Risk-Based Determination of the Exposure Dwell Time to Lethal Agents Required to Achieve a Desired Sterility Assurance Level.

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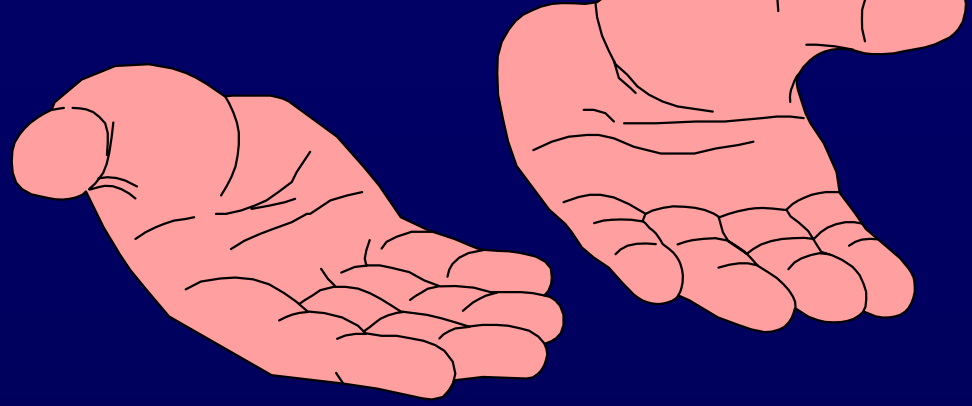
The National Center for Food Safety & Technology (NCFST)

IFTPS Annual Meeting 2009
San Antonio, Texas.

Outline

Risk as a significant component of processes

Techniques that may assist to place bounds on risk while defining the exposure dwell to a lethal agent.



Consumers are demanding miracle foods that are totally natural, have zero calories, zero fats and cholesterol, delicious taste, total nutrition, low price, environmentally friendly production, 'green' packaging….and that guarantee perfect bodies, romance and immortality

(Carol Brookins, Global Food and Agriculture Summit, 1999)

Some Recent US Food Safety Issues

August, 2006 *E. coli* in bagged spinach 204 illnesses, in 26 states, three deaths.

September 2006 Recall of refrigerated carrot juice due to btulinum toxin, 4 cases

September *2006* *Salmonella* in tomatoes sickened 183 illnesses in 2 states.

December 2006: Iceberg lettuce contaminated with *E. coli* fast food restaurants, 152 illnesses.

February 2007: peanut butter contaminated with *Salmonella* 425 illnesses in 44 states.

March 2007: One hundred brands of pet food distributed nationwide were recalled after illnesses and deaths of cats and dogs due to melamine contamination.

June 2007: Veggie Booty snacks contaminated with Salmonella caused 65 illnesses in 20 states.

Some Recent US Food Safety Issues

June 2007: Ground beef contaminated with *E. coli* caused 14 illnesses leading to a recall of ground beef that had been shipped to 11 western states.

July 2007: Canned chili and meats containing C*lostridium botulinum* were recalled after causing eight illnesses in three states.

August 2007: Nationwide recall of fresh spinach due to suspected Salmonella contaimanition.

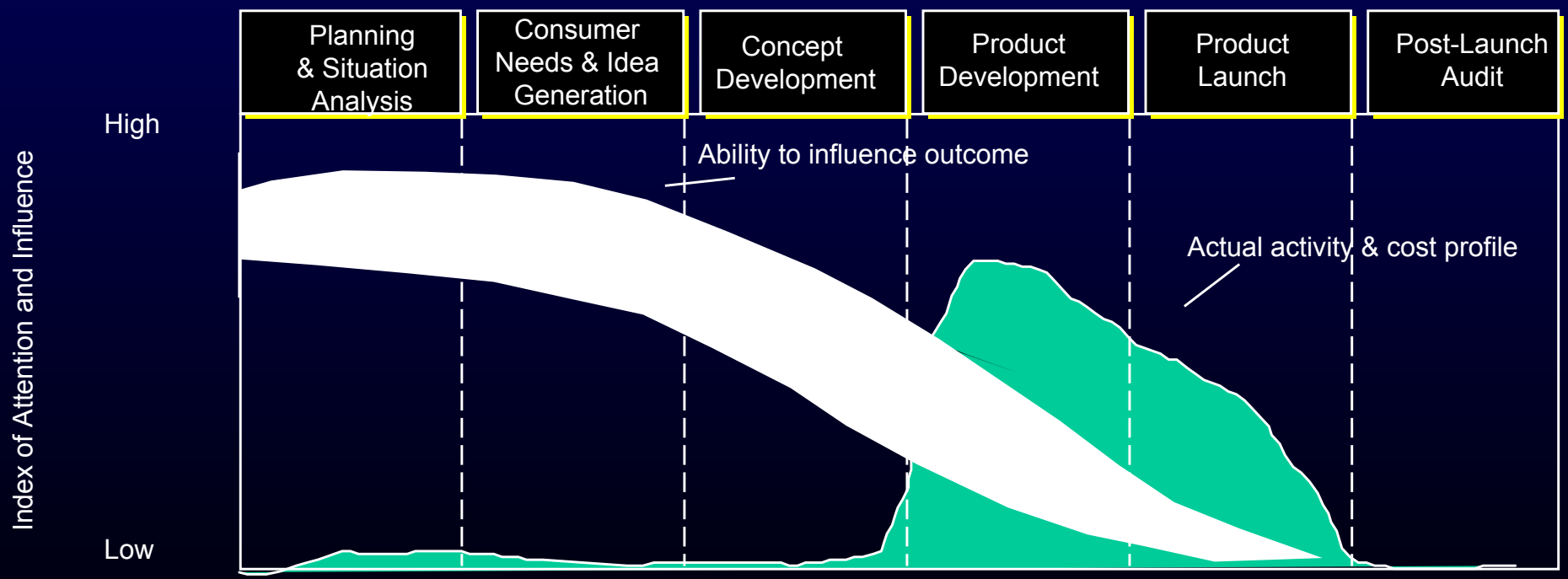
September 2007: The second largest beef recall in U.S. history (21.7 million pounds) due to *E. coli* contamination of Frozen Hamburgers and Patties

October 2007: Recall of Turkey and Chicken Pot Pies recalled due to Salmonella contamination, Illnesses in 31

Managing the risk of Innovation’

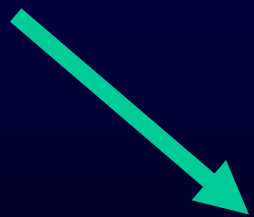
- The opportunity to influence the success of a new product is greatest he early stages
- Innovation is about being ‘brave’ not ‘foolish’
- Collaboration in pre-competitive validation stage helps to reduce risk

nportance of the Front-End



Reforms to Managing Food Safety

Command & Control
Prescriptive
Point Testing
Constraint to Innovation



Risk based
Flexible
Through Chain
Supports Innovation
More Complex

New Approaches to Risk Management

ALAR

ie 'As low as Reasonable'

BUT:

-Technological capabilities vary

-Idea of 'reasonable' varies

→

Public Health Based Goals

-eg yearly incidence of Listeriosis below 4 cases/million of pop.

BUT:

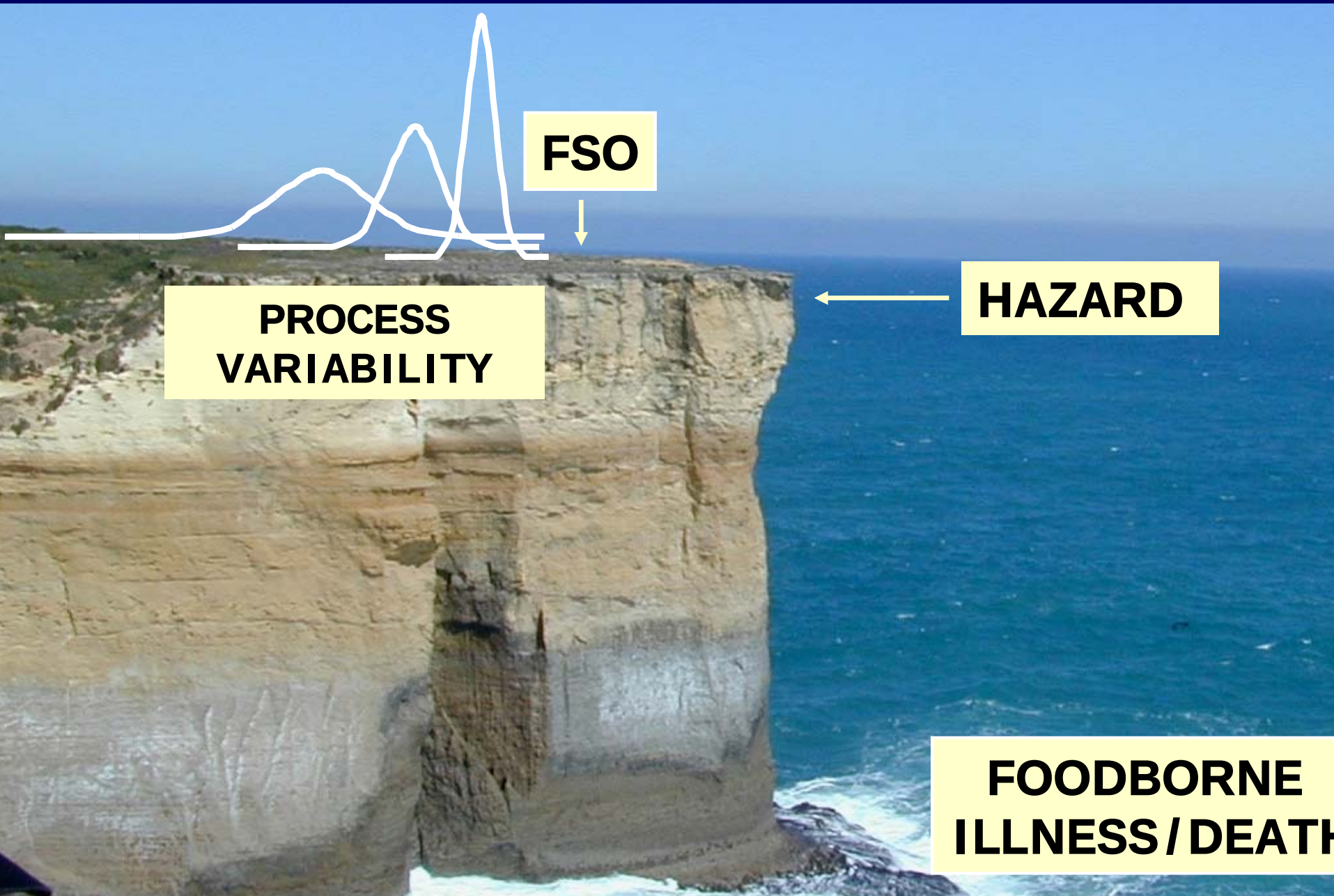
-in terms of population

-not related to specific foods

The Issue Behind the Issue:

Equivalence: Do two systems of food safety risk management (e.g. inspection, HACCP, processing) provide the same degree of public health protection?

Managing the 'Food Safety Cliff'



Food Safety Objectives

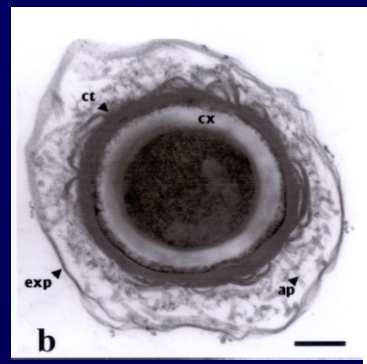
$$H_0 + \Sigma I + \Sigma R \leq FSO$$

- FSO = food safety objective
- H_o = initial level of the hazard
- ΣI = total increase in hazard,through growth or contamination
- ΣR = total death (reduction of hazard; negative number)

Impact of New Risk Management

- Increased flexibility....innovation
- Science based & increased transparency
- Will impact
  - Shared responsibility across chain
  - Stringency of HACCP
  - Micro Criteria more science based
  - Equivalency of new processes

Conclusions, & some Unanswered Questions



CATEGORY: SHELF-STABLE LOW-ACID FOODS

The Challenge of Bacterial Spores

An Expert Panel Discussion in Print

Bacterial sporeformers, such as *Clostridium botulinum* and *Bacillus cereus* and their toxins, do not get industry's attention like *Listeria monocytogenes* and *E. coli* O157:H7, but that doesn't mean these microbial contaminants aren't on the radar screen for food manufacturers. This may be related to the fact that since the implementation of the low acid canned food regulations, there has been a precipitous decline in the number of incidents of reported botulism outbreaks in the U.S. But, as food companies strive both to develop products with extended shelf life and meet regulatory mandates for improved food safety and defense, these spoilage and potential public health contaminants must be addressed anew.

The National Center for Food Safety and Technology (NCFST), a unique food safety and engineering research consortium composed of scientist from academia, industry and the U.S. Food and Drug Administration (FDA) located at the Illinois Institute of Technology's Moffet Campus, has been investigating microbial behavior of sporeforming organisms in order to foster scientific and technical exchange to better understand the science and research needs. NCFST experts note that while little spore research has been conducted since the 1970s, due to the advent of new food preservation (sterilization) technologies, there is a need to look at more closely the testing methods for determining resistance, the mechanisms of spore inactivation, and methods of production control. By studying resistance of spore populations to various food preservation technologies, particularly novel technologies, the food industry will have a better opportunity to create ambient shelf-stable, low-acid food products that consumers want, as well to implement new technologies to attain production efficiencies and food safety goals.

This *Food Safety Magazine* (FSM) panel, comprised of NCFST experts

- How does wet heat kill spores?
- How does the cortex control core water content?
- What is the state of water in the core?
- What is the physical state of core cytoplasm
- What is the role of CaDPA in the core?
- What is the cause of poor germination kinetics (and the consequent lack of success Tyndallisation procedures)? (& can it be overcome?)
- Can we exploit lysozyme germination?
- Can we exploit bacteriocins other than nisin as outgrowth inhibitors ?
- Can we exploit some aspects of the spore's resistance mechanisms, e.g. for the des novel, ambient-stable, preservation systems?

NCFST Project: Framework for Setting and Validation of Novel Sterilization Processes

$$H_o - \sum_{i=1}^{n} R_i + \sum_{i=1}^{m} I_i \leq FSO$$

- Publication of a white paper addressing the use of new risk management schemes (i.e., ICMSF) for determining performance criteria and validation strategies for sterilization processes utilizing new technologies

Anderson et al, NCFST FSO Sterilization Project

Definition: Two events A and B are independent if and only if

$P(B|A) = P(B)$

And

$P(A|B) = P(A)$

Otherwise A and B are dependent.

Theorem two events are independent if and only if

$P(A \cap B) = P(A)P(B)$

Therefore, to obtain the probability that two independent objects will both occur, we simply find the product of their individual probabilities.

Walpole & Myers

One possible way to reach very low probabilities of failure (such as required by sterilization processes) is to take advantage of this theorem:

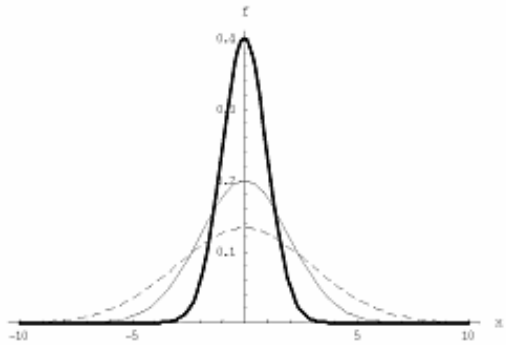
Start with a bounded low probability of failure for a feasible (worst case condition). This is our subject.

Combine it with the (low) probability that the worst case condition will actually occur.

Distribution analysis.

Skewness

The third moment of a distribution and the first shape parameter. The skewness is measure of the symmetry of the distribution. A skewness of zero means the distribution is symmetrical like the normal distribution shown below:

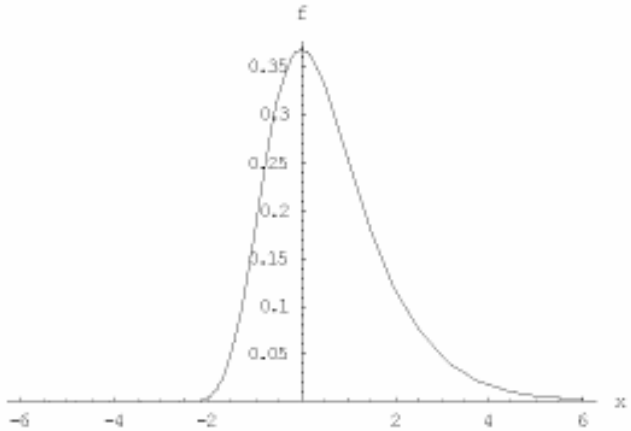


A skewness value of 1 and above or -1 and below represents a sizable departure from normality. The formula used for estimating the skewness from a set of data is:

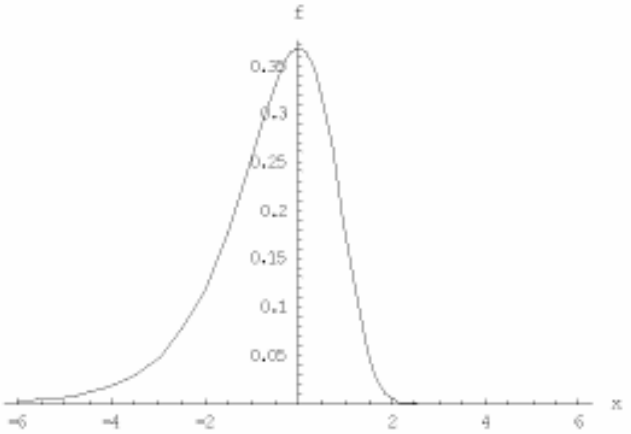
$$\frac{n}{(n-1)(n-2)} \quad \frac{\sum_{i=1}^{n}(x_i - \overline{X})^3}{S^3}$$

where n is the sample size, x_i represents the data points, $\overline{X}$ is the average and S is the standard deviation.

A positive skewness means the upper tail is longer than the lower tail like the Largest Extreme Value distribution with a skewness of 1.14 shown below:

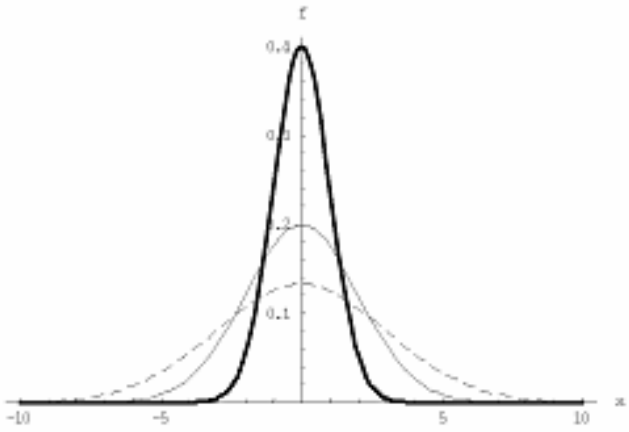


A negative skewness means the lower tail is longer than the upper tail like the Smallest Extreme Value distribution with a skewness of -1.14 shown below:

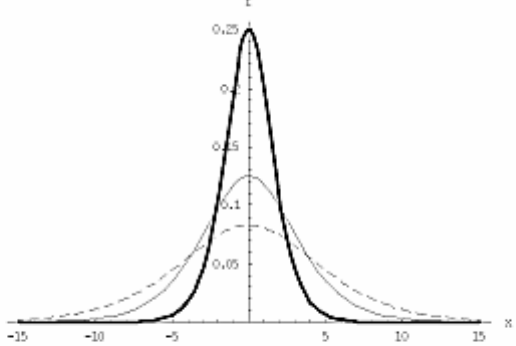


Kurtosis

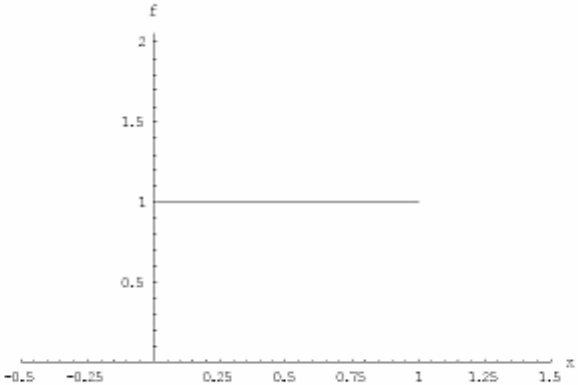
The fourth moment of a distribution and the second shape parameter. The kurtosis is a measure of the heavy the tails are. The normal distribution, shown below, has a kurtosis of 3:



A kurtosis greater than 3 means the tails are heavier than the normal distribution.



A kurtosis less than 3 means the tails are lighter than the normal distribution like the Uniform distribution with a kurtosis of 1.8 shown below:



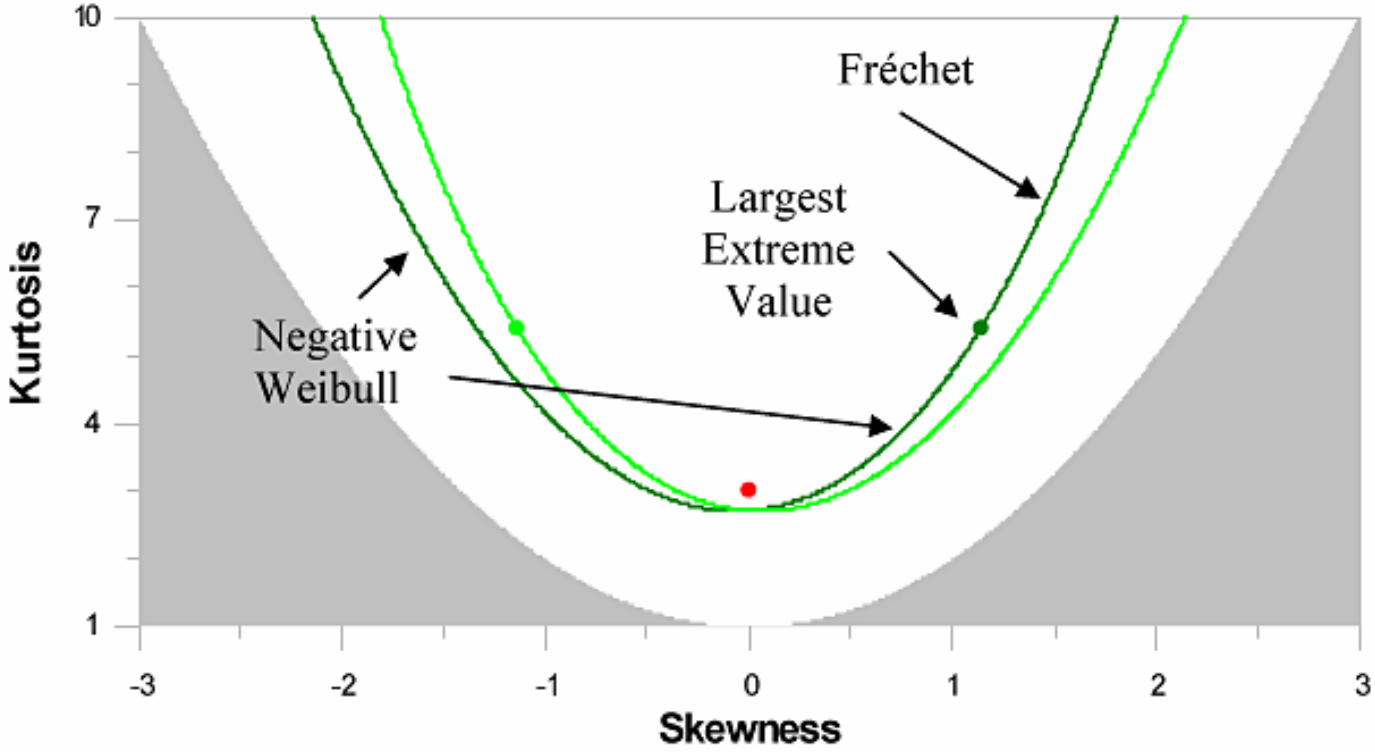
A kurtosis value of 4 and above or 2 and below represents a sizable departure from normality. The formula used for estimating the kurtosis from a set of data is:

$$\frac{n(n+1)}{(n-1)(n-2)(n-3)} \frac{\sum_{i=1}^{n}(x_i-\overline{X})^4}{S^4} - \frac{3(3n-5)}{(n-2)(n-3)}$$

where n is the sample size, x_i represents the data points, $\overline{X}$ is the average and S is the standard deviation.

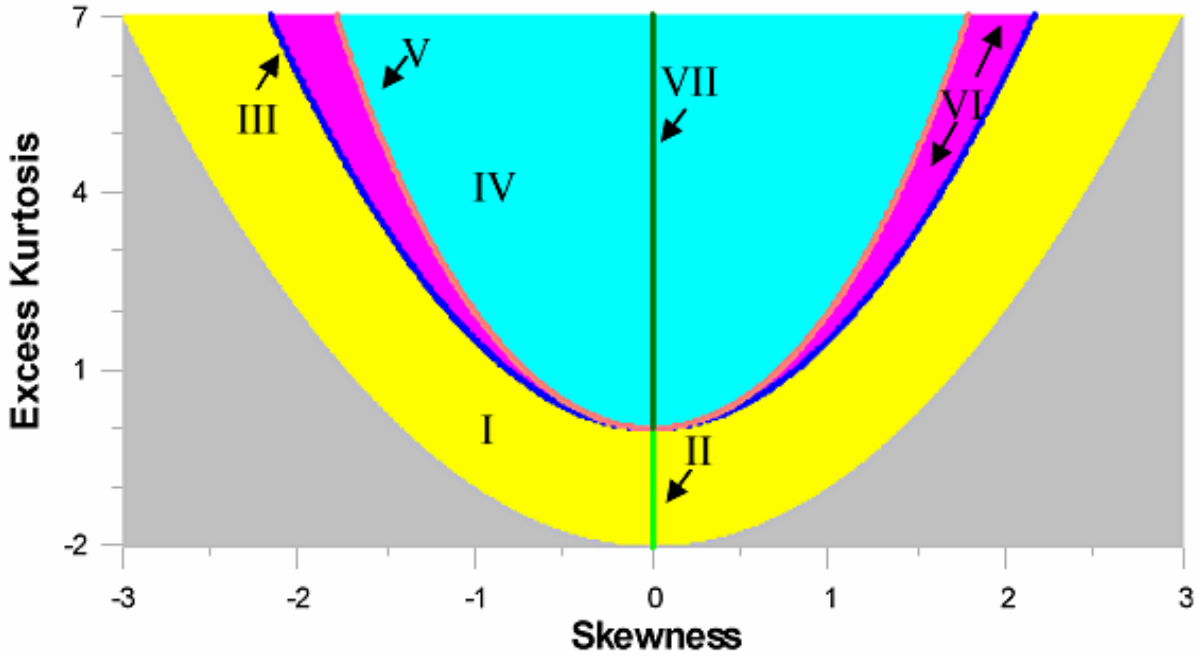
The excess kurtosis = kurtosis - 3. This results in the normal

Shape: The largest extreme value family of distributions is made up of three distributions: Fréchet, negative Weibull and largest extreme value. It covers any specified average, standard deviation and any skewness below 5.6051382. Together they form a 3-parameter family of distributions that is represented by a curve on a skewness-kurtosis plot as shown below. The Fréchet distribution covers the portion of the curve with skewness above 1.139547. The negative Weibull distribution covers the portion of the curve with skewness below 1.139547. The largest extreme value distribution handles the remaining case of skewness equal to 1.139547.



- Type I: Beta Distribution
- Type II: Special case of beta distribution that is symmetrical
- Type III: Gamma Distribution
- Type IV: Region above Type V
- Type V: 3 parameter distribution represented by curve
- Type VI: Region between Gamma and Type V
- Type VII: Special case of Type IV that is symmetrical

The special cases can be ignored (II and VII). Type I and III are alias for distribution already covered. That leaves Type IV, V and VI as new distributions.



Test of Fit: Two normality tests are performed. When no transformation is selected, these tests are applied directly to data values and test for normality. When a transformation/distribution is selected, these tests are applied to the transformed values and test for whether the selected distribution fits. The first test is a general test for all departures from normality. The Skewness-Kurtosis All test (SK All) is the default test but the Anderson-Darling test (AD) and Shapiro-Wilks test (SW) are also available. They can be selected using the *Analysis Options* dialog box or the popup menu described below. The p-value and decision are given. The test passes if the p-value > 0.05. The second test is the Skewness-Kurtosis Specific test (SK Spec). This test is designed to only reject for those departures from normality that invalid the tolerance interval and confidence statement relative to the spec limits. Passing this test indicates the statements are valid. Only the pass/fail decision is given. If the normality test fails, one can state: "With 95% confidence the data is not from the normal distribution." If it passes, one can state: "No significant departure from normality was detected."

P_p

Capability index that compares process variation to the width of the spec limits:

$$P_p = \frac{(\text{Upper Spec Limit} - \text{Lower Spec Limit})}{6 \text{ Standard Deviations}}$$

The numerator is the width of the spec limits. The denominator is 6 standard deviations, which can be thought of as the width of the process. For the normal distribution 99.7% of values fall within ±3 standard deviations of the average or into an interval 6 standard deviations wide. A P_p value of 1 means the process variation fills the spec limits. A P_p of 2 means the specs are twice as wide as the process. The larger P_p is, the better the capability.

P_{pk}

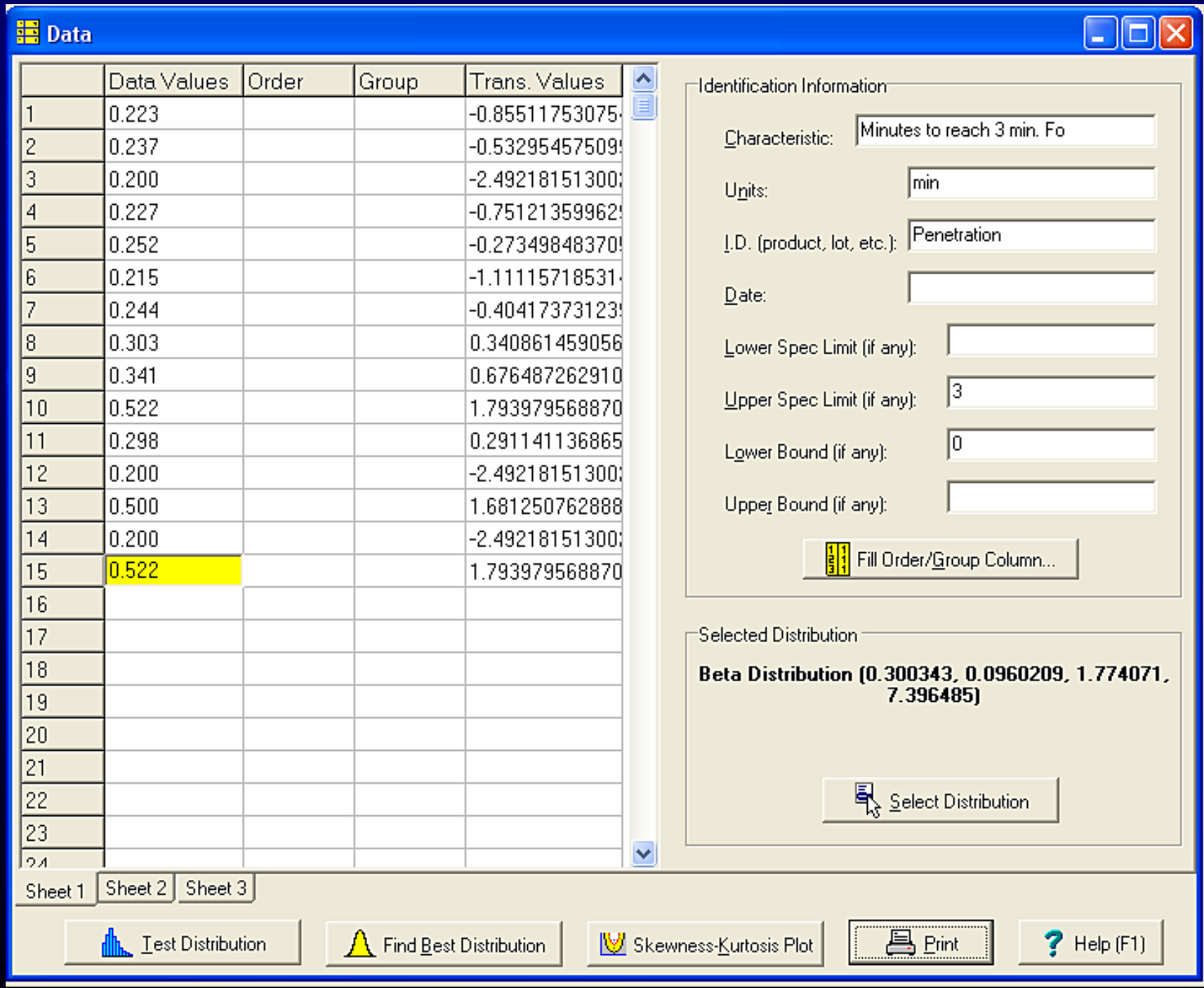
Capability index that measure the relative distance to the nearest spec limit:

$$P_{pk} = \text{Minimum}\left(\frac{\text{Upper Spec Limit} - \text{Average}}{3 \text{ Standard Deviations}}, \frac{\text{Average - Lower Spec Limit}}{3 \text{ Standard Deviations}}\right)$$

The numerator is the distance to the nearest spec limit. For a one-sided spec limit (lower spec only or upper spec only) only use the portion of the formula for that spec limit. The denominator is 3 standard deviations, which can be thought of as the half the width of the process. For the normal distribution 99.7% of values fall within ±3 standard deviations of the average or into an interval 6 standard deviations wide. A P_{pk} value of 1 means the distance between the average and the nearest spec limit is 3 standard deviations and thus the process fills this interval and touches the spec limit. A P_{pk} value of 2 means the distance between the average and the nearest spec limit is 6 standard deviations and thus the process fills only half this interval. This leaves a safety margin. The larger P_{pk} is, the better the capability.

	Data Values
1	0.223
2	0.237
3	0.200
4	0.227
5	0.252
6	0.215
7	0.244
8	0.303
9	0.341
10	0.522
11	0.298
12	0.200
13	0.500
14	0.200
15	0.522

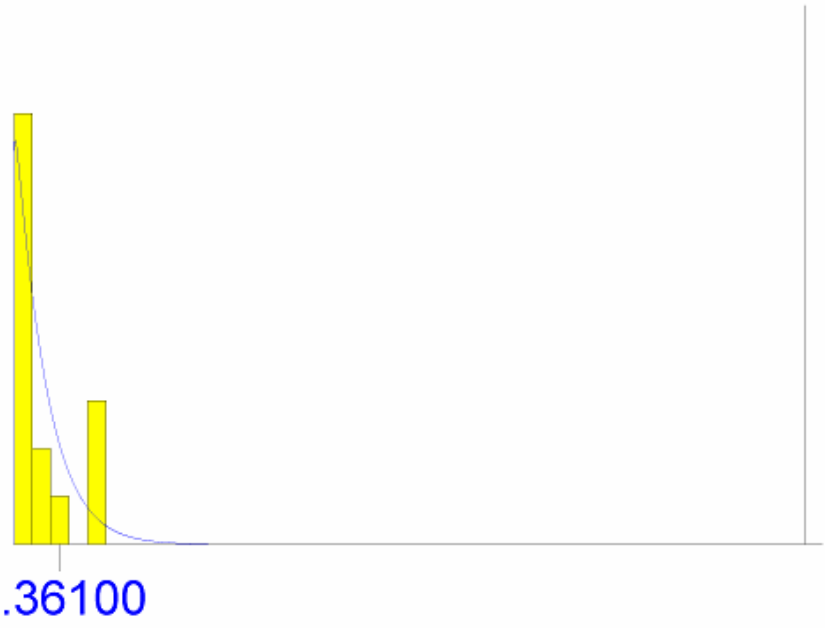
Time in minutes needed to reach 3 minutes of Fo


Data
Data Values
Order
Group
Trans. Values
1 0.223 -0.85511753075
2 0.237 -0.53295457509
3 0.200 -2.49218151300
4 0.227 -0.75121359962
5 0.252 -0.27349848370
6 0.215 -1.11115718531
7 0.244 -0.40417373123
8 0.303 0.340861459056
9 0.341 0.676487262910
10 0.522 1.793979568870
11 0.298 0.291141136865
12 0.200 -2.49218151300
13 0.500 1.681250762888
14 0.200 -2.49218151300
15 0.522 1.793979568870
16
17
18
19
20
21
22
23
Identification Information
Characteristic: Minutes to reach 3 min. Fo
Units: min
I.D. (product, lot, etc.): Penetration
Date:
Lower Spec Limit (if any):
Upper Spec Limit (if any): 3
Lower Bound (if any): 0
Upper Bound (if any):
Fill Order/Group Column...
Selected Distribution
Beta Distribution (0.300343, 0.0960209, 1.774071, 7.396485)
Select Distribution
Sheet 1
Sheet 2
Sheet 3
Test Distribution
Find Best Distribution
Skewness-Kurtosis Plot
Print
Help (F1)

Minutes to reach 3 min. Fo (min) - Penetration

Beta Distribution (0.300343, 0.0960209, 1.774071, 7.396485)

Sample Size =	15
Average =	0.2989
Standard Deviation =	0.1190
Skewness =	1.25
Excess Kurtosis =	0.08
Test of Fit: p-value =	0.7633
(SK All) Decision =	Pass
(SK Spec) Decision =	Pass
Pp =	---
Ppk =	1.94
Est. % In Spec. =	100.000000%



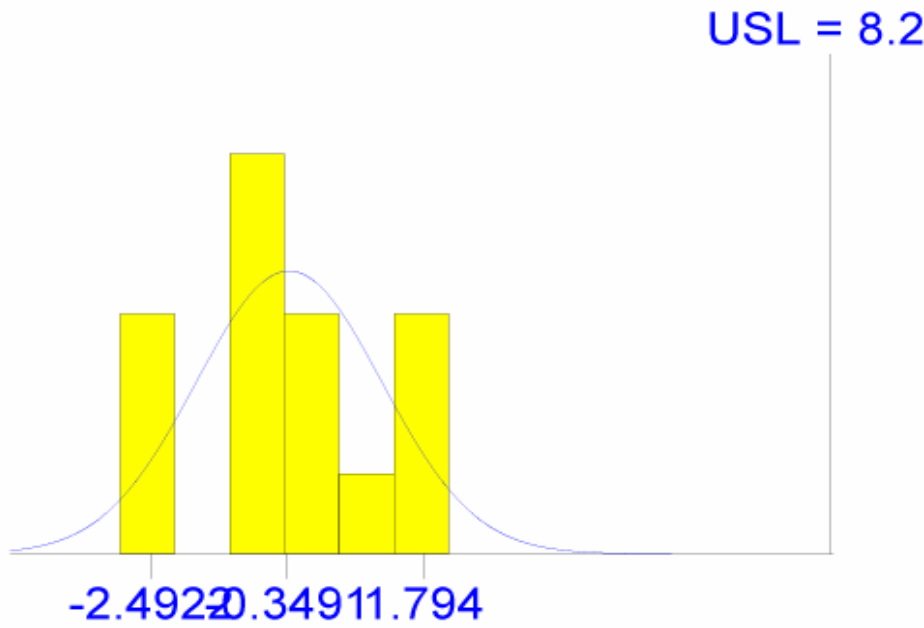
With 99% confidence more than 99% of the values are below 1.66113

With 99% confidence more than 99.9474% of the values are in spec.

Minutes to reach 3 min. Fo (min) - Penetration

sformation = NORMINV(BETADIST(X,1.03632737221423,29.0013020670302, (1.66472858429911 - 2.93101754615536/ 2.0), (1.66472858429911 + 2.93101754615536/ 2.0)),0,1)

Sample Size =	15
Average =	-0.3218
Standard Deviation =	1.4652
Skewness =	-0.08
Excess Kurtosis =	-0.80
Test of Fit: p-value =	0.7633
(SK All) Decision =	Pass
(SK Spec) Decision =	Pass
Pp =	---
Ppk =	1.94
Est. % In Spec. =	100.000000%



With 99% confidence more than 99% of the values are below 5.865
With 99% confidence more than 99.9474% of the values are in spec.

Distribution Analyzer 1.2 Validation Package

Contains reproductions of the following two documents:

Report Number: TE-07-2

Protocol Number: TE-07-2

Original documents and supporting evidence are on file at:

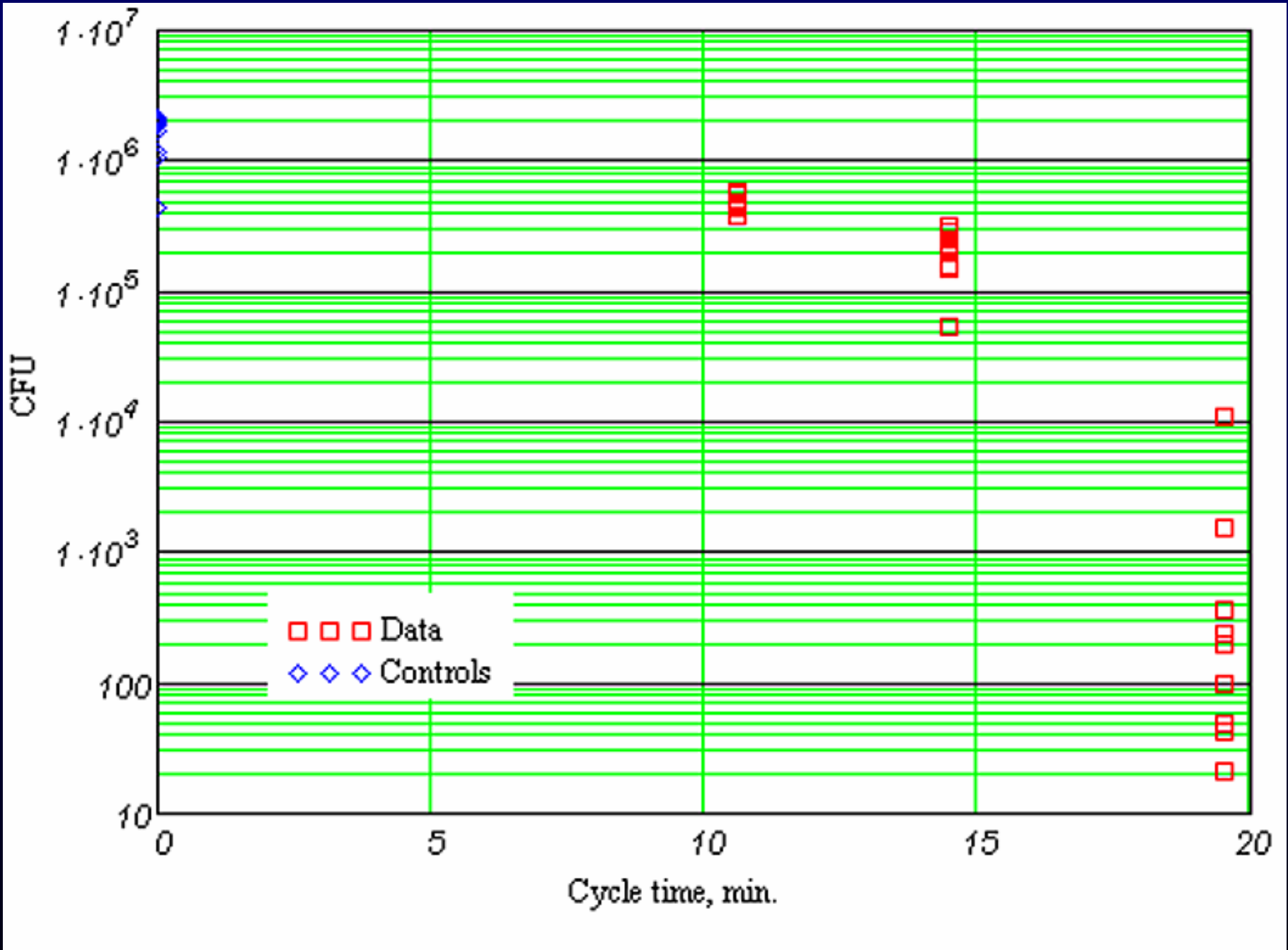
Taylor Enterprises, Inc.
5510 Fairmont Rd., Suite A
Libertyville, IL 60048 USA

Office: (847) 367-1032
Fax: (847) 367-1037
Email: info@variation.com
Web: www.variation.com

Program has been validated and can be used for regulatory submissions to the FDA.

Prediction intervals on fractional exposure data.

Inoculated packs distributed randomly in the load (distribution gradient previously demonstrated to be random) or in the coldest region.

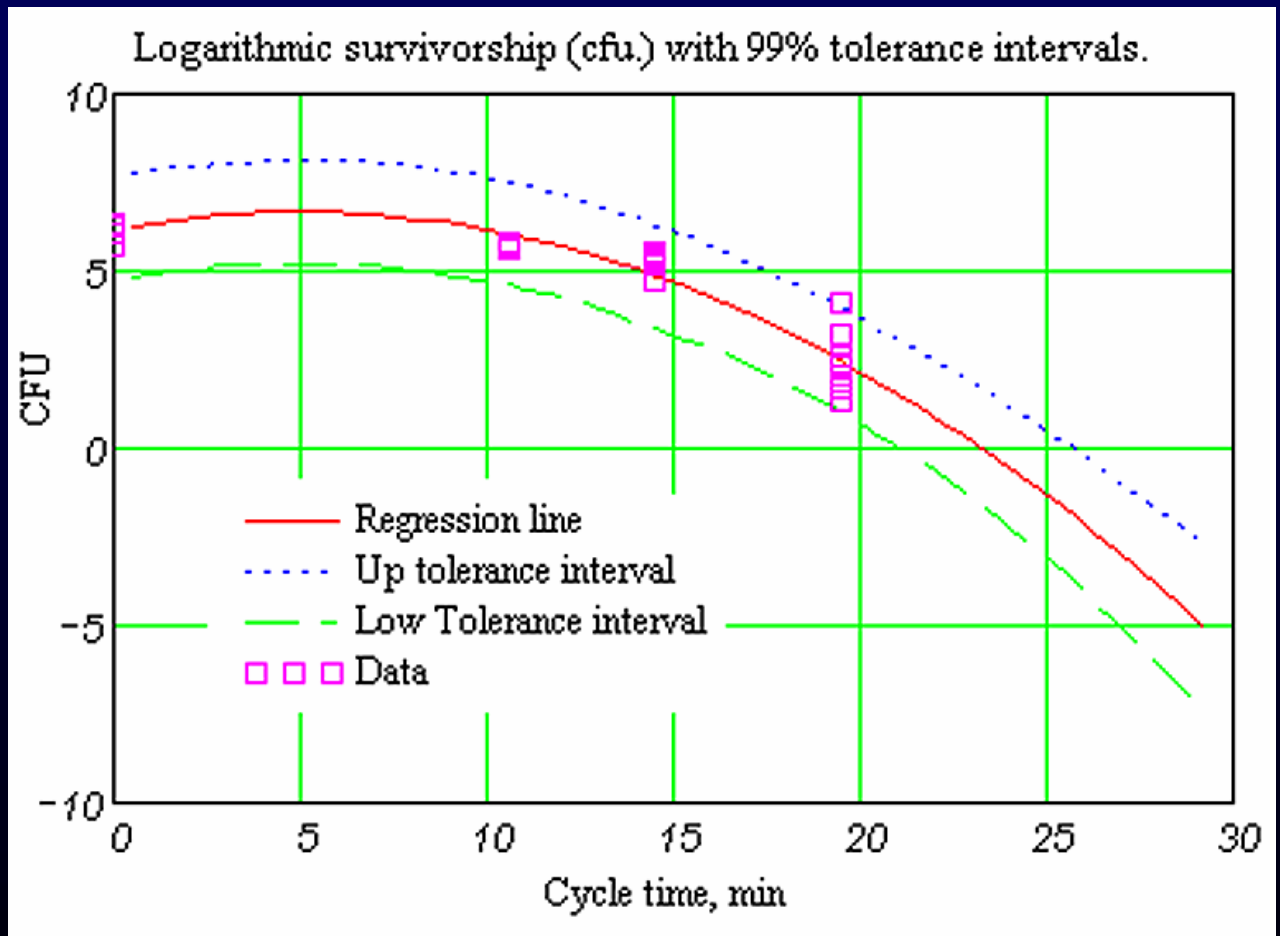

1·10^7
1·10^6
1·10^5
1·10^4
1·10^3
100
10
CFU
0
5
10
15
20
Cycle time, min.
Data
Controls

$$b = \begin{pmatrix} 6.1240239542 \\ 0.2006286003 \\ -0.019945765 \end{pmatrix}$$

Coefficients for the quadratic model.

$$RSQUARED := \frac{SSR}{SSTO}$$

RSQUARED = 0.898 Coefficient of determination:



Calculate time required to reach logarithmic survivorship of -1 at the upper 99% prediction interval.

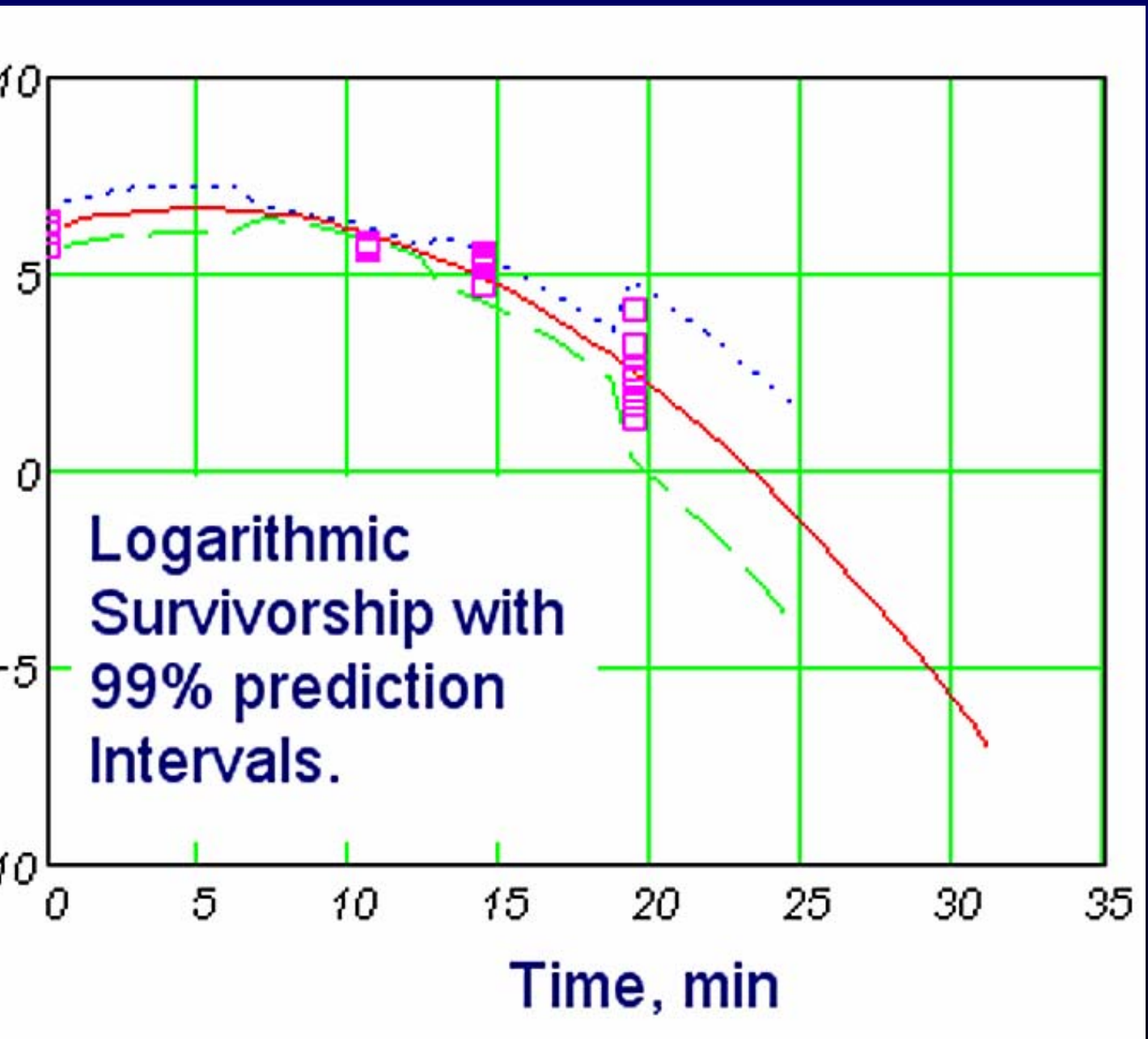
$t := 40$ Initial guess.

Given $\text{linterp}(x_o, UP, t) = -1$ $\text{timeNeeded99} := \text{Find}(t)$

$\text{timeNeeded99} = 27.051$

$\text{Exposure99} := \text{ceil}(\text{timeNeeded99} - \text{exposureStart})$

$\text{Exposure99} = 17$



Prediction intervals calculated with variable standard deviation.

References

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