

A Presentation for the National HBPA Summer 2014

**On Medication Thresholds
By Wayne Carlton Duer , PhD**

**A MEDICATION THRESHOLD IS A
MEDICATION CONCENTRATION IN
WEIGHT PER VOLUME. IF THE SAMPLE
FROM A HORSE EXCEEDS THIS
CONCENTRATION THEN IT IS ASSERTED
THAT THE MEDICATION RULE WAS
VIOLATED AND A FINE MAY BE ISSUED.**

**IDEALLY A MEDICATION THRESHOLD
SHOULD BE SET IN SUCH A WAY AS TO
MINIMIZE THE CHANCES OF FALSELY ACCUSING
SOMEONE OF A VIOLATION. A REVIEW OF AVAILABLE
LITERATURE SUGGESTS THAT THIS IS NOT NECESSARILY
ALWAYS THE PRACTICE.**

**IDEALLY THE THRESHOLD WOULD BE
LIKE A SPEEDOMETER THAT ONE COULD
CLEARLY SEE. HOWEVER, LIFE IS NOT
SO SIMPLE. COMPLEXITIES EXIST NOT
ONLY IN THE SETTING OF A THRESHOLD
BUT ALSO IN ITS IMPLEMENTATION.**

What the literature and practice look like today.



"Well, lemme think. ...You've stumped me, son.
Most folks only wanna know how
to go the other way."

Outline of Forensic Toxicology

Specimen Collection

Specimen Preservation

Sampling of Specimen

Detection of Components of Interest

Isolation and Purification of Components

Quantification or Quantitation

Report

Interpretation

Testimony in Court



CHAIN
OF
CUSTODY

**DISTRIBUTIONS EXIST BECAUSE OF
VARIABILITY.**

**NOT ALL HORSES ARE THE SAME IN
THE WAY IN WHICH THEY CHANGE
AND DISTRIBUTE SUBSTANCES IN THEIR
BLOOD OR ELIMINATE SUBSTANCES IN THEIR
URINE.**

**ALL CHEMICAL TESTS ALSO HAVE INHERENT
VARIABILITY .**

A DISTRIBUTION CAN LOOK LIKE

A MOUNTAIN RANGE.

A DISTRIBUTION CAN LOOK

LIKE A BAR CHART.

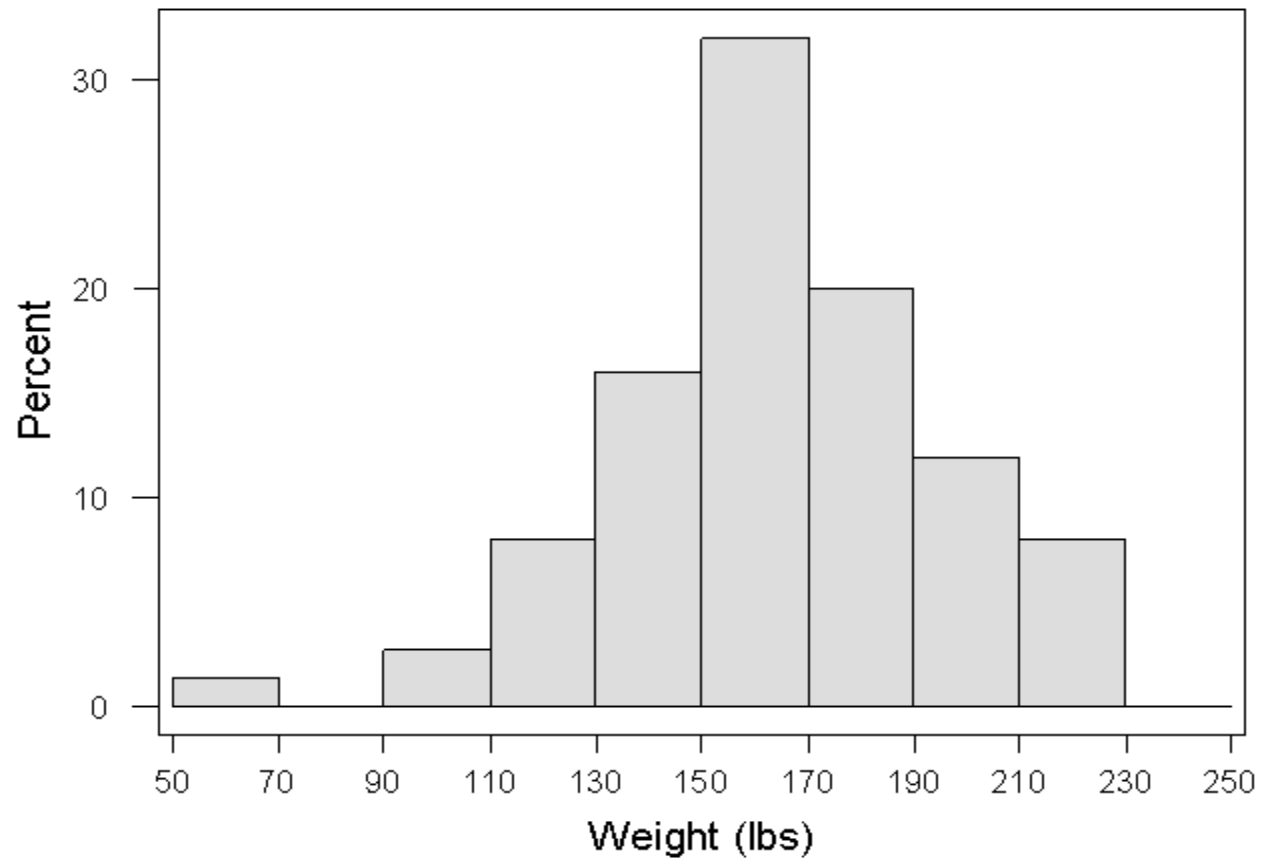
DISTRIBUTIONS ARE THE HEART

OF MATHEMATICAL STATISTICS AS

APPLIED TO REAL WORLD PROBLEMS

LIKE DETERMINING A THRESHOLD.

**IN CHEMICAL TESTS THESE DISTRIBUTIONS
ARE GRAPHS THAT CAN LOOK LIKE MOUNTAIN
RANGES OR BAR CHARTS. THE BOTTOM OR
HORIZONTAL AXIS OF THESE GRAPHS IS A
MEASURED VALUE SUCH AS CONCENTRATION
OR OTHER MEASURED PROPERTY.
THE VERTICAL AXIS IS THE NUMBER OF
SPECIMENS HAVING THIS CONCENTRATION
OR PROPERTY.**

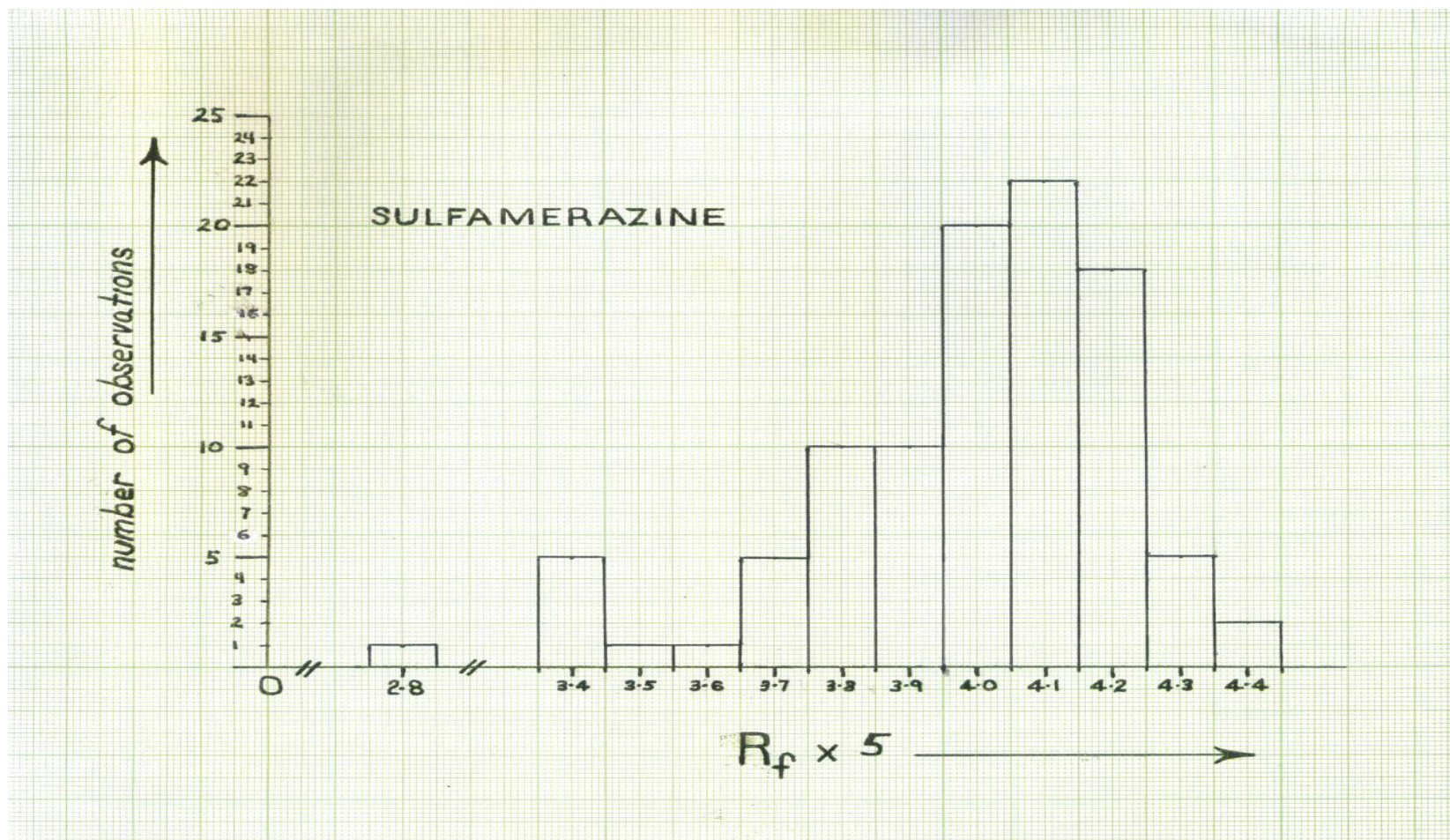


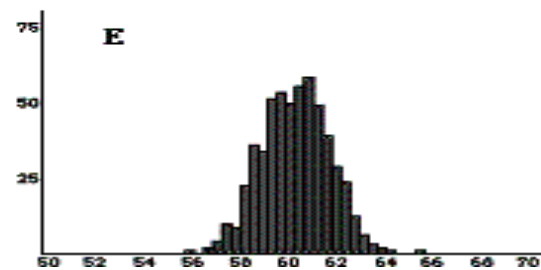
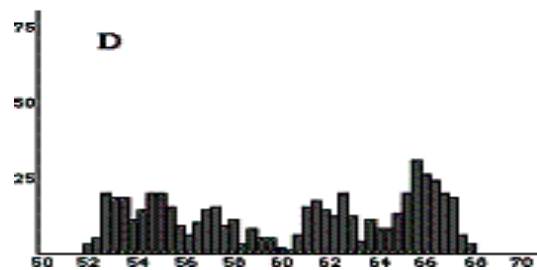
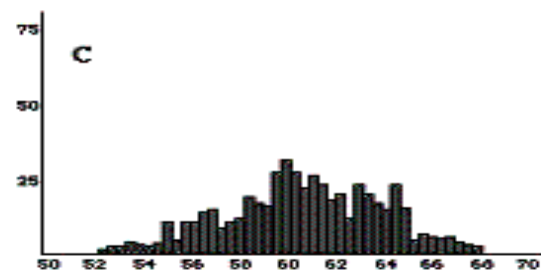
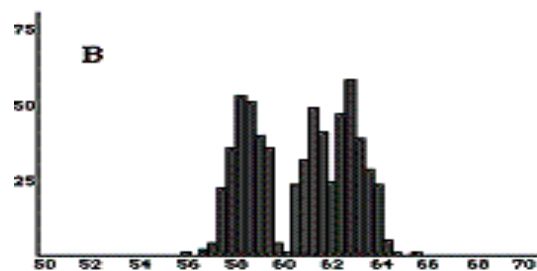
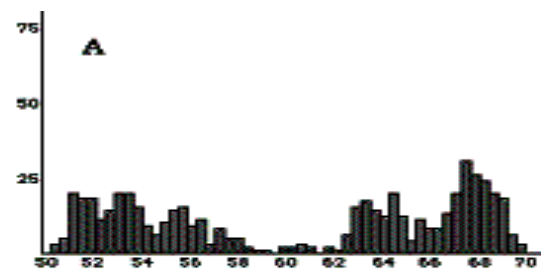
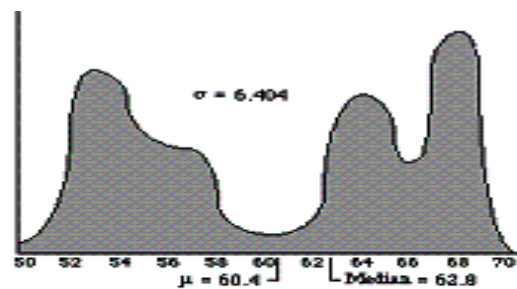
AVERAGE OR MEAN IS 163

MALE WEIGHTS

Example Data for Analytical Methods

Thin Layer Chromatography 3





SCIENTISTS WISH FOR A NORMAL
OR GAUSSIAN DISTRIBUTION. THIS IS BECAUSE THE NORMAL
DISTRIBUTION HAS SOME VERY CONVENIENT PROPERTIES.
IF THEIR DATA DOES NOT CONFORM TO
A NORMAL DISTRIBUTION OFTEN THEY WILL USE
ANY MATHEMATICAL FUNCTION OR OPERATOR
TO TRY TO GET IT TO LOOK SOMETHING
LIKE NORMAL. THIS MAY NOT WORK OUT WELL.

SOME MATHEMATICAL FUNCTIONS HAVE BEEN USED

TO ATTEMPT TO TRANSFORM DATA TO A NORMAL LOOKING

DISTRIBUTION. A FEW OF THESE FUNCTIONS ARE:

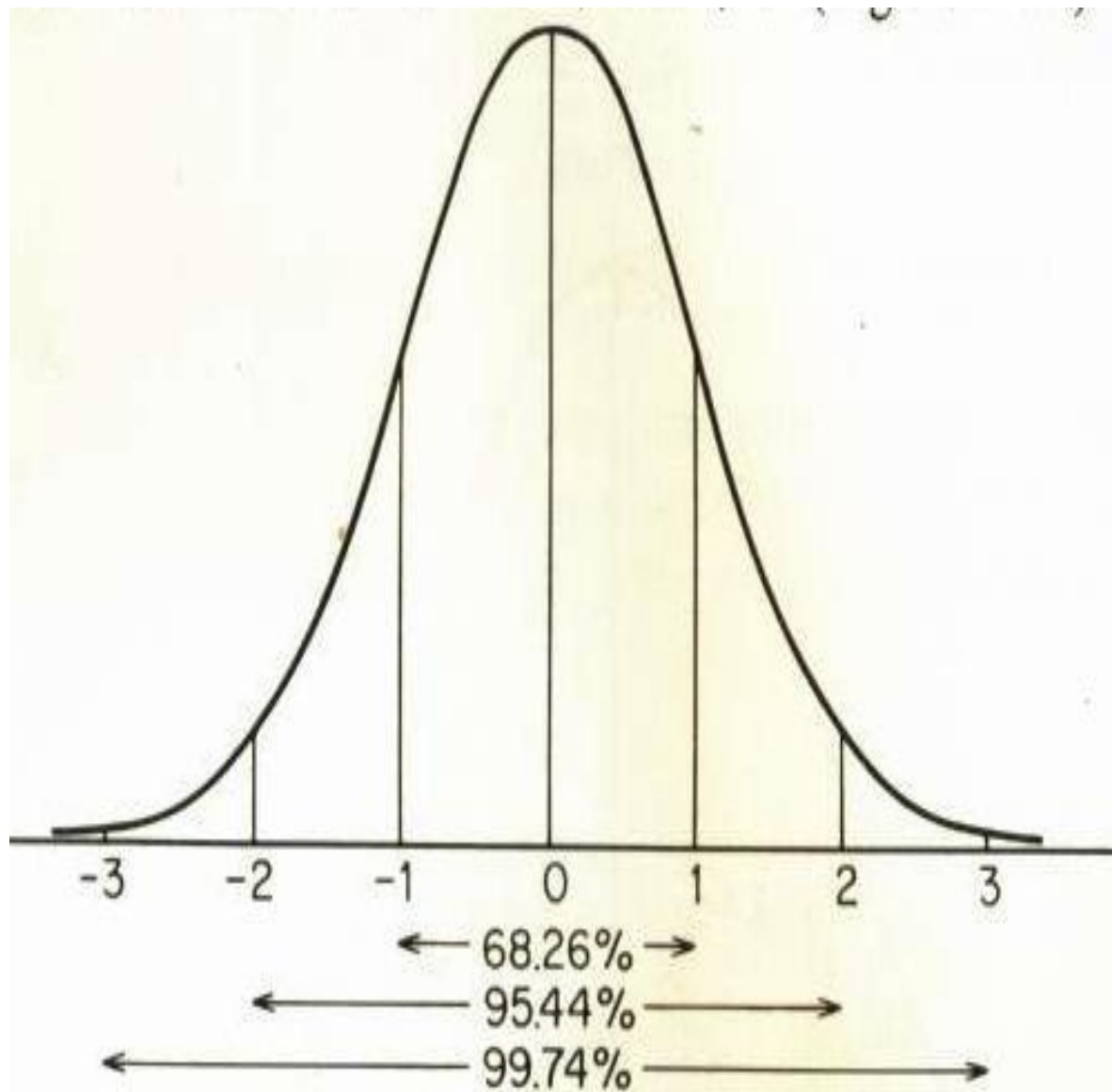
LOGARITHM, EXPONENTIAL, SQUARE ROOT , CUBE ROOT, GEOMETRIC, BURR, JOHNSON, LOG-LOGISTIC.

AFTER USING THE TRANSFORMATION, INVOLVED MATHEMATICAL TESTS SUCH AS

KOLMOGOROV-SMIRNOV CAN BE APPLIED TO SEE IF NORMAL APPROXIMATION

HAS BEEN ACHIEVED . BACK TRANSFORMATIONS MUST THEN BE APPLIED

WHICH ARE NOT UNAMBIGUOUS. THEY CONSTITUTE NO ABSOLUTE PROOF.

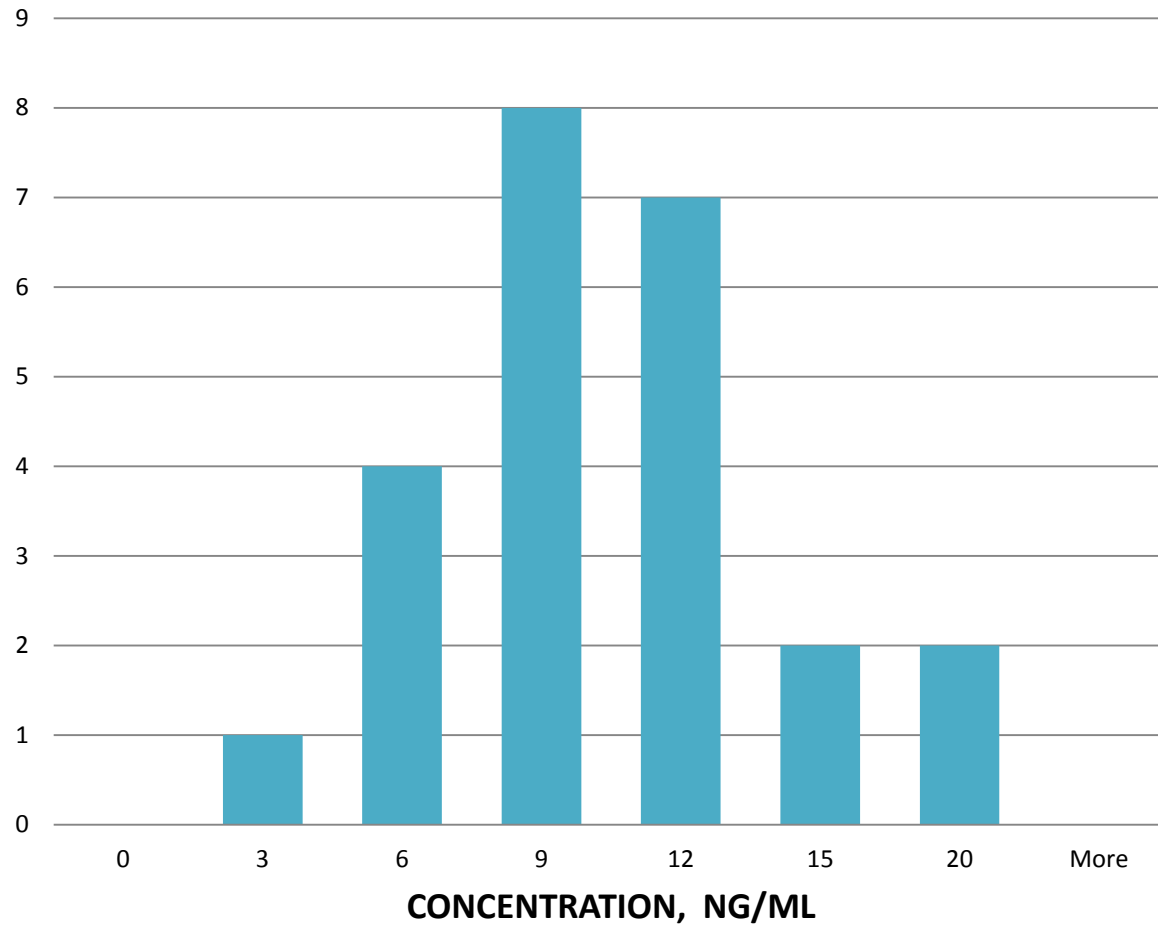


BEFORE USING ANY DATA, INDUSTRIAL QUALITY CONTROL STATISTICIANS WILL TEST ASSUMPTIONS. FIVE OF THESE ARE:

1. SUFFICIENT NUMBER OF DATA POINTS
2. UNCORRELATED MEASUREMENTS
3. NORMALITY
4. HOMOGENEITY OF VARIANCES
5. HOMOGENEITY OF MEANS

IF ANY ASSUMPTION IS FALSE USE OF THE DATA MUST BE RESTRICTED.

FLUNIXIN



THE PREVIOUS HISTOGRAM REPRESENTS PLASMA RESULTS AT 24 HOURS AFTER ADMISITRATION OF 500 MG. FROM SUCH DATA, THE RACING MEDICATION AND TESTING CONSORTIUM, INC. RECOMMENDED A THRESHOLD OF 20 NG/ML, WHICH IS THE PRESENT THRESHOLD OF THE CALIFORNIA HORSE RACING BOARD. IN A 2006 PRESENTATION DR. SCOTT STANLEY DISCUSSED CALIFORNIA'S PREVIOUS EXPERIENCE WITH THIS LEVEL. BASICALLY, MANY POSITIVES WERE FOUND. DR. STANLEY HAD THOUGHT THAT A THRESHOLD OF ABOUT 50 WAS NEEDED FOR THE 500MG, 24HR PRACTICE.

https://ua-rtip.org/symposium_racing_gaming

FROM A PRESENTATION BY H. KNYCH, R. SAMS, R. ARTHUR,

and S. STANLEY, <http://ua-rtip.org/sites/ua-rtip.org/files/stanley.pdf>,

THEIR METHOD OF DERIVING THRESHOLDS INVOLVES TRANSFORMING

THE DATA WITH THE NAPERIAN LOGRITHM, PERFORMING CALCULATIONS

AND THEN BACKTRANSFORMING FOR A THRESHOLD. USING 12 HORSES

THEY FOUND A THRESHOLD OF 47.7, USING 31 HORSES GAVE A 40.9.

THE METHOD WHICH THEY USED MAY BE CALLED

DISTRIBUTION DEPENDENT. ONLY ABOUT 20 HORSES WERE

SUGGESTED TO BE USED. THIS IS TOO SMALL OF A NUMBER.

Type I Calculation (UCD)

	N = 12	N = 31
Mean	2.5849	2.3307
SD	0.6663	0.6324
Mean + k x SD	4.869	4.089
Concentration, ng/mL	47.4	40.9

A 1.1 MG/KG IV DOSE OF FLUNIXIN AS FLUNIXIN MEGLUMINE BRAND OF BANAMINETM WAS ADMINISTERED TO 16 HORSES AND BLOOD SAMPLES WERE COLLECTED AT VARIOUS TIMES AFTER ADMINISTRATION. PLASMA FLUNIXIN CONCENTRATIONS WERE DETERMINED BY A VALIDATED LIQUID CHROMATOGRAPHY MASS SPECTROMETRIC METHOD. THE PLASMA FLUNIXIN CONCENTRATIONS WERE ABOVE 20 NG/ML AT 24 HOURS IN SAMPLES FROM 4 OF 16 HORSES. www.rmtcnet.com

**THERE HAVE BEEN MANY ARTICLES
PUBLISHED CONCERNING THE USE OF
DISTRIBUTION DEPENDANT METHODS
FOR THRESHOLD CALCULATIONS. A
NUMBER OF PROBLEMS HAVE
BEEN FOUND TO EXIST IN THEM.
THREE INDICATE AT LEAST 120 SUBJECTS
OR HORSES ARE NEEDED TO HAVE A
CHANCE OF DEFINING A DISTRIBUTION.**

**ALTERNATIVELY, DISTRIBUTION-FREE
METHODS HAVE BEEN PROPOSED AND
USED. THESE INVOLVE FEWER
ASSUMPTIONS AND THEREFORE
OFFER ADVANTAGES.**

**ONE OF THESE STEMS FROM THE
STATISTICIAN DR. HARALD CRAMÉR.**

**USING THE DATA FROM THE HISTOGRAM FOR
FLUNIXIN WITH EQUATIONS OF CRAMÉR
AND CHOOSING A PROBABILITY OF 1/10000
FOR MAKING A FALSE ACCUSATION YIELDS
A THRESHOLD = 264 .**

ONE MAY USE THE RMTC EQUATIONS AND THEIR THRESHOLD
TO CALCULATE THE RISK FOR FALSE ACCUSATIONS.

FOR FLUNIXIN WITH THE 20NG/ML THRESHOLD, THIS RISK IS
104/10000 OR 1.04%. IN OTHER WORDS ONE IN EVERY
ONE HUNDRED ACCUSATIONS WILL LIKELY BE FALSE.

THE RISK WHEN USING THE CRAMÉR METHODS FOR
FLUNIXIN WITH A THRESHOLD OF 264 IS 1/10000 OR 0.01%.
IN OTHER WORDS ONE IN EVERY TEN THOUSAND
ACCUSTIONS WILL LIKELY BE FALSE.

<u>RISK</u>	<u>THRESHOLD</u>
1/10000	264 ng/mL
1/5000	164
1/1000	85
1/500	44
1/100	35

**THE REAL QUESTION IN CHOOSING A THRESHOLD
IS THE FOLLOWING.**

**WHAT PERCENTAGE OF ACCUSATIONS
SHOULD BE ALLOWED TO BE FALSE?
1% OR 0.01% OR SOME THING ELSE?**

**THE USE OF CRAMÉR ALLOWS ONE
TO CHOOSE THE LIKELY PERCENTAGE
OF FALSE ACCUSATIONS AT THE
OUTSET SO THAT EVERYONE
INVOLVED CAN UNDERSTAND THE
IMPLICATIONS OF A RULE.**