PROCESS SAFETY ENGINEERING (0905477)

06- DOSE RESPONSE

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The superior man, when resting in safety, does not forget that danger may come…. When all is orderly, he does not forget that disorder may come. Confucius (551 BC – 479 BC)

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Outline

- Toxicological Study
- Factors Affecting A Toxicological Study
- Dose-Response
- Crash Review of Statistics
- Analysis for Toxicological Study
- LD, ED and TD Curves
- Mixtures of Chemicals
- Models for Dose-Response Curves
- The Probit (**Pro**bability Un**it**)
- Linearization of Response-Curve
- The Causative Factor
- Relating TLV and LD50

Toxicological Studies

- A major objective of a toxicological study is to quantify the effects of the suspect toxicant on a target organism.
- For most toxicological studies animals are used, usually with the hope that the results can be extrapolated to humans.
- Once the effects of a suspect agent have been quantified, appropriate procedures are established to ensure that the agent is handled properly.
- Baseline toxicological studies are based on samples with no toxicants as a reference.

Raises some ethical issues?

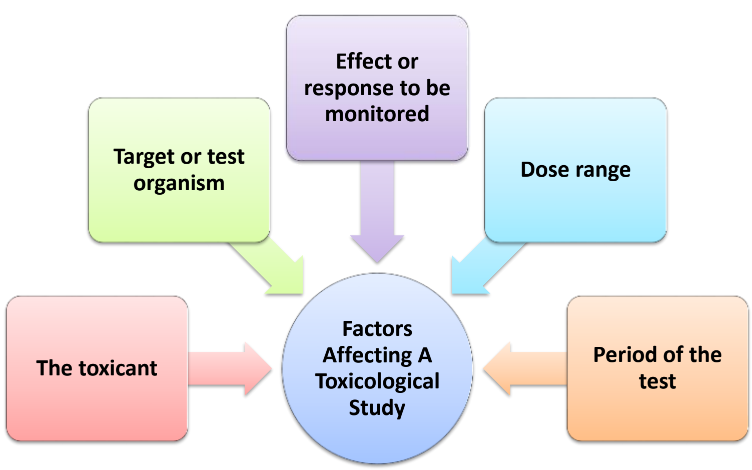
Difficulties Encountered in Toxicological Studies

- Baseline study required (control group)
- Response not necessarily numerical
- Specificity of individual response
  - Allergy or immunity
  - Statistical study required
  - Organism specific response, not applicable to humans
  - Dosage response
  - Response time, latency, acute versus chronic
  - Difficulty in measuring intended variable (lead in liver measured by lead in blood)

- Major Problem
  - No ethical way to get human volunteers, hence need to use “model” systems of rats, cats, dogs, rabbits, etc.
- Hinders production of a new chemical, almost as stringent as a new drug
  - Currently averages 17 years and 1 million pages

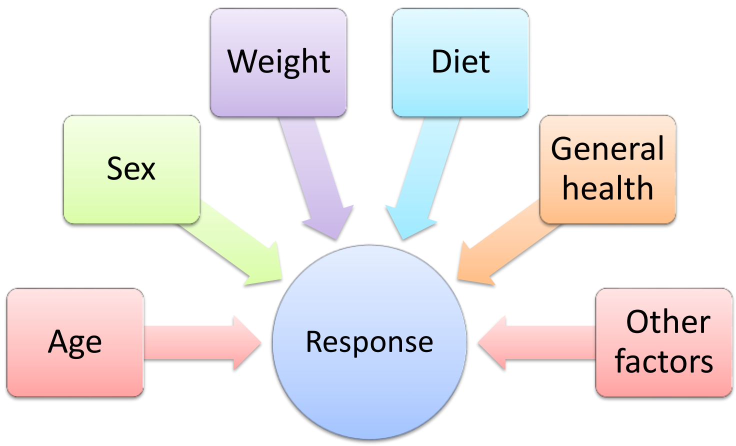
Factors Affecting A Toxicological Study

- Before undertaking a toxicological study, the following items must be identified:



Factors Affecting Dose-Response

- Biological organisms respond differently to the same dose of a toxicant.



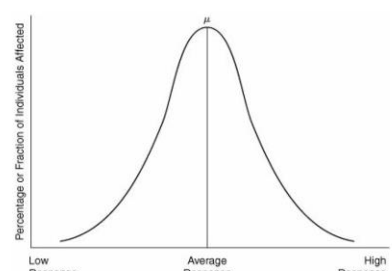
Crash Review of Statistics

x = response
$f(x)$ = probability (or fraction) of individuals experiencing a specific response.
μ = the arithmetic mean defined as

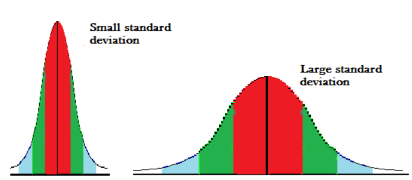
$$\mu = \frac{\sum_{i=1}^{n} x_i f(x_i)}{\sum_{i=1}^{n} f(x_i)}$$

σ = the standard deviation defined from the variance as

$$\sigma^2 = \frac{\sum_{i=1}^{n} (x_i - \mu)^2 f(x_i)}{\sum_{i=1}^{n} f(x_i)}$$

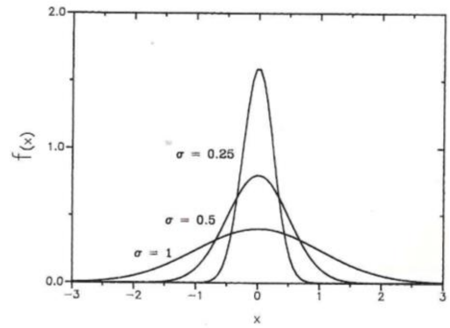


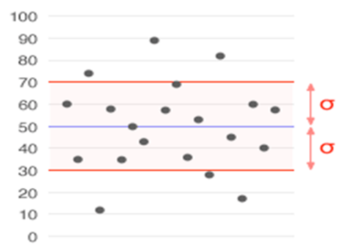
$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{-1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}$$

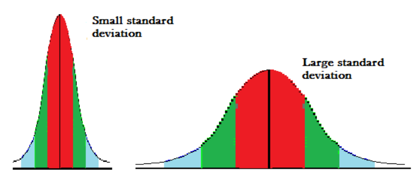


Standard Deviation

- Standard deviation measures how the data are spread out with respect to the mean.
- The higher the value of σ, the more spread the data are

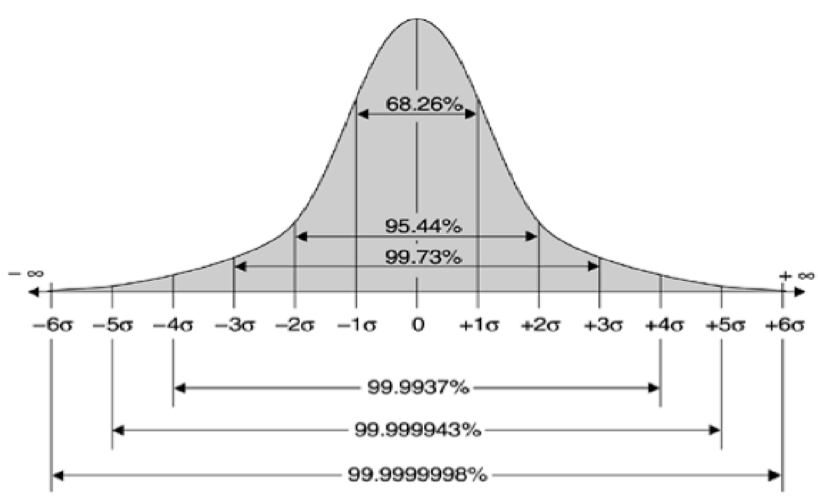






Area Under the Curve (AUC)

- Area under the curve represents the percentage of individuals affected for a specific response interval

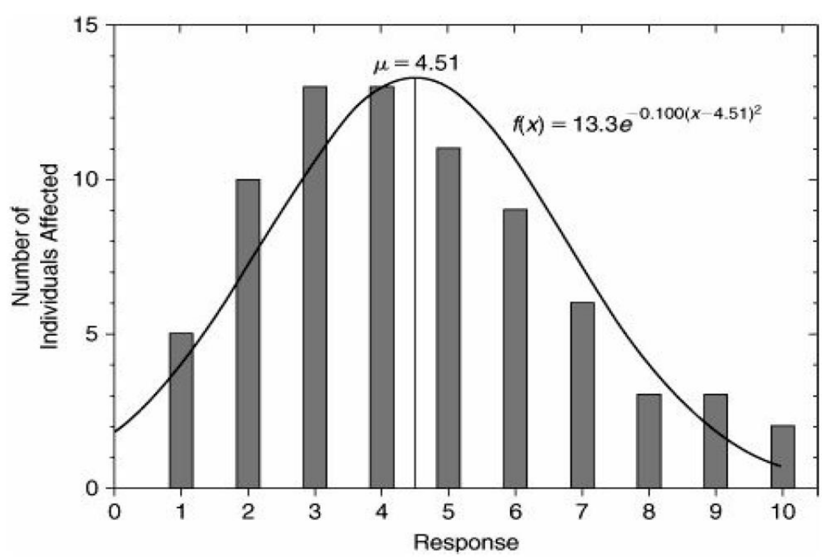


Example 2.1

Seventy-five people are tested for skin irritation because of a specific dose of a substance. The responses are recorded on a scale from 0 to 10, with 0 indicating no response and 10 indicating a high response. The number of individuals exhibiting a specific response is given in the given table.

a) Plot a histogram of the number of individuals affected versus the response.
b) Determine the mean and the standard deviation.
c) Plot the normal distribution on the histogram of the original data.

Response	Number of individuals affected
0	0
1	5
2	10
3	13
4	13
5	11
6	9
7	6
8	3
9	3
10	2
	75



Percentage of individuals affected based on response

$$\mu = \frac{(0\times0)+(1\times5)+(2\times10)+(3\times13)+(4\times13)+(5\times11)+(6\times9)+(7\times6)+(8\times3)+(9\times3)+(10\times2)}{75}$$

$$= \frac{338}{75} = 4.51.$$

$$\sigma^2 = [(1-4.51)^2(5) + (2-4.51)^2(10) + (3-4.51)^2(13) + (4-4.51)^2(13) + (5-4.51)^2(11) + (6-4.51)^2(9) + (7-4.51)^2(6) + (8-4.51)^2(3) + (9-4.51)^2(3) + (10-4.51)^2(2)]/75 = 374.7/75 = 5.00,$$

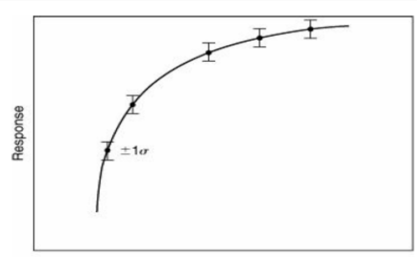
$$\sigma = \sqrt{\sigma^2} = \sqrt{5.00} = 2.24.$$

$$f(x) = \frac{1}{(2.24)\sqrt{6.28}} e^{-\frac{1}{2}\left(\frac{x-4.51}{2.24}\right)^2}$$

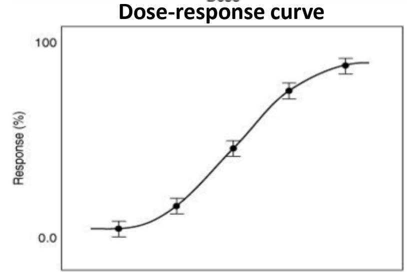
$$= 0.178 e^{-0.100(x-4.51)^2}.$$

Analysis for Toxicological Study

1. Run test on “large” population.
2. Given same dose (usually in dose/body mass).
3. Determine the number or fraction of individuals that have a response.
4. The toxicological experiment is repeated for **a number of different doses,** and normal curves are drawn.
5. The standard deviation and mean response are determined from the data for each dose.
6. A complete dose-response curve is produced by plotting the cumulative mean response at each dose.
7. Error bars are drawn at ±σ around the mean.
8. For convenience, the response is plotted versus the **logarithm of the dose. Forms Sigmoid shaped curve.**



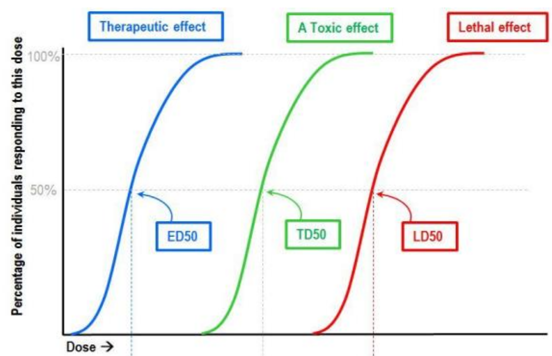
Dose-response curve



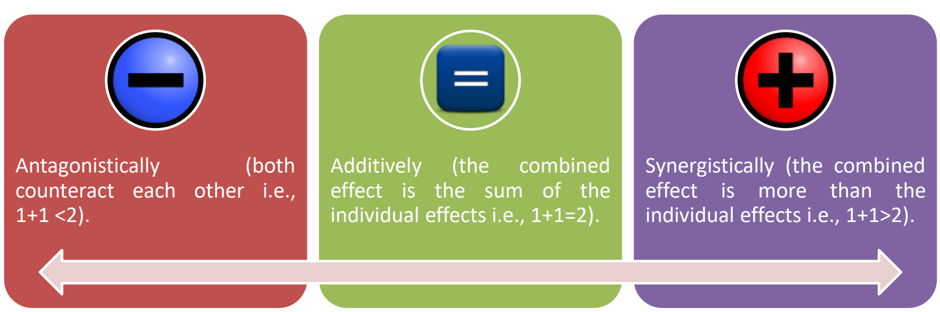
Response versus log dose curve

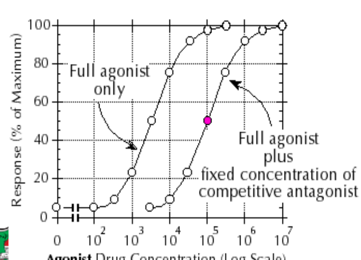
LD, ED and TD Curves

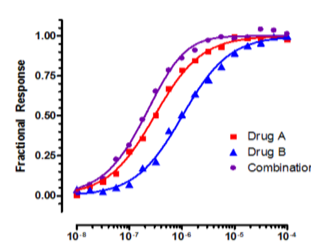
- If the response of interest is death or lethality, the response versus log dose curve is called a **lethal dose** curve (LD).
- If the response to the chemical or agent is minor and reversible (such as minor eye irritation), the response–log dose curve is called the **effective dose** curve (ED).
- if the response to the agent is toxic (an undesirable response that is not lethal but is irreversible, such as liver or lung damage), the response–log dose curve is called the **toxic dose** curve (TD).



Mixtures of Chemicals

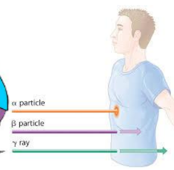


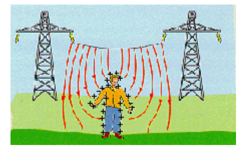




Models for Dose-Response Curves

- Response versus dose curves can be drawn for a wide variety of exposures, including exposure to:
  - heat,
  - pressure,
  - radiation,
  - impact, and
  - sound.





- For computational purposes the response versus dose curve is not convenient; an analytical equation is preferred.

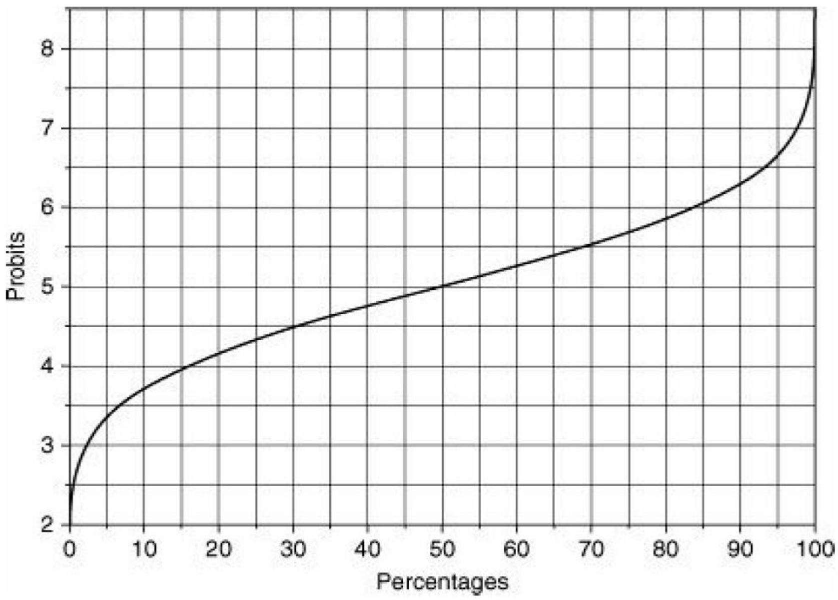
The Probit (**Pro**bability Un**it**)

- Many methods exist for representing the response-dose curve.
- For single exposures the probit (**probit ≡ probability unit**) method provides a straight-line equivalent to the response-dose curve.
- The probit variable Y is related to the probability P by:

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{Y-5} e^{-u^2/2} du$$

$$= 50\left[1 + \frac{Y-5}{|Y-5|} \operatorname{erf}\left(\frac{|Y-5|}{\sqrt{2}}\right)\right]$$

- Plotted in Figure 2-9 and tabulated in Table 2-4.



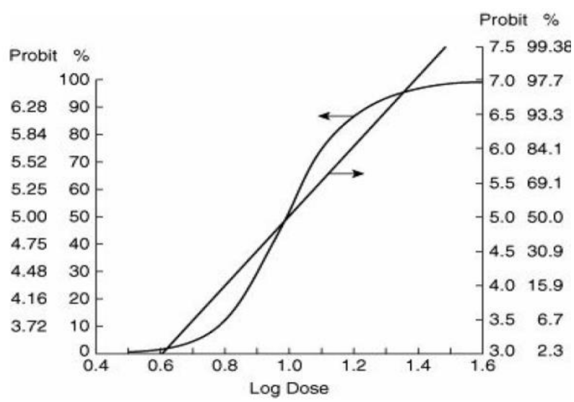
The relationship between percentages and probits

Transformation from Percentages to Probits

%	0	1	2	3	4	5	6	7	8	9
0	–	2.67	2.95	3.12	3.25	3.36	3.45	3.52	3.59	3.66
10	3.72	3.77	3.82	3.87	3.92	3.96	4.01	4.05	4.08	4.12
20	4.16	4.19	4.23	4.26	4.29	4.33	4.36	4.39	4.42	4.45
30	4.48	4.50	4.53	4.56	4.59	4.61	4.64	4.67	4.69	4.72
40	4.75	4.77	4.80	4.82	4.85	4.87	4.90	4.92	4.95	4.97
50	5.00	5.03	5.05	5.08	5.10	5.13	5.15	5.18	5.20	5.23
60	5.25	5.28	5.31	5.33	5.36	5.39	5.41	5.44	5.47	5.50
70	5.52	5.55	5.58	5.61	5.64	5.67	5.71	5.74	5.77	5.81
80	5.84	5.88	5.92	5.95	5.99	6.04	6.08	6.13	6.18	6.23
90	6.28	6.34	6.41	6.48	6.55	6.64	6.75	6.88	7.05	7.33
%	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
99	7.33	7.37	7.41	7.46	7.51	7.58	7.65	7.75	7.88	8.09

Linearization of Response-Curve

- The probit relationship transforms the sigmoid shape of the normal response versus dose curve into a straight line when plotted using a linear probit scale.
- Standard curve-fitting techniques are used to determine the best-fitting straight line.



The Causative Factor: Fires

- Table 2-5 lists a variety of probit equations for a number of different types of exposures.
  - The causative factor represents the dose V.
  - The probit variable Y is computed from

$$Y = k_1 + k_2 \ln V$$

Type of injury or damage	Causative variable	Probit parameters k_1	Probit parameters k_2
Fire[a]			
Burn deaths from flash fire	$t_e I_e^{4/3}/10^4$	−14.9	2.56
Burn deaths from pool burning	$t I^{4/3}/10^4$	−14.9	2.56

t_e = effective time duration (s)
I_e = effective radiation intensity (W/m^2)
t = time duration of pool burning (s)
I = radiation intensity from pool burning (W/m^2)

A pool fire is a turbulent diffusion fire burning above a horizontal pool of vaporizing hydrocarbon fuel where the fuel has zero or low initial momentum.

The Causative Factor: Explosions

Type of injury or damage	Causative variable	Probit parameters k_1	Probit parameters k_2
Explosion[a]			
Deaths from lung hemorrhage	p^o	−77.1	6.91
Eardrum ruptures	p^o	−15.6	1.93
Deaths from impact	J	−46.1	4.82
Injuries from impact	J	−39.1	4.45
Injuries from flying fragments	J	−27.1	4.26
Structural damage	p^o	−23.8	2.92
Glass breakage	p^o	−18.1	2.79

p^o = peak overpressure (N/m^2)
J = impulse (N s/m^2)

The Causative Factor: Toxic Releases

Type of injury or damage	Causative variable	Probit parameters k_1	Probit parameters k_2
Toxic release[b]			
Ammonia deaths	$\Sigma C^{2.0}T$	−35.9	1.85
Carbon monoxide deaths	$\Sigma C^{1.0}T$	−37.98	3.7
Chlorine deaths	$\Sigma C^{2.0}T$	−8.29	0.92
Ethylene oxide deaths[c]	$\Sigma C^{1.0}T$	−6.19	1.0
Hydrogen chloride deaths	$\Sigma C^{1.0}T$	−16.85	2.0
Nitrogen dioxide deaths	$\Sigma C^{2.0}T$	−13.79	1.4
Phosgene deaths	$\Sigma C^{1.0}T$	−19.27	3.69
Propylene oxide deaths	$\Sigma C^{2.0}T$	−7.42	0.51
Sulfur dioxide deaths	$\Sigma C^{1.0}T$	−15.67	1.0
Toluene	$\Sigma C^{2.5}T$	−6.79	0.41

C = concentration (ppm)
T = time interval (min)

Example 2-2

- Determine the percentage of people who will die as a result of burns from pool burning if the probit variable *Y* is 4.39. Compare results from Table 2-4 and Equation 2-6.

Solution

The percentage from Table 2-4 is 27%. The same percentage can be computed using Equation 2-6, as follows:

$$P = 50\left[1 + \frac{4.39 - 5}{|4.39 - 5|}\operatorname{erf}\left(\frac{|4.39 - 5|}{\sqrt{2}}\right)\right]$$

$$= 50\left[1 - \operatorname{erf}\left(\frac{0.61}{\sqrt{2}}\right)\right] = 50[1 - \operatorname{erf}(0.4314)]$$

$$= 50[1 - 0.458] = 27.1\%,$$

where the error function is a mathematical function found in spreadsheets, Mathcad, and other software programs.

Time-Varying Doses

- When the exposed subjects receive different doses as a function of time

A risk assessment study scenario involves 1000 people being exposed to chlorine vapors due to a train car rupture in a suburban area.

People	Exposure time (min)	Concentration (ppm)
500	50	200
	30	100
	20	50
500	150	200
	50	100
	20	50

Predict the potential deaths.

Solution

From Handout

Chlorine $a = -13.22$, $b = 1.0$, $n = 2.3$

$$Y = -13.22 + 1.0 \ln \overline{C^n t}$$

For different exposure times

$$\overline{C^n t} = \int_{t_1}^{t_2} C^n dt = \sum C_i^n \Delta t.$$

So

$$Y = -13.22 + \ln \sum C^{2.3} \Delta t$$

First Group - 500 Individuals

time	Conc	$Con^{2.3}$	$C^{2.3}\Delta t$
50	200	196,051	9,802,550
30	100	39,810	1,194,300
20	50	8,084	161,680

$$Y = -13.22 + \ln(9.80\times10^6 + 1.19\times10^6 + 1.62\times10^5) = 3.01$$

From Table 2.4 → 2.35%

So 2.35% of people died or 11.76 = 12 people

2nd Group

time	Conc	$C^{2.3}$	$C^{2.3}t$
150	200	196,051	29,407,650
50	100	39,810	1,990,500
20	50	8,084	161,680

$$Y = -13.22 + \ln\left[29.41\times10^6 + 1.991\times10^6 + 0.1616\times10^6\right]$$

$$Y = 4.05$$

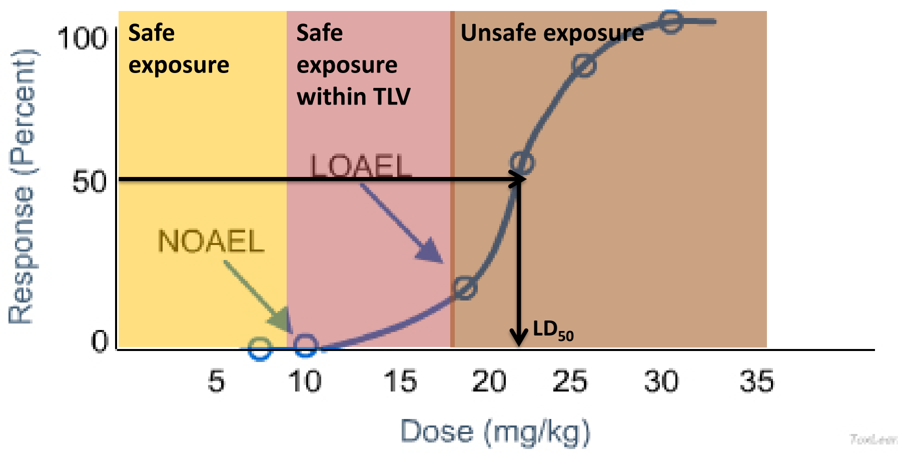
Table 2-4 → 17%

So 17% of people die or 85 people in this group

over all 12 + 85 = 97 deaths

~ 10% die

Relating TLV and LD50



Highest dose at which **no observable adverse effect** is seen (NOAEL) or the **lowest dose at which an adverse effect is observed** (LOAEL)

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