CLENBUTEROL

Blood and urine clearance as a function of dose and time and its relevance to the RMTC recommended threshold

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Warning

The information on the Racing Medication and Testing Consortium Therapeutic Medications List does not constitute and is not a guarantee, warranty or assurance that the use of any of the therapeutic medications at the dosage and withdrawal time listed will not result in a positive post-race test. The Racing Medication and Testing Consortium is not responsible for results differing in any way from those herein.

Use of this document and its information does not lessen or relieve any trainer's responsibility for affirming that, during a horse race, a horse is free of any therapeutic medication listed in his or her state's racing commission rulebook, and for complying with provisions of the state racing commission's regulations.

Owners, trainers or any other persons responsible for the care of a racehorse are strongly advised to consult a veterinarian and the state racing commission regulatory veterinarian for guidance and advice on the use and withdrawal times of all therapeutic medications, as testing methodologies may change with little or no notice.

The guidelines provided in this document are not consistent with foreign regulations or laboratory methods.

RMTC
Racing Medication & Testing Consortium

Substance	**Clenbuterol**
Restricted Administration Time	**14 days**
Threshold Route of Administration Experimental Administration	**140 pg/mL of urine or LOD in plasma**
Dosage	**Oral 0.8 mcg/kg**

Immunopharmacology and Immunotoxicology, 2010; 32(1): 171–176

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healthcare

RESEARCH ARTICLE

Detection of urine and blood clenbuterol following short-term oral administration in the horse

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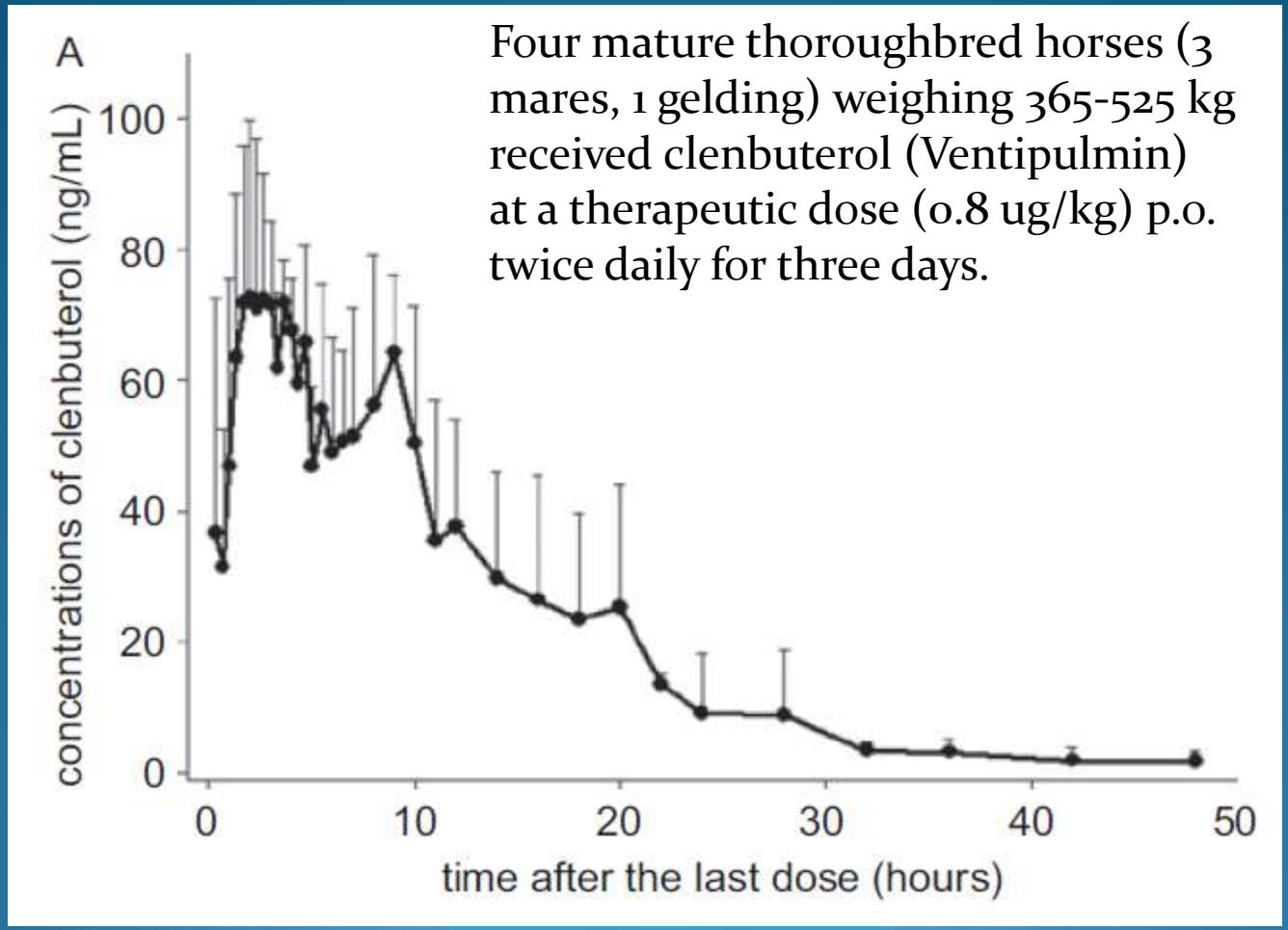
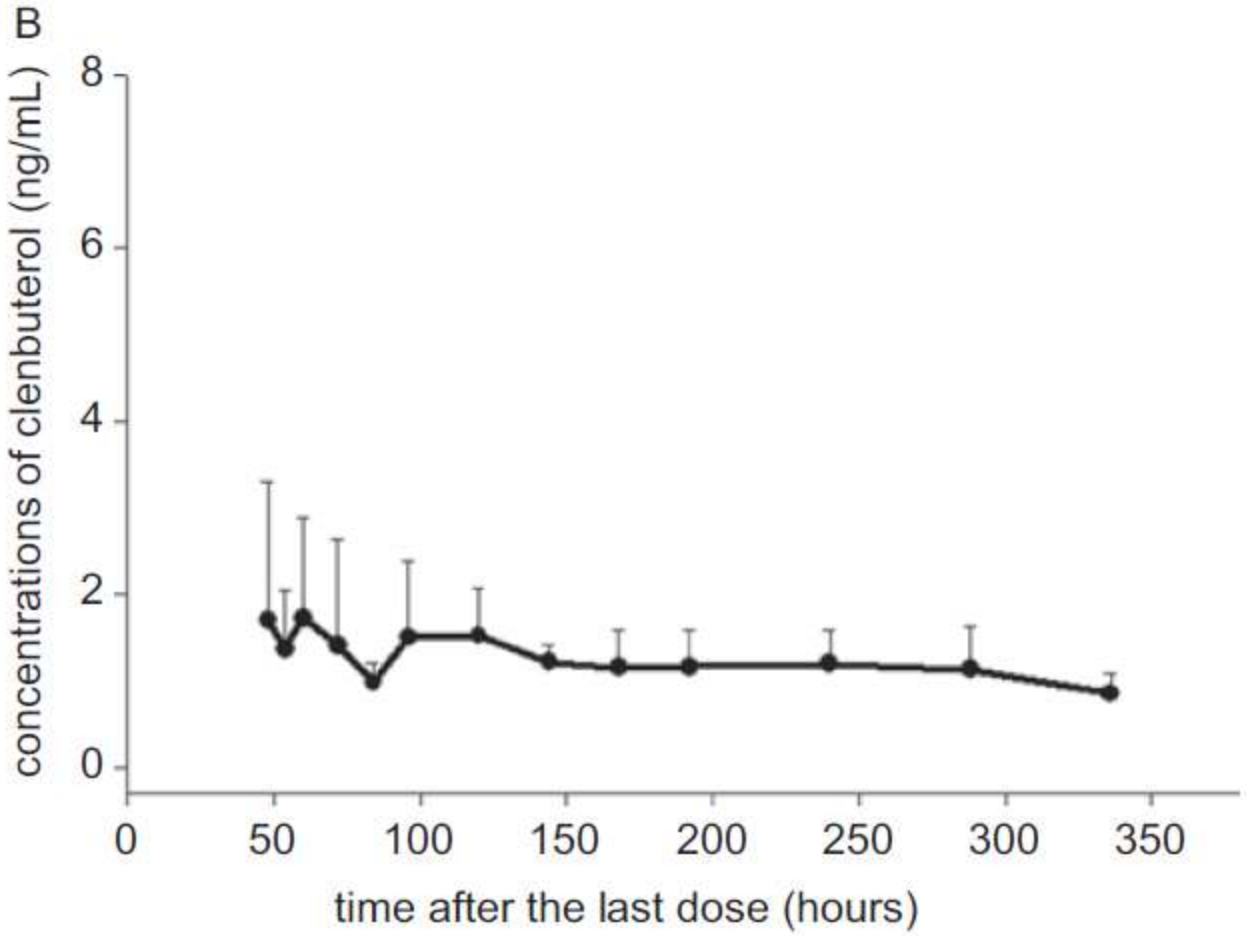
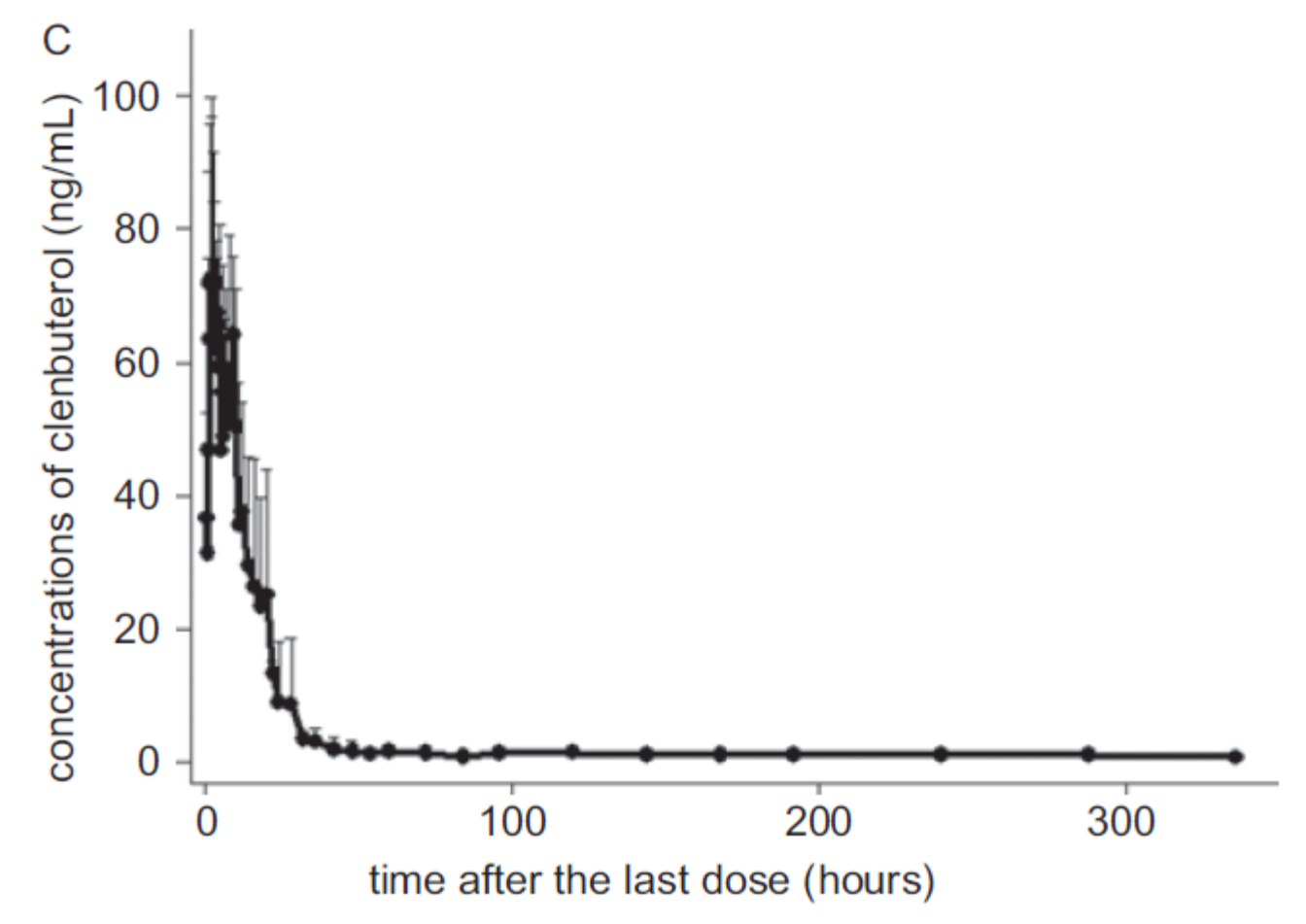


Four mature thoroughbred horses (3 mares, 1 gelding) weighing 365-525 kg received clenbuterol (Ventipulmin) at a therapeutic dose (0.8 ug/kg) p.o. twice daily for three days.

Figure 2. (A) The average concentrations of urinary clenbuterol in the first 48 hours,



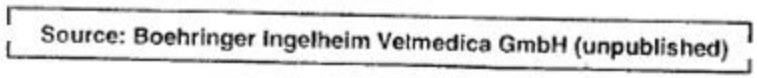
(B) from day 2 to day 14 (336 hours)



and (C) in totally 14 days after the last dose.

Elimination Kinetics of Clenbuterol in Horses in Training

Following treatment with Ventipulmin®



Kleemann et al., 1999

Product: Ventipulmin® oral syrup

Horses:	Number:	14
	Breed:	German Warmblood
	Age:	2-18 years (mean: 7.4)
	Sex:	6 male and 8 female
	Training:	Daily, adapted to age, individual competition level, and physical condition

Drug Treatment:	**0.8 µg/kg b.w. clenbuterol morning and evening for 10 days**
Blood Sampling:	**Pre-dosing on Day 1 and daily immediately after training for 5 days following the final dose**
Urine Sampling:	**Pre-dosing on Day -1 and daily for 15 days following the final dose (spontaneously voided within 1 hour after training)**
Analysis for *clenbuterol*:	**Method: GC-MS Limit of Quantification 0,05 ng/ml Limit of Detection 0,025 ng/ml**

Depletion of Clenbuterol in Equine Urine

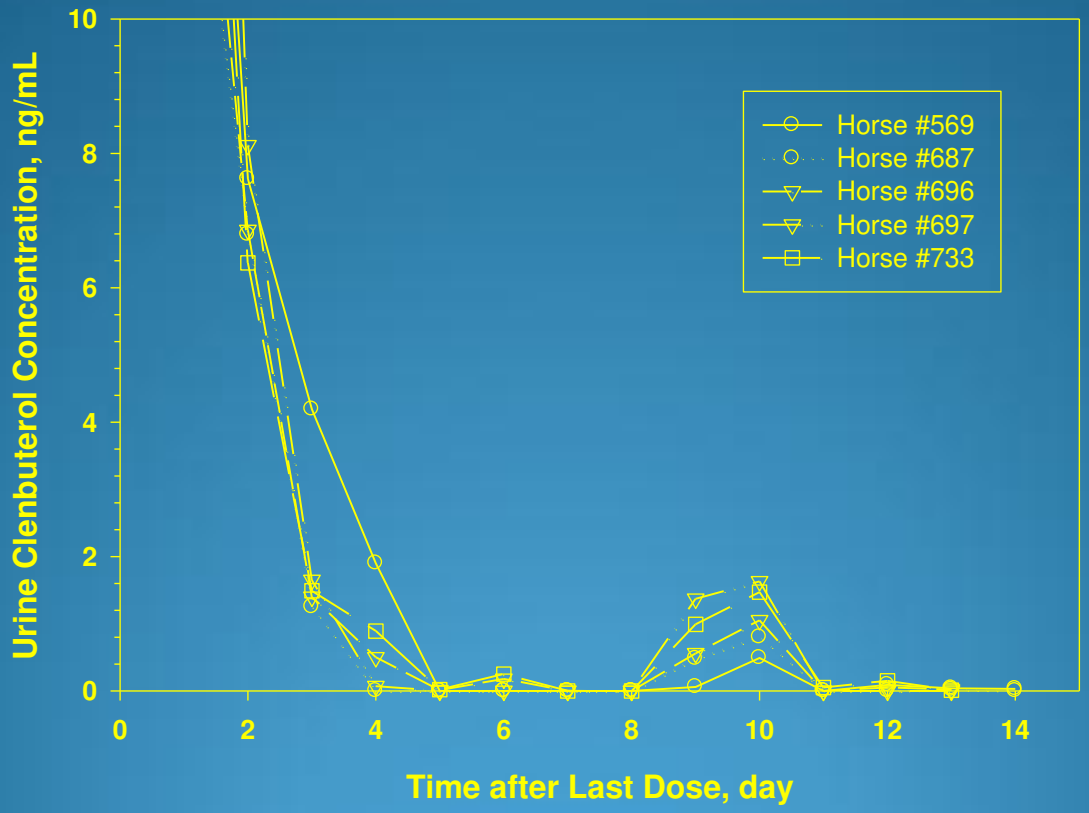
Days Post Final Dose	Number of Horses	Number which were		Clenbuterol (ng/ml) in Positives	
		Negative*	Positive	Range	Mean ± SD
1	11	0	11	6.1 - 22.2	10.50 ± 5.27
2	14	0	14	1.1 - 7.1	2.60 ± 2.56
3	12	1	11	0.1 - 1.9	0.98 ± 0.55
4	14	3	11	0.05 - 1.1	0.45 ± 0.33
5	11	3	8	0.07 - 0.85	0.41 ± 0.26
6	12	6	6	0.14 - 0.58	0.31 ± 0.18
7	14	9	5	0.08 - 0.44	0.20 ± 0.16

* Below the limit of quantitation

Days Post Final Dose	Number of Horses	Number which were		Clenbuterol (ng/ml) in Positives	
		Negative*	Positive	Range	Mean ± SD
8	14	11	3	0.15 - 0.22	0.18 ± 0.04
9	14	12	2	0.13 - 0.30	0.21 ± 0.12
10	14	13	2	0.05 - 0.29	0.17 ± 0.17
11	14	13	1	— 0.32	
12	14	13	1	— 0.06	
13	14	13	1	— 0.13	
14	14	14	0	—	

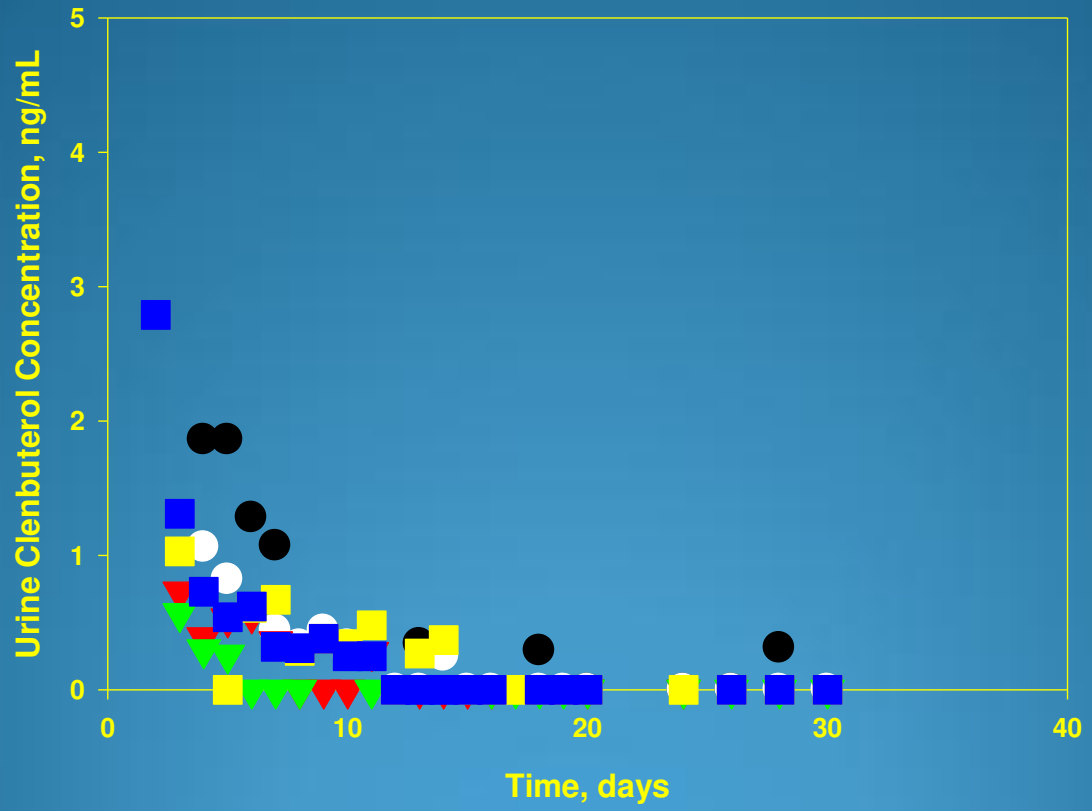
* Below the limit of quantitation

Oral Clenbuterol, 400 μg Twice Daily



Source: Tobin *et al.*

- Richard Sams, PhD
  - Analytical Toxicology Laboratory
- OSU College of Veterinary Medicine



Conclusions

- Clenbuterol detected and identified after repeated oral administration
  - low dose: 28 days > 0.25 ng/mL
  - high dose: 28 days > 0.25 ng/mL

- Richard Sams, PhD
- Analytical Toxicology Laboratory
- OSU College of Veterinary Medicine

J. vet. Pharmacol. Therap. 27, 71–77, 2004. DRUG METABOLISM, PHARMACOKINETICS AND TOXICOLOGY

Pharmacokinetics and disposition of clenbuterol in the horse

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Soma, L. R., Uboh, C. E., Guan, F., Moate, P., Luo, Y., Teleis, D., Li, R., Birks, E. K., Rudy, J. A., Tsang, D. S. Pharmacokinetics and disposition of clenbuterol in the horse. *J. vet. Pharmacol. Therap.* **27**, 71–77.

The pharmacokinetics of clenbuterol (CLB) following a single intravenous (i.v.) and oral (p.o.) administration twice daily for 7 days were investigated in thoroughbred horses. The plasma concentrations of CLB following i.v. administration declined mono-exponentially with a median elimination half-life ($t_{1/2k}$) of 9.2 h, area under the time–concentration curve (*AUC*) of 12.4 ng·h/mL, and a zero-time concentration of 1.04 ng/mL. Volume of distribution (V_d) was 1616.0 mL/kg and plasma clearance (*Cl*) was 120.0 mL/h/kg. The terminal portion of the plasma curve following multiple p.o. administrations also declined mono-exponentially with a median elimination half-life ($t_{1/2k}$) of 12.9 h, a *Cl* of 94.0 mL/h/kg and V_d of 1574.7 mL/kg. Following the last p.o. administration the baseline plasma concentration was 537.5 ± 268.4 and increased to 1302.6 ± 925.0 pg/mL at 0.25 h, and declined to 18.9 ± 7.4 pg/mL at 96 h. CLB was still quantifiable in urine at 288 h following the last administration (210.0 ± 110 pg/mL). The difference between plasma and urinary concentrations of CLB was 100-fold irrespective of the route of administration. This 100-fold urine/plasma difference should be considered when the presence of CLB in urine is reported by equine forensic laboratories.

At 72–96 h the concentration of CLB in plasma had declined to ~35 and ~20 pg/mL, respectively which is a reduction of approximately 96–97%. Thus, these low concentrations of CLB at 72–96 h postadministration should be considered a reasonable withdrawal time. The result of this study also suggested that the plasma rather than urine CLB concentrations should be used for forensic purposes.

QUESTIONS

1. What data were used to establish a 14 day withdrawal and a 140 pg/ml threshold in urine for clenbuterol?
2. If the threshold is based on a dose of 0.8 ug/ml, what frequency of administration is permitted? Once, twice a day? For how many days?
3. Was a “safety factor” included in the deliberations?
4. Why was blood not chosen as the regulatory sample?
5. Is this a de facto ban on the use of clenbuterol?
6. Is the threshold based on science or technology?
7. Does the fact that a LOD in plasma is established open trainers to being called positive as new technology is developed?

The ARCI/RMTC must produce the documents, discussions and final basis for the decisions made in order for racing jurisdictions to defend against arguments that these thresholds are arbitrary and capricious, as well as other cogent arguments.

The ARCI/RMTC must produce the scientific basis for these thresholds (pharmacology, pharmacodynamics) and explain how these decisions meet the standard mandated by the various States of protecting the horses, race participants and the betting public.

Illegal clenbuterol was being sold by compounding pharmacies and being distributed by veterinarians, all in the name of profits. Some preparations were 10- 70 times the Ventipulmin concentration (72.5 ug/ml) and were responsible for several deaths. Most was mixed to be 100 ug/ml, allowing administration of smaller doses and a greatly reduced cost. This no doubt was also used to try to accomplish an anabolic effect by some trainers/veterinarians. However, how much of what was being observed was due, not to clenbuterol, but ractopamine, zilpaterol and/or dermorphin (frog juice)?

The industry should demand action by State and Federal agencies to end drug manufacturing practices by compounding pharmacies and the direct sale of drugs for use in racehorses with the expressed intent of effecting performance.

Banning or making the use of drugs specifically approved by the FDA for use in horses illegal or impossible to use therapeutically only serves to force the use of other substances not approved for use or even tested for safety.

Medication regulations should be based on the science of pharmacology, not hysteria, political agendas, financial considerations or technology. The RMTC has failed to follow its own charter of providing the industry with scientifically based thresholds.