Toxicodynamics

Refer lecturer for course updated notes.

Students are oblidged to follow the courses for evaluation process and presented notes are preliminary drafts for the whole evaluation process.

Definition

- What body does to the xenobiotic= toxicokinetic
- What xenobiotic does to the body= toxicodynamic

- Toxicodynamics, termed pharmacodynamics in pharmacology, describes the dynamic interactions of a toxicant with a biological target and its biological effects

- Molecular, Biochemical, Physiologica, Pharmacologial effects of Toxicants or their Metabolites in Biological systems

- Interaction with the toxicant with a molecular target

- Toxicant refers: parent xenobiotic, its metabolite, or even a generated reactive oxygen species that actually causes cellular damage
- Target: molecule that interacts with the ultimate toxicant

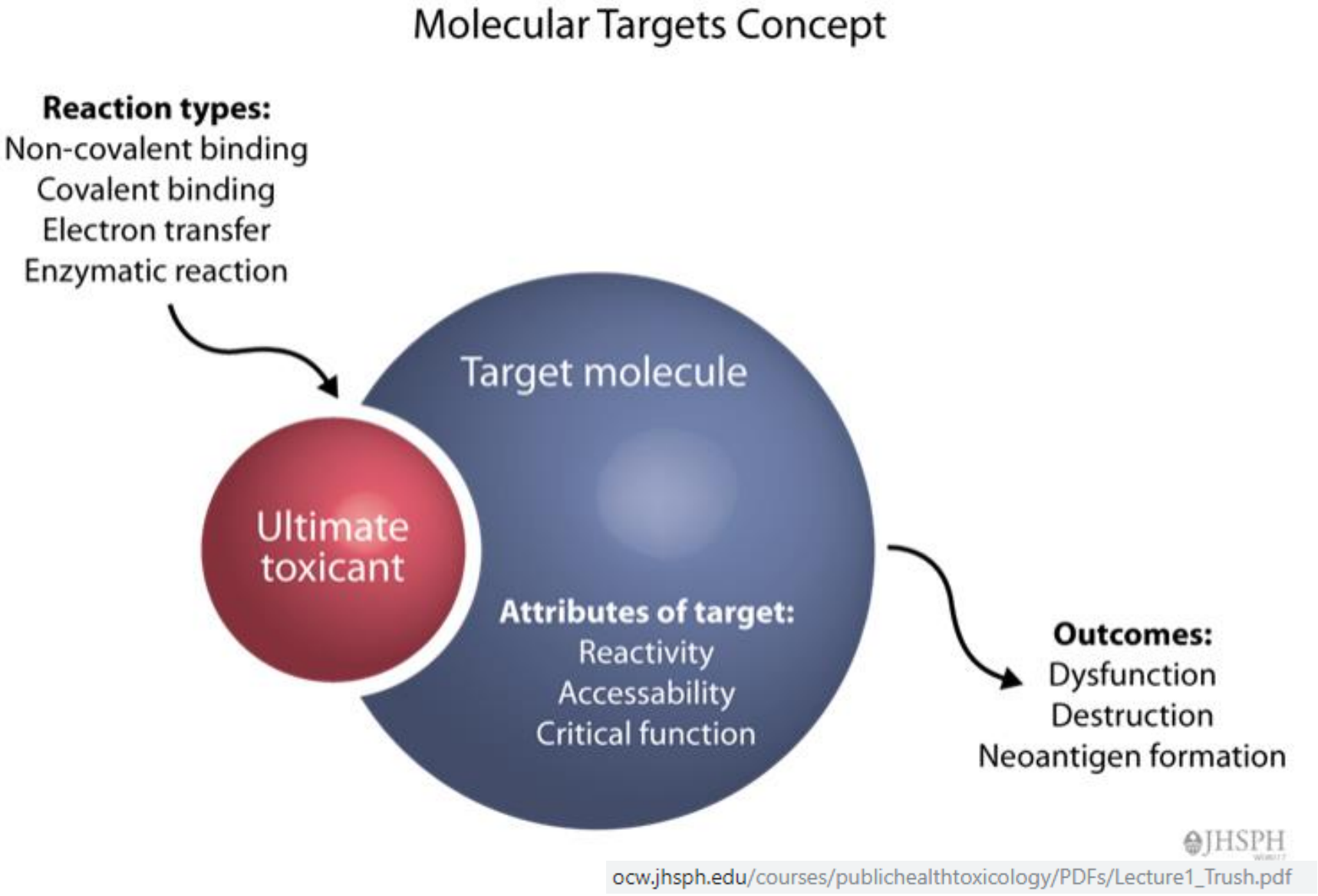
- Distribution&Biotransformation limit the toxicant to the target cell(s)

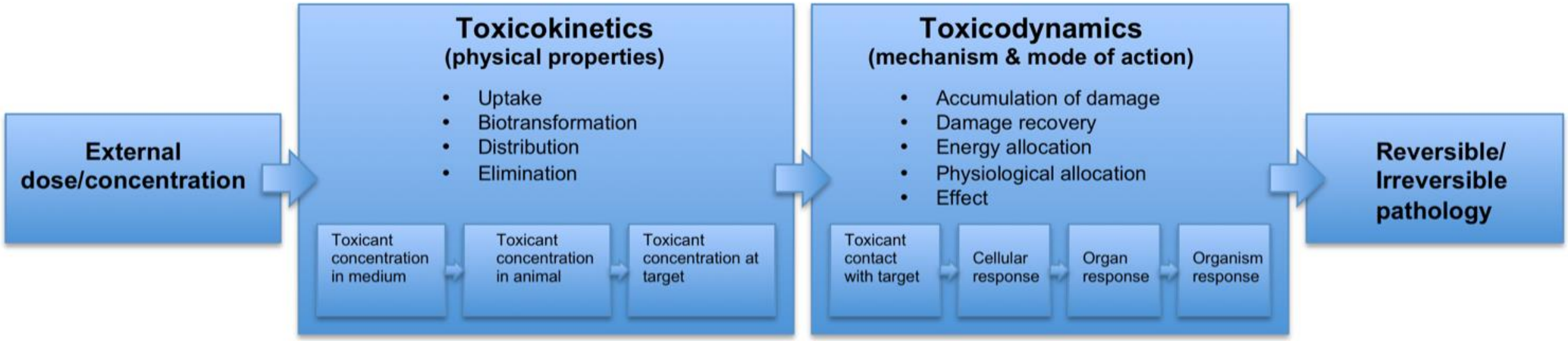
- Toxic action is the consequence of the pysicohemical interaction with the toxicant and target

Biological Target/Site of Action

- binding proteins
  - Arylhydrocarbon receptor-Dioxin
- Lipids (carbon tetrachloride)
- ion channels,
- DNA (aflatoxin)
- variety of other receptors (endocrine disrupting compounds-androgen/estrogen/thyroid receptor)

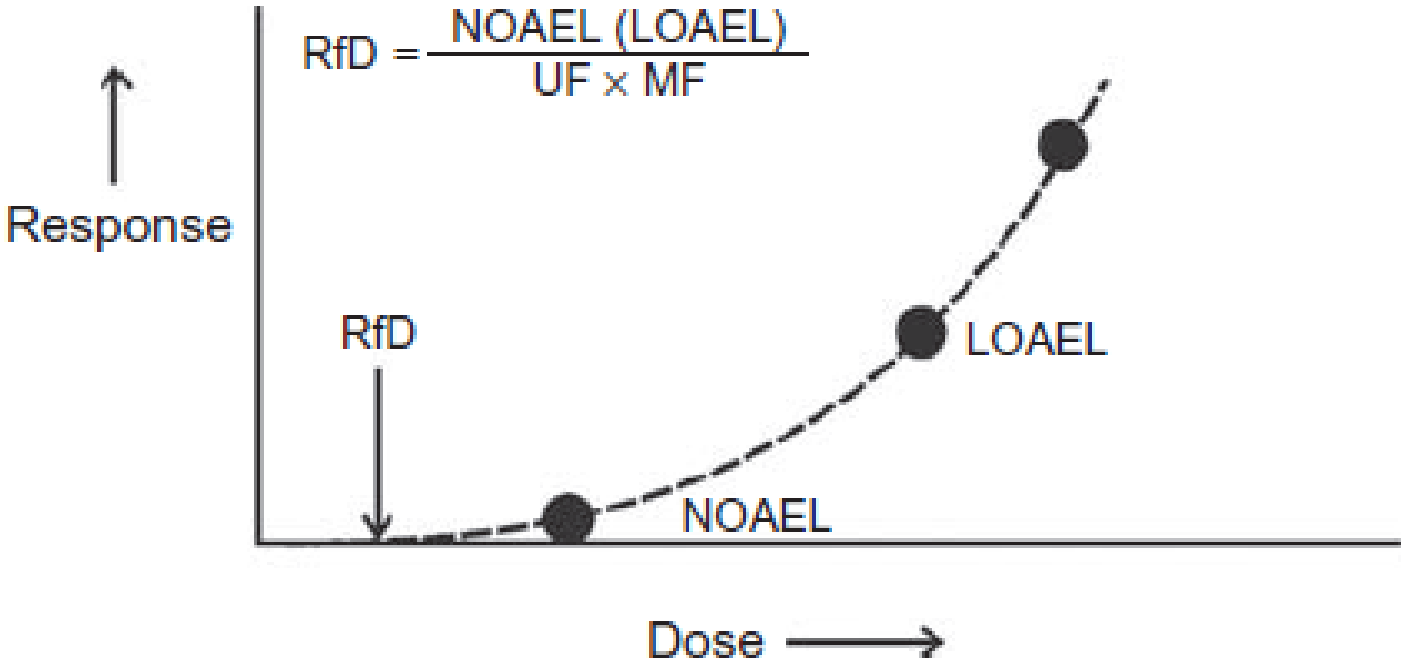
- interact with these receptors and produce structural or functional alterations.





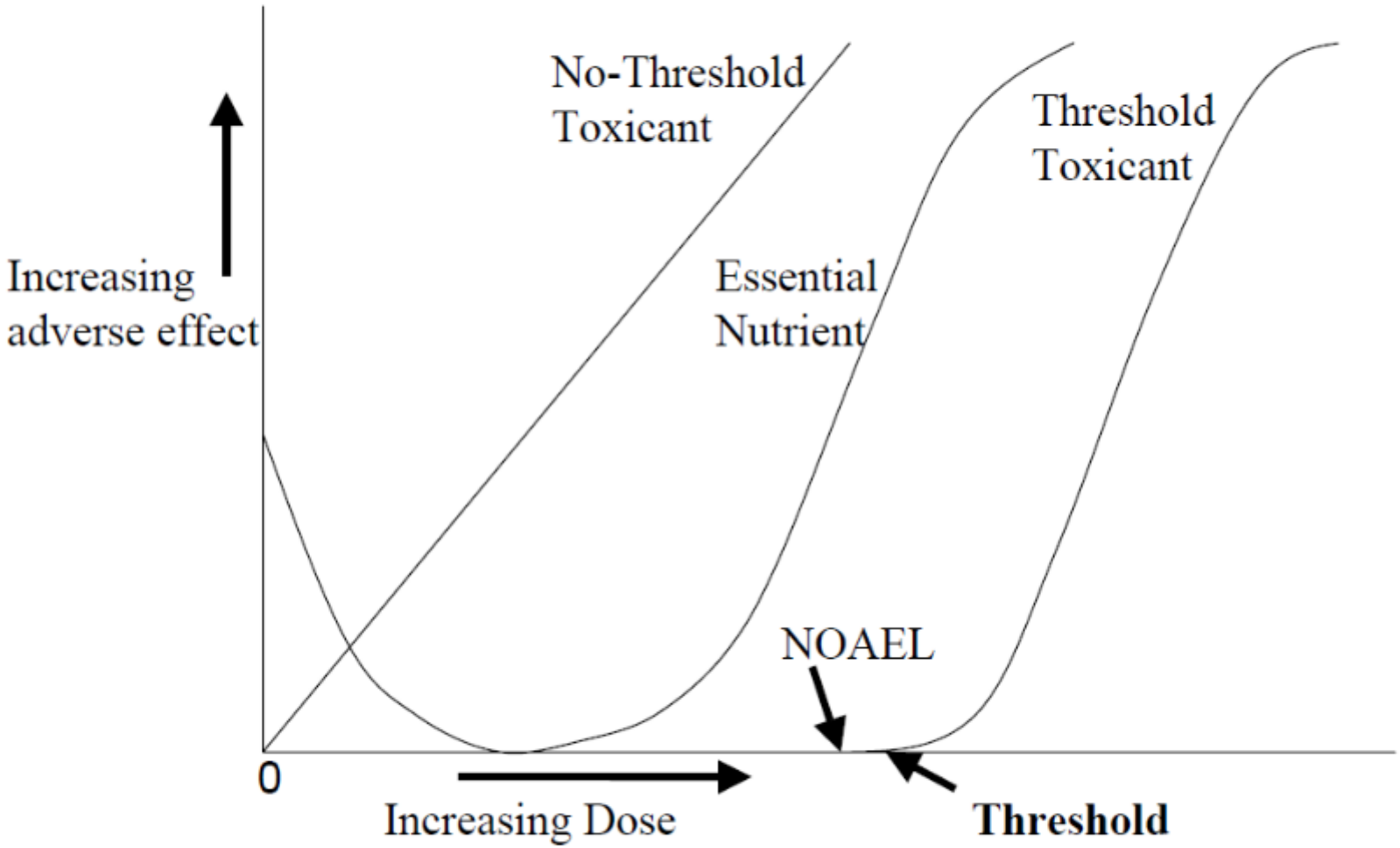
Dose-Response Relationship

- No Observed Effect (NOEL) Level, the highest exposure level for which no effects are observed and the
- NOAEL, the highest exposure level that produces no adverse effects.
- LOAEL, the highest exposure level at which an adverse effect is observed.

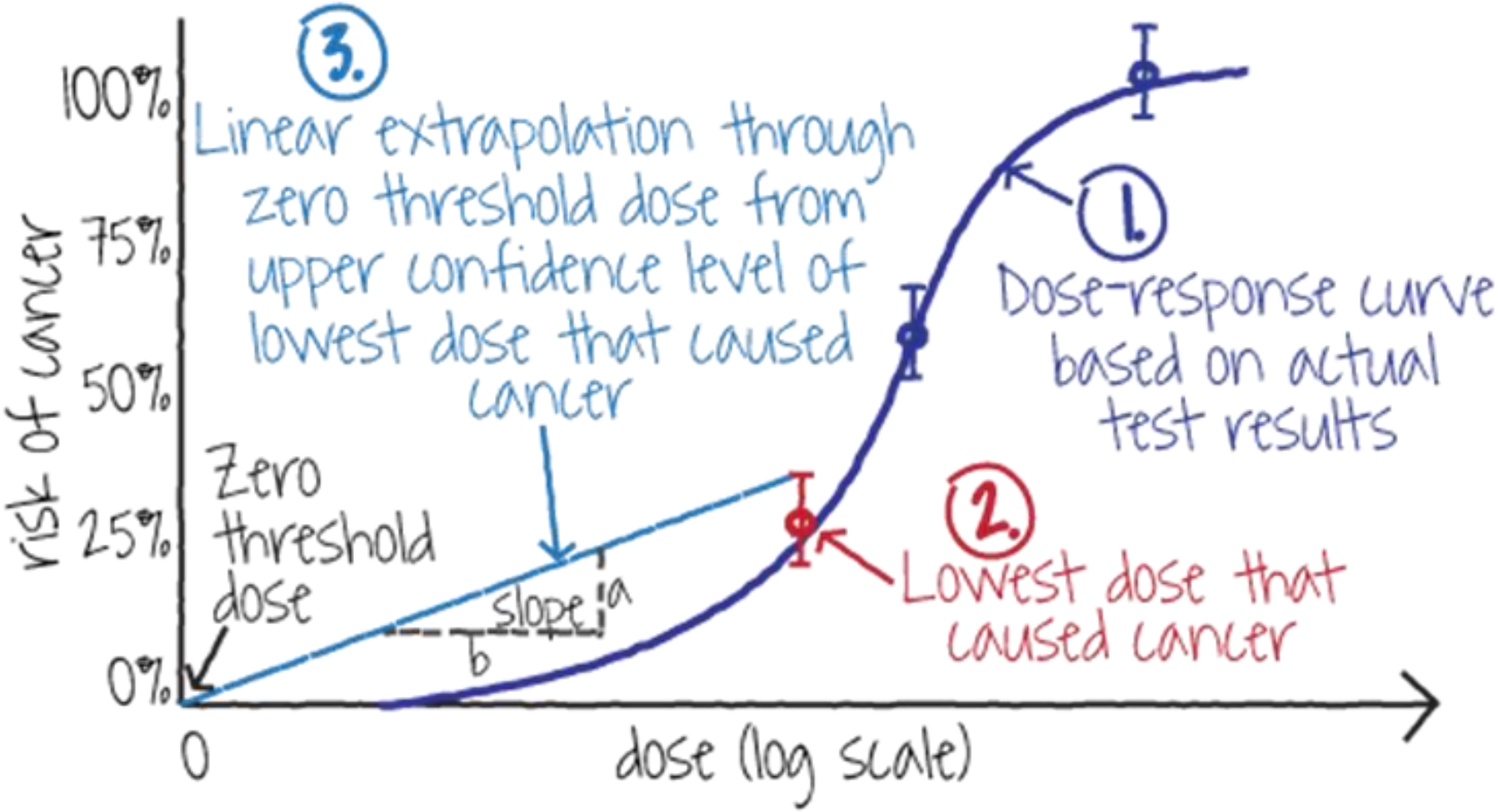


$UF = UF_H \cdot UF_A \cdot UF_S \cdot UF_L$
UF_H = Human variability (10×)
UF_A = Animal to human (10×)
UF_S = Subchronic to chronic (10×)
UF_L = LOAEL to NOAEL (10×)
MF = Modifying factor for completeness of data (1–10×)
RfD = Reference dose

Dose-Effect Curves



Duffus & Worth, ©IUPAC


3.
Linear extrapolation through zero threshold dose from upper confidence level of lowest dose that caused cancer
100%
75%
50%
25%
0%
risk of cancer
Zero threshold dose
slope = a/b
1.
Dose-response curve based on actual test results
2.
Lowest dose that caused cancer
0
dose (log scale)

The cumulative curve is used to show data

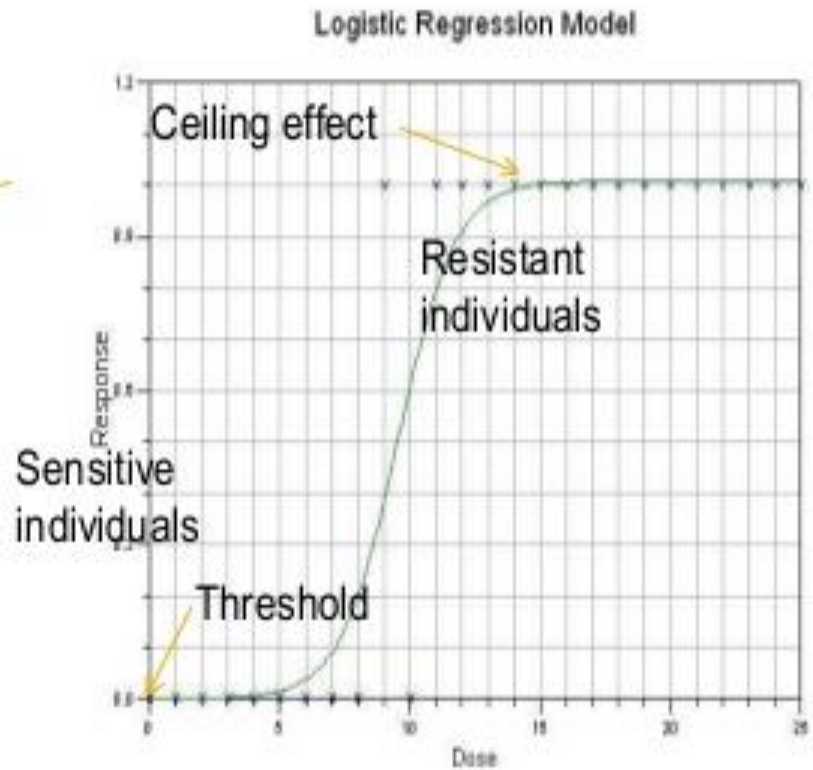
Y-axis: Response % (lethality, toxic response, effective drug dose)

X-axis: Dose (mg) Dose may be on a linear or a log scale

No response below thres-hold

Ceiling effect: no difference once all individuals are affected

100%



According to effected parts-1

- ***Local toxicity:***

Occur at the area of the body which has been in contact with the chemical.

External tissue injuries from acids or lung injuries from inhaled reactive gases.

- ***Systemic toxicity***

Occur after the chemical has been absorbed and distributed from the entry point to other parts of the body.

Most substances produce systemic effects, but some substances may cause *both* types of effects.

tetraethyl lead, which is a gasoline additive and produces skin effects at the contact site. It may also be absorbed and transported into the body causing adverse effects on the central nervous system and on other organs.

According to effected parts-2

- ***Target organ toxicity***
- The degree of the toxic effect is not the same in all organs.
- Usually there are one or two organs which show the major toxic effect. These are referred as target organs of toxicity of the particular substance.
- CNS is the target organ of toxicity most frequently involved in systemic effects.
- The blood circulation system, liver, kidneys, lungs and skin follow in frequency of systemic effects.
- Some substances attack muscle and bones.
- Both the male and female reproductive systems are susceptible to adverse and often debilitatingimpacts from many substances. ***gan toxicity***

Mechanism of Action of Toxicants

1. Specific Action of Toxicant

- **1. Receptor mediated events**:
- The actions at the specific receptors for neuro-transmitters, hormones, and drugs either as agonists or as antagonists are responsible for numerous toxic responses.
- This is most important for neurotoxins acting within and outside the central nervous system,
- e.g. strychnine, morphine and atropine.

- **2. Enzyme mediated events**:
- Interact directly with specific enzymes which catalyze some important physiologic processes to produce their toxic effects.
- The severity and duration of poisoning can be influenced by the strength of toxicant-enzyme interaction.
- e.g. Organophosphorus and carbamate insecticides produce their toxicity through inhibition of cholinesterses.
- HCN by cytochrome oxides.
- Lead via inhibition of membrane bound Na+-K+, - ATPase, δ-aminolevulinic acid synthetase and ferrochelate, etc.

drjaggyvpt.blogspot.com/2016/02/mechanisms-of-action-of-toxicants.html

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

1. Physical toxicants:

- Certain toxicants act by their physical deposition in body tissues, and organs like lungs, e.g. industrial and heavy metals dust, silicon, and asbestos.

2. Direct chemical injury:

Direct chemical injury to tissues either causes protoplasmic precipitation or alters the membrane dependent homeostatic control of cell functions. Damage is usually immediate, localized and non-specific.

Damage occurs when cell membranes contact strong corrosives, caustics or compounds that coagulate proteins or damage lipids, e.g. acids, bases, phenols, aldehydes, alcohols, petroleum distillates and some salts of heavy metals.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

3. Necrosis of epithelial cells:

- Systemic toxins can cause epithelial necrosis mainly by producing ischaemia (reduced blood flow) resulting in damage to metabolically active cells.

- Damage mainly occurs due to cellular anoxia which further leads to an energy deficit, e.g. carbon monoxide, cyanide, and nitrite.

Mechanism of Action of Toxicants
2. Non-specific Action of Toxicants

4. Interference with body metabolism or synthesis: This leads to loss of products used for energy, structural components and growth. This may take place in following ways:

- **a. *Uncoupling of oxidative phosphorylation****:*** The release of energy in the electron transport chain becomes uncoupled from the formation of energy. This results in no phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). The energy is dissipated as heat rather than stored in high energy phosphate bonds. Thus, body temperature rises, e.g. dinitrophenol and chlorophenol fungicides, and arsenates.
- **b. *Inhibition of oxidative phosphorylation***: This results in limited oxygen uptake with lower ATP formation. The effects of fatigue and weakness are similar to that of oxidative uncouplers but there is no fever.
- **C. *Inhibition of nucleic acid and protein synthesis***: This can occur by toxicants that injure DNA or that bind to ribosomes during transcription or translocation, e.g. aflatoxins, organomercurials, and trichothcccncs,
- **d. *Interference with fat metabolism****:*** This occurs when toxins affect the rough endoplasmic reticulum resulting in reduced synthesis of lipid acceptor proteins or reduced incorporation of phospholipids and triglycerides into transport lipoproteins. This leads to fat accumulation in the cell, e.g. carbon tetrachloride, ethionine, yellow phosphorus, and puromycin.

Mechanism of Action of Toxicants
2. Non-specific Action of Toxicants

5. Injury to blood, vascular and respiratory system:

- Hypoplasia or aplasia of cellular components of blood may result from direct toxic effects on bone marrow precursor cells. e.g. Chloramphenicol, radiations, etc.
- Coagulopathy from toxic interference with Vit. K results in spontaneous haemorrhages. e.g. rodenticides such as warfarin and brodifacoum prevent the reactivation of Vit. K needed for the synthesis of prothrombin and factors VII, IX and X.
- Causing lysis of erythrocytes: e.g. Haemotoxic venoms.
- Inactivating haemoglobin: e.g. Nitrites, CO, Chlorate, etc.
- Interfering with oxygen exchange in pulmonary alveoli: ANTU, paraquat, etc.
- Interfering with cellular utilization of oxygen: Cyanide, H_2S, Fluoroacetate, etc.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

6. Deposition in tissues/organs: Certain toxicants have special affinity for some organ and tissue, thus producing their toxicity.

- For example, fluoride deposition in bones and teeth produces exostosis of bones and mottling of teeth; and sulphonamide and oxalate crystals deposition in kidneys produces nephrotoxicity.
- Causing abnormalities in long bones – Fluorine, Lead, Selenium, Copper, etc.
- Causing painful lesions in feet: Ergot and other mold toxins, fluorine, etc.
- Bone cartilages and joints: Fluoroquinolones.
- Liver: CCl4, Chloroform, paracetamol, lantadenes, pyrrolizidine alkaloids, etc.
- Kidney: lead, mercurial salts, aminoglycoside, etc.
- CNS: lead, mercury, barbiturates, strychnine, etc.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

7. Action on ion permeability/channels:

- Excitable membranes are critical to the function of nerves and muscles to generate and propagate action potential. Interaction with ion-channels and membrane ion-pumps can be influenced by a variety of toxic compounds.
- e.g. neurotoxicity of chlorinated hydrocarbons (DDT, aldrin) and pyrethroids (fluvalinate, deltamethrin), tetrodotoxin, saxitoxin, etc. is the result of interference with sodium channels.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

8. Altered calcium homeostasis: Calcium ions have critical roles in cellular function whose concentration is tightly controlled by a variety of compartmentation processes and transport mechanisms. Various toxicants can disrupt these with marked deleterious effects on the cell, i.e. changes in the cytoskeleton, leakage from plasma membrane, impaired mitochondrial function and activation of calcium dependent degradative enzymes (proteases, phospholipases, endonucleases), e.g. free radicals, quinones and peroxides.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

- **9. Formation of secondary toxic metabolites**: Certain compounds after their biotransformation, results in metabolites which are more toxic. For example, urea toxicity occurs due to release of ammonia, and carcinogenicity is produced by active metabolites of aflatoxins.
- **10. Action similar to normal metabolite or nutrient**: Some toxicants resemble endogenous substances in their structure and can mimic their activity but in higher magnitude which produces toxic effects. For example, oestrogenic mycotoxins (zearalenone), plants, and feed additives may alter reproductive cycle due to their structural resemblance with endogenous oestrogens.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

- **11. Immuno-deficiency**: Toxicants can affect both humoral and cell mediated immunities. Reduced antibody synthesis, interference with complement, altered neutrophil function and reduced lymphoblastogenesis are all toxic effects mediated by various agents, e.g. heavy metals (lead, nickel), digoxin, mycotoxins, drugs, and insecticides.
- **12. Developmental defects**: These defects occur primarily *in utero* as a result of toxicants affecting susceptible cells during organogenesis. Most teratogenic effects altering the morphology of the foetus occur in the first trimester of pregnancy e.g. benzimidazole anthelmintics. Toxicant exposure in the third trimester results in reduced growth of a foetus, e.g. thalidomide, tetracyclines, heavy metals, and quinine.

Mechanism of Action of Toxicants

2. Non-specific Action of Toxicants

- **13. Carcinogenesis**: Promotion of carcinogenesis is caused by chemicals that produce tissue irritation or damage to macromolecules resulting in expression of the cancer process. This is mainly due to DNA damage, e.g. insecticides (DDT), hormones (oestrogen), and saccharrin.
- **14. Deficiency of nutrients**: Certain toxicants produce deficiency of essential nutrients in the body. However, such effects produced by these chemicals are secondary. For example, molybdenum produces toxicity due to deficiency of copper; oxalate chelates Ca^{++} in the rumen and blood to produce hypocalcaemia (oxalate poisoning).
- **15. Non-specific action on enzymes**: Certain toxicants inhibit certain non-specific enzymes to produce their toxic effects. For example, rubratoxins inhibit cytochrome P450 mixed function oxidases besides certain ATP-ases.