BHARATHIDASAN UNIVERSITY
Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
Course Code : BM35C7

Unit-V
Toxicology- Part 2

Dr. P.S.Dhivya
Guest Lecturer
Department of Biomedical Science

MUTAGENICITY-MECHANISM OF MUTAGENESIS

MUTAGENICITY

- **Mutagenicity** refers to the ability or capacity of a chemical, physical, or biological agent (a **mutagen**) to induce changes or mutations in the genetic material (DNA) of an organism. Mutations can be alterations in the DNA sequence, such as base substitutions, insertions, deletions, or chromosomal rearrangements.
- Mutagenicity is significant because mutations can result in harmful effects, such as cancer, genetic disorders, or developmental abnormalities. However, mutations can also be a source of genetic diversity, contributing to evolutionary processes.

Spontaneous mutagenesis refers to the occurrence of mutations in an organism’s DNA that happen naturally, without any external influence or deliberate intervention. This process is a fundamental aspect of genetics and contributes to the genetic diversity of populations over time.

Spontaneous Mutagenesis

Replication Errors:

Mispairing: Incorrect base pairing during DNA replication can lead to point mutations.

Slipped-strand mispairing: This occurs when DNA polymerase slips and either inserts or deletes nucleotides, causing frameshift mutations.

Depurination and Deamination:

Depurination: Loss of a purine base (adenine or guanine) can lead to a deletion mutation.

Deamination: Conversion of cytosine to uracil or adenine to hypoxanthine can result in point mutations.

Oxidative Damage: Reactive oxygen species (ROS) can cause damage to DNA bases and sugar-phosphate backbone, leading to various types of mutations.

Induced Mutagenesis

Chemical Mutagens:

Base analogs: These DNA bases and can be incorporated into the DNA during replication, leading to mispairing.

Alkylating agents: These add alkyl groups to DNA bases, causing mispairing or DNA strand breaks.

Intercalating agents: These insert between DNA base pairs, causing frameshift mutations.

Physical Mutagens:

Ionizing radiation: This can cause DNA strand breaks and base damage.

Ultraviolet radiation: This can cause thymine dimers, which can interfere with DNA replication and repair.

Biological Mutagens: Transposable elements: These DNA sequences can move within the genome, disrupting genes and causing mutations.

Viruses: Some viruses can insert their genetic material into the host genome, leading to mutations.

CARCINOGENICITY

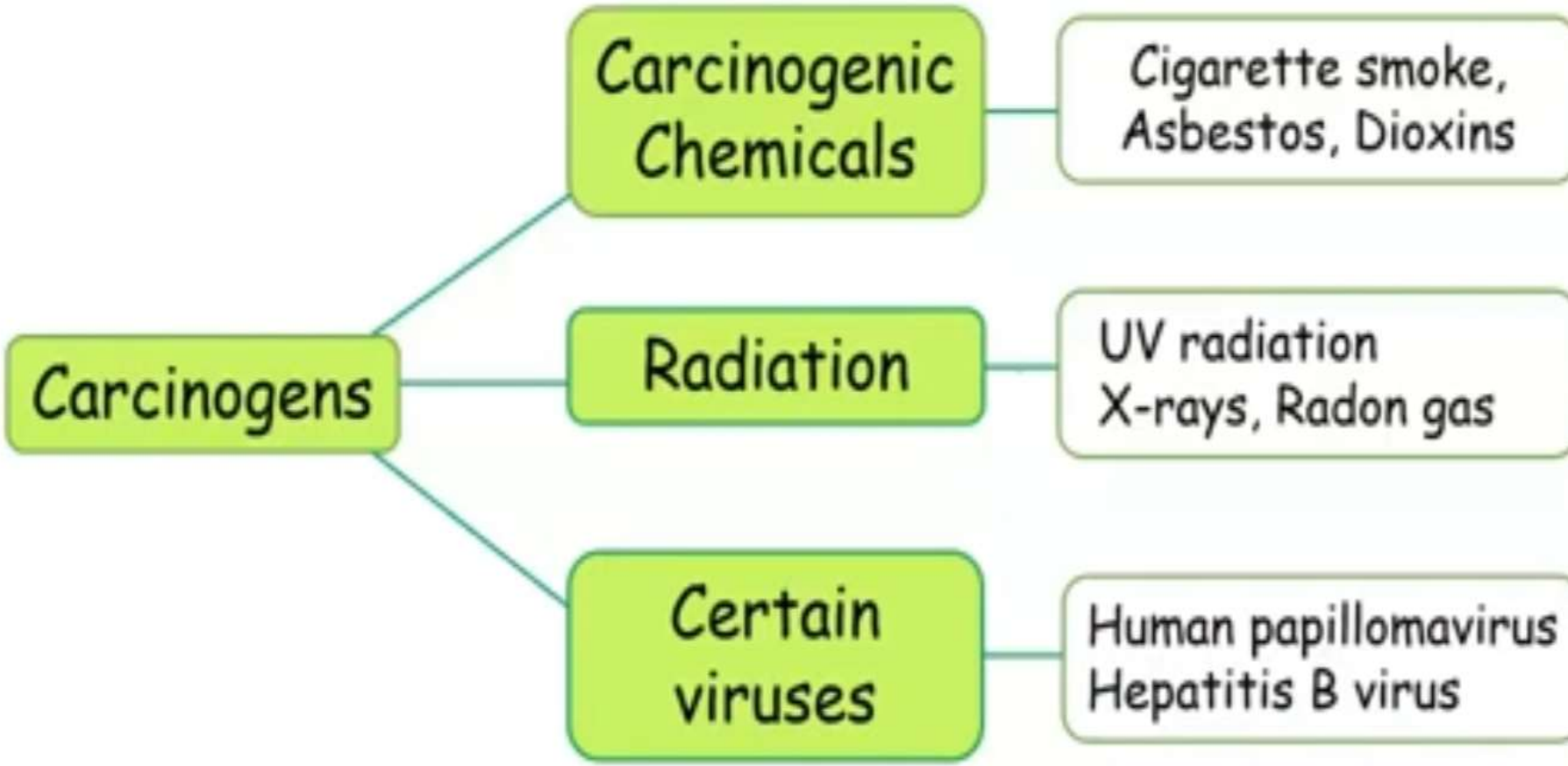
&

TOXICOKINETICS

CARCINOGENICITY:

- A carcinogen is any substance, radionuclide or radiation that is an agent directly involved in causing cancer. This may be due to ability to damage the genome or to the disruption of cellular metabolic processes.
- Radioactive substances are gamma rays and alpha particles .
- Non- radioactive substances are certain dioxins and tobacco smoke.

Types & Examples Of Carcinogens



How Do Carcinogen enter the body??

- Skin absorption: Many solvents and other chemicals go directly through the skin.
- Ingestion: Swallowing of a carcinogen.
- Inhalation: Breathing gases, fumes and vapour is the most common form of exposure.

Organs to carcinogens attack:

- Liver
- Lungs
- Kidney
- Reproductive system
- Skin
- Many other organs and tissues

TOXICOKINETICS

Definition

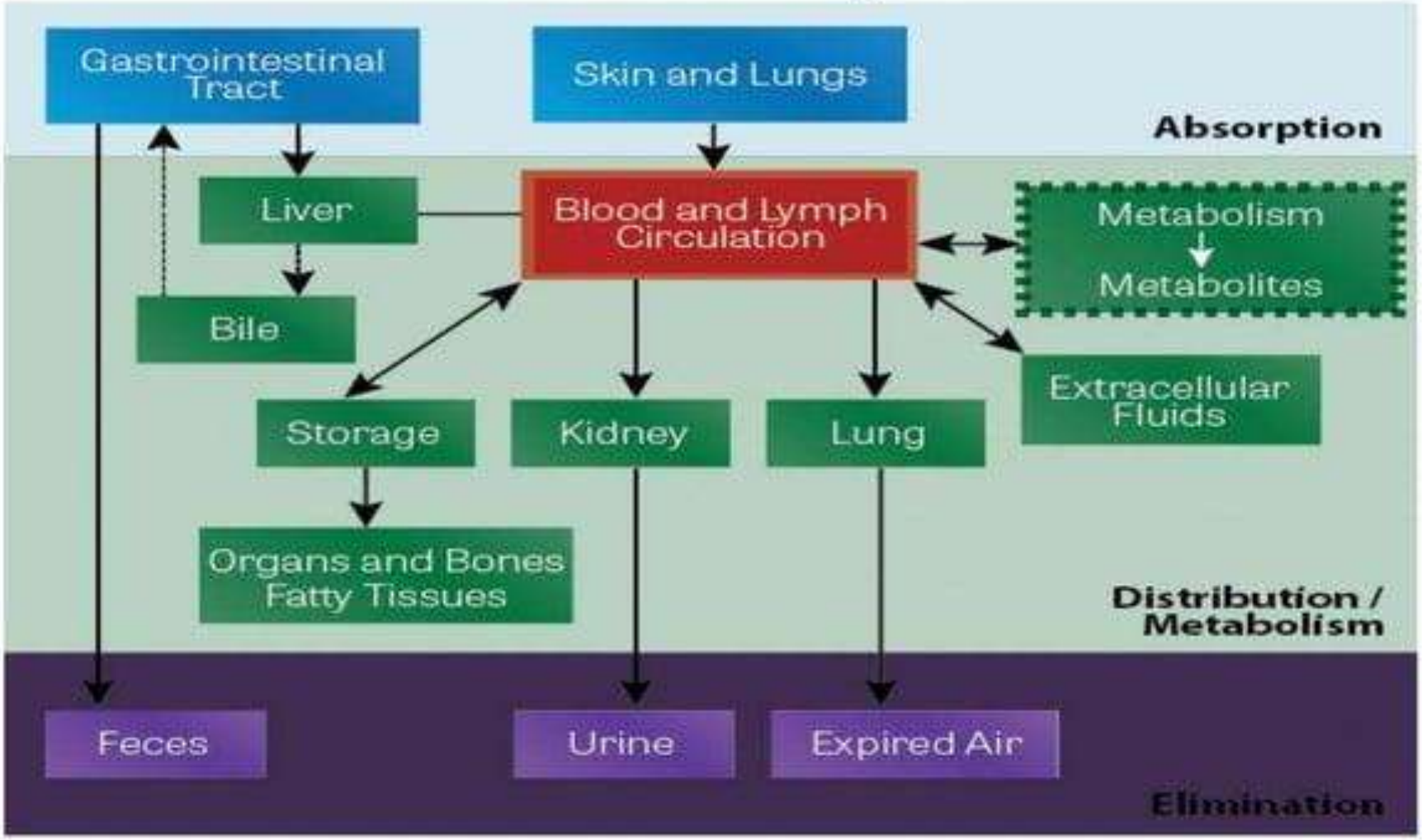
- **Toxicokinetics** describes the rate of a chemical enter the body and how the compound metabolise and excrete once it is in the body.
- Simply, how a substance gets into the body and what happens to it in the body.

- Toxicokinetics deals with what the body does with a drug when given a relatively high dose relative to the therapeutic dose.
- The science of toxicology has evolved to include environmental and occupational chemicals as well as drugs.
- Toxicokinetics is thus the appropriate term for the study of the kinetics of all substances at toxic dose/exposure levels.

Four processes are involved in toxicokinetics:

- **Absorption** — the substance enters the body.
- **Distribution** — the substance moves from the site of entry to other areas of the body.
- **Biotransformation** — the body changes (transforms) the substance into new chemicals(metabolites).
- **Excretion** — the substance or its metabolitesleave the body.

Absorption, distribution, biotransformation, and elimination are inter-related processes as illustrated in Figure



Difference between pharmacokinetics and toxicokinetics

Pharmacokinetics	Toxicokinetics
• It has been with us for many years . • Extensive collaboration with pharmacology. • Lower doses than toxicokinetics	• It is a far more recent discipline. • It need extensive collaboration with toxicologist, toxicokinetics and pharmacokinetics. • Much higher doses are used

RISK ASSESSMENT IN REPRODUCTIVE TOXICITY

WHAT IS REPRODUCTIVE TOXICITY?

Reproductive toxicity refers to harmful effects on the reproductive system or its functions caused by exposure to certain chemicals or drugs. This toxicity can affect both men and women, potentially causing issues such as infertility, developmental disorders in offspring, hormonal imbalances, and complications during pregnancy

Drugs Known to Cause Reproductive Toxicity

Chemotherapy Agents

Methotrexate: This folic acid antagonist is teratogenic and can cause fetal malformations or miscarriage

Cyclophosphamide:

An alkylating agent that can affect both male and female fertility, leading to ovarian or testicular damage and fetal harm.

Phenytoin

Known to cause fetal hydantoin syndrome, which involves facial abnormalities, growth delays, and intellectual disabilities.

Retinoids

Isotretinoin (Accutane)

Used for severe acne but highly teratogenic, causing severe birth defects, miscarriage, or fetal death.

Acitretin

Used for severe psoriasis, it poses risks similar to isotretinoin and is contraindicated in pregnancy.

NSAIDs and Certain Antibiotics

Aspirin (in high doses): Linked with fetal bleeding risks and can potentially affect implantation and fetal kidney development.

Tetracyclines

Known to cause discoloration of teeth and bone development issues in fetuses.

Immunosuppressants

Mycophenolate mofetil: Known to cause malformations in offspring, including ear, eye, and heart defects

Methods to identify reproductive toxicity

Hormone Analysis: Measures levels of reproductive hormones such as estrogen, progesterone, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-Müllerian hormone (AMH). Changes in these hormones can reflect reproductive system impairment.

Menstrual Cycle Monitoring: Observing irregularities in menstruation can provide insights into hormonal balance and ovarian function.

Pregnancy Outcome Analysis: Evaluates miscarriage rates, preterm birth, stillbirth, or fetal abnormalities. These indicators can reflect reproductive toxicity effects during gestation.

Blood Analysis: These are the most common matrices for detecting toxicants like pesticides, heavy metals, and endocrine-disrupting chemicals. Regular biomonitoring of these fluids helps identify exposure trends that could lead to reproductive toxicity.

Placental Analysis: Used in pregnant women to detect in-utero exposure to toxins, which could impact fetal development and future reproductive health.

SAFETY MEASURES

- **Avoiding Hazardous Drugs and Chemicals**: Many pharmaceuticals (like certain chemotherapy agents and anticonvulsants) are known to be reproductive toxicants. These drugs should only be used when essential and under strict medical supervision .
- **Occupational Safety**: For workers in industries where they may encounter reproductive toxicants should enforce protective measures such as regular monitoring, and limiting work hours in toxic environments.
- **Dietary Changes**: Reducing intake of foods high in pesticides or contaminants can also limit exposure. Eating organic, washing fruits and vegetables thoroughly, and avoiding high-mercury fish can reduce toxicant intake.

Smoking Cessation and Limiting Alcohol

Smoking and excessive alcohol consumption are associated with reproductive toxicity. Quitting smoking and reducing alcohol intake can protect reproductive organs and improve hormonal balance.

Managing Stress and Sleep

Chronic stress and poor sleep quality disrupt hormonal cycles, potentially impacting fertility. Regular exercise, stress management techniques, and maintaining a consistent sleep schedule can help mitigate these effects.

Fertility Treatments

For individuals experiencing fertility issues due to exposure, assisted reproductive technologies like in vitro fertilization (IVF) or intrauterine insemination (IUI) may be options

Effects of Reproductive Toxicity

- **Reduced Fertility**: Reduced quality or motility of sperm, and menstrual irregularities.
- **Fetal Abnormalities**: Physical deformities, developmental delays, or prenatal death.
- **Endocrine Disruption**: Imbalance in sex hormones leading to issues such as irregular menstruation, polycystic ovary syndrome (PCOS), or hypogonadism.
- **Increased Risk of Miscarriage and Preterm Birth**: Higher rates of pregnancy loss or premature birth.
- **Postnatal Developmental Issues**: Neurological impairments, growth restrictions, and behavioral changes.

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.