DOSE RESPONSE CURVE

DR SHAMS SULEMAN

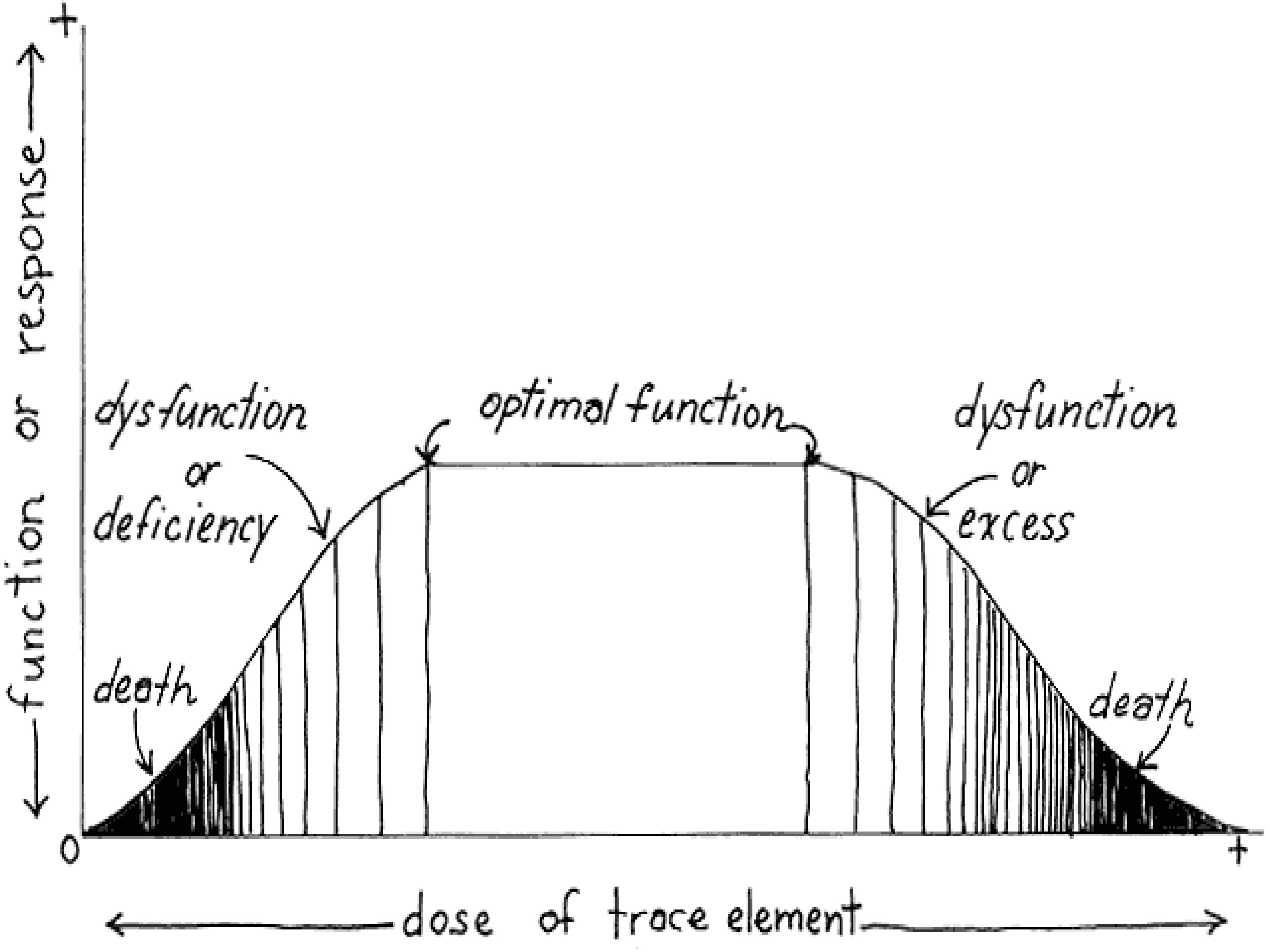
LEARNING OBJECTIVES

- Define Dose response curve, Graded dose-response curve and Quantal dose-response curve.
- Describe Graded dose-response curve and Quantal dose-response curve.
- Describe the limitations of graded dose-response curve and its remedy in a Quantal dose-response curve.
- Describe the significance of constructing dose-response curves.
- Explain the advantages of taking log dose values on the dose axis

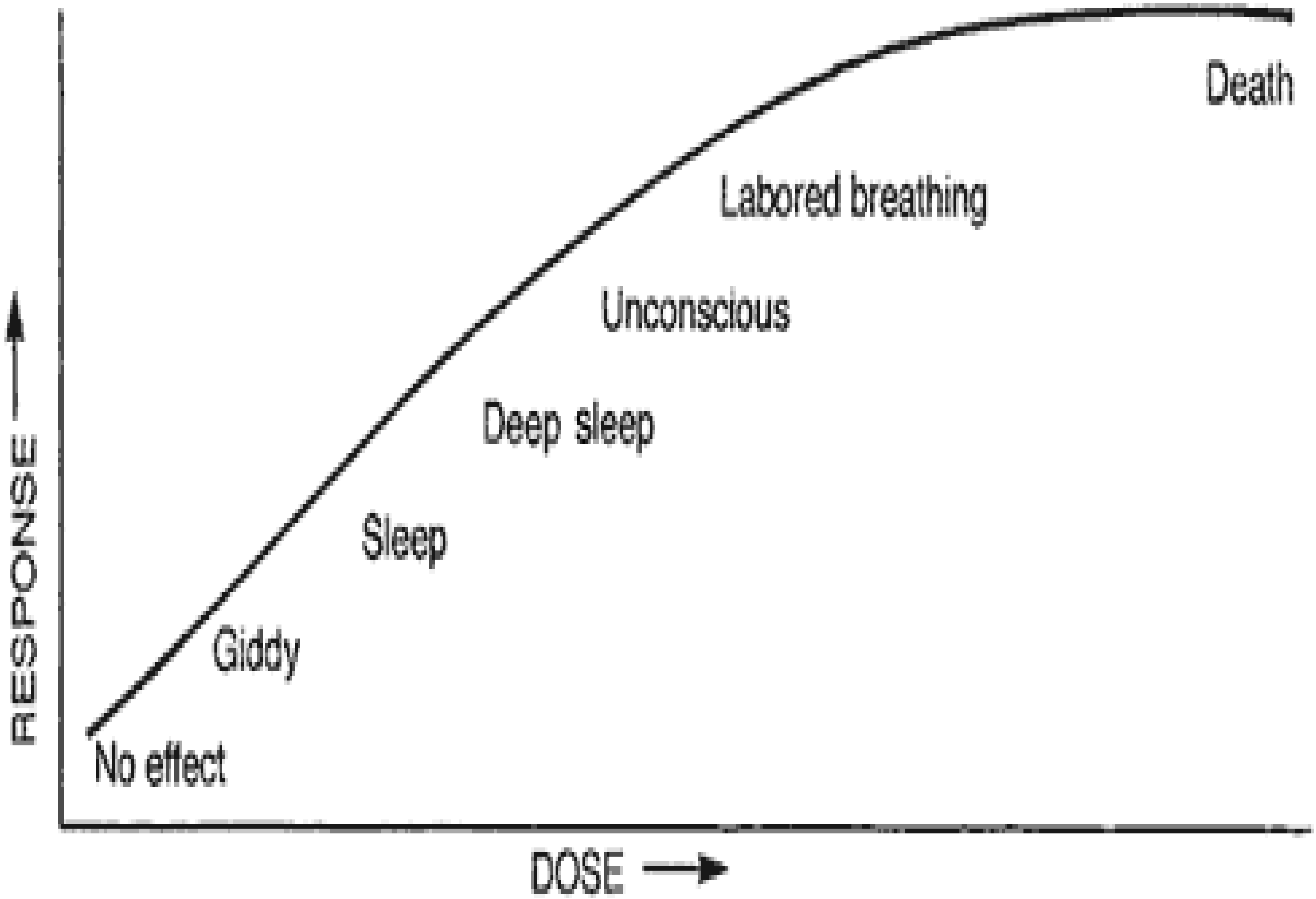
Relation between drug concentration & Response

It may be:

- Complex as observed clinically in patients.
- Simple in carefully controlled *in vitro* systems.
- It can be described mathematically & represented graphically.



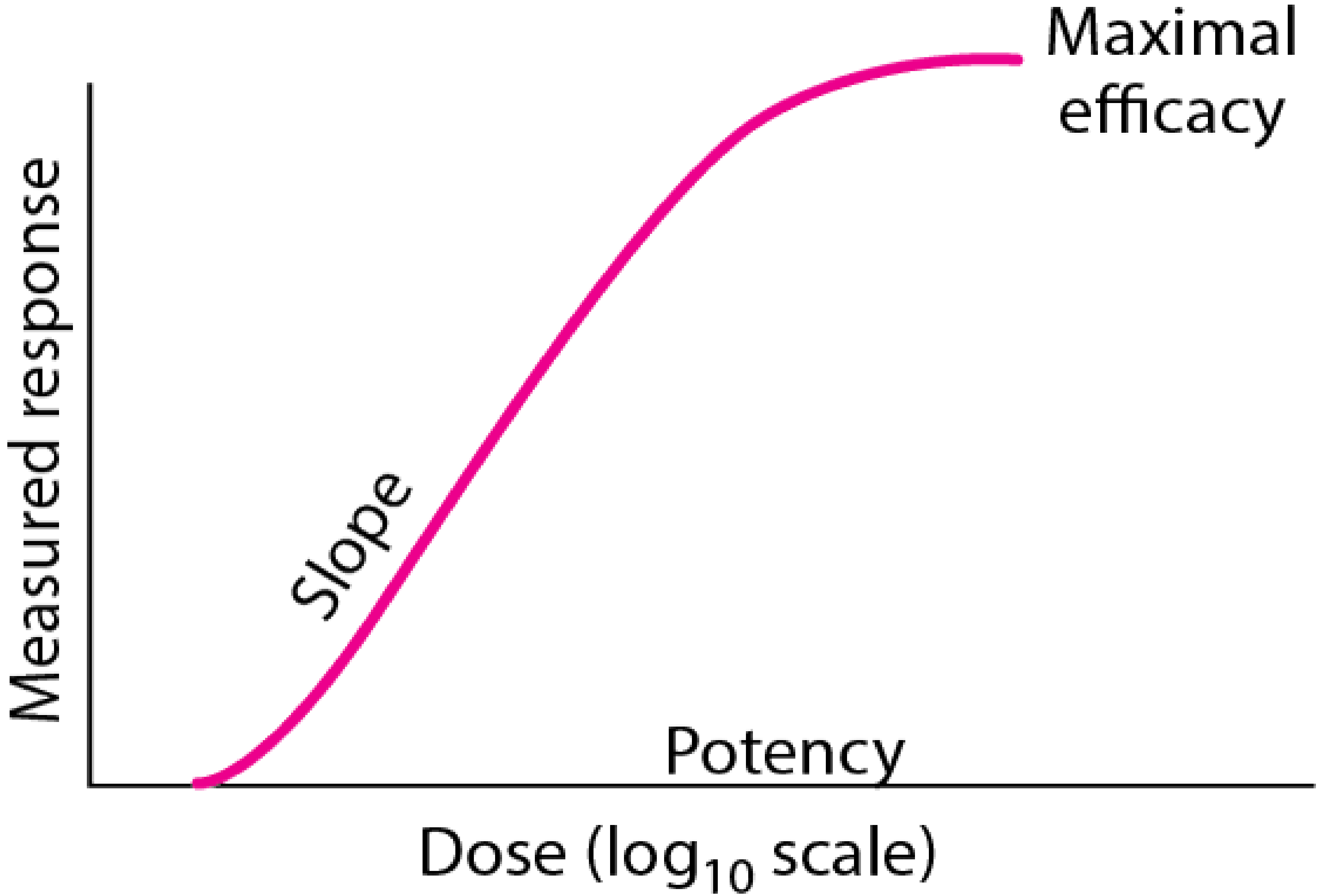
function or response
+
0
dysfunction
or
deficiency
death
optimal function
dysfunction
or
excess
death
+
dose of trace element

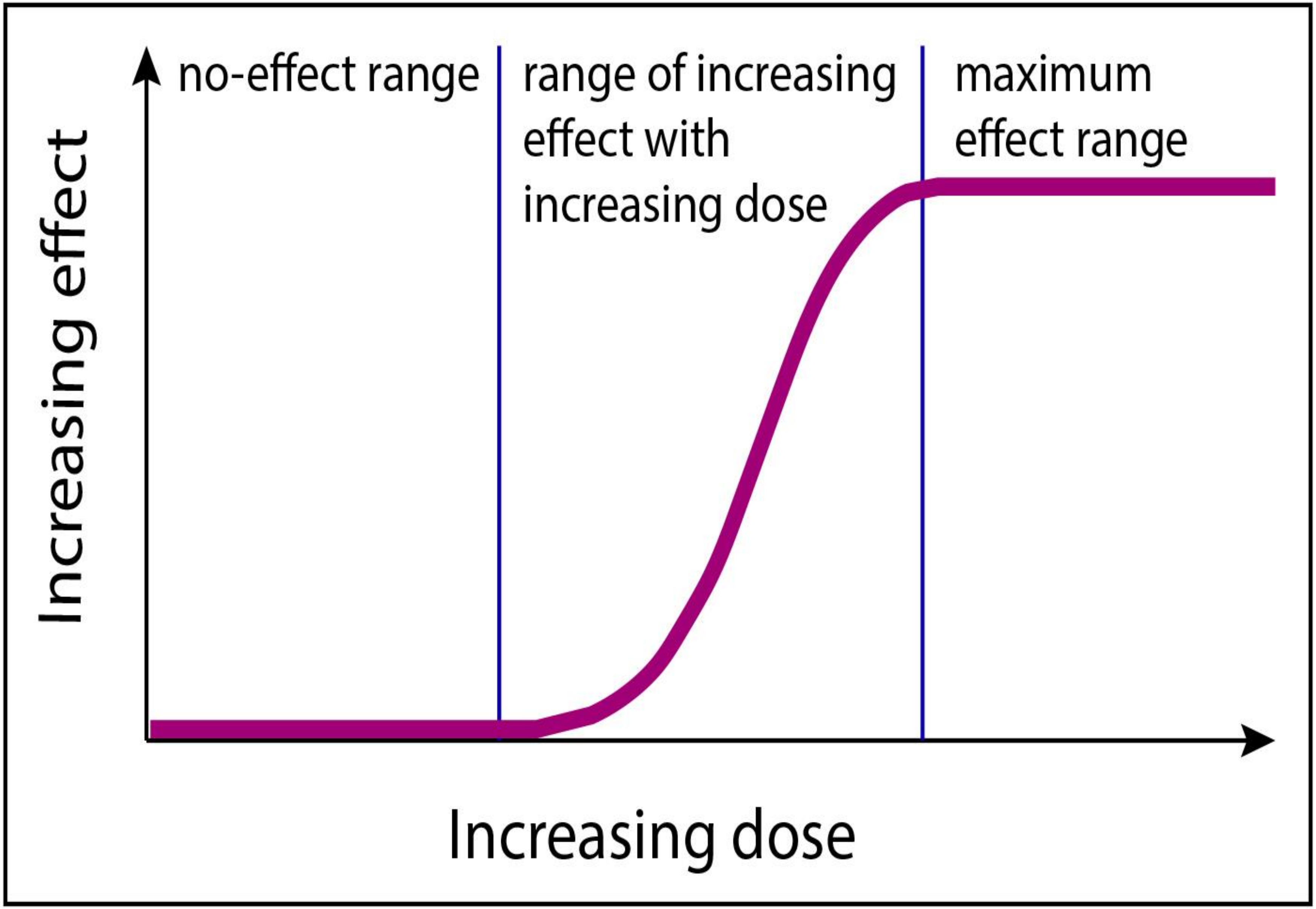

Death
Labored breathing
Unconscious
Deep sleep
Sleep
Giddy
No effect
RESPONSE
DOSE

Dose-response relationships

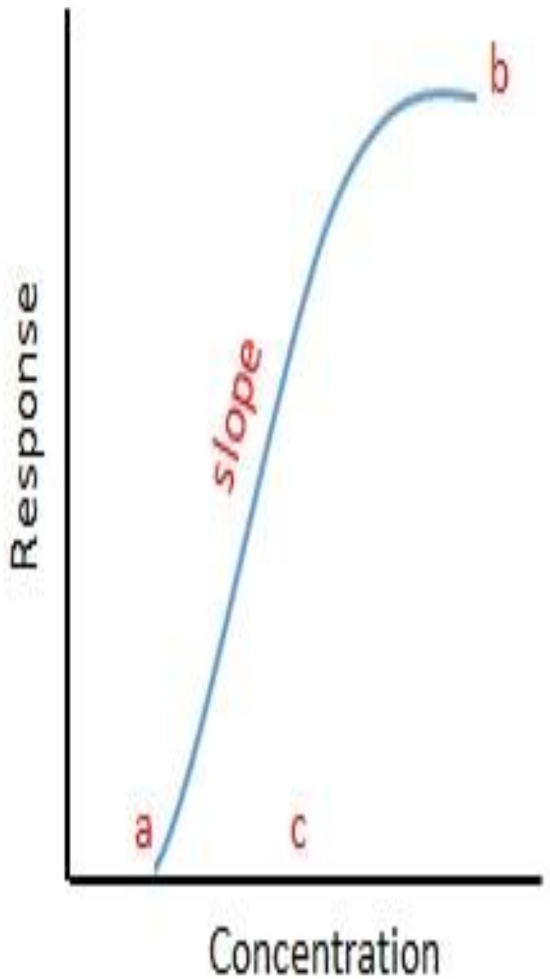
- The relationship between the concentration of drug at the receptor site and the magnitude of the response is called the dose-response relationship

- Depending on the purpose of the the studies, this relatioship can be described in terms of a graded (continous) response or a quantal (all-or-none) response


Maximal
efficacy
Measured response
Slope
Potency
Dose (log_{10} scale)


no-effect range
range of increasing effect with increasing dose
maximum effect range
Increasing effect
Increasing dose

1. A hypothetical dose-response curve



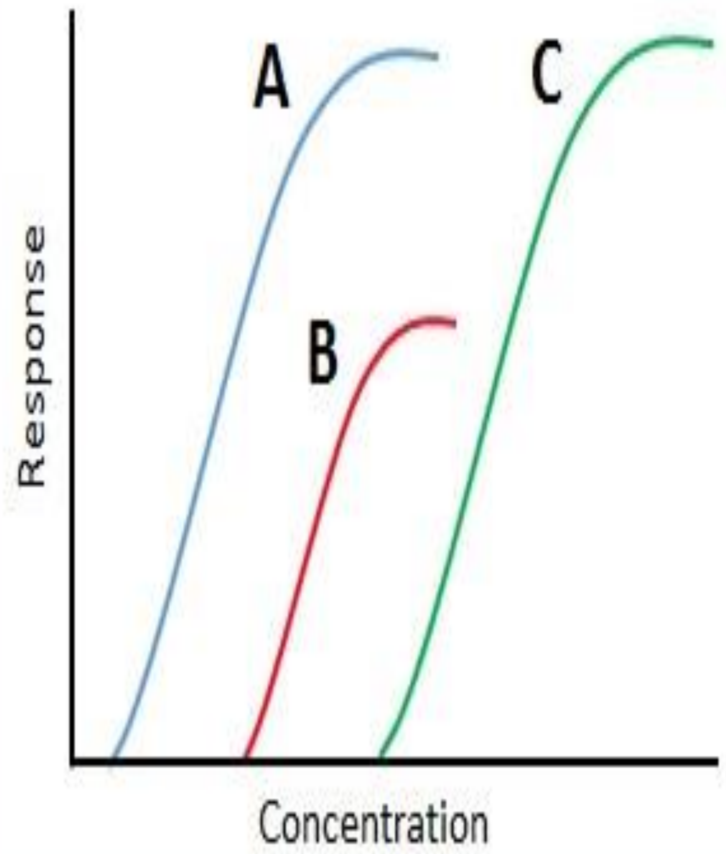
1. A hypothetical dose-response curve

Dose-response graphs typically have the dose on the X-axis and the measured effect (i.e. the measured response) on the y- axis. Plotting the logarithm of the concentration generally results in sigmoidal plots as shown on the left.

The main parameters that can be identified by dose-response curves are

- Potency- the position of the curve along the x-axis **a**
- Maximal efficacy- the greatest response attainable **b**
- Slope- change in response per unit dose (and half maximal dose **c**)

2. Comparison of dose-response curves



2. Comparison of dose-response curves

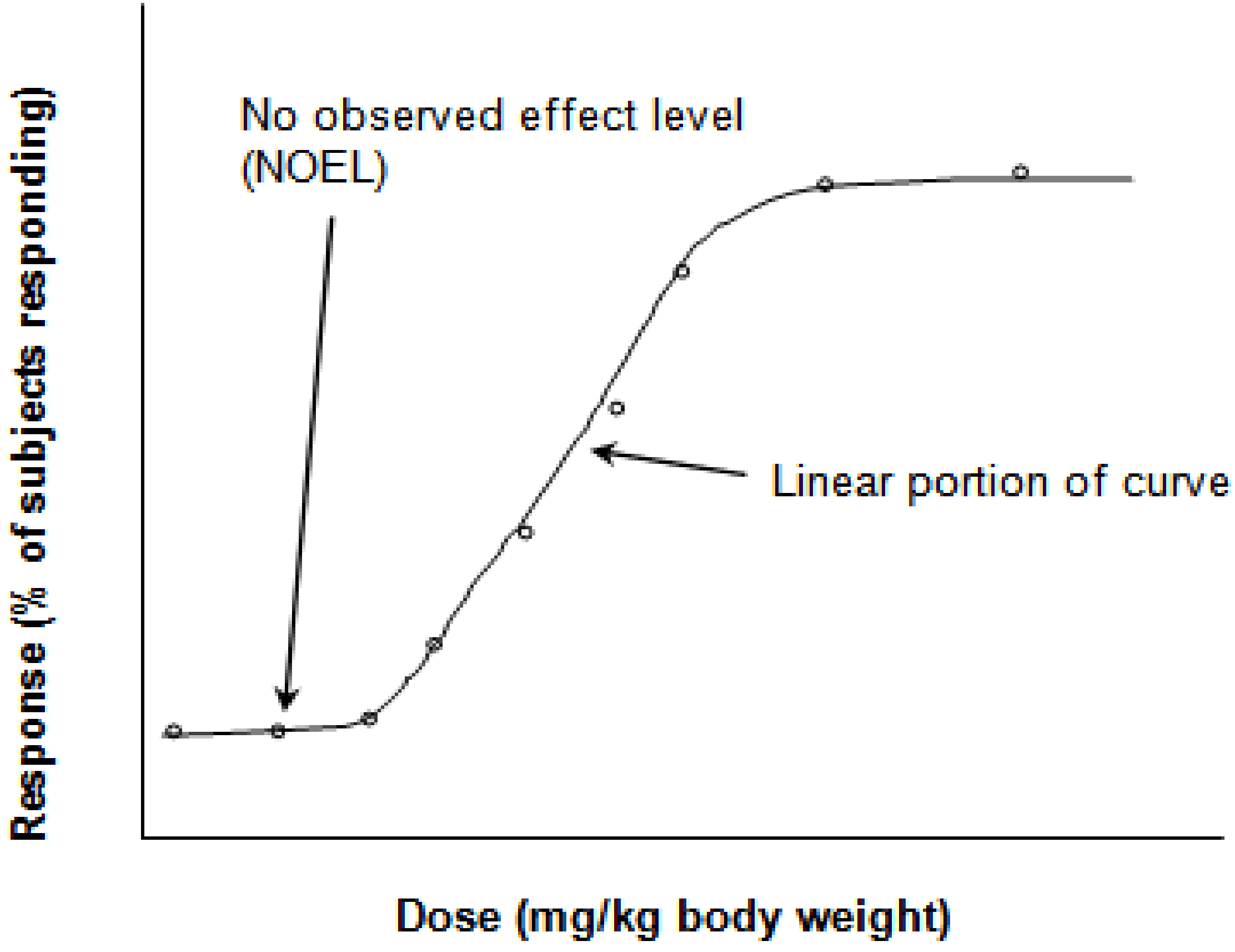
The pharmacologic profiles of individual drugs can be differentiated by comparing their dose-response curves.

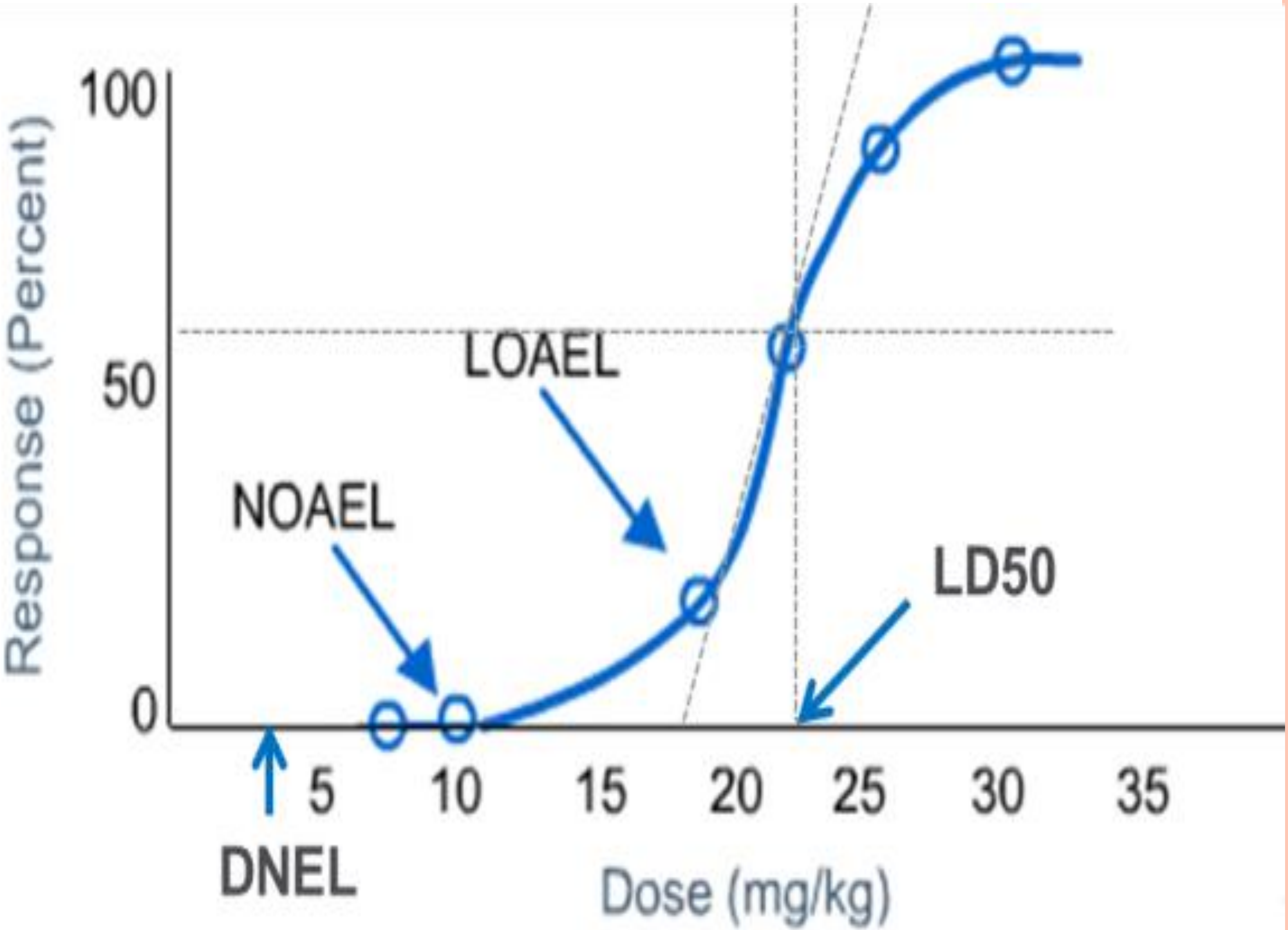
In the graph on the left, drug **A** has greater biological activity per dosing unit and is therefore considered to be more potent than drugs **B** or **C**- shown by its left-shifted position on the x-axis. Drugs **A** and **C** have equal efficacy- indicated by their maximal attainable response (ceiling effect). Drug **B** is more potent than drug **C**, but its maximal efficacy is lower.

Shape of the curve

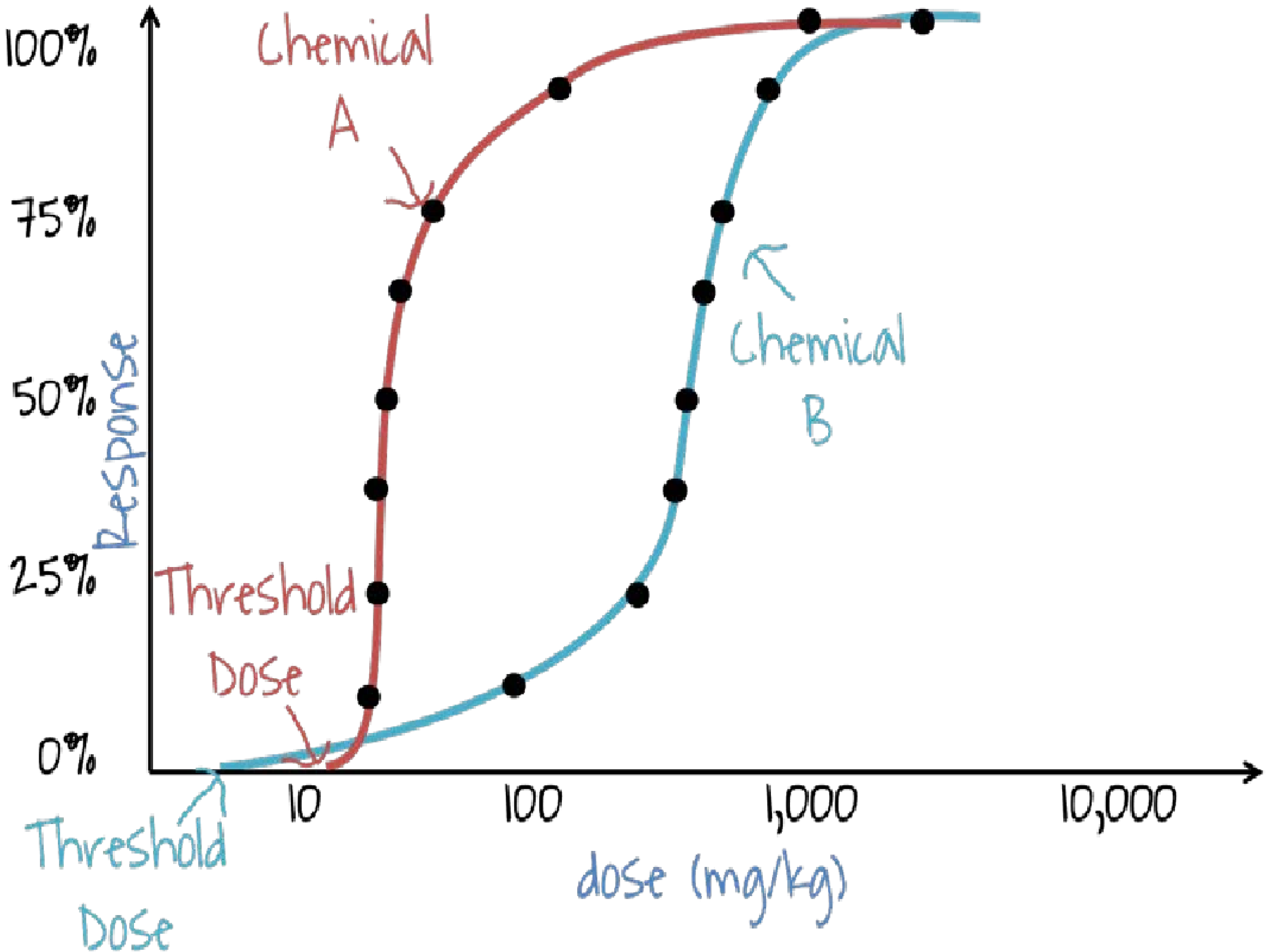
- A standard dose-response curve is defined by four parameters:
- the baseline response (Bottom),
- the maximum response (Top),
- the slope, and the
- drug concentration that provokes a response halfway between baseline and maximum (EC50).

Dose-Response Curve Showing a Threshold





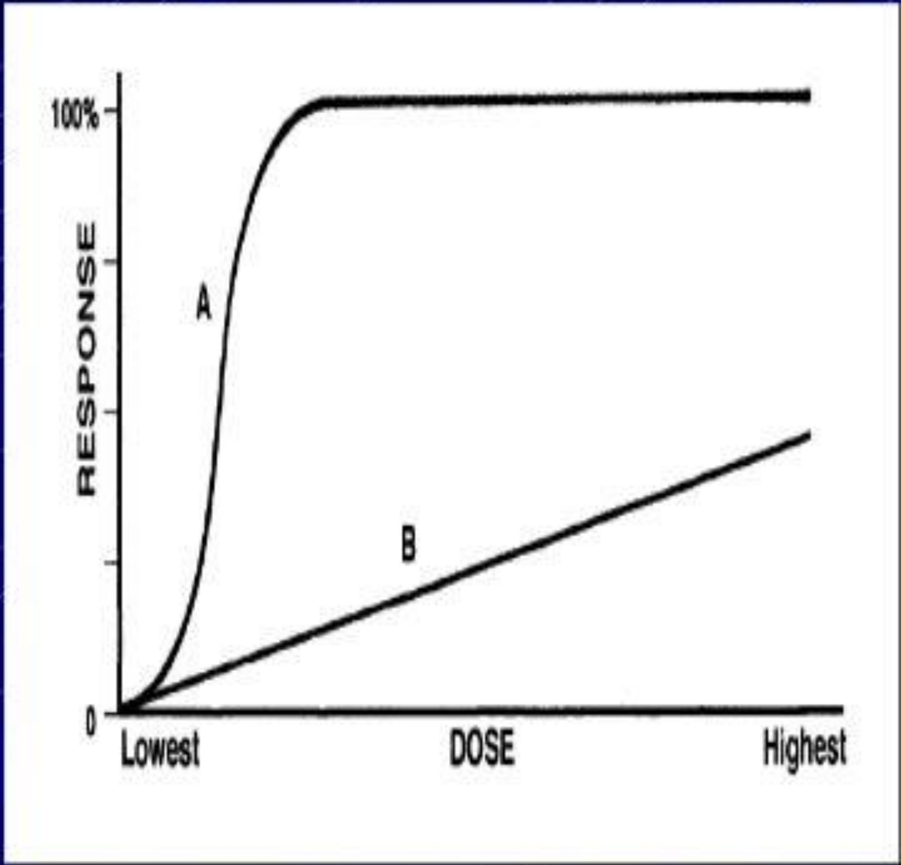
100
50
0
Response (Percent)
LOAEL
NOAEL
LD50
5
10
15
20
25
30
35
DNEL
Dose (mg/kg)



3 – The dose-response curve for hypothetical Chemical B is added, with a slope initially much lower than Che

- A sharp increase in slope suggest increasingly higher risk of toxic response as the dose increases

relatively flat slope suggest that effect of an increasing dose is minimal



DOSE RESPONSE CURVES

- Bioassay/ Quantitative analysis

TYPES

- Graded dose response = hyperbola
- Quantal dose response = sigmoid
- Time dependent response

INTERPRETATIONS

- Steep rise = frusemide
- Early plateau = thiazides

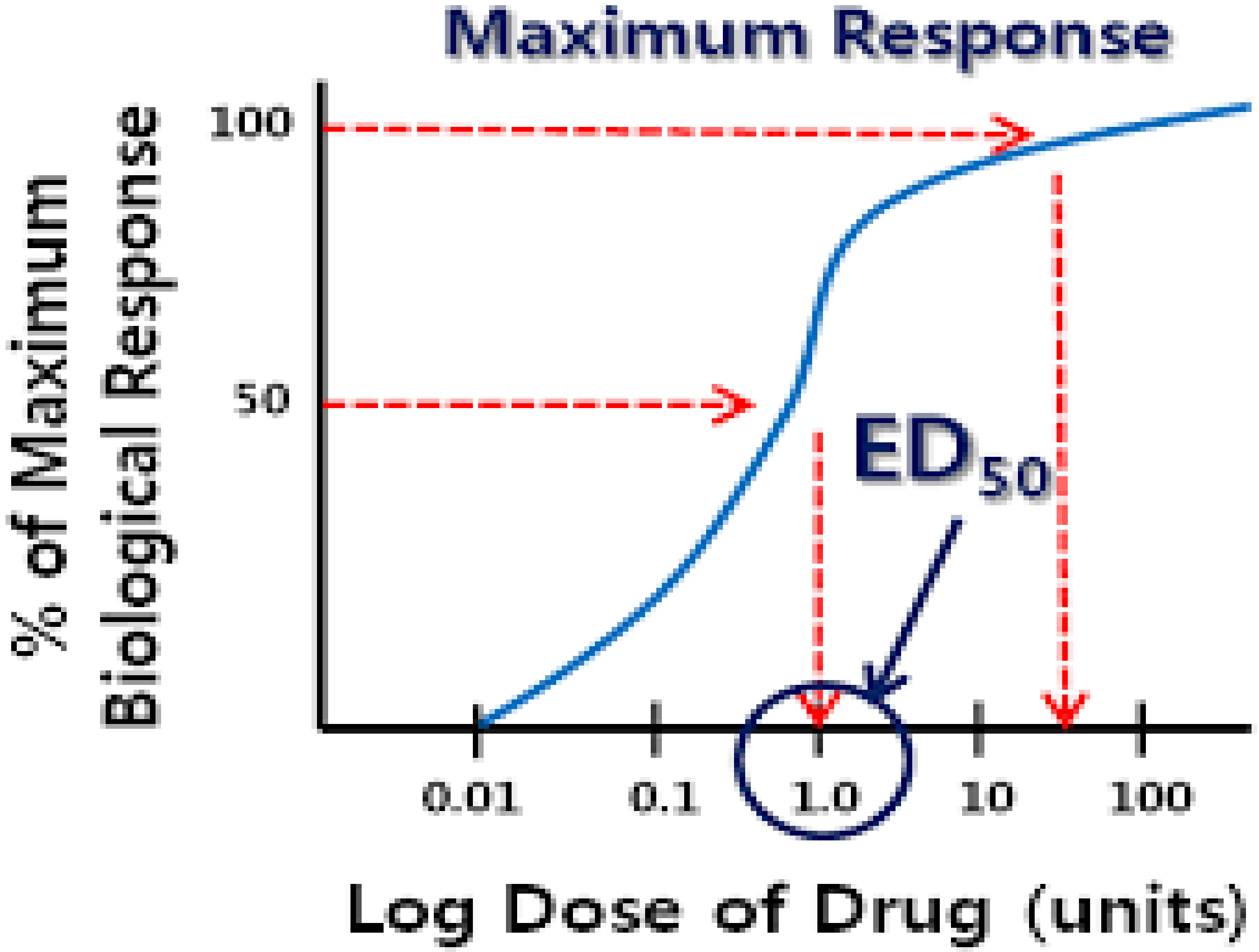
Graded-dose response relationship

- The response to a drug is a graded effect, meaning that the measured effect is continuous over a range of doses

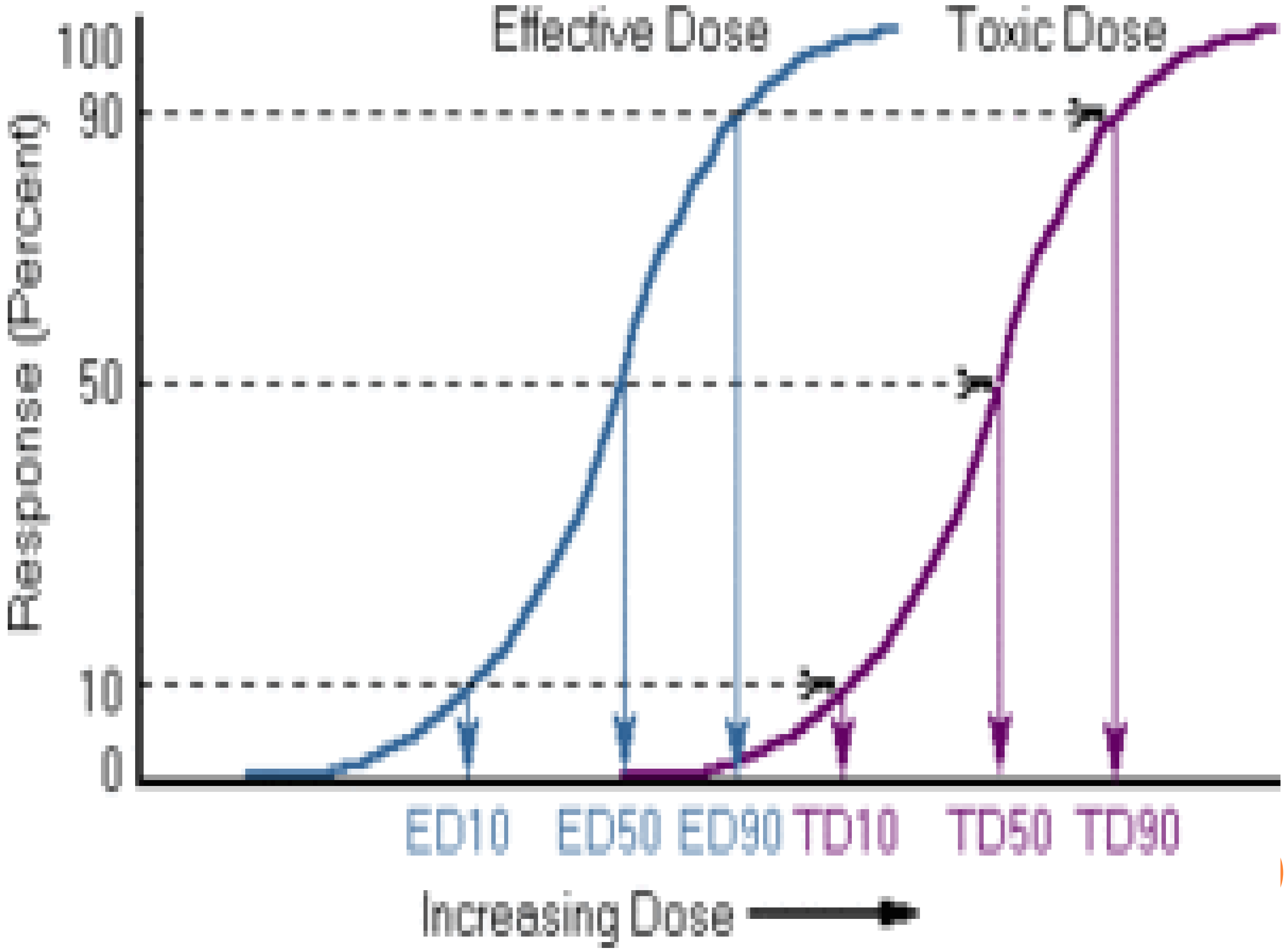
- Graded dose response curves are constructed by plotting the magnitude of the response against increasing doses of a drug (or log dose)

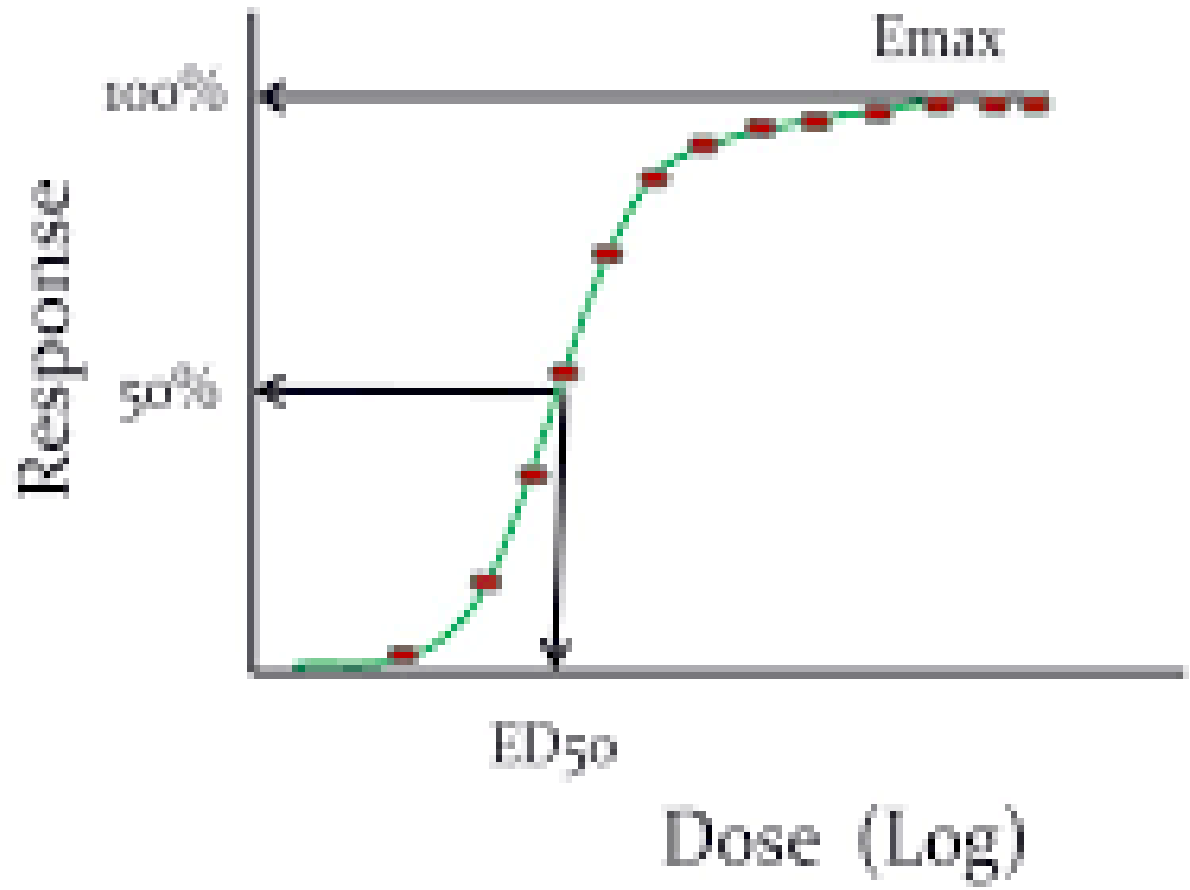
GRADED DOSE RESPONSE

- The response is ***elicited*** is expressed in terms of **Percentage of the maximal response**
- ***Plotted*** against the **Log dose of the drug**
- ***Illustrates*** the relationship among
  - Drug dose
  - Receptor occupancy
  - Magnitude of physiological event
- ***Obeys*** Law of mass action
  - **E = Emax * D / KD + D**
- ***Unmasks*** the spare receptors



Maximum Response
% of Maximum
Biological Response
100
50
ED50
0.01
0.1
1.0
10
100
Log Dose of Drug (units)

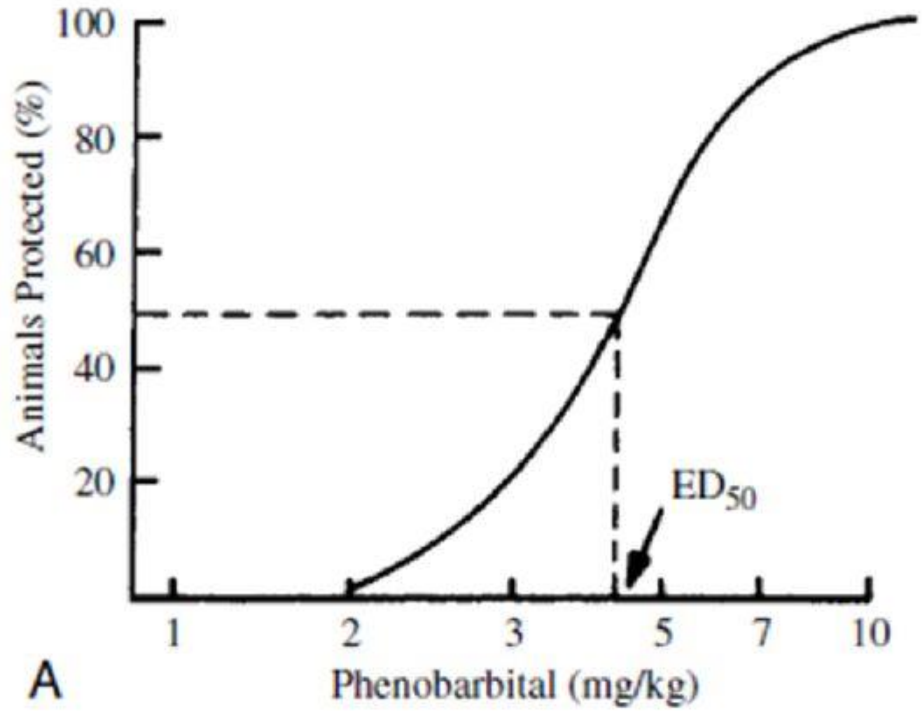

Effective Dose
Toxic Dose
Response (Percent)
100
90
50
10
0
ED10
ED50
ED90
TD10
TD50
TD90
Increasing Dose

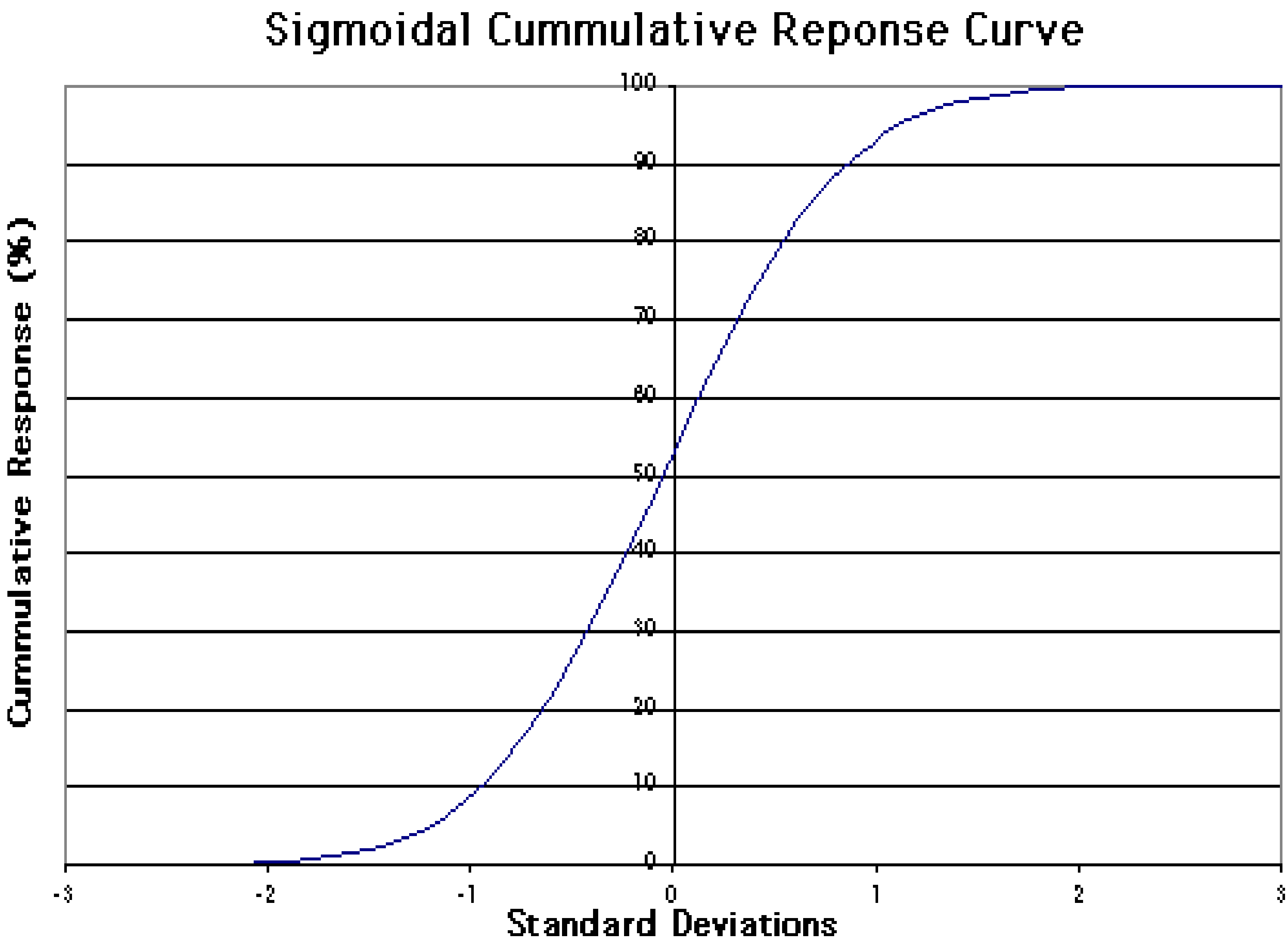


Graded dose response curve

Quantal Dose-Response Curve: Effective Dose

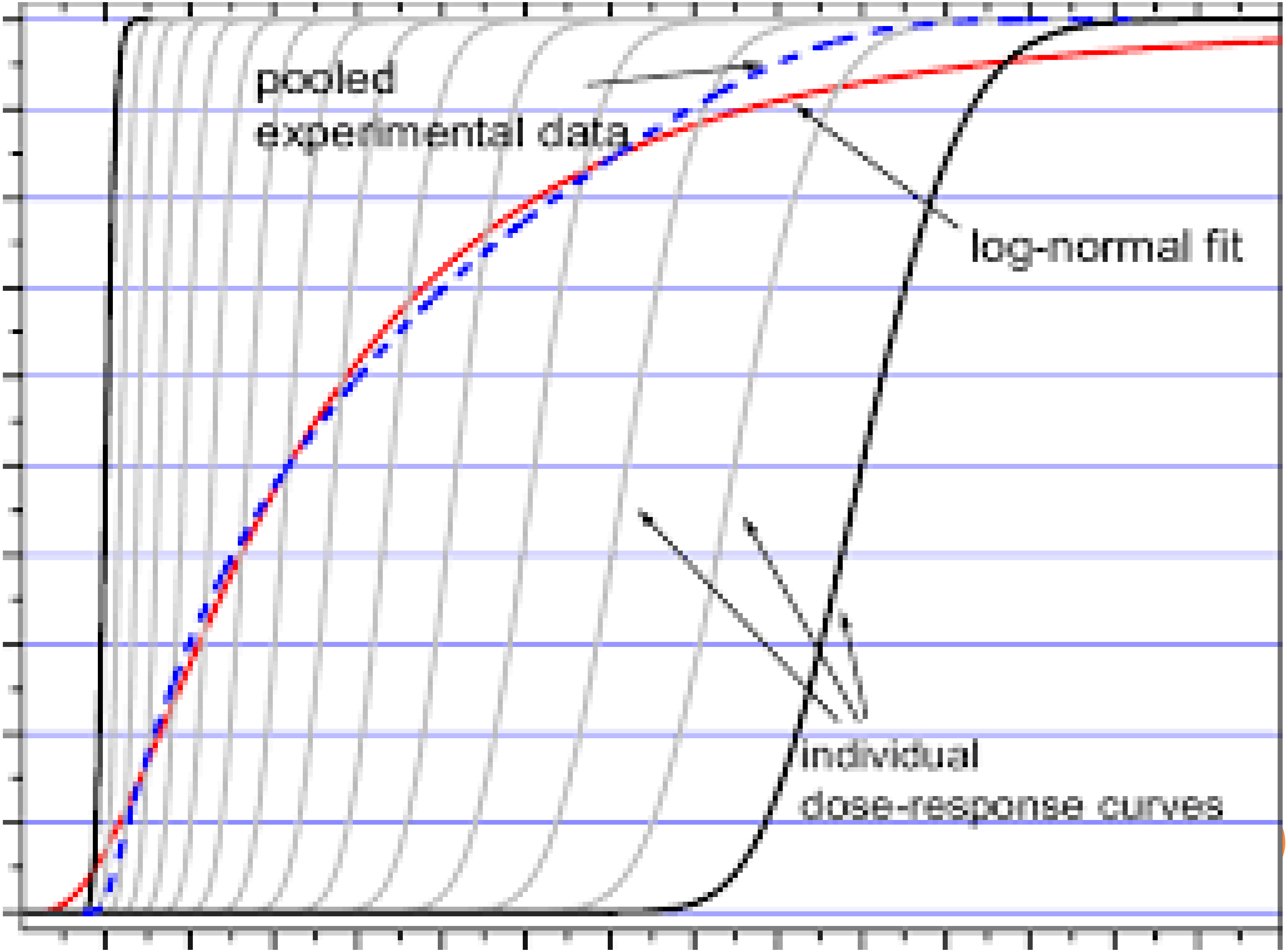
- The quantal dose–response curve represents estimates of the frequency with which each dose elicits the desired response in the population
- This is done through the calculation of an ED50, the dose that would protect 50% of the animals




Sigmoidal Cummulative Reponse Curve
Cummulative Response (%)
100
90
80
70
60
50
40
30
20
10
0
-3
-2
-1
0
1
2
3
Standard Deviations

Quantal-dose response relationship

- The quantal (all or none) dose-effect curve often characterizes the distribution of responses to different doses in a *population* of individual organisms
  - Median toxic dose(TD_{50}): the dose at which 50% of individuals/population exhibit a particular toxic effect
  - If the toxic effect is death of the animal, a median lethal dose (LD_{50}) may be experimentally defined
  - Median effective dose (ED_{50}) is the dose that produces a quantal effect (all or nothing) in 50% of the population that takes it


pooled
experimental data
log-normal fit
individual
dose-response curves

Difference graded-quantal

Quantal: *fraction* of animals responding

- *e.g.* 8 out of 20 = 0.4
- always between 0% and 100%
- no standard deviations

Graded: *degree* of response of the animal

- *e.g.* 85 eggs or body weight of 23 g
- usually between 0 and infinite
- standard deviations when >1 animal

THERAPEUTIC USES

THE NEED FOR DOSE RESPONSE CURVES

- ‘Drug Potency’ and ‘Drug Efficacy’ used interchangeably
- However, they are **NOT** synonymous
- Refer to different characteristics of the drug.
- The two can vary independently: Easily demonstrated on curves
  - § Aspirin is less potent as well as less efficacious analgesic than morphine.
  - § Pethidine is less potent but equally efficacious analgesic as morphine.
  - § Furosemide is less potent but more efficacious diuretic than Metolazone.
  - § Diazepam is more potent but less efficacious CNS depressant than Pentobarbitone.

Both curves provide

Information regarding

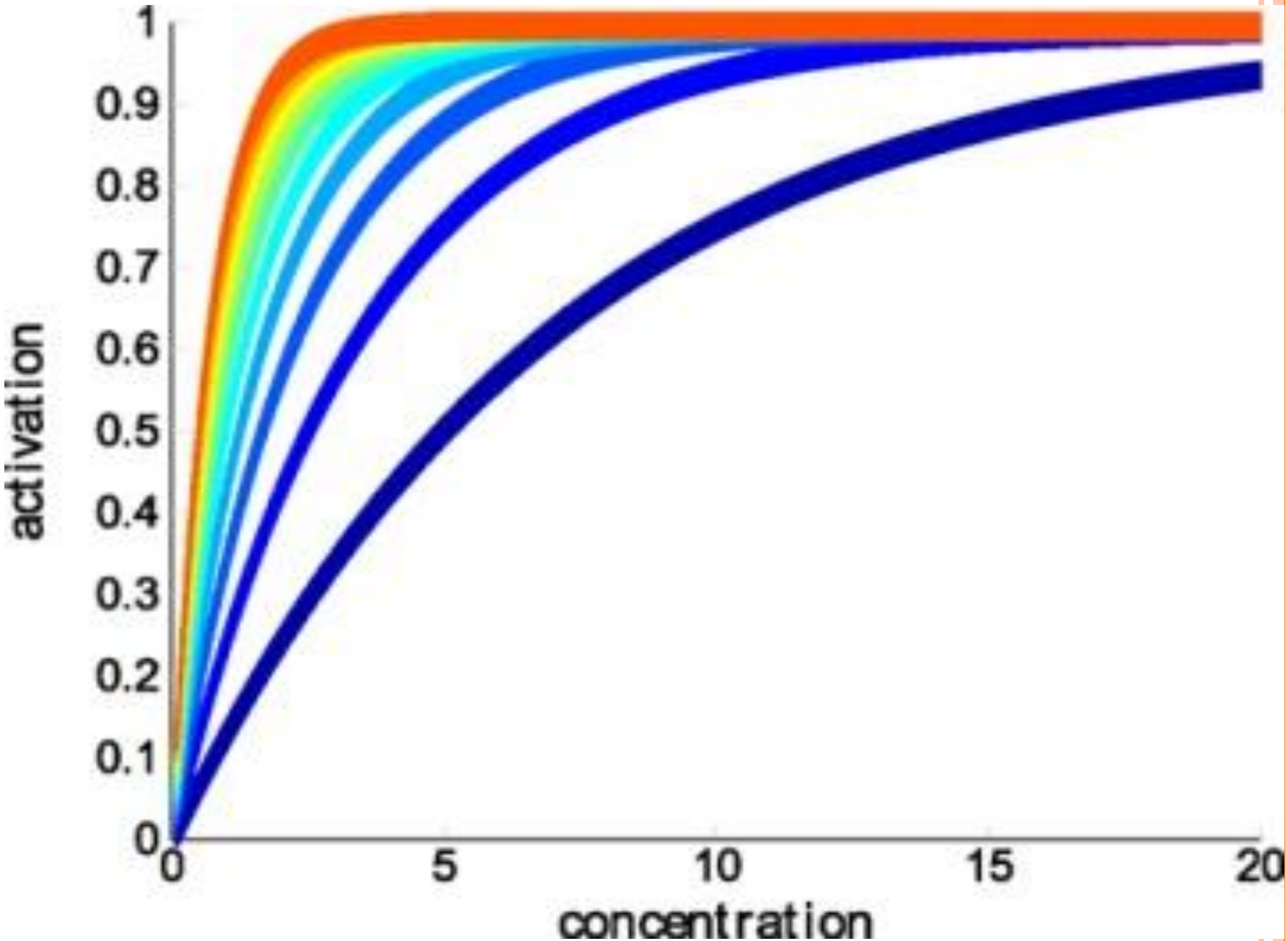
- potency.
- Selectivity

But

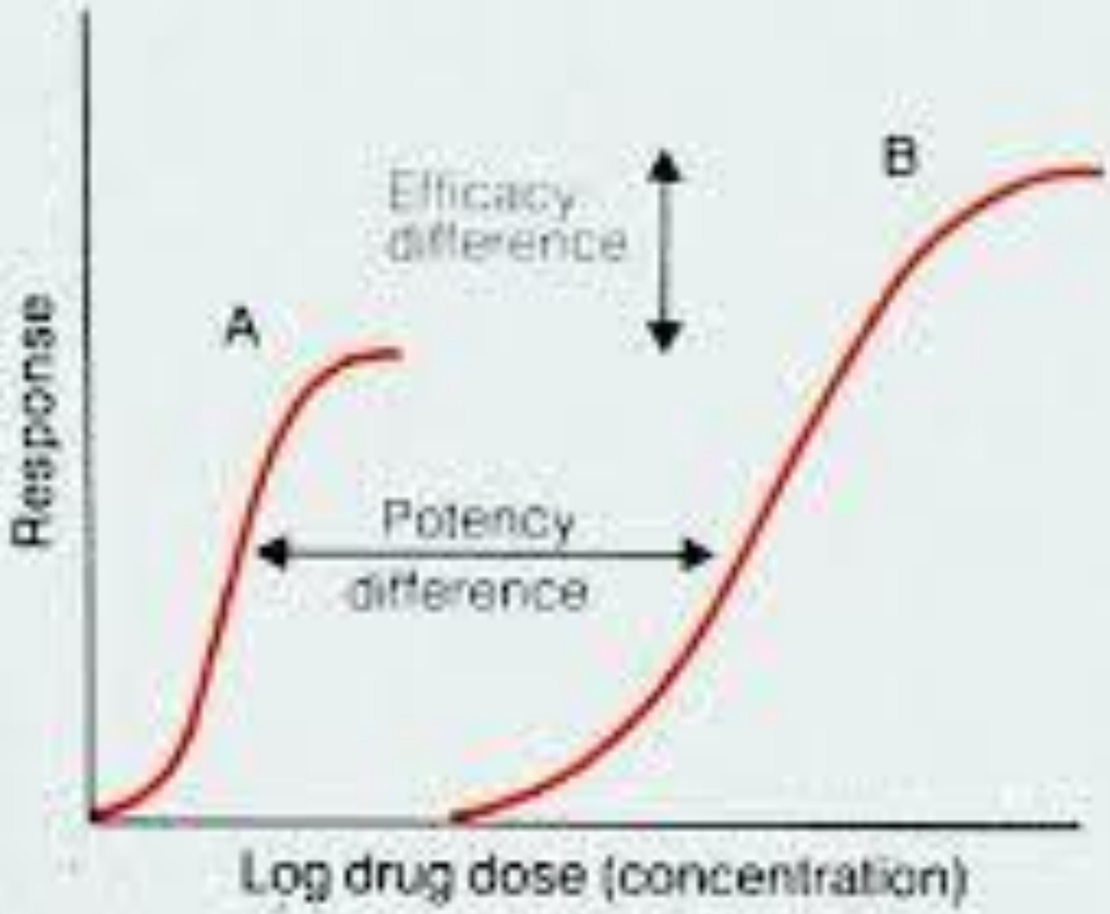
- **Graded dose response** curve indicates maximum efficacy
- **Quantal dose response** indicates potential variability of responsiveness among individuals

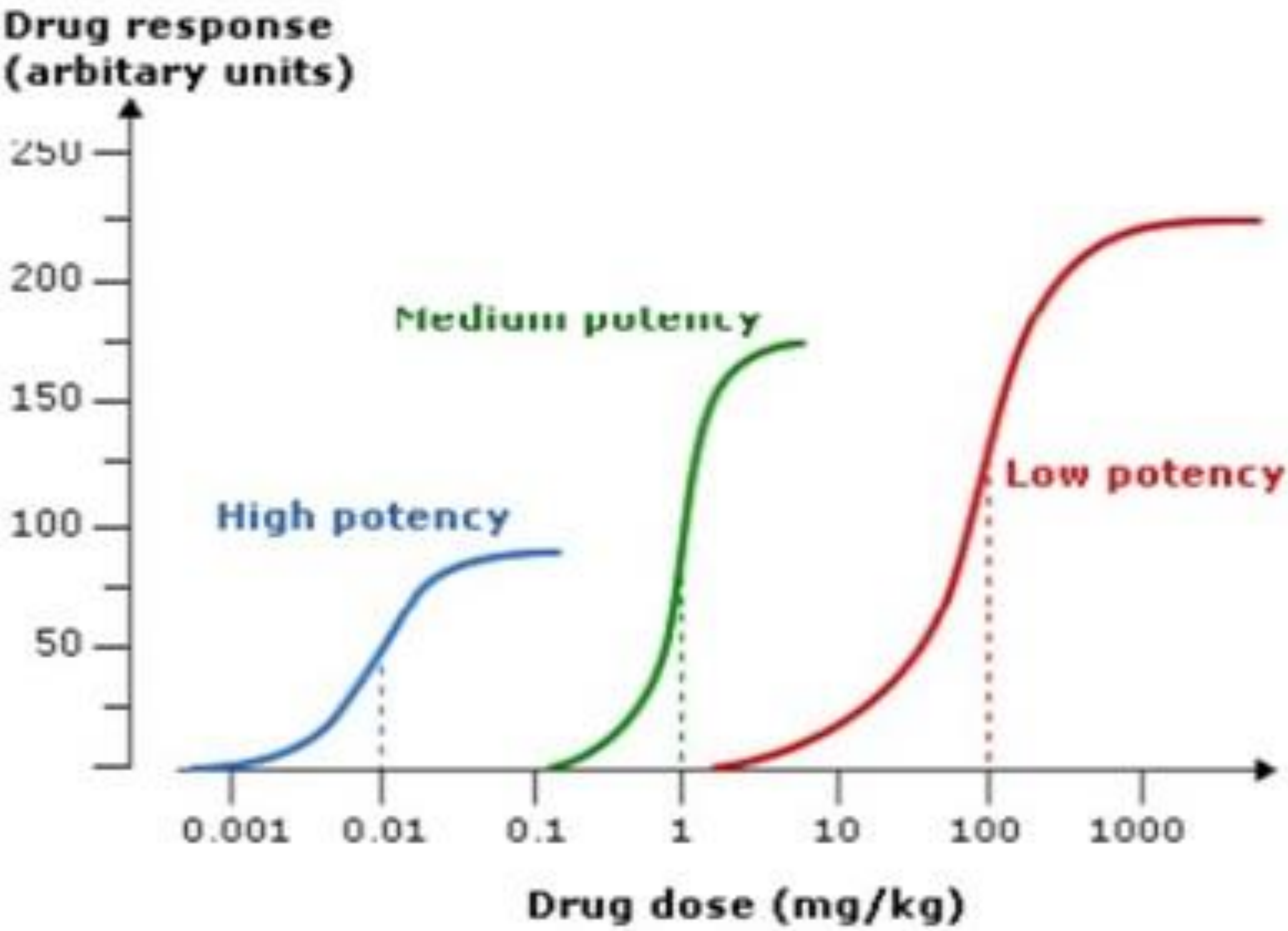
GRADED DOSE RESPONSE

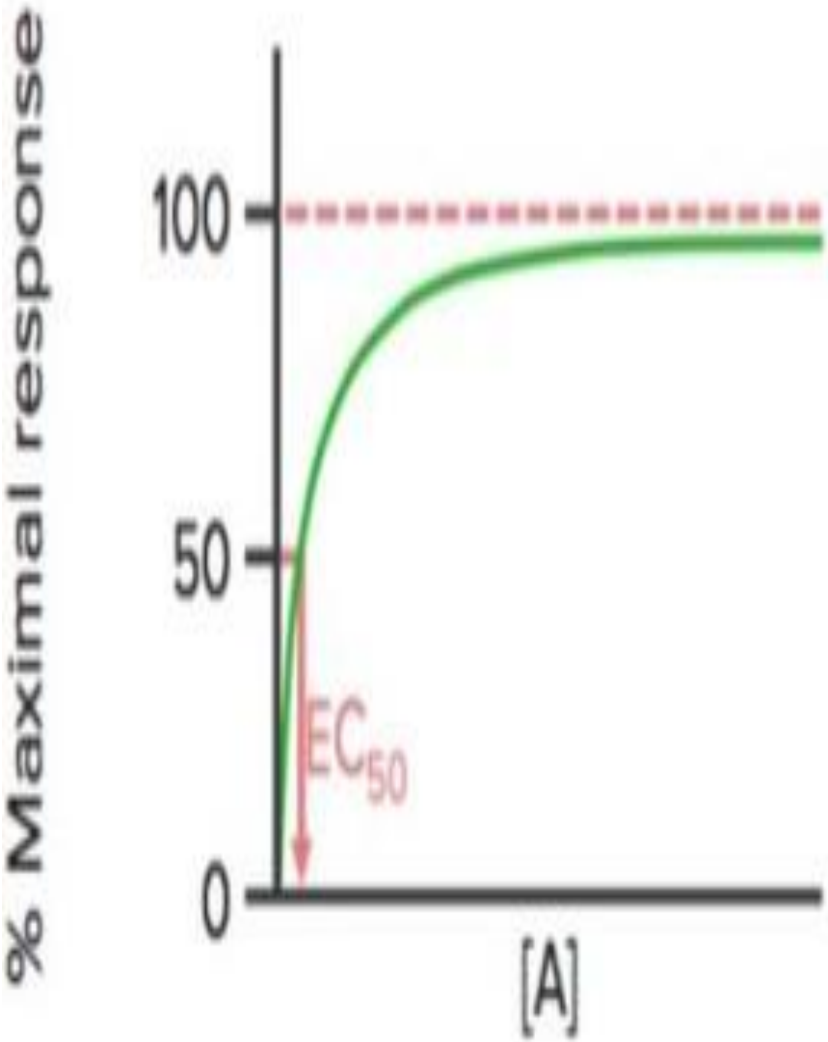
- **USES**
  - Maximum efficacy :::: **Emax;** the highest limit of dose response on response axis
  - **Potency:** the smallest the Emax the greater the potency
  - **Comparison** of relative efficacy and potency of drugs that elicit the same response


activation
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
concentration

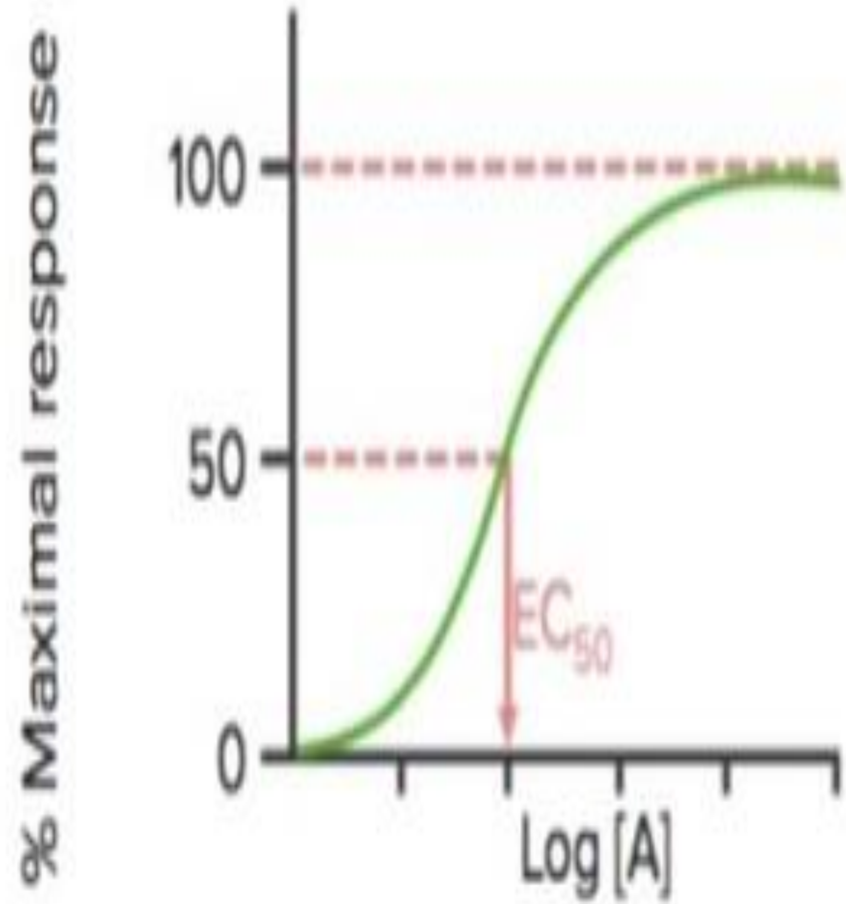
The difference between 'potency' (affinity) and 'efficacy' (activity)



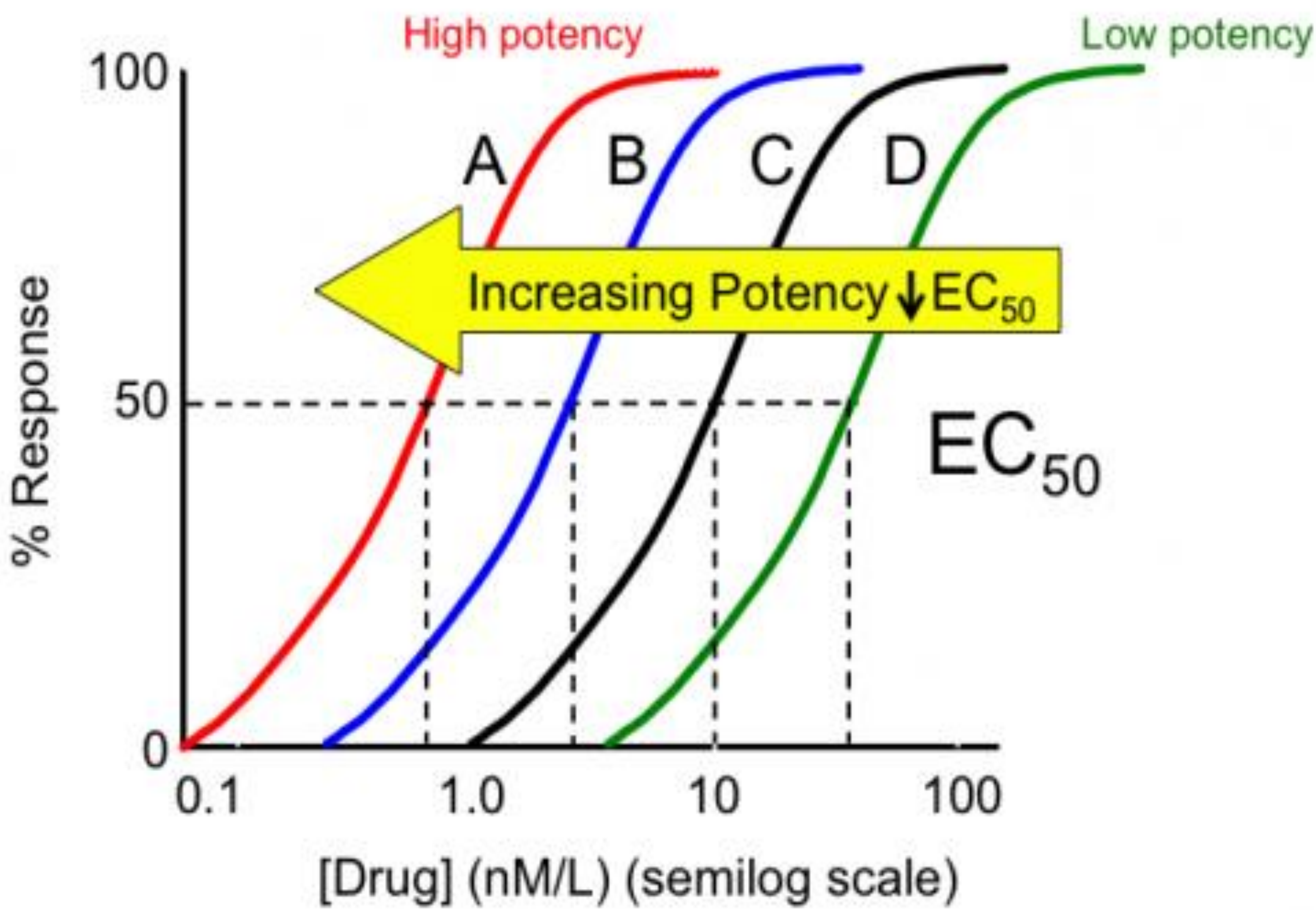

Drug response
(arbitary units)
250
200
150
100
50
Medium potency
High potency
Low potency
0.001
0.01
0.1
1
10
100
1000
Drug dose (mg/kg)



Dose vs. Response



Log of dose vs Response


High potency
Low potency
100
50
0
A
B
C
D
Increasing Potency ↓EC50
EC50
% Response
0.1
1.0
10
100
[Drug] (nM/L) (semilog scale)

Quantal D/R curves used to define

- median effective (and toxic) doses,
- concept of "therapeutic index"
- the potential range of inter-subject variability in drug response.

THERAPEUTIC WINDOW

Optimal therapeutic effect exerted only over a narrow range of plasma drug concentrations or drug doses

- Both below and above this range, beneficial effects are suboptimal,
  - § Tricyclic (Imipramine) exert maximal antidepressant effect when their plasma concentration is maintained between 50–150 ng/ml.
  - § Clonidine lowers BP over a plasma concentration range of 0.2–2.0 ng/ml; BP may rise at concentrations above 2 ng/ml.
  - § Glipizide exerts poorer glycaemia control at doses > 25 mg/day.

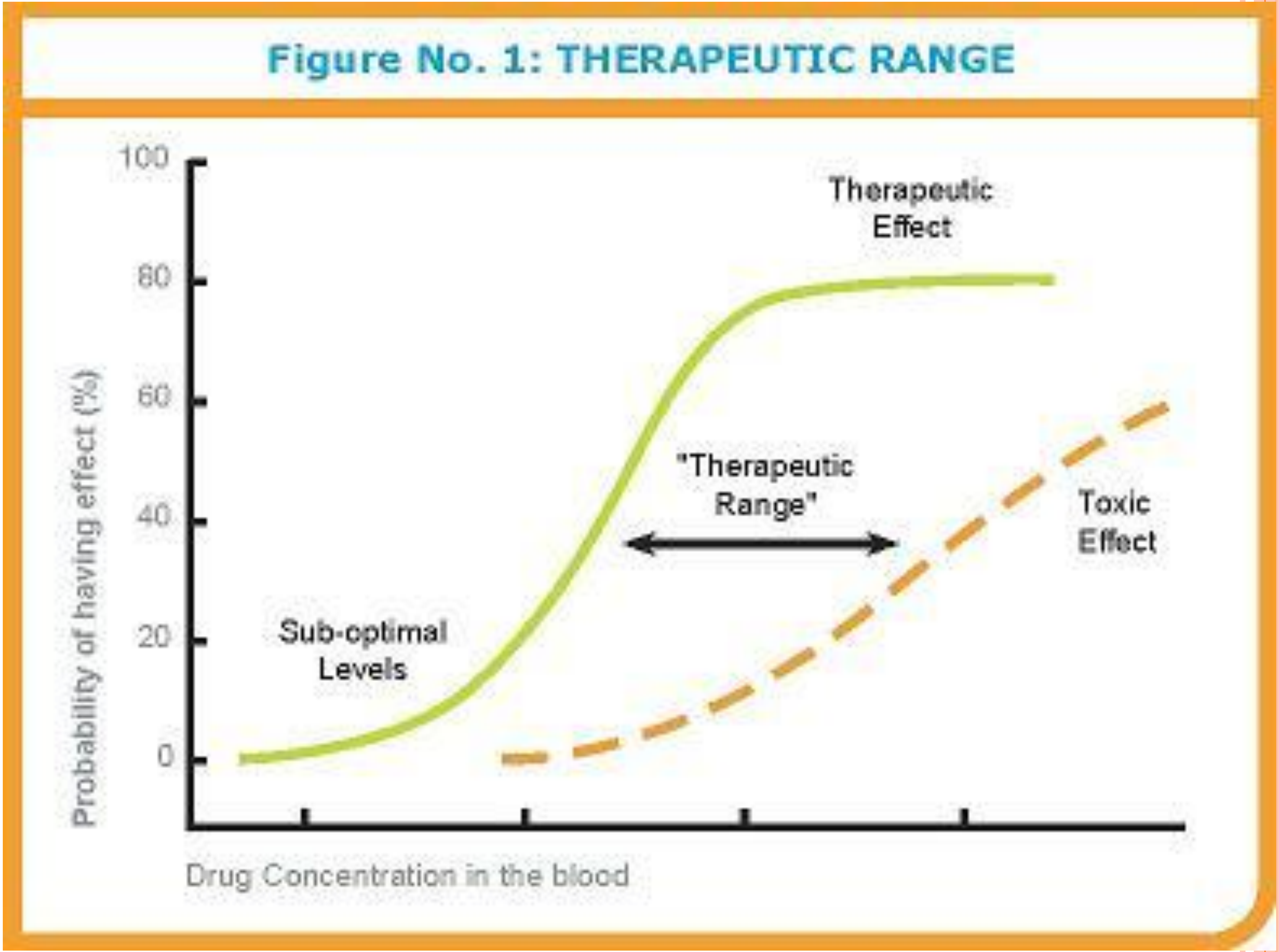
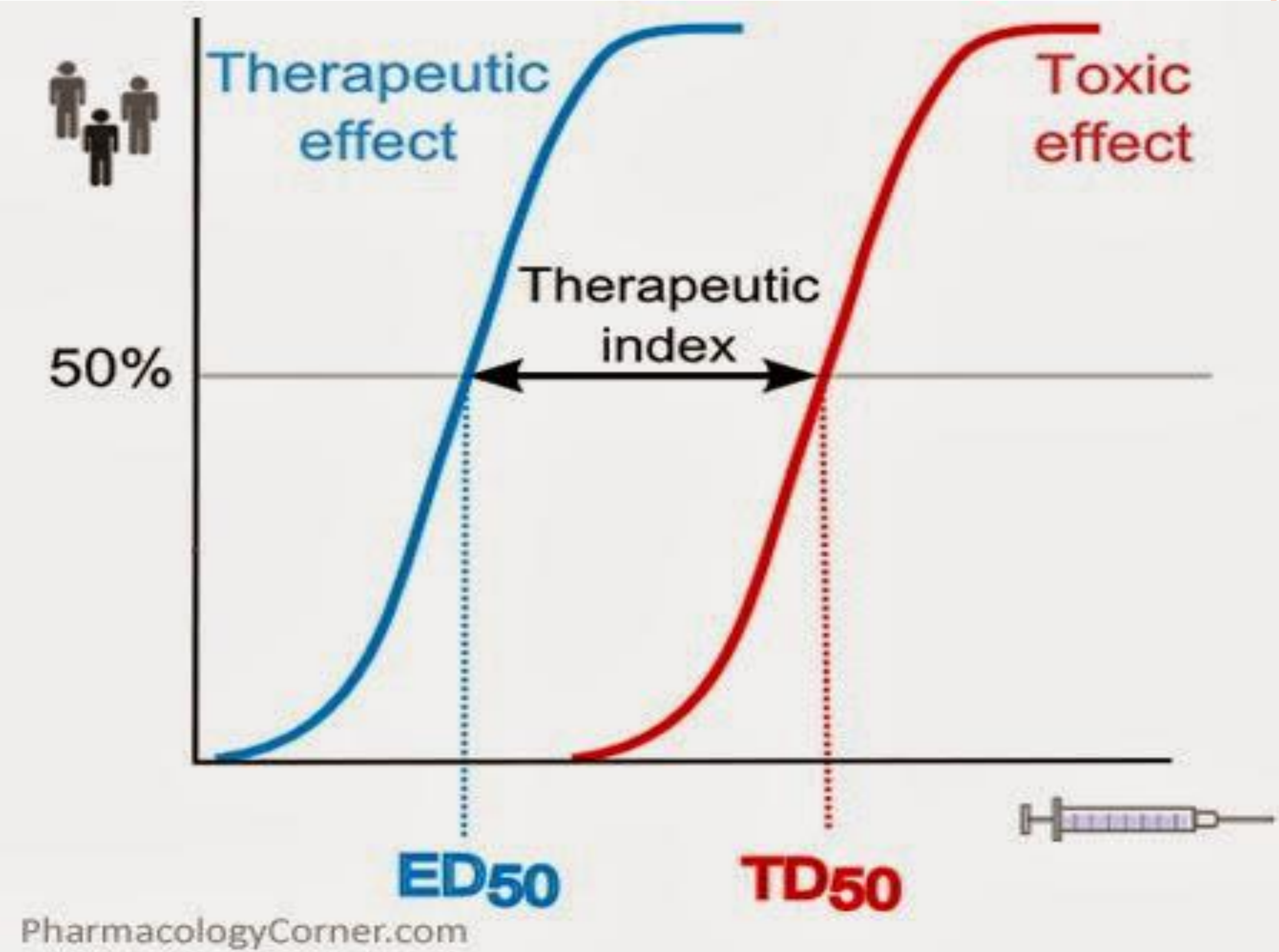
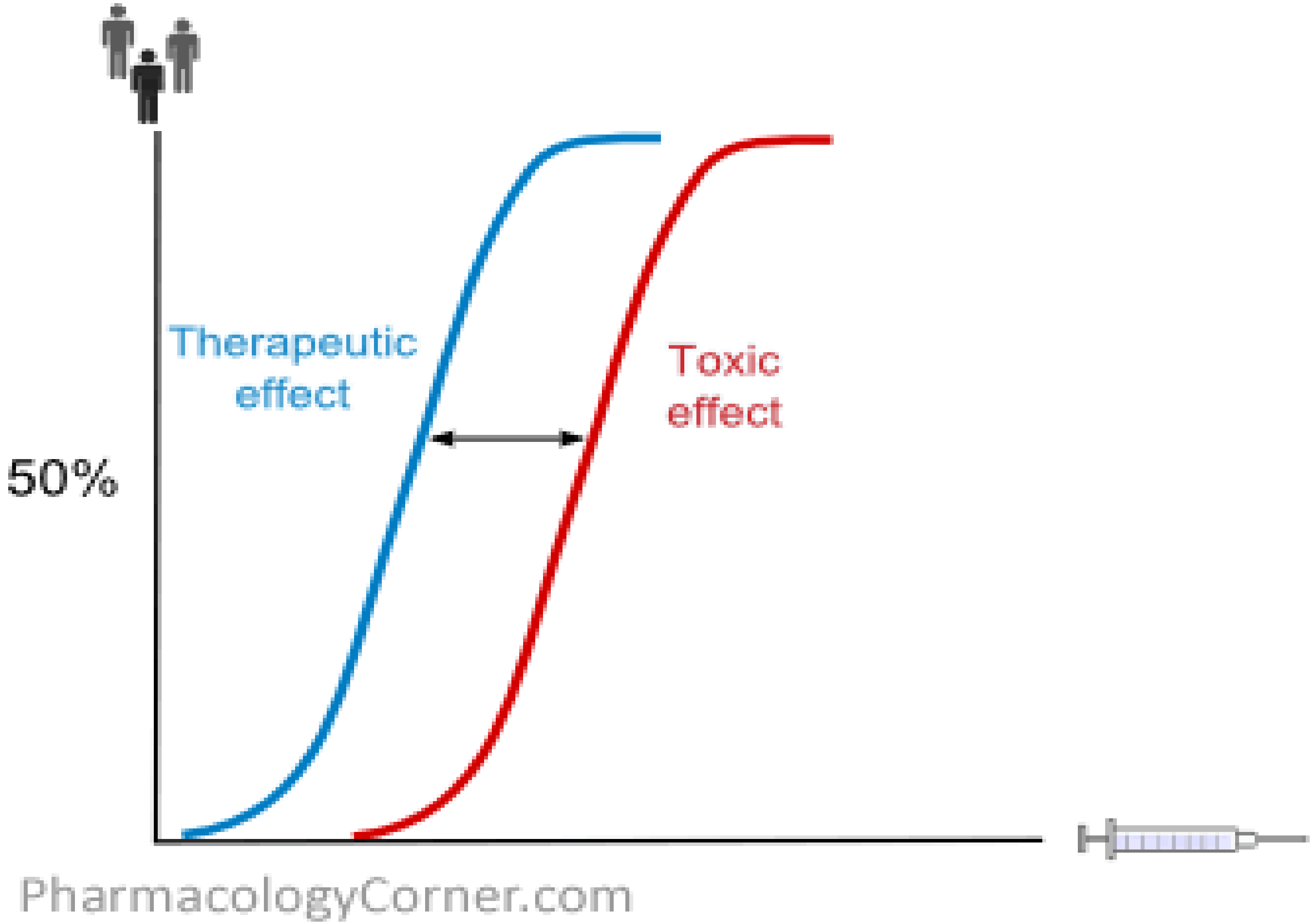


Figure No. 1: THERAPEUTIC RANGE
100
80
60
40
20
0
Probability of having effect (%)
Therapeutic Effect
"Therapeutic Range"
Toxic Effect
Sub-optimal Levels
Drug Concentration in the blood

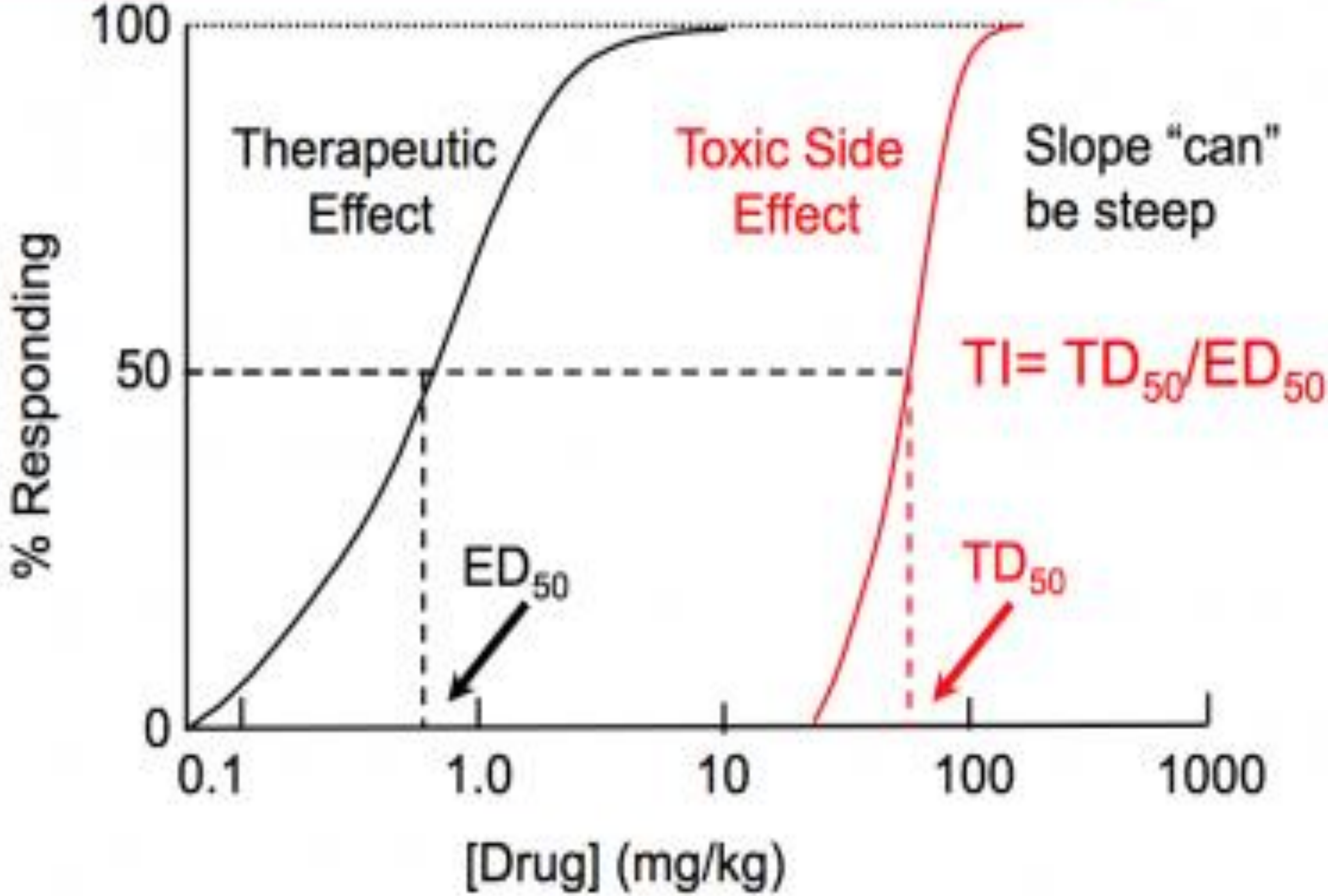

Therapeutic effect
Toxic effect
50%
Therapeutic index
ED50
TD50
PharmacologyCorner.com

Narrow TI



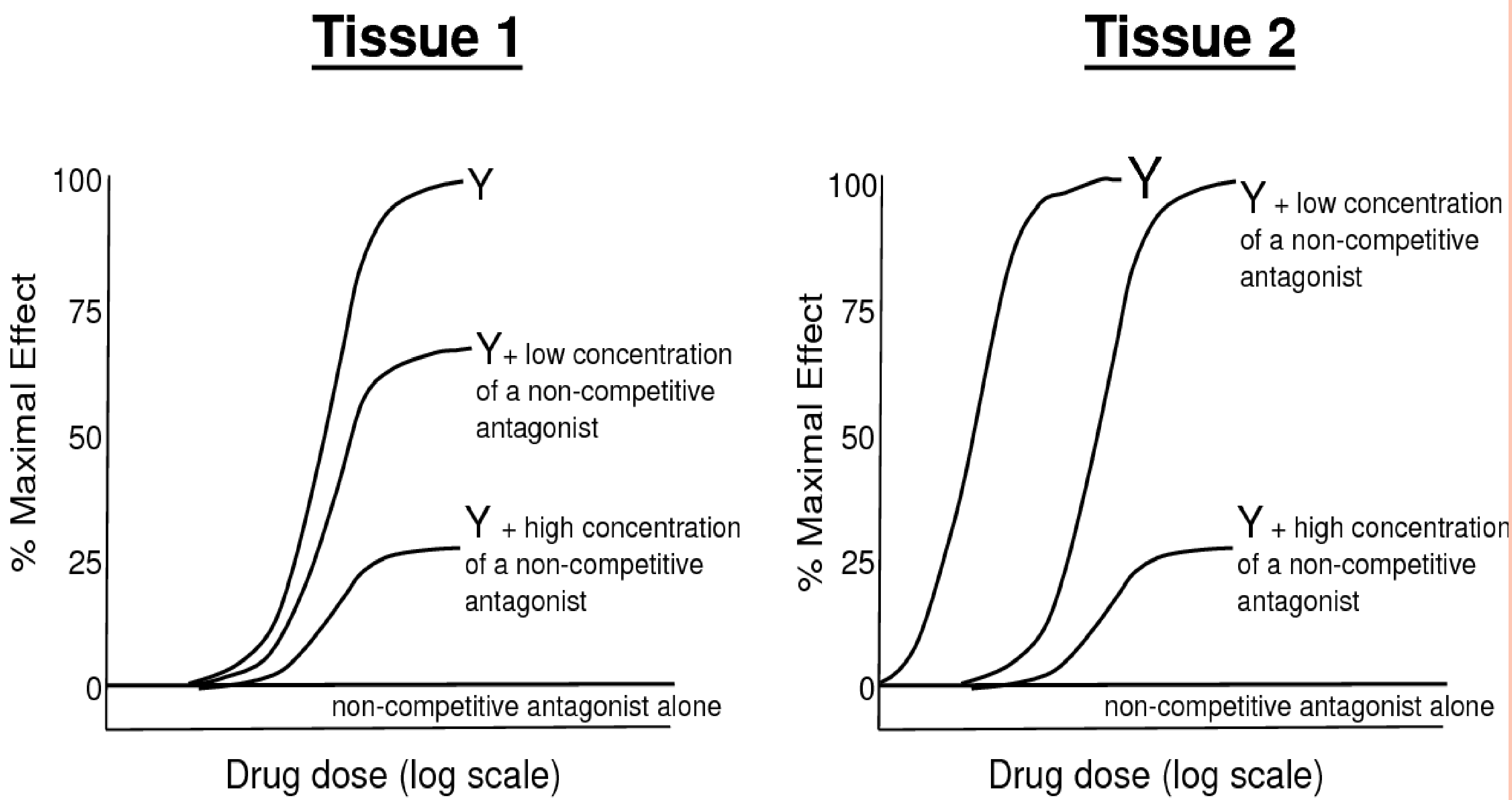
Therapeutic effect
Toxic effect
50%
PharmacologyCorner.com

Drug Safety - Therapeutic Index



CHARACTER OF ANTAGONISM

Figure 2



The Log Dose-Response Curve

- Advantages of expression as log versus response
  - Dose-response relationship expressed as a nearly straight line over a large range of drug doses.
  - Wide range of doses can be plotted on a single graph, allowing easy comparison of different drugs.
  - Use of log dose-response curves to compare different drugs which produce the same response

Physiological Salt solution

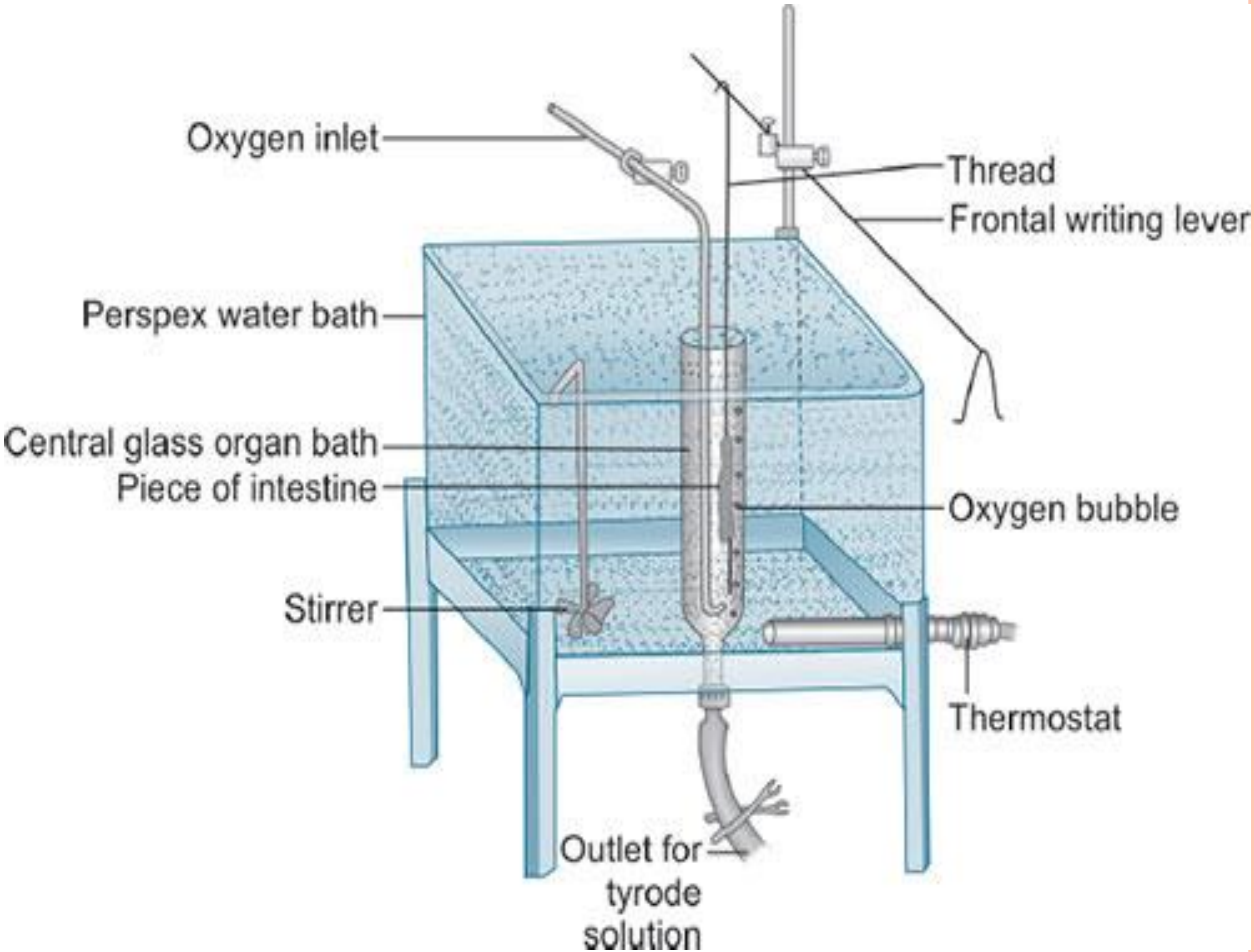
Constituents	Frog's ringer soln.	Mammalian ringer soln.	Tyrode soln.	Krebs Henseleit salt solution	Ringer locke solution	De-jalon solution
NaCl	6.5g	9.2g	8.0g	6.90g	9.15g	9.00g
KCl	1.4g	0.42g	0.2g	0.35g	0.42g	0.42g
MgCl2	0.3g	----	0.1g	0.11g	----	---
MgSO4.7H2O	----	----	---	---	---	---
NaH2PO4.2H 2O	0.1g	----	0.05g	0.14g	----	----
KH2PO4	----	----	----	----	----	----
Glucose	2.0g	----	1.0g	2.0g	1.00g	0.50g
NaHCO3	0.2g	0.2g	0.1g	2.10g	0.15g	0.50g
Sodium lactate	-----	----	----	----	3.10g	----
CaCl2	0.12g	0.24g	0.2g	0.28g	0.24g	0.06g

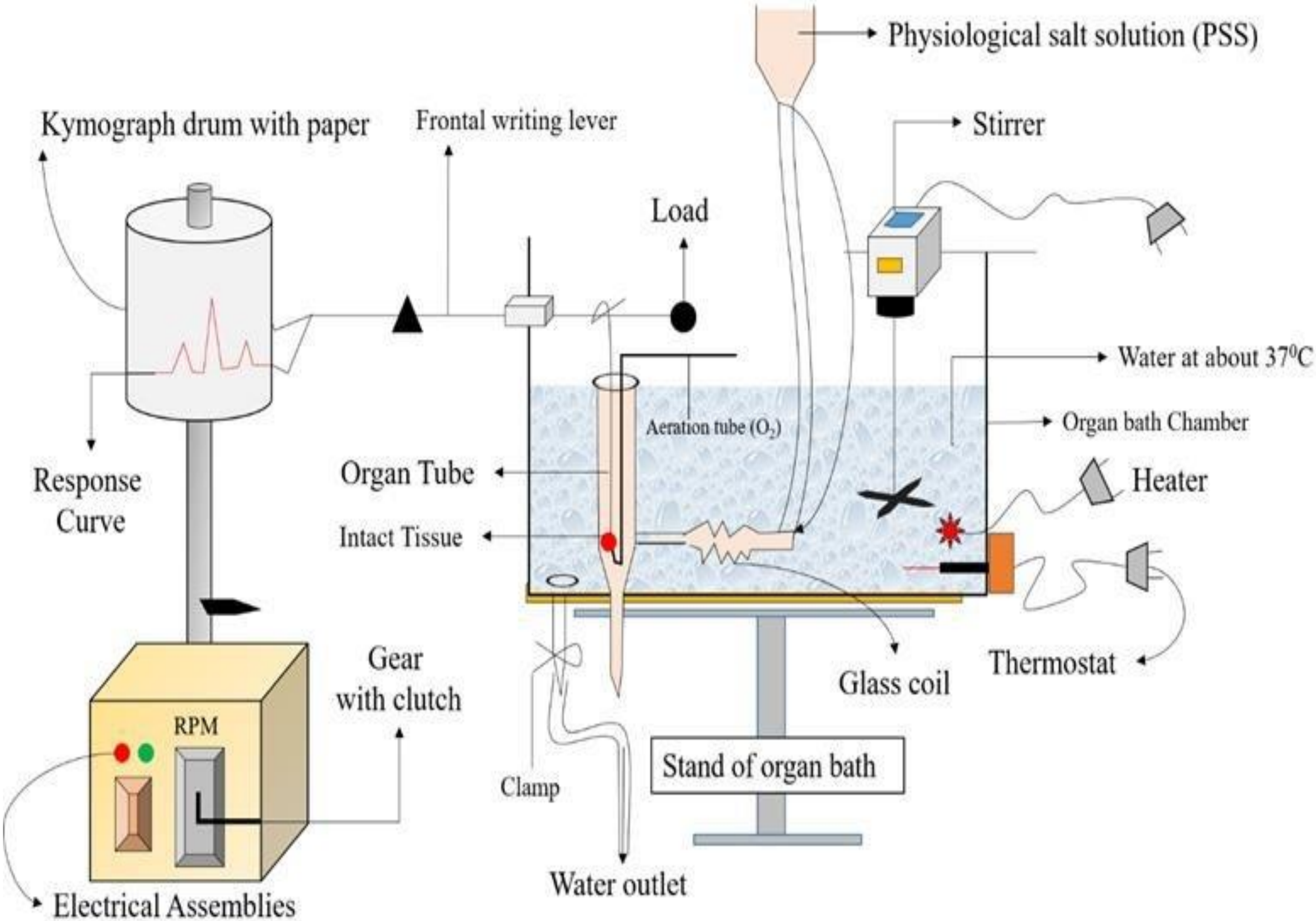

EcoCyte Bioscience
NTS-1
Normal Tyrode's Solution
EcoCyte Bioscience
NTS-2
Normal Tyrode's Solution

Preparation of Tyrode solution (PSS)

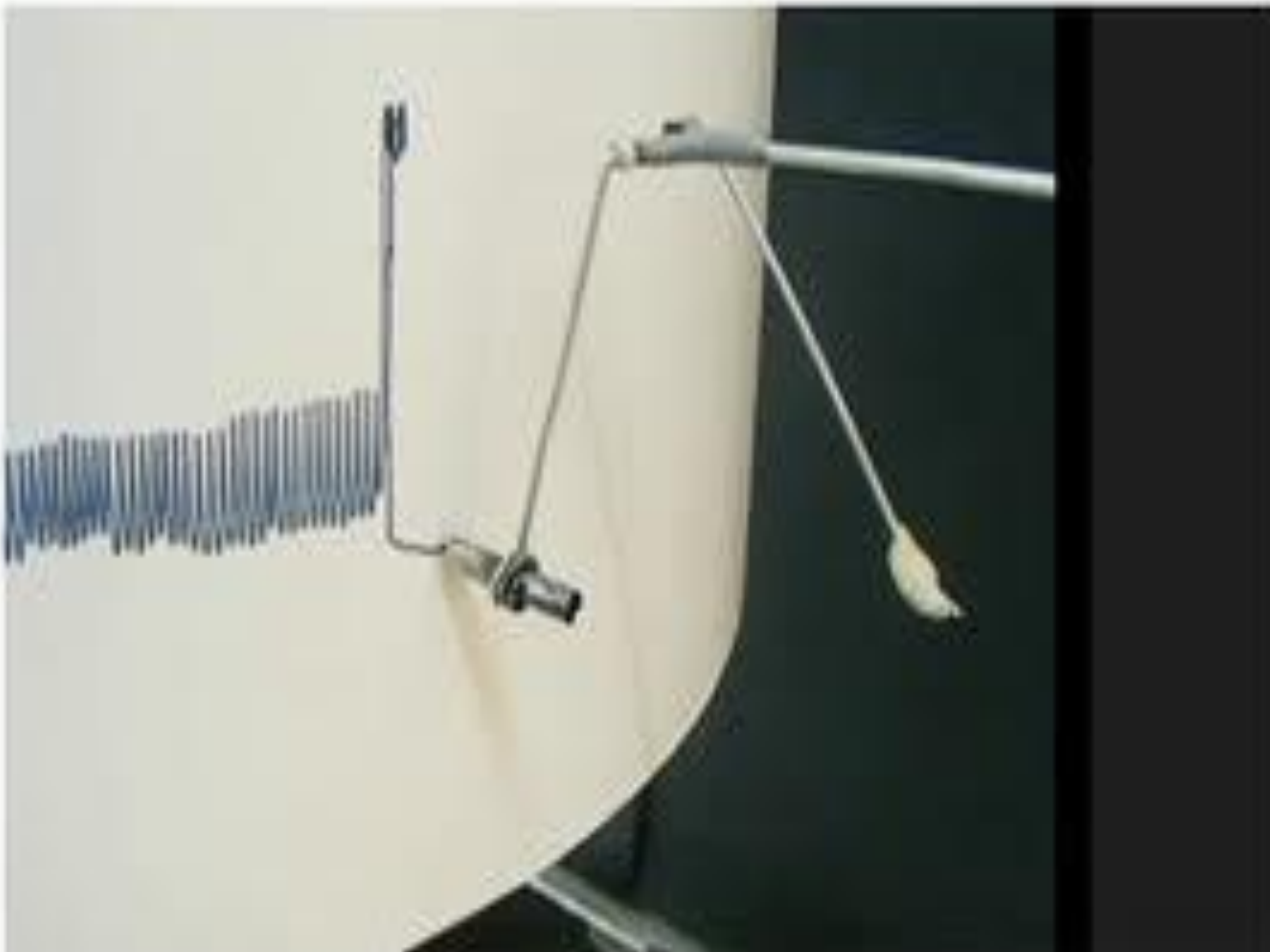
- Prepare 1 litre of Tyrode solution by dissolving NaCl (8.0 g), KCl (0.2 g), $MgCl_2$ (0.1 g), $NaHCO_3$ (1.0 g), NaH_2PO_4 (0.05 g) and glucose (2.0 g) in distilled water.
- $MgCl_2$ should be added at last.
- $CaCl_2$ (0.2 g) should be dissolved separately in distilled water to avoid chances of precipitation of salt.
- Mix $CaCl_2$ solution to the higher volume of PSS.

	Tyrode® solution	K^+-Tyrode® solution
NaCl (mmol/l)	137.0	122.0
KCl (mmol/l)	5.0	20.0
$CaCl_2$ (mmol/l)	2.0	2.0
$MgCl_2$ (mmol/l)	1.0	1.0
NaH_2PO_4 (mmol/l)	1.0	1.0
$NaHCO_3$ (mmol/l)	12.0	12.0
Glucose (mmol/l)	11.0	11.0


Oxygen inlet
Thread
Frontal writing lever
Perspex water bath
Central glass organ bath
Piece of intestine
Oxygen bubble
Stirrer
Thermostat
Outlet for tyrode solution



Physiological salt solution (PSS)
Kymograph drum with paper
Frontal writing lever
Stirrer
Load
Water at about 37^{0}C
Aeration tube (O_2)
Organ bath Chamber
Response
Curve
Organ Tube
Heater
Intact Tissue
Gear
with clutch
Thermostat
Glass coil
RPM
Stand of organ bath
Clamp
Water outlet
Electrical Assemblies




ADINSTRUMENTS
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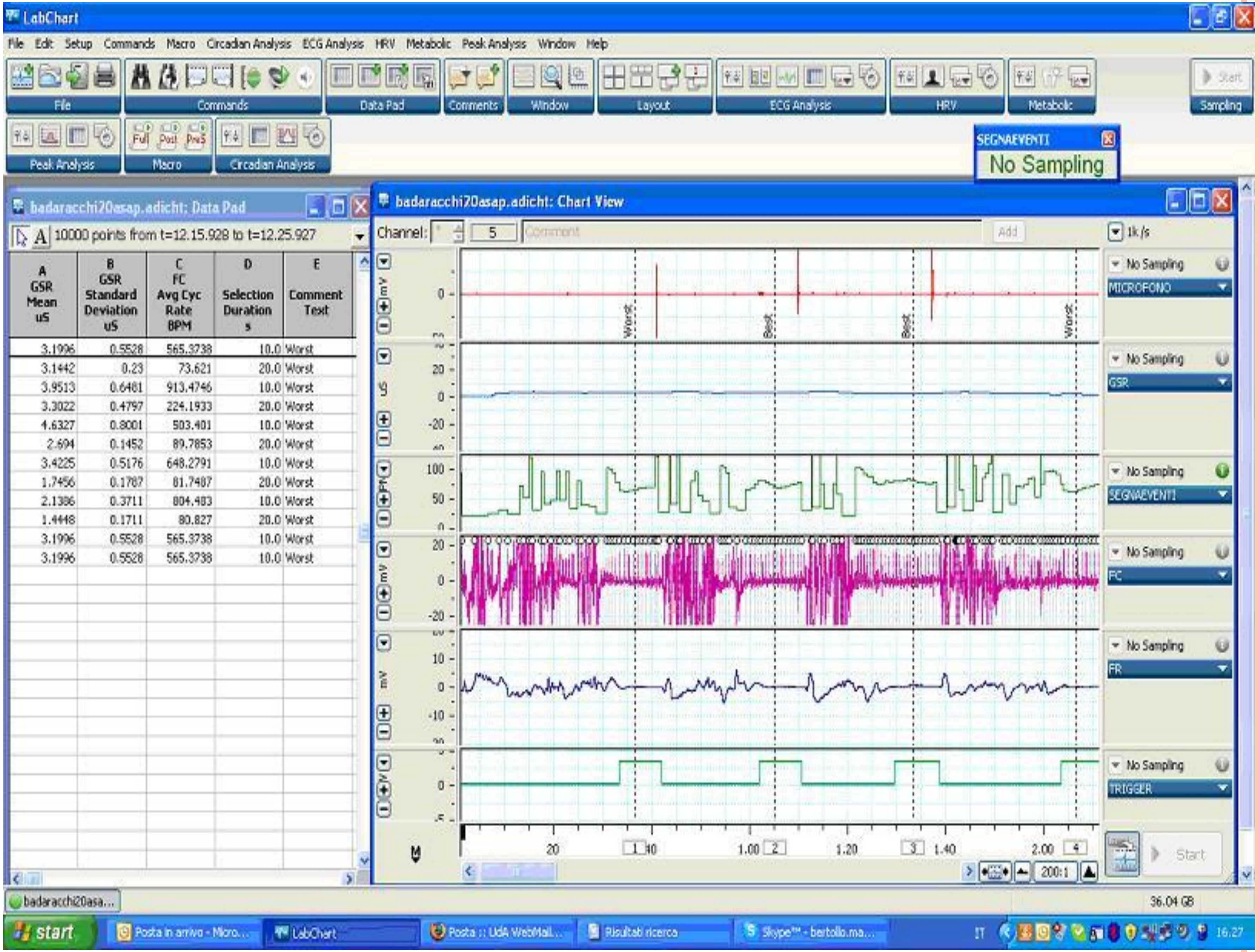
LabChart
File Edit Setup Commands Macro Circadian Analysis ECG Analysis HRV Metabolic Peak Analysis Window Help
File
Commands
Data Pad
Comments
Window
Layout
ECG Analysis
HRV
Metabolic
Sampling
Peak Analysis
Macro
Circadian Analysis
SEGNAEVENTI
No Sampling
badaracchi20asap.adicht: Data Pad
10000 points from t=12.15.928 to t=12.25.927
A GSR Mean uS
B GSR Standard Deviation uS
C FC Avg Cyc Rate BPM
D Selection Duration s
E Comment Text
3.1996 0.5528 565.3738 10.0 Worst
3.1442 0.23 73.621 20.0 Worst
3.9513 0.6481 913.4746 10.0 Worst
3.3022 0.4797 224.1933 20.0 Worst
4.6327 0.8001 503.401 10.0 Worst
2.694 0.1452 89.7853 20.0 Worst
3.4225 0.5176 648.2791 10.0 Worst
1.7456 0.1787 81.7487 20.0 Worst
2.1386 0.3711 804.483 10.0 Worst
1.4448 0.1711 80.827 20.0 Worst
3.1996 0.5528 565.3738 10.0 Worst
3.1996 0.5528 565.3738 10.0 Worst
badaracchi20asap.adicht: Chart View
Channel:
5
Comment
Add
1k/s
Worst
Best
Best
Worst
No Sampling
MICROFONO
No Sampling
GSR
No Sampling
SEGNAEVENTI
No Sampling
FC
No Sampling
FR
No Sampling
TRIGGER
Start
200:1
36.04 GB
badaracchi20asa...
start
Posta in arrivo - Micro...
LabChart
Posta :: UdA WebMail...
Risultati ricerca
Skype™ - bertollo.ma...
IT
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- Goodman & Gilman's The Pharmacological Basis of Therapeutics: Brunton LL. 12th Edition

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