renndatums, des Namens des Trainers, des Namens des Pferdes, der Rasse, des Standorts, das Labor, der Testmatrix und der angegebenen Konzentration (sofern verfügbar).*

Date	Trainer	Horse	Breed	Location	Lab	Matrix	Concentration
3/19/23	Brewer	Ilovemywoody	Standardbred	Miami Valley Raceway	Ohio Department of Agriculture Analytical Toxicology Laboratory	Plasma	253 pg/ml
11/26/22	Hagerman	Dashintothe-beach	Standardbred	Northfield Park	Ohio Department of Agriculture Analytical Toxicology Laboratory	Blood	130 pg/ml
	McGinnis	HP Maestro	Standardbred		Ohio Department of Agriculture Analytical Toxicology Laboratory	Blood	113 pg/ml
11/8/22	Rhoades	Sheswildnfree		Northfield Park	Ohio Department of Agriculture Analytical Toxicology Laboratory	Blood	645 pg/ml
	Sharp				Kenneth L. Maddy Analytical Chemistry Laboratory/split sample	Blood	30 pg/ml

test is requested within seven days of the original identification) confirms the presence of the detected substance. HIWU states that this grace period, usually about three weeks, will (in the opinion of HIWU) allow the trainer to investigate the source of the prohibited substance and provide an explanation to HIWU. HIWU, however, apparently will NOT assist the trainer in his or her investigations (our emphasis on NOT). In this regard we specifically note the critical role of the Ontario Racing Commission (ORC) drug testing personnel in identifying the unusual origins of the "cluster" of methamphetamine identifications described by *Brewer* et al. 2106[1], and the central role that their high sensitivity analysis of samples taken from the suspected horse trailer played in the identification of the horse trailer source of the trace level urinary methamphetamine identifications involved in this Ontario Racing Commission matter.

Clandestine (street) synthesis of methamphetamine

Clandestine laboratories synthesizing methamphetamine are reported as largely using the synthetic method of Akira Ogata, who in 1919 first synthesized methamphetamine by combining ephedrine, iodine and red phosphorus[15] .

The starting material for this methamphetamine synthesis is ephedrine, typically (-)-1R,2S-ephedrine (Fig. 5) from cold medications and by the early 1990s[16] was able to report that the "*hydroidic acid-red phosphorus*" method was the most common clandestine synthesis route to methamphetamine, used in clandestine laboratories since the early 1980s. The reaction scheme is shown in Fig. 6 as the "Red Phosphorus" method, and *Skinner*[16] reported that reduction of l-ephedrine or d-pseudoephedrine resulted in formation of d-methamphetamine.

Optimal reaction yields in established laboratory settings are as high as 92%, while clandestine synthetic yields are likely to be in the 50–75% range. Hypophosphorus acid apparently also works well in place of red phosphorus, at least in smaller scale syntheses[17] .

Regulatory responses to clandestine synthesis of methamphetamine

Responding to these clandestine synthesis of methamphetamine events, the US Congress passed the "Combat Methamphetamine Epidemic Act in 2005", wherein the most important provision involved restrictions on the availability of pseudo-

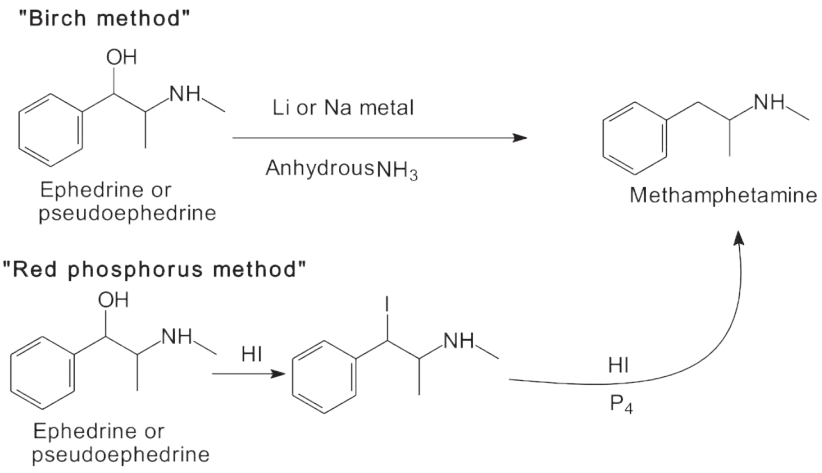

Fig. 6 Common routes to methamphetamine starting from ephedrine or pseudoephedrine. The "Birch method" is a chemical reduction method relying on reaction with ammonia in the presence of alkali metal catalysts. The "Red phosphorus method" requires hydrogen iodide and the phosphorus allotrope known as red phosphorus. The Birch method has been common throughout the American Midwest, whereas the red phosphorus method has been more frequently used in Mexican laboratories for mass production. | *Gängige Wege zu Methamphetamin ausgehend von Ephedrin oder Pseudoephedrin. Die „Birch-Methode" ist eine chemische Reduktionsmethode, die auf der Reaktion mit Ammoniak in Gegenwart von Alkalimetallkatalysatoren beruht. Die „Rote-Phosphor-Methode" erfordert Jodwasserstoff und das als roter Phosphor bekannte Phosphorallotrop. Die Birch-Methode ist im gesamten Mittleren Westen der USA verbreitet, wohingegen die Methode mit rotem Phosphor in mexikanischen Labors häufiger für die Massenproduktion eingesetzt wird.*

Table 3 Synthetic methods and their methamphetamine stereoisomer production. The first three methods have been used in clandestine laboratories, whereas the bottom two methods are considered too challenging for significant clandestine laboratory synthesis. | *Synthesemethoden und ihre Herstellung von Methamphetamin-Stereoisomeren. Die ersten drei Methoden wurden in geheimen Laboren verwendet, während die beiden unteren Methoden als zu anspruchsvoll für eine umfangreiche Synthese im geheimen Labor gelten.*

Starting compound	Available in	Reaction type	Product	Reference
1-phenyl-2-propanone	Readily synthesized from phenylacetic acid	Leuckart method or Reductive amination	Racemic methamphetamine	[36] *Kunalan* et al., 2009 [37] *Cunningham*, et al., 2010
(+)-pseudoephedrine	OTC decongestants	Birch reduction	S (+)-methamphetamine	[20] *Abbruscato* & *Trippier*, 2018
(-)-ephedrine	OTC decongestants	Birch reduction	S (+)-methamphetamine	[20] *Abbruscato* & *Trippier*, 2018
(-)-norephedrine	OTC decongestants and appetite suppressants	Hydrogenation of carbodiimide product	R (-)-methamphetamine	[38] *Hazama* et al., 2008
D-phenylalanine	Dietary supplements	LiAlH4 reduction & benzyl chloroformate reaction	S (+)-methamphetamine	[39] *Repke* et al., 1978

ephedrine and other key synthetic components [18]. The Mexican authorities followed suit, but Mexican laboratories have largely turned to alternative synthetic routes starting from phenyl-2-propanone. Figure 7 shows two routes from phenyl-2-propanone (phenylacetone) to methamphetamine by either reductive amination with methylamine or the Leuckart reaction. These latter approaches are capable of high production yields but produce racemic methamphetamine (dl) [19, 20].

These synthetic procedures and the methamphetamine enantiomer status of the synthetic product are summarized in Table 3. Simply put, the Leuckart method starting with 1-phenyl-2-propanone yields racemic methamphetamine, while the Birch reduction method starting with d-pseudoephedrine or l-ephedrine both yield l-methamphetamine.

Pharmacokinetics and pharmacodynamics of d- and l-methamphetamine

With regard to the comparative pharmacokinetics of the d- and l-forms of methamphetamine, *Mendelson* [19] studied the methamphetamine stereoisomer pharmacokinetics (PK) and found they showed similar PK parameters, and at high doses, l-methamphetamine intoxication is similar to that of d-methamphetamine, but the psychodynamic effects of l-methamphetamine were shorter-lived and less desired by recreational users. The authors concluded that racemic and d-methamphetamine have similar effects and would be expected to have comparable abuse liabilities. More recently [21] reviewed methamphetamine stereoisomeric effects focusing on l-methamphetamine and confirmed that cardiovascular and subjective effects from d-methamphetamine (0.5 mg/kg) were much longer-lasting than those from l-methamphetamine (0.5 mg/kg).

The National Institute of Drug Abuse (NIDA) [18] in 2019 claimed significant decreases of up to 80% of lab incidents owing to successful reduction in the availability of methamphetamine precursors, a claim supported prospectively in the earlier review by *McKetin* et al. [22]. Given that illicit methamphetamine synthesis involves many hazards beyond physiological addiction, with hazards including explosive chemicals such as anhydrous ammonia, drain cleaners, paint thinner, metallic lithium, hydrochloric or sulfuric acids, starter fluid, camping fuel, and others that can damage the respiratory tract, mucous membranes, eyes, and skin [23], legal restrictions designed to reduce the ability to synthesize methamphetamine continue. One approach involves development of new pseudoephedrine compositions that make extraction of the active component difficult [24]. However, *Presley* et al. [25] raise doubts about the efficacy of such formulations. Meanwhile, illicit labs have developed masking agents to make detection of precursors and products more difficult for analytical labs; five commonly employed protecting groups – acetyl, p-tosyl, methoxycarbonyl, Fmoc, and t-Boc – were recently studied by *Mayer* et al. [26] in efforts to assist labs in the recognition of masked compounds.

Regulatory significance of the d- and l-isomers of methamphetamine

The regulatory distinction between d-methamphetamine and l-methamphetamine raises an interesting regulatory/forensic point, namely that identifying only the l-enantiomer is consistent with exposure of the horse to the less active l-enantiomer isomer, as has happened in Kentucky [27]. On the other hand, identification of predominantly d-methamphetamine may be evidence of exposure to either commercially approved synthesized, purified and marketed d-methamphetamine product, or illegal synthesis from ephedrine or pseudoephedrine. Identification of a mixture of approximately equal concentrations of the d- and l-methamphetamine enantiomers may suggest exposure to an illicitly synthesized and not enantiomerically purified mixture of d- and l-methamphetamines, i.e., racemic methamphetamine.

The pharmacokinetics and pharmacodynamics of methamphetamine in horses

To our knowledge there are only two published studies addressing the pharmacokinetics and pharmacodynamics of methamphetamine in horses. In the early seventies, *Ray* and colleagues [28] administered 150 mg of Desoxyn®, namely d-methamphetamine to six horses, one of which was a Thoroughbred. As shown in Figure 8 replotted from *Ray* et al. 1972 [28], plasma concentrations of d-methamphetamine in this Thoroughbred horse peaked rapidly at 1 hour post-administration and then declined to be present at less than

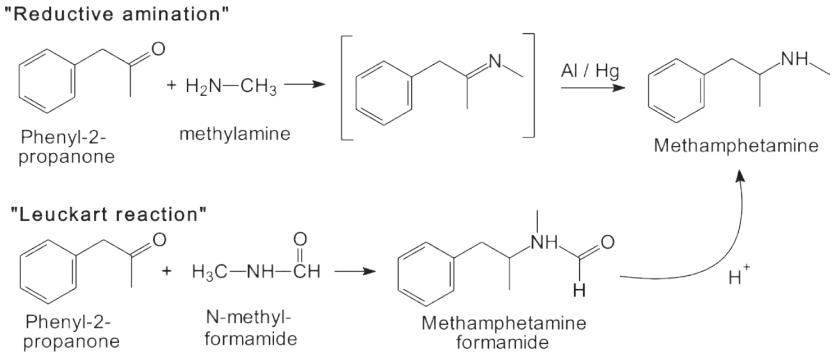

Fig. 7 Synthetic routes to methamphetamine from phenyl-2-propanone, a.k.a. phenylacetone. The "Reductive amination" route combines phenyl-2-propanone and methylamine to create an N-methylimine that undergoes reduction catalyzed by aluminum amalgam. The "Leuckart reaction" relies on nucleophilic attack of the phenyl-2-propanone carbonyl carbon by N-methylformamide to produce a methamphetamine formamide product that is converted by treatment with acid to methamphetamin. | *Synthesewege zu Methamphetamin aus Phenyl-2-propanon, auch als Phenylaceton bekannt. Der Weg der „reduktiven Aminierung" kombiniert Phenyl-2-propanon und Methylamin, um ein N-Methylimin zu erzeugen, das einer durch Aluminiumamalgam katalysierten Reduktion unterliegt. Die „Leuckart-Reaktion" beruht auf einem nukleophilen Angriff des Phenyl-2-propanon-Carbonylkohlenstoffs durch N-Methylformamid, um ein Methamphetamin-Formamid-Produkt zu erzeugen, das durch Behandlung mit Säure in Methamphetamin umgewandelt wird.*

5.7 ng/ml at 8 hours post-administration. We specifically note that this 150 mg/horse d-methamphetamine dose used by *Ray* et al. is an approximately six-fold greater dose than the suggested human daily dose of Desoxyn® and *Ray* et al. [28] did not report any behavioral changes in any of their six horses administered this IM dose of d-methamphetamine.

Clandestinely synthesized methamphetamine and trace level identifications in horses

Given its relative ease of synthesis and worldwide use as a recreational substance, methamphetamine is a widely illicitly synthesized and marketed substance, as exemplified by the Canadian horse trailer methamphetamine events [1]. In the United States during 2015–2018 an estimated 1.6 million US adults aged 19 and over reported past year methamphetamine use. Of these, 52.9 % had a methamphetamine misuse disorder, i.e., US individuals misusing methamphetamine, essentially all of which was the product of illicit synthesis, hereinafter "street" methamphetamine.

This pattern of illicit synthesis and presumably variable chemical presentations and packaging of street methamphetamine adds to the variables influencing the likelihood of inadvertent transfer of trace amounts to horses. In the first place, street methamphetamine is unlikely to be presented to street users in a chemically and mechanically stable pill format. A further consideration is that as an abused substance methamphetamine is likely to be used recreationally by individuals at far higher doses than medically approved doses. While the medically approved human dose of Desoxyn® is 2.5–10 mg daily and not to exceed 60 mg/day, common recreationally abused doses are 100–1,000 mg/day and up to 5,000 mg/day in chronic binge use. These product format and use variables that apply principally to street methamphetamine greatly increase the variability in the amounts of a recreational substance such as methamphetamine that a horse is likely to be inadvertently exposed to, as compared to exposure to amounts of prescribed or over the counter human medications.

High jugular blood concentrations following mucous membrane exposure of horses to methamphetamine

The second and most recent study of the pharmacokinetics and pharmacodynamics of methamphetamine is that of *Knych* et al. 2019 [29]. In this study *Knych* et al. administered d-methamphetamine from Sigma-Aldrich to six exercised Thoroughbred horses. Intravenous administration of 10 mg of methamphetamine produced mean peak post-injection plasma concentrations of 9.90 ng/ml, which plasma concentrations declined following a two-compartment model, rapidly at first and then more slowly to fall below the Limit of Detection (LOD) of 5 picograms/ml between 12- and 18-hours post-administration. This relatively small equine dose of methamphetamine was deliberately selected for this study based on the *"high likelihood that inadvertent exposure (to methamphetamine) would be to lower amounts of the drug"*, in other words an important goal of this *Knych* study was to address the matter of random oral exposure of racing horses to relatively small amounts of methamphetamine.

Addressing this random mucous membrane exposure matter *Knych* et al. [29] administered this same 10 mg dose of methamphetamine *"transmucosally"* meaning that the *"Methamphetamine powder was applied directly to/rubbed onto the oral mucosa by an individual wearing a glove"*. As set forth in Figure 9, peak jugular blood plasma/serum concentrations following transmucosal administration occurred rapidly, between zero to 15 or 30 minutes post-administration and were widely variable, ranging from about 4 ng/ml to an unexpected 88.4 ng/ml, presumably reflecting both the skill of the individual performing the "rubbing" and the cooperativeness of the equine involved. By far the most important take home message from these data is that mucous membrane application of a 10 mg dose of methamphetamine produced jugular vein blood concentrations on average four-fold greater than the peak plasma concentration following intravenous administration and in one horse at least as high as 88,400 picograms/ml, dashed line in figure 9. The words "at least as high" allude to the fact that the 88,400 picograms/ml plasma concentration in Figure 9 replotted from *Knych* et al. [29] presents as an apparently declining plasma concentration of methamphetamine, with the true peak plasma concentration of methamphetamine in this horse likely being higher than the presented 15-minute time point, with the actual peak jugular blood/plasma/serum concentration occurring at some time between 0 and 15 minutes following the oral transmucosal administration procedure.

The reason for these fourfold and higher jugular vein blood concentrations observed after transmucosal oral administration of methamphetamine is that the jugular vein drains the oral cavity and as such is actually delivering the high local

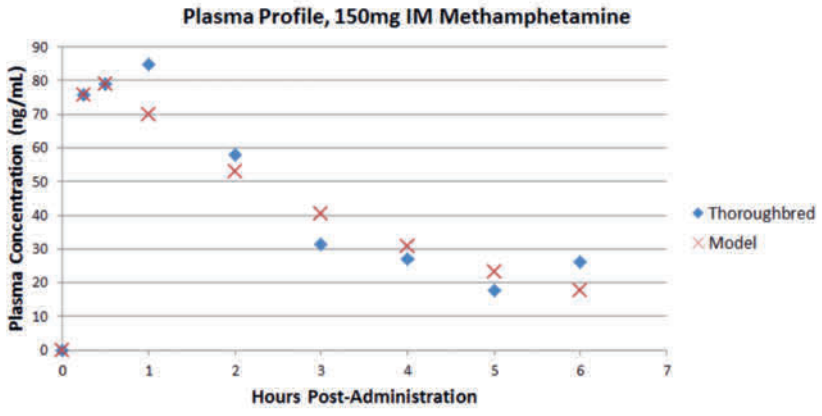

Fig. 8 The blue diamonds show the plasma concentrations of methamphetamine in a Thoroughbred horse administered 150 mg of methamphetamine IM replotted from Ray et al. [28]. The crosses show a first pass best fit kinetic model of these data obtained by back stripping. | *Die blauen Rauten zeigen die Plasmakonzentrationen von Methamphetamin bei einem Vollblutpferd, dem 150 mg Methamphetamin IM verabreicht wurden, neu aufgetragen von Ray et al. [28]. Die Kreuze zeigen ein kinetisches First-Pass-Best-Fit-Modell dieser Daten, das durch Back-Stripping erhalten wurde.*

oral tissue concentration of methamphetamine to the systemic circulation of the horse. This is a factor that must be kept in mind when evaluating the pharmacological or regulatory significance of jugular blood concentrations of a substance that may have entered the horse by oral transmucosal absorption, such as in this case methamphetamine. Review of the *Knych* data [29] from horse #8 shows a declining plasma concentration of 88.4 nanograms/ml at 15 minutes post-oral 10 mg transmucosal administration, suggesting that a 100 microgram oral transcutaneous exposure to methamphetamine could be expected to give rise to a 884 picogram/ml jugular blood plasma identification of methamphetamine, a dose 1,500-fold less than the dose administered by *Ray* and his colleagues and well below any dose expected to produce a pharmacological response in the horse in question and above the range of all of the more recent serum/plasma methamphetamine concentrations as presented in Tables 1 and 2 .

Previously in place or proposed screening limits for methamphetamine

Reviewing the urinary methamphetamine identifications reported in Canadian racing in 2016, *Brewer* et al. [1] proposed an interim 15 nanogram/ml Screening Limit in urine based on the concentrations reported in these Canadian urinary identifications. At about the same time the Oklahoma Horse Racing Commission (OHRC) published a urinary Screening Limit of 100 ng/ml, based on their regulatory experience in Oklahoma [30]. This higher Screening Limit presented by the OHRC is consistent with the fact that methamphetamine has a pKa of 9.8, meaning that it will carry a positive charge and may be expected to trap at high concentrations in acidic pH urines. These chemical characteristics mean that post-administration urinary concentrations of methamphetamine are highly variable as shown by *Ray* et al. [28] where the peak urinary concentrations of methamphetamine ranged from 1,145 ng/ml in one horse to 17,930 in another, approaching a 16-fold range in peak urinary concentrations following administration of the same dose of methamphetamine to non-exercised horses. Even more compelling is the highly variable relationship between the peak plasma and peak urinary concentrations, the urinary concentrations of methamphetamine in one horse being, at 17,930 ng/ml, a 996-fold greater concentration amount than the 18 ng/ml peak plasma concentration observed in that particular horse. Simply put, urinary concentrations of methamphetamine are highly variable, presumably largely driven by the ability of methamphetamine, as a basic medication, to concentrate in acidic urine [31], similar to the 1,000-fold concentrating effect of acidic post-exercise urinary pH on urinary lidocaine concentrations [32] and also consistent with the well-recognized inherent variability of post-race urinary pH values and resultant equine urinary drug concentrations [33,24]. In short, regulatory thresholds and regulatory evaluations involving methamphetamine are best based on plasma data, given the extreme variability in urinary methamphetamine concentrations as presented in the paper of *Ray* et al. [28].

Suggested evaluation process for an equine methamphetamine identification

To correctly evaluate the pharmacological and regulatory significance of a claimed methamphetamine identification in a jugular blood sample from a racing horse, we suggest the following approaches. First, given that the currently in place HISA/HIWU penalties for a trace level methamphetamine identification can be career terminating for a horseperson, it is incumbent on the parties involved to rigorously evaluate all available chemical and other evidence. The evidence evaluated should therefore include quantitative blood and urinary analysis for both methamphetamine isomers. Quantitative analysis of a suitably timed post-event hair sample from the

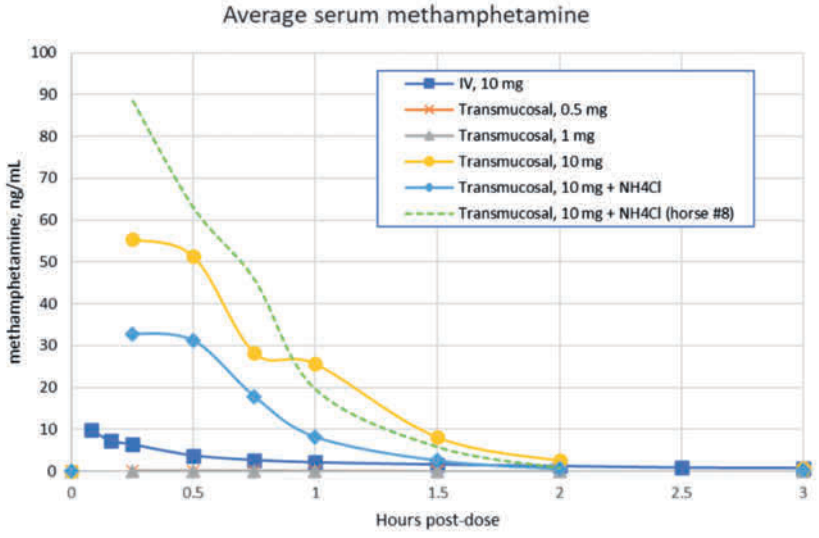

Fig. 9 Comparison of IV and transmucosal administrations of 10 mg doses of d-methamphetamine to six thoroughbreds. The blue squares (■) starting at 0.08-hr present mean serum concentrations of methamphetamine following IV administration (10 mg/horse to six horses). Traces for the remaining symbols (×,Δ,●,♦) present mean serum concentrations following oral transmucosal administration of 0.5, 1, 10 and 10 (NH_4Cl) mg/horse, respectively. The last of these included 165 g ammonium chloride administered via nasogastric tube 10 hr prior to methamphetamine administration. Transmucosal administration results represent the average of two horses, except for those given NH_4Cl, three horses. The one horse in this six-horse experiment with the highest serum methamphetamine values following oral transmucosal administration is shown with the dashed line. Data replotted *from Table 2 of Knych et al. 2019.* [30] | *Vergleich der intravenösen und transmukosalen Verabreichung von 10-mg-Dosen d-Methamphetamin an sechs Vollblüter. Die blauen Quadrate (■), beginnend bei 0,08 Stunden, zeigen die mittleren Serumkonzentrationen von Methamphetamin nach intravenöser Verabreichung (10 mg/Pferd bis sechs Pferde). Spuren für die übrigen Symbole (×,Δ,●,♦) zeigen mittlere Serumkonzentrationen nach oraler transmukosaler Verabreichung von 0,5, 1, 10 bzw. 10 (NH_4Cl) mg/Pferd. Die letzte davon umfasste 165 g Ammoniumchlorid, die 10 Stunden vor der Methamphetaminverabreichung über eine Magensonde verabreicht wurden. Die Ergebnisse der transmukosalen Verabreichung stellen den Durchschnitt von zwei Pferden dar, mit Ausnahme von drei Pferden, denen NH_4Cl verabreicht wurde. Das eine Pferd in diesem Sechs-Pferde-Experiment mit den höchsten Methamphetamin-Serumwerten nach oraler transmukosaler Verabreichung ist mit der gestrichelten Linie dargestellt. Daten aus Tabelle 2 von Knych et al. 2019.*

horse in question should be included in a full investigation of any methamphetamine positive to distinguish between incidental environmental exposure and intentional administration. [35]

Review of the *Knych* et al. data [29] presented in Figure #9 shows that oral transmucosal exposures to 10 mg of methamphetamine gave rise to a jugular vein blood/plasma/serum methamphetamine reading of 88,400 picograms/ml in one of the six horses used in these experiments. On this basis, exposure to 0.1 mg of methamphetamine may reasonably be expected to give rise to jugular vein methamphetamine identifications of 884 picograms/ml or thereabouts. Given that 0.1 mg of methamphetamine is in the order of 1,500-times less than the 150 mg IM dose used by *Ray* and his colleagues [28] and which dose produced no reported behavioral effects, it is reasonable to assume that transmucosal exposure to sub-milligram amounts of methamphetamine can give rise to readily detectable picogram/ml jugular blood/plasma/serum concentrations of methamphetamine. Based on these data, a simple low nanogram/ml or less identification of methamphetamine in a jugular blood/plasma/serum sample is most likely evidence of nothing more than inadvertent environmental exposure of the horse to a pharmacologically insignificant amount of environmental methamphetamine.

Absence of, or a very low concentration of, methamphetamine in the corresponding urine sample would be evidence that the exposure resulting in the jugular blood sample identification was of relatively recent occurrence, namely within 60 minutes or so of the urine sample collection time, which time frame may be of assistance in identifying the circumstances under which the exposure event occurred. Finally, absence of a detectable concentration of the correct enantiometic forms of methamphetamine in an appropriately timed hair sample from the horse would be evidence that the jugular blood/plasma/serum identification was a transient trace level detection associated with environmental exposure of the horse to methamphetamine and not in any way associated with a deliberate horseperson-related administration to the horse of a pharmacologically significant amount of methamphetamine.

In closing, given the clandestine synthesis and widespread street availability and use of methamphetamine including recreational use by racetrack personnel and its detection in ship-in stalls, simple identification of a jugular blood/plasma/serum sub-nanogram amount of methamphetamine is most likely evidence of innocent and inadvertent exposure of the horse to environmental methamphetamine. If the horse person is at risk of significant penalty for such an unpredictable occurrence, the horseperson should be allowed to pursue all of the above presented scientific approaches to establish that a simple trace level detection in jugular blood/plasma/serum is not *per se* evidence of a knowing and deliberate administration of a pharmacologically significant amount of methamphetamine to the horse or horses in question. Based on the data available to date, identification of less than 1 nanogram/ml in jugular vein plasma serum can be associated with oral exposure of the horse to amounts of methamphetamine in the order of 1,500-fold less than a pharmacologically effective dose. A jugular blood plasma/serum concentration of 1 nanogram/ml of methamphetamine is thus a highly conservative regulatory "cut-off" or Screening Limit of Detection" concentration and, based on the data presented in Figure 9, a jugular blood plasma serum concentration of up to 3 nanograms/ml would not be inconsistent with "*incidental transfer from a human substance abuser or a similar inadvertent environmental source.*"

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ARCI	Association of Racing Commissioners International
DEA	Drug Enforcement Administration
DQ	DisQualification.
FEI	Federation Equestre Internationale
HISA	Horseracing Integrity and Safety Authority.
HIWU	Horseracing Integrity and Welfare Unit.
MDMA	3,4-MethyleneDioxyMethAmphetamine
NIDA	National Institute on Drug Abuse
OHRC	Oklahoma Horse Racing Commission
ORC	Ontario Racing Commission
OTC	Over-The-Counter
PK	PharmacoKinetics
TRC	Texas Racing Commission
US	United States

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Author's contributions

TT conceived and directed the project and TT, CKF of the North American Association of Racetrack Veterinarians (NAARV), GAM, Director of the New York Drug Testing and Research Program, RLH of Holland Management Inc., and AMB of Caracas, Venezuela and Dubai, United Arab Emirates reviewed the data interpretation and analysis and approved the proposed regulatory guidelines from an equine practitioner, researcher, and regulatory scientist's perspective.

KB and AFL performed the data searching, chemical structure evaluations and statistical analyses and TT coordinated and edited all drafts of this manuscript with ongoing contributions from all authors and all authors reviewed approved the final manuscript submitted for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available in the public domain as referenced in the manuscript or from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate are not applicable: As a review of the relevant scientific and regulatory literature, no ethics approval or consent to participate was necessary or required and all the authors have consented to publication of this case report and analysis.

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