

## Examining the Plausibility of Drug Positives

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From LAHBPA

*LEVAMISOLE ALERT: Jan. 20, 2013*

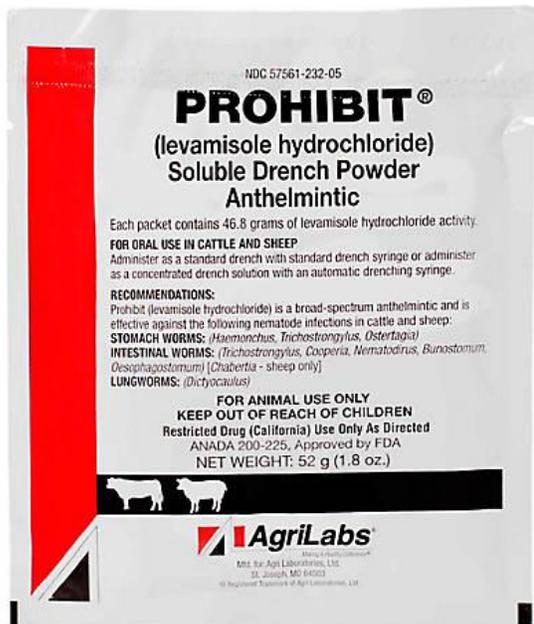
*A Levamisole positive has just been called in Kentucky. Levamisole is classified by the ARCI as a Class 2 Penalty Class B substance. A Levamisole-caused positive recently turned up in NY (Tioga Downs) in spite of, reportedly, being administered more than 100 hours before the race. There have also reportedly been some Pemoline positives in England following Levamisole administration.*

*Levamisole has long been used in veterinary medicine as an anthelmintic (wormer) and immune stimulant. In a horse, Levamisole metabolizes to Aminorex and Pemoline both banned ARCI Class 1 STIMULANT drugs.... **ADVISE YOUR HORSEMEN AND VETS TO AVOID LEVAMISOLE/ TETRAMISOLE IN HORSES.***

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Above is the levamisole alert sent out to Louisiana horsemen and veterinarians in early 2013. There are alerts currently on the ARCI and THA websites. There are numerous articles written about horses identified as having levamisole in their systems in both the States and overseas. In multiple sources including veterinary literature and product labeling, the use of levamisole as a dewormer is not recommended for use in horses due to its narrow margin of safety. The only exception seems to be the extra-label use of levamisole as an adjunct therapy in combination with decoquinatate for the treatment of Equine Protozoal Myeloencephalitis (EPM). This is why it was surprising when eight of trainer Joe Sharp's horses tested positive for levamisole recently in Louisiana.

Sharp explained to the Paulick Report that the positives were the result of his use of a dewormer he had purchased at Tractor Supply. Identified in the racing commission rulings as Prohibit, a cattle and sheep drench dewormer, Sharp stated that he had "talked to one of my vets about it and they didn't alert us to any concern," before proceeding to treat his horses with Prohibit.



## PROHIBIT® Soluble Drench Powder

### Levamisole Hydrochloride

#### Anthelmintic

Each 52 g pouch contains 46.8 g of levamisole hydrochloride activity.  
ANADA 200-286, Approved by FDA.  
Each 605 g bottle contains 545.5 g of levamisole hydrochloride activity.  
ANADA 200-225, Approved by FDA.

Cattle and Sheep Dewormer: For Oral Use.  
Administer as a standard drench with standard drench syringe or administer as a concentrated drench solution with an automatic drenching syringe.  
Mixes as a clear solution.

#### INDICATIONS:

Prohibit® (Levamisole Hydrochloride) is a broad-spectrum anthelmintic and is effective against the following nematode infections in cattle and sheep:

**SHEEP: STOMACH WORMS:** (*Haemonchus contortus*, *Trichostrongylus axei*, *Ostertagia circumcincta*), **INTESTINAL WORMS:** (*Trichostrongylus colubriformis*, *Cooperia curticei*, *Nematodirus spathiger*, *Bunostomum phlebotomum*, *Desmophagostomum columbianum*, *Chabertia ovina*), **LUNGWORMS:** (*Dictyocaulus filaria*).

**CATTLE: STOMACH WORMS:** (*Haemonchus placei*, *Trichostrongylus axei*, *Ostertagia circumcincta*), **INTESTINAL WORMS:** (*Trichostrongylus axei*, *Ostertagia circumcincta*, *Cooperia punctata*, *Nematodirus spathiger*, *Bunostomum phlebotomum*, *Desmophagostomum radiatum*), **LUNGWORMS:** (*Dictyocaulus viviparus*).

#### DOSAGE AND ADMINISTRATION

**CATTLE-STANDARD DRENCH SOLUTION:** Place the contents of each pouch in a 1 quart (946 mL) container. Fill with water, swirl until dissolved. Administer as a single drench dose according to the following table:

Weight	Drench Dosage	Each Pouch Will Treat
200 lb	1.0 fl. oz.	84 head
400 lb	1.5 fl. oz.	52 head
600 lb	1.5 fl. oz.	21 head
800 lb	2.0 fl. oz.	16 head

**CATTLE-CONCENTRATED DRENCH SOLUTION:** For use with 20 mL Automatic Syringe. Place the contents of each pouch in a standard household measuring container and add water to the 3/4 fl. oz. level. Swirl until dissolved. Give 2 mL (0.067 fl. oz.) per 100 lb body weight. Refer to the table above for the number of cattle each pouch will treat.

**SHEEP-STANDARD DRENCH SOLUTION:** Place the contents of each pouch in a 1 gallon (128 fl. oz.) container. Fill with water, swirl until dissolved. Administer as a single drench dose according to the following table:

Weight	Drench Dosage	Each Pouch Will Treat
40 lb	0.5 fl. oz.	250 head
100 lb	1.0 fl. oz.	100 head
150 lb	1.5 fl. oz.	84 head
200 lb	2.0 fl. oz.	64 head

**SHEEP-CONCENTRATED DRENCH SOLUTION:** For use with 20 mL Automatic Syringe. Place the contents of each pouch in a standard household measuring container and add water to the 1 1/2 fl. oz. level. Swirl until dissolved. Give 2 mL per 50 lb body weight. Refer to the table above for the number of sheep each pouch will treat.

**GALLON BOTTLE:** When you are ready to deworm your cattle or sheep, add water to the powder in this bottle up to the 3 liter mark. Swirl to mix thoroughly before using. If any solution is left over, it may be stored for up to 3 months in this tightly capped bottle, shake well before using.

Administer as a single drench dose as follows:

**Cattle -- 2 mL per 100 lb. body weight**

Weight	Drench Dosage	Each Bottle Will Treat
100 lb	2 mL	1,500 head
1,000 lb	4 mL	500 head
500 lb	10 mL	300 head
100 lb	14 mL	214 head
1,000 lb	20 mL	150 head

**Sheep -- 1 mL per 50 lb. body weight**

Weight	Drench Dosage	Each Bottle Will Treat
100 lb	2 mL	1,500 head
1,000 lb	4 mL	500 head
500 lb	10 mL	300 head
100 lb	14 mL	214 head
1,000 lb	20 mL	150 head

**NOTE:** Careful weight estimates are essential for proper performance of this product. Prepare solutions as needed. However, excess solutions may be stored in clean closed containers up to 90 days without loss of anthelmintic activity.

Cattle and sheep maintained under conditions of constant health exposure may require retreatment within 2 to 4 weeks after the first treatment.

**WARNING:** Do not administer to cattle within 48 hours of slaughter for food. Do not administer to sheep within 72 hours of slaughter for food. To prevent residues in milk, do not administer to dairy animals of breeding age.

**CAUTION:** Mucous foam may be observed. However, this reaction will disappear within a few hours. If this condition persists, a veterinarian should be consulted. Follow recommended dosage carefully. Consult veterinarian before using in severely debilitated animals.

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

Store between 15° and 30°C (59° and 86°F).

**WARNING:** Keep out of reach of children.

For Animal Use Only.

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Manufactured for Agri Laboratories, L.L.C., St. Joseph, MO 64503

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It was puzzling that a trainer of high-class stock would purchase a cattle and sheep drench dewormer at a local Tractor Supply when the equine section of the store is full of known, safe, and approved horse dewormers, but this is the story told by Sharp and accepted by Louisiana stewards. Sharp only received a \$1,000 fine for each occurrence. The lenient penalty leaves one to question whether the stewards contemplated not only the plausibility of the explanation but the science that could bolster or contradict its likelihood.

In all species studied, levamisole has a very short elimination half-life. The elimination half-life is the amount of time required for the plasma concentration of a drug to decrease by one-half the initial dose. According to the Veterinary Drug Handbook published June 20, 2017, the half-life of levamisole in horses is 2 hours and it's undetectable by day 7 in all tissues in all animals. Other literature gives a half-life range of 2 to 4 hours. In further support of just how quickly levamisole leaves the body, the warning label on Prohibit advises to not administer the product to cattle within 48 hours or to sheep within 72 hours of slaughter for food.

One can only speculate on the levamisole dosage given to the Sharp horses since it's not approved for use in equines and therefore there are no dosage instructions for equines. Assuming Sharp gave the dosage directed for cattle (1/2 ounce per 200 lbs), we arrive at a dosage of 3 ounces or 4.39 grams of levamisole for a 1200 lb horse. For this exercise we will assume that 100% of the levamisole is absorbed almost instantaneously from the gastrointestinal tract and then rapidly distributed in the blood. On average a 1200 lb. horse would be expected to have approximately 54.5 liters of blood and therefore the 4.39 grams dose of levamisole would result in a peak serum concentration of approximately 80,550 ng/ml.

It is likely the actual plasma concentration was significantly less because drugs are rarely 100% bioavailable and are not absorbed that rapidly and entirely into the bloodstream. Nevertheless,

using the most generous of calculations underscores the point that Sharp's explanation is unconvincing.

For example, if we start with a plasma concentration of 80,550 ng/ml and we assume an elimination half-life of 4 hours, as shown in the table below, all of Sharp's horses would have been treated within about 80 hours of their race. If we assume the half-life was 2 hours, the horses would have been treated within about 40 hours of their race. The test results of the eight Sharp horses are to the right of the table.

Hour 0 (administration)	80,550 ng/ml	
Hour 4	40,275 ng/ml	
Hour 8	20,137.50 ng/ml	
Hour 12	10,068.75 ng/ml	
Hour 16	5,034.375 ng/ml	
Hour 20	2,517.188 ng/ml	
Hour 24	1,258.594 ng/ml	
Hour 28	629.297 ng/ml	
Hour 32	314.648 ng/ml	
Hour 36	157.324 ng/ml	
Hour 40	78.662 ng/ml	
Hour 44	39.331 ng/ml	
Hour 48	19.666 ng/ml	
Hour 52	9.833 ng/ml	
Hour 56	4,916 ng/ml	
Hour 60	2.458 ng/ml	1.173 ng/ml Tempt Fate (12/6/19)
Hour 64	1.229 ng/ml	.700 ng/ml Sweet N Salty Kiss (12/1/19)
Hour 68	0.615 ng/ml	.214 ng/ml Sycamore Run (12/21/19)
Hour 72	0.307 ng/ml	.203 ng/ml Midnight Fantasy (12/14/19)
Hour 76	0.154 ng/ml	.169 ng/ml Classy Act (12/19/19)
Hour 80	0.077 ng/ml	.156 ng/ml Robinson (12/7/19)
Hour 84	0.038 ng/ml	.114 ng/ml O Seraphina (12/22/19)
Hour 88	0.019 ng/ml	.067 ng/ml Tracksmith (12/28/19)
Hour 92	0.0096 ng/ml	
Hour 96	0.0048 ng/ml	

It is known that Sharp has levamisole positive cases pending in Kentucky and he also received another levamisole positive on January 18, 2020 in Louisiana. We were able to deduce the identity of three of the Kentucky horses through racing commission rulings but we do not yet know the reported concentration in the plasma:

Street Dazzle (11/23/19 at CD)  
 Art Collector (11/30/19 at CD)  
 Blackberry Wine (11/30/19 at CD)  
 Blackberry Wine (1/18/20 at FG)

In a February 8, 2020 DRF article by Byron King, Sharp claimed that “as soon as we found out [about the levamisole positives], we took it out of the barn on Dec. 12.” However, five of Sharp’s horses tested positive after December 16, more than four days (96 hours) after Sharp states he could have possibly given the horses their last dose. The plasma concentrations of levamisole found in these five horses are not consistent with a withdrawal time of four days. One may think that an occasional horse may be an outlier but five of eleven horses is a high percentage of outliers.

We used the following formula (again assuming a 4-hour half-life) to arrive at the dosage each horse would have received on December 12 to have the plasma concentrations present at the time the samples were collected. In the case of Blackberry Wine, we used a level of .010 ng/ml since we do not yet know the level detected in his plasma:

$$\text{Initial Dose} = \text{Amount Detected} \times 2^{x/y}$$

$x = \# \text{ hours since administered}$   
 $y = 1/2 \text{ life in hours}$

Classy Act (7 days, .169 ng/ml)	40,508 kg
Sycamore Run (9 days, .214 ng/ml)	210 million kg
O Seraphina (10 days, .114 ng/ml)	7.16 billion kg
Tracksmith (16 days, .067 ng/ml)	289 quintillion kg
Blackberry Wine (37 days, .010 ng/ml)	3.67 octodecillion kg

Clearly, these dosages are fantastically absurd and could not have possibly been administered to the Sharp horses. The lowest is more than the weight of a half-dozen African elephants while the dosage estimated for Blackberry Wine is far larger than the mass of the sun. This seems to leave us with two possible explanations: Sharp did not stop all levamisole administration on December 12, 2019 as he stated, or he has a very high percentage of levamisole outliers.

Another cause for questioning the plausibility of this being a case of “deworming-gone-wrong” is the likely deworming schedule of a trainer’s stable. One would think that all or the majority of a stable would be treated on a single day in the monthly, semi-monthly or quarterly schedule. The wide range of dates of the positives appears to indicate that horses were being treated individually on all dates on the calendar.

Racing’s regulators owe it to the owners, trainers, handicappers, and sport to do their very best to ensure that our races are run fairly. They owe it to the horses to protect them from any drugs being administered for reasons other than legitimate therapeutic use. When confronted with positive drug tests, racing’s regulators should scrutinize the plausibility of the explanations as well as where the science points when considering appropriate penalties.