



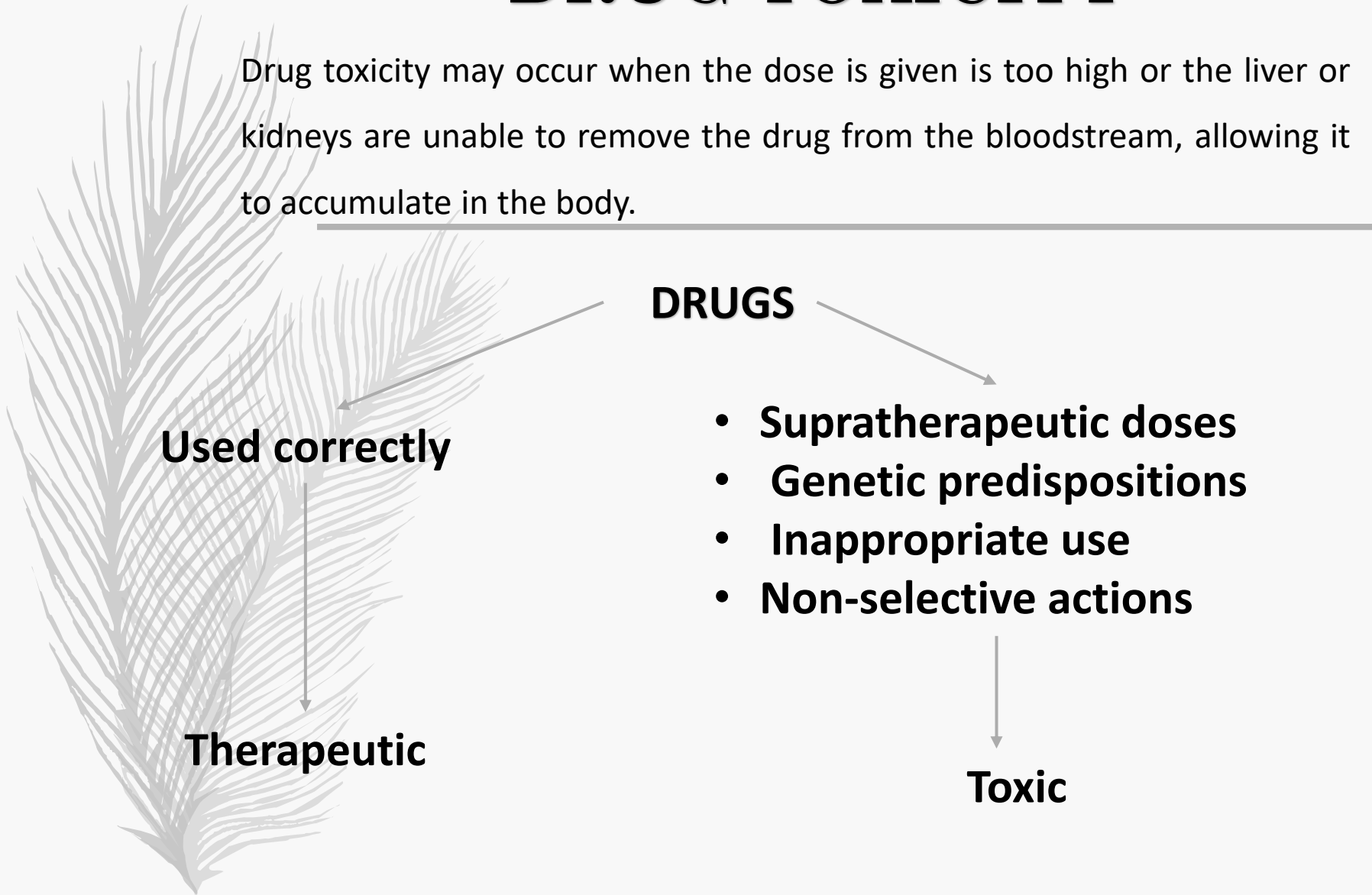
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# **Drug toxicity and toxicity caused by agrochemicals**

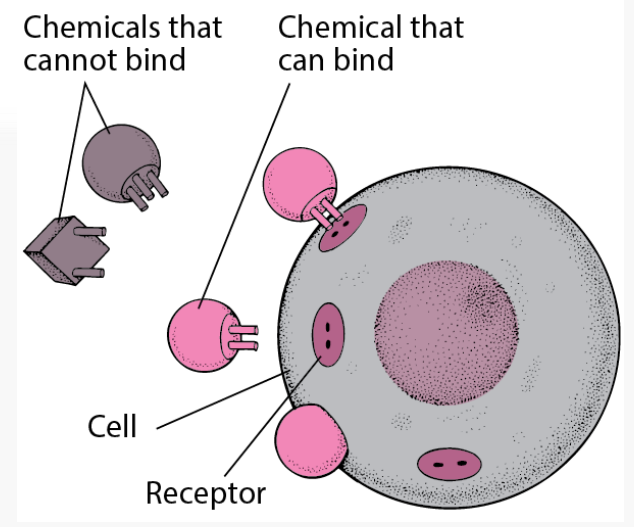
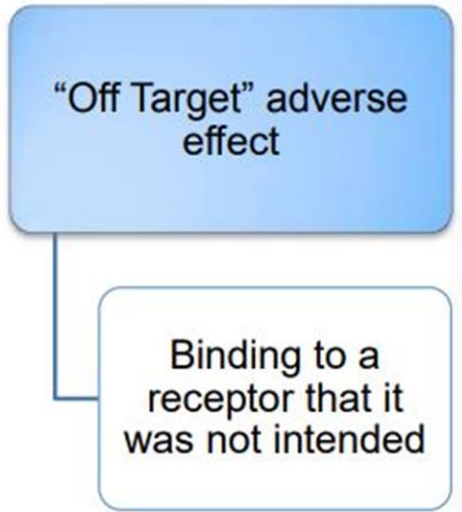
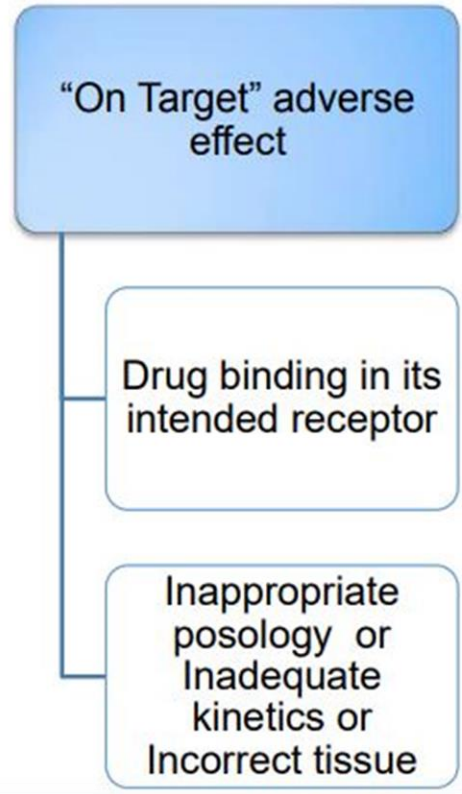
# DRUG TOXICITY

Drug toxicity may occur when the dose is given is too high or the liver or kidneys are unable to remove the drug from the bloodstream, allowing it to accumulate in the body.

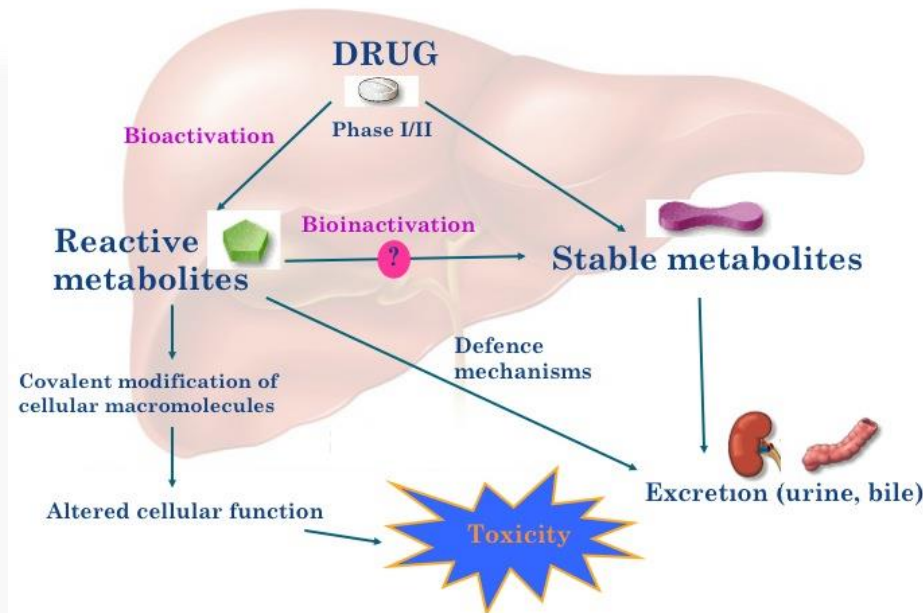
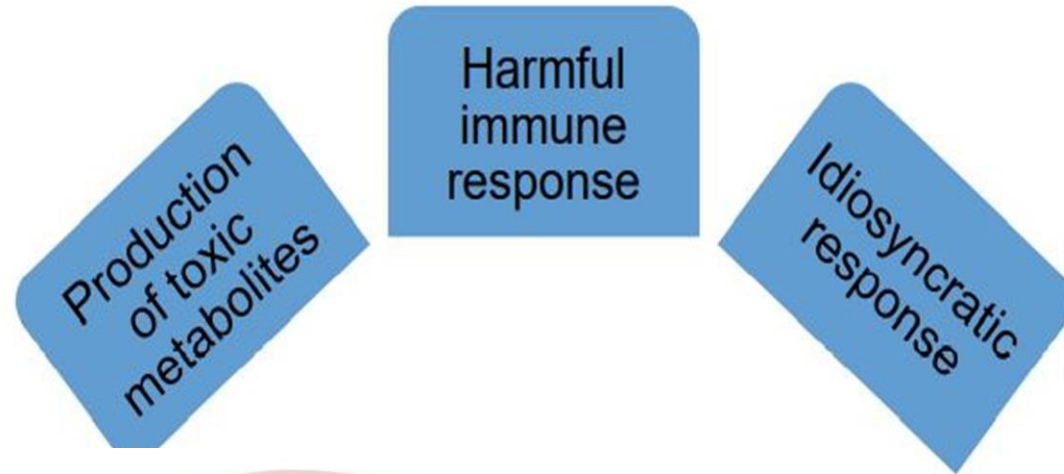
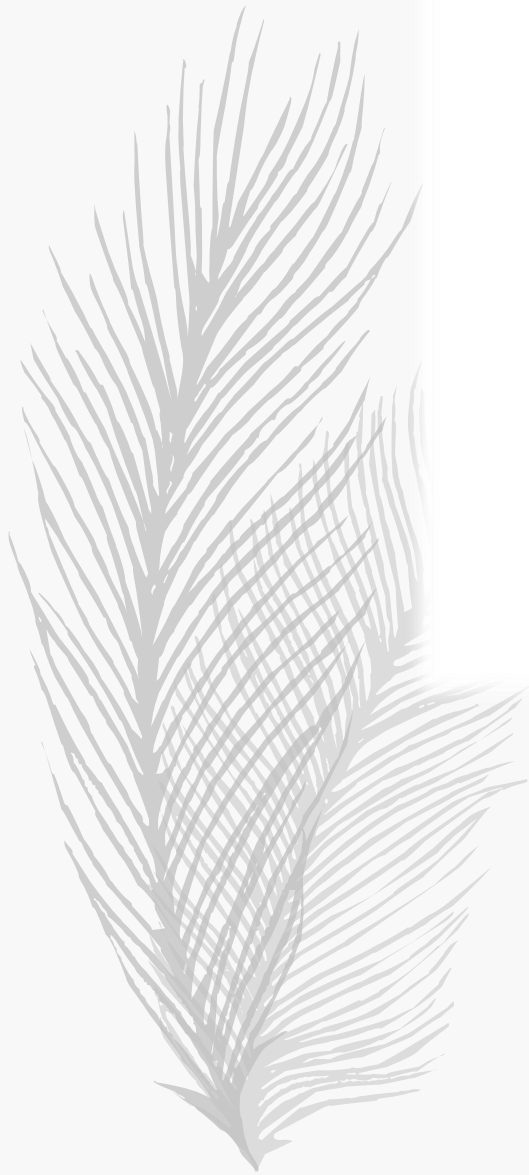
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# DRUG TOXICITY CLASSIFICATION



# OTHER CLASSIFICATIONS





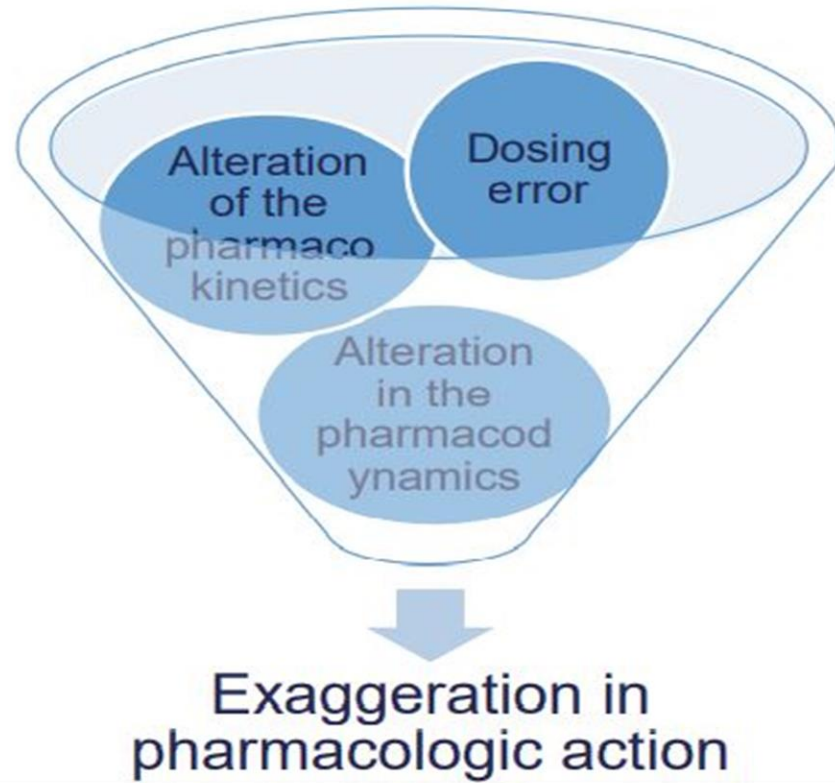
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## **Examples of Metabolic Conversions Leading to Toxic Metabolites**

A. Acetaminophen. The analgesic acetaminophen (4-hydroxyacetanilide, paracetamol) exhibits lethal hepatotoxicity.

B. Tienilic Acid. Tienilic acid is a uricosuric diuretic drug that may cause immunoallergic hepatitis.

# CAUSES OF ON-TARGET EFFECTS



**On-target effects refers to exaggerated and adverse pharmacologic effects at the target of interest in the test system.**



# Mechanism: On Target Effects

- On-target adverse effects, which are the result of the drug binding to its intended receptor, but at an inappropriate concentration, with suboptimal kinetics, or in the incorrect tissue
- An adverse effect may be an exaggeration of the desired pharmacologic action due to alterations in exposure to the drug.
  - Deliberate or accidental dosing error
  - Alterations in the pharmacokinetics of the drug
  - By changes in the pharmacodynamics of the drug-receptor interaction that alter the pharmacologic response
- All this causes an increase in the effective concentration of the drug and thus to an increased biological response.



## EXAMPLE: ANTIHISTAMINE DIPHENHYDRAMINE

- Used to reduce allergic reaction
- Minimize histamine release by interacting with H1 receptors.
- Pass the blood-brain barrier
- Causes drowsiness by interacting with H1 receptor in the brain.



# MECHANISM OF DRUG TOXICITY: Off-Target adverse effect

Off-target refers to adverse effects as a result of modulation of other targets; these may be related biologically or totally unrelated to the target of interest.

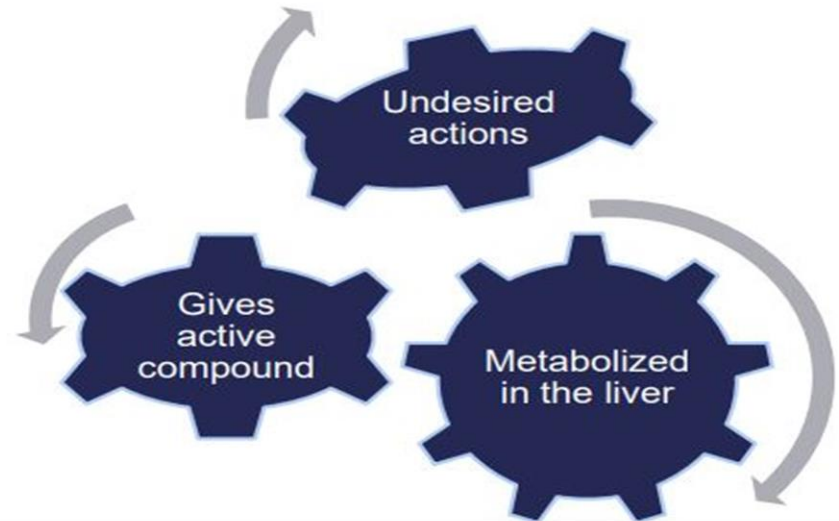
## EXAMPLE: ANTIHISTAMINE TERFENADINE

- Inhibits histamine release in the blood
- Also inhibits cardiac potassium channels
- Causes fatal cardiac arrhythmias
- Withdrawn from the market
- Now usage of fexofenadine
- Have affinity to cardiac potassium channels but to a much lesser degree than terfenadine

# MECHANISM OF DRUG TOXICITY: Production of toxic metabolites



## DRUG METABOLISM





## EXAMPLE: LOSARTAN AND EBASTIN

- Losartan is converted to the active E3174
- Ebastin is converted to carebastine
- Both are active inside the body and may cause damage.

**Losartan**, sold under the trade name Cozaar among others, is a medication mainly used to treat high blood pressure. It is also used for diabetic kidney disease, heart failure, and left ventricular enlargement.

**Ebastine** is a H<sub>1</sub> antihistamine with low potential for causing drowsiness

# ACETAMINOPHEN: Mechanism of Acetaminophen toxicity

WITH NORMAL DOSES

Acetaminophen enter through the digestive tract

Heavily metabolized by the liver by Liver enzymes

P450 will metabolize it into intermediate "N-acetyl-p-benzoquinoneimine (NAPQI)"

Finally it is excreted from the body

Then it is further conjugated with glucuronate and sulfate

NAPQI is then immediately conjugated with glutathione

## WITH HIGH DOSE ADMINISTERED

The high levels of acetaminophen will saturate the conjugation enzymes

First the glucuronate transferase and the sulfate transferase will be saturated

This will eventually saturate the glutathione transferase

When that happens high levels of NAPQI will accumulate inside the cell

NAPQI will react with other hepatic proteins giving other toxic compounds

This will cause hepatotoxicity and will cause death

This is solved by giving the patient N-acetylcysteine

