Toxicology

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Introduction

History

- Phillip von Hohenheim (1493 -1541),(Paracelcius) was an alchemist, physician,astrologer and known as the“ **father of toxicology**“→ “All things are poison and nothing is without poison, only the dose permits something not to be poisonous.”

Definition Of Terms

- **Toxin**
  - Toxic substances that are produced naturally (nature origin)
- **Toxic**
  - This term relates to poisonous or deadly effects on the body
- **Toxicants**
  - Any chemical that can injure or kill humans, animals, or plants; a poison
- **Toxicity**
  - Describes the degree to which a substance is poisonous or can cause injury. The toxicity depends on a variety of factors: dose, duration and route of exposure, shape and structure of the chemical itself, and individual human factors.

What is Toxicology

- Science of poison→ The study of how natural or man-made poisons cause undesirable effects in living organisms.
- Poison → any substance that can cause severe injury or death, with excessive exposure
- Sub-disciplines of Toxicology
  - Environmental Toxicology , Occupational (Industrial) Toxicology, Regulatory Toxicology, Food Toxicology, Clinical Toxicology, Forensic Toxicology and others.

Occupational Toxicology

- Involved with health effects from **exposure** to chemicals in the workplace
- This field grew out of a need to save workers from toxic substances and to make their work environment safe.

Exposure

- Exposure→ Concentration of chemical involved and frequency of its interaction with people
- Degree of exposure→ determined during risk assessment
- Excessive Exposure→ The amount of exposure that lead to **injury or adverse effects** e.g. Median Lethal Dose (LD50) of Ethanol is &7000 mg/kg, it means that by ingesting 7000 mg/kg Ethanol, half of the rat population in the experiment died

Injury

- Adverse effects→ abnormal, undesirable harmful change following exposure
  - Irreversible Change & causes damage – 1. Toxic, 2. Harmful
  - Reversible change – 3. Harmless
- Injury depends on = property of chemical + nature of exposure + health & developmental state of the person

Route of Exposure

Routes of Exposure

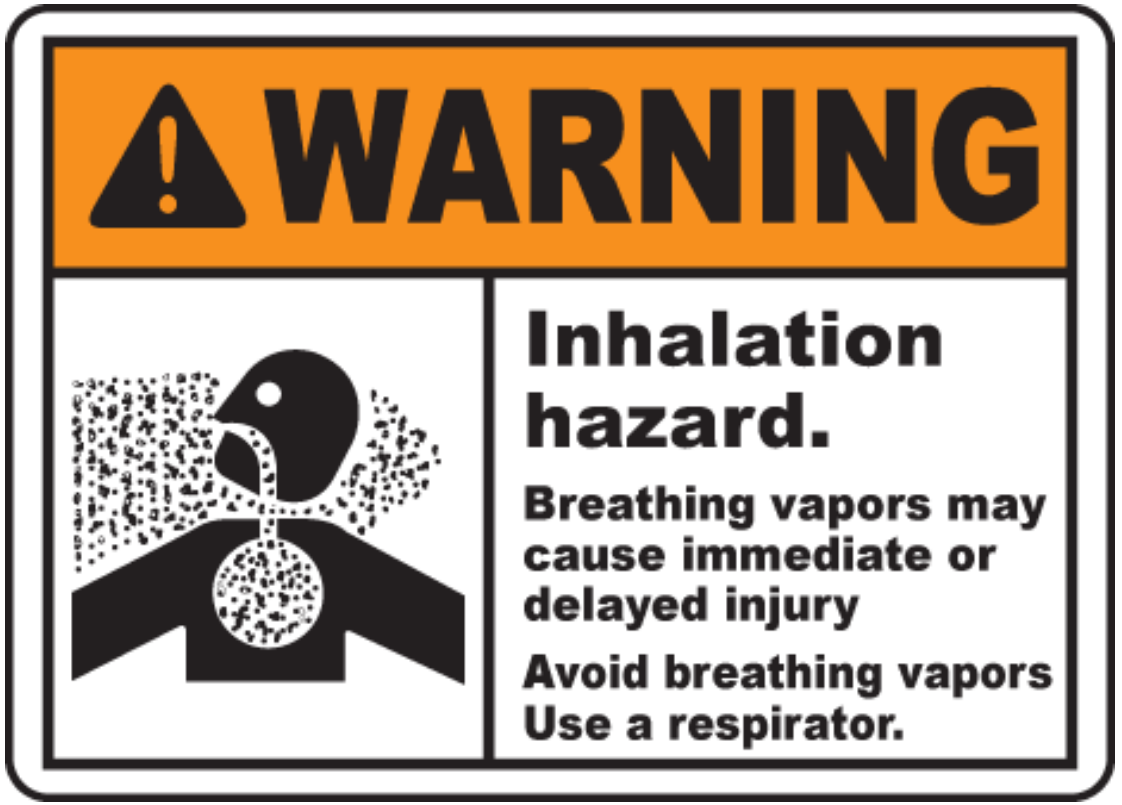
- Skin & mucous membrane
- Lung (Inhalation)
- Ingestion
- Eye

Routes of Exposure

- Skin
  - Chemicals that can penetrate healthy intact skin – aniline, hydrogen cyanide, organophosphate, etc.
  - Absorption through skin from the chemical that absorbed through clothing is far more worse

Routes of Exposure

- Lung (Inhalation)
  - Depends on
    - Size & Shape of particles
    - Rate of physical work (Tidal Volume increase by exertion)



Routes of Exposure (Lung)

- Size & Shape of particles
  - Size – effective aerodynamic diameter
  - Shape – dust, microorganism
  - Larger diameter (>10 micro meter)→ lodge in bronchi/bronchioles→ mucocilliary clearance→ oesophagus→ Gut
  - Smaller Diameter(<2 micro meter)→ persist in alveoli→ cause harm
  - e.g. Insoluble particle (Asbestos)→ macrophage tried to engulf but damaged → hydrolytic enzyme leak→ local tissue damage→ fibrosis

Routes of Exposure (Lung)

- Rate of physical work
  - Advice to avoid physical activity during haze

Routes of Exposure

- Ingestion
  - Mostly we can control (unlike airborne)
  - Airborne particle also can be ingested
  - Depends on
    - Concentration
    - Time
      - Continuous
      - Intermittent
      - Sometimes can accumulate and cause harm in later life e.g. Lead which accumulates in bones cause little harm but once broken, can cause harm to the body

Adverse effect

- Characteristics
  - Local
  - Systemic
  - Both Local & Systemic e.g. Allergic reaction
  - Accumulation
    - Chemical e.g. Adipose tissue accumulate organochloride pesticide and does not cause harm
    - Damage e.g. death of nerve cell following repetitive exposure
- Factors
  - Balance between Absorption and excretion
  - Balance between injury and repair
  - Immediate or delayed effect
  - Reversible or irreversible

Adverse effect

- Local
  - Irritants
  - Corrosive
- Systemic e.g. Organophosphate poisoning

Chemical Interaction

- Additive effects (1 + 1 = 2)
- Synergistic Effects (1 + 1 = 4)
- Antagonist (1 + 5 = 2)

Tolerance and resistance

- Decrease in sensitivity to a chemical following exposure
- Resistance → complete insensitivity towards chemical

Classification

Classification of toxic agents

- Toxic substances are classified into the following
    1. Heavy Metals
    2. Solvents and Vapours
    3. Radiation and Radioactive Materials
    4. Dioxin/Furans
    5. Pesticides
    6. Plant Toxins
    7. Animal Toxins

Effect of toxic agents (Heavy metal)

- **Arsenic**
  - Inorganic arsenic is a known carcinogen and can cause cancer of the skin, lungs, liver and bladder
- **Barium**
  - Barium is not known to cause cancer
  - Short term exposure can cause vomiting, abdominal cramps, diarrhoea, difficulties in breathing, increased or decreased blood pressure, numbness around the face, and muscle weakness
  - Large amounts of barium intake can cause, high blood pressure, changes in heart rhythm or paralysis and possibly death.

Effect of toxic agents (Heavy metal)

- **Cadmium**
  - Cadmium and cadmium compounds are known human carcinogens
  - Smokers get exposed to significantly higher cadmium levels than non-smokers
  - Severe damage to the lungs may occur through breathing high levels of cadmium
- **Lead**
  - Exposure to high lead levels can severely damage the brain and kidneys and ultimately cause death
  - In pregnant women, high levels of exposure to lead may cause miscarriage
  - High level exposure in men can damage the organs responsible for sperm production.

Effect of toxic agents (Heavy metal)

- **Mercury**
  - Exposure to high levels can permanently damage the brain, kidneys, and developing foetuses
  - Effects on brain functioning may result in irritability, shyness, tremors, changes in vision or hearing, and memory problems
- **Selenium**
  - Chronic oral exposure to high concentrations can produce selenosis
  - Major signs of selenosis are hair loss, nail brittleness, and neurological abnormalities
  - Brief exposures to high levels in air can result in respiratory tract irritation, bronchitis, difficulty breathing, and stomach pains
  - Longer-term exposure can cause respiratory irritation, bronchial spasms, and coughing.

Effect of toxic agents (Solvent and vapours)

- **Benzene**
  - Benzene enters the body through inhalation and it may pass through the skin
  - Exposure to low concentrations may cause dizziness, lightheadedness, headache, loss of appetite and stomach upset
  - High exposures to benzene may cause irregularities in the heart beat which can lead to death
  - It has carcinogenic effect as well.

Effect of toxic agents (Solvent and vapours)

- **carcinogens** (e.g., benzene, carbon tetrachloride, trichloroethylene)
- **reproductive hazards** (e.g., 2-ethoxyethanol, 2-methoxyethanol, methyl chloride)
- **neurotoxins** (e.g., n-hexane, tetrachloroethylene, toluene)

Effect of toxic agents (Radiation and radioactive material)

- **Short-Term Health Effects of Radiation Exposure and Contamination**
  - Acute Radiation Syndrome (ARS)→ a serious illness that can happen when a person is exposed to very high levels of radiation, usually over a short period of time.
  - Symptoms of ARS may include nausea, vomiting, headache, and diarrhea
- **Long-Term Health Effects of Radiation Exposure and Contamination**
  - Cancer
  - Prenatal radiation exposure
  - Mental health

Effect of toxic agents (Dioxin/ furans)

- **Short-term exposure** of humans to high levels of dioxins may result in skin lesions, such as chloracne and patchy darkening of the skin, and altered liver function
- **Long-term exposure** is linked to impairment of the immune system, the developing nervous system, the endocrine system and reproductive functions.

Effect of toxic agents (Pesticides)

- **Organochlorines** → cause a loss of sensation around the mouth, hypersensitivity to light, sound, and touch, dizziness, tremors, nausea, vomiting, nervousness, and confusion
- **Organophosphates and Carbamates** → causes signs and symptoms of excess acetylcholine, such as increased salivation and perspiration, narrowing of the pupils, nausea, diarrhea, decrease in blood pressure, muscle weakness, and fatigue
- **Pyrethroids** → Pyrethroids can cause an allergic skin response, and some pyrethroids may cause cancer, reproductive or developmental effects, or endocrine system effects

Effect of toxic agents (Plant toxins)

Plants produce a range of chemicals designed to fend off predators or discourage consumption by insects or animals.

- **Philodendron, poison ivy, cashew** → allergic dermatitis
- **Grasses**→ allergic rhinitis
- **Lily family, glory lily, crocus, horse chestnut** → affects the GIT tract

Effect of toxic agents (Plant toxins)

- **Red alga (red tide), green alga, mushrooms, Coffee bean, tea, cola nut mint family** → affects the nervous system
- **Fungus that grows on peanuts, walnuts** → liver cancer
- **Legumes (Astrogalus); bitter melon seeds (Momordica)** → affects the reproductive system

Effect of toxic agents (**Animal toxins)**

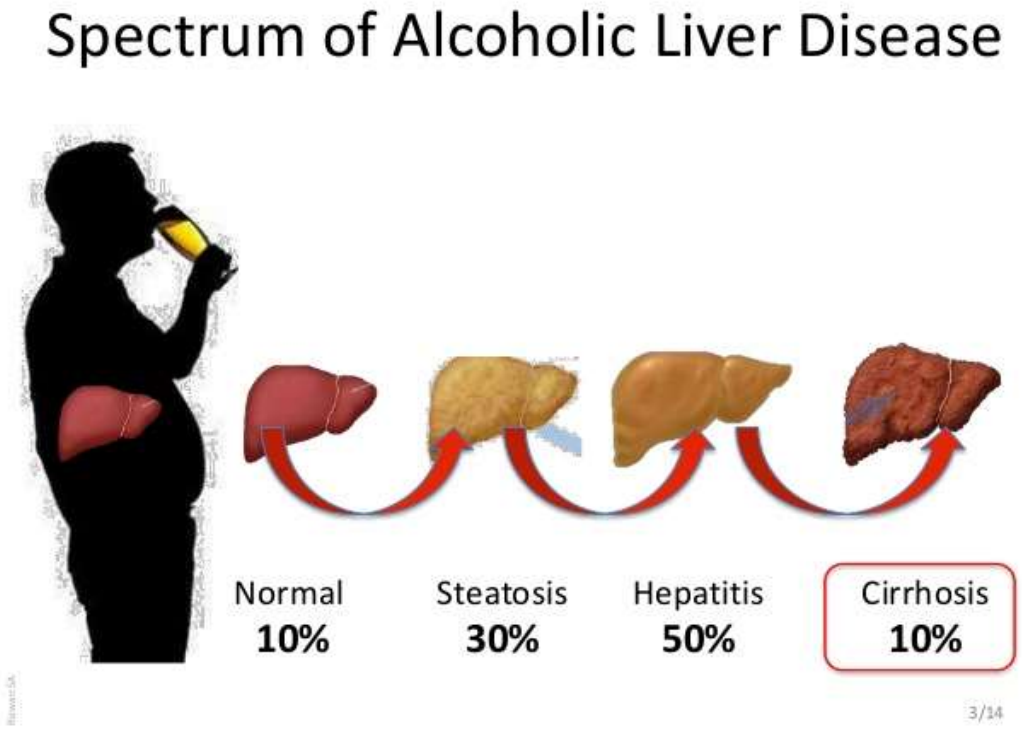
These toxins can result from venomous or poisonous animal releases

- For examples
  - **scorpions, spiders , ticks** → produces neurotoxin
  - **Rattlesnakes, cobras, coral snakes** → produces very complex enzyme-based venoms and neurotoxin

Toxicokinetic & Toxicodynamic

Toxicodynamic

- Toxic (The Chemical) + Dynamic (Changes, *Perubahan*)
- Toxic action on living system
- E.g. excessive ethanol injure liver by blocking metabolism of fat & carbohydrate, and scar tissue replace healthy tissue causing Liver cirrhosis→ this process is toxicodynamic



Toxicodynamic

- Dose-Toxicity relationship
  - Dose-effect relationship
  - Biological effect monitoring
  - Dose –Response relationship
  - Acute & Chronic effects
- Toxicity testing & health risk

Toxicity Testing

- Dose-Response and Concentration response relationship
- Fixed dose testing
  - Toxic
  - Very Toxic
  - Harmful

Dose-Response relationship

- Incidence of defined biological effect in an exposed population, expressed by percentage
- LD_n = Dose of toxicants lethal to n % of population
- LD_{50} = Single dose of chemical that can cause death in 50% of population in an experimental condition e.g. death of mice
- LD_{50} does no tell sub lethal toxicity & does not explain shape of dose-response curve that it derive (Figure 1.2)
- Threshold dose → minimal dose required for detectable response, expressed as NOEL/LOEL (No/Lowest Observed Effect Level)

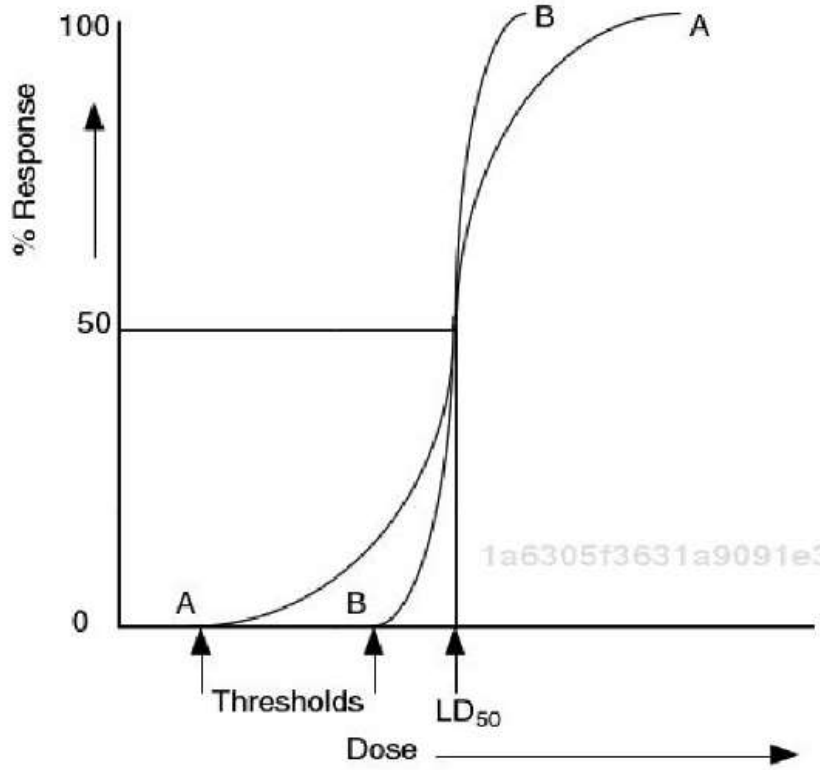


Figure 1.2 *Two substances with the same LD_{50} but different lower lethal thresholds*

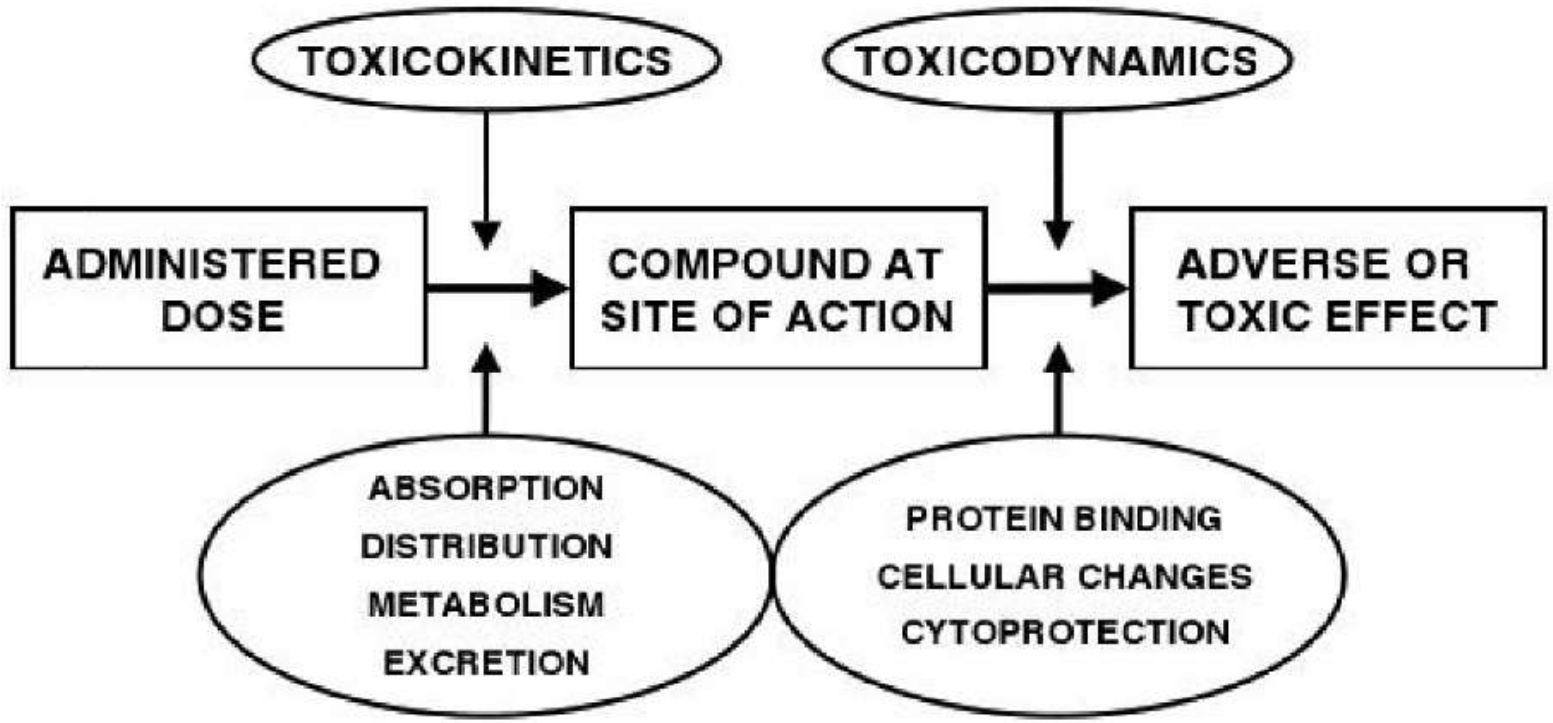


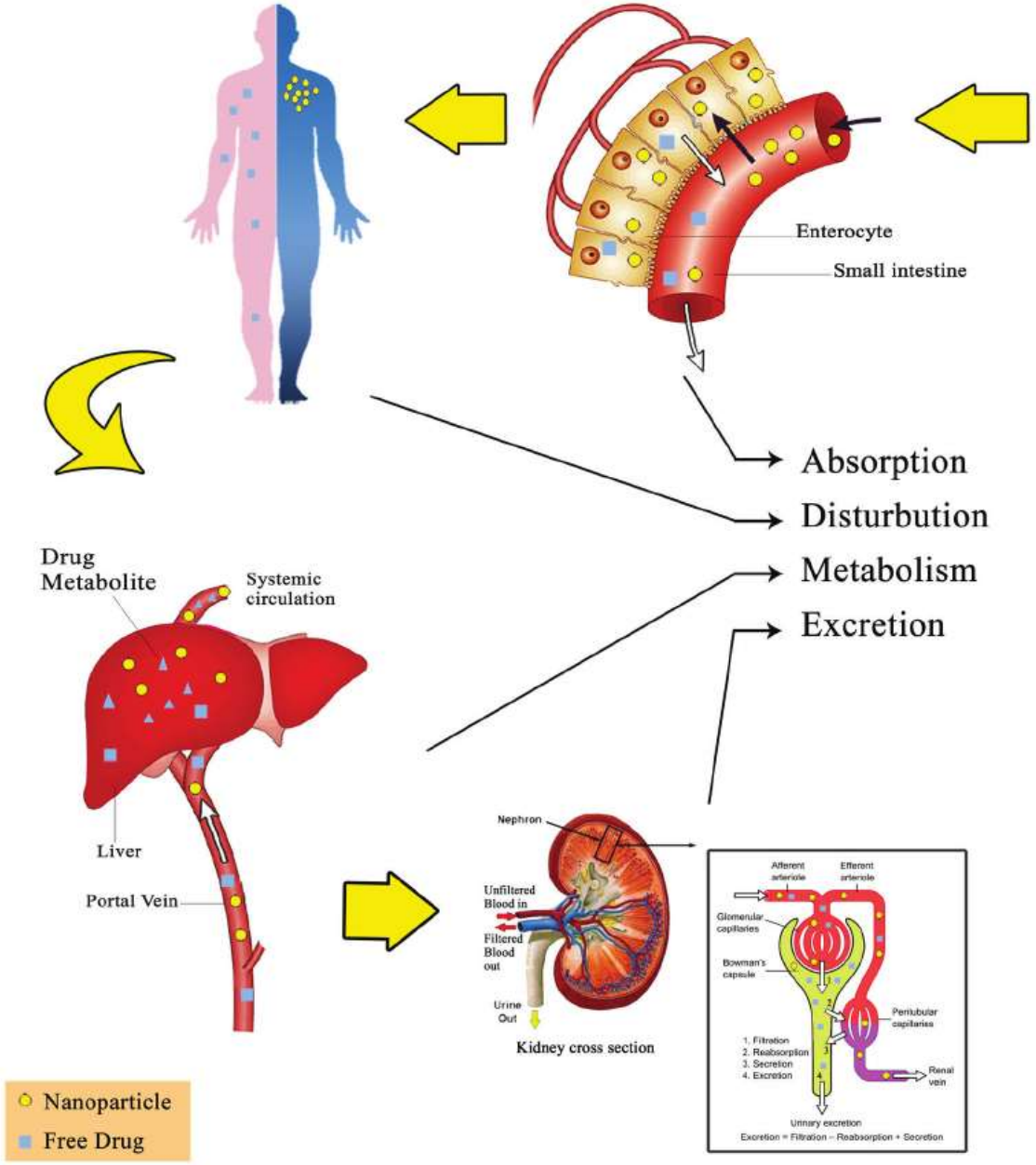
Figure 3.1 *The relationship between delivery of the administered dose to the target site and the generation of the adverse or toxic response*

Toxicokinetic

- Toxico + Kinetics (*Pergerakan*)= movement of chemicals around the body
- E.g. Ethanol from Beer→ Acetaldehyde→ Acetic Acid → nasty odour, used in breathalyser = This is Toxicokinetic (The way body handle potentially toxic substance)

Toxicokinetic

- The study of
  - Absorption
  - Distribution
  - Metabolism
  - Excretion



Toxicokinetic

- Absorption
  - Transfer of chemical from absorption site to general circulation
  - Rate of absorption
    - Determine peak plasma concentration
    - Depends on
      - Vehicle e.g. absorption slow with oily vehicle
      - Lipid Solubility e.g. lipid soluble cross cell membrane easily and absorbed more rapidly than water soluble
      - Place e.g. gut & lung provide larger permeable surface thus enhance absorption
  - Extent of absorption
    - The extent of chemical being transformed prior to reach general circulation e.g. in Gut Lumen

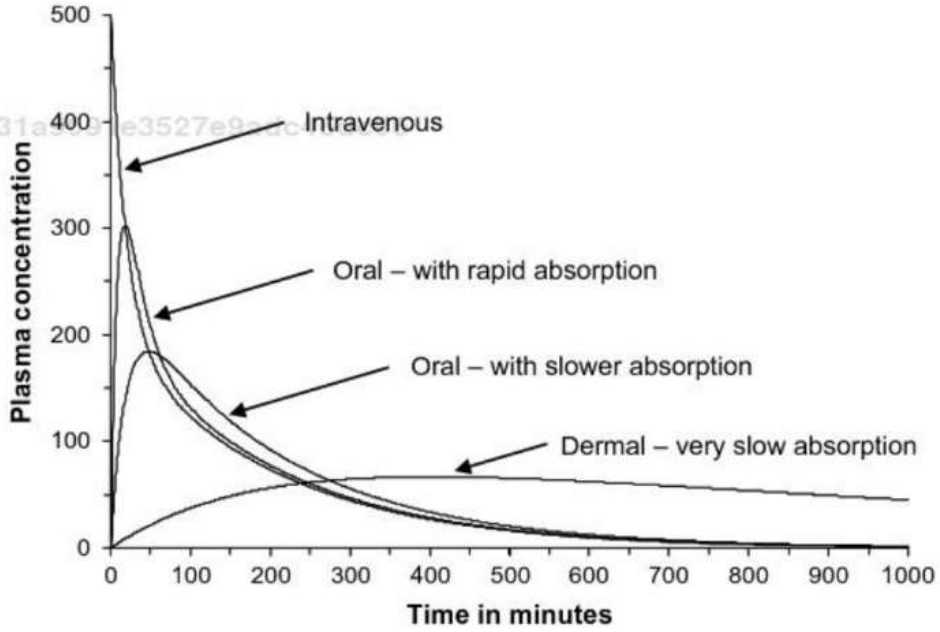
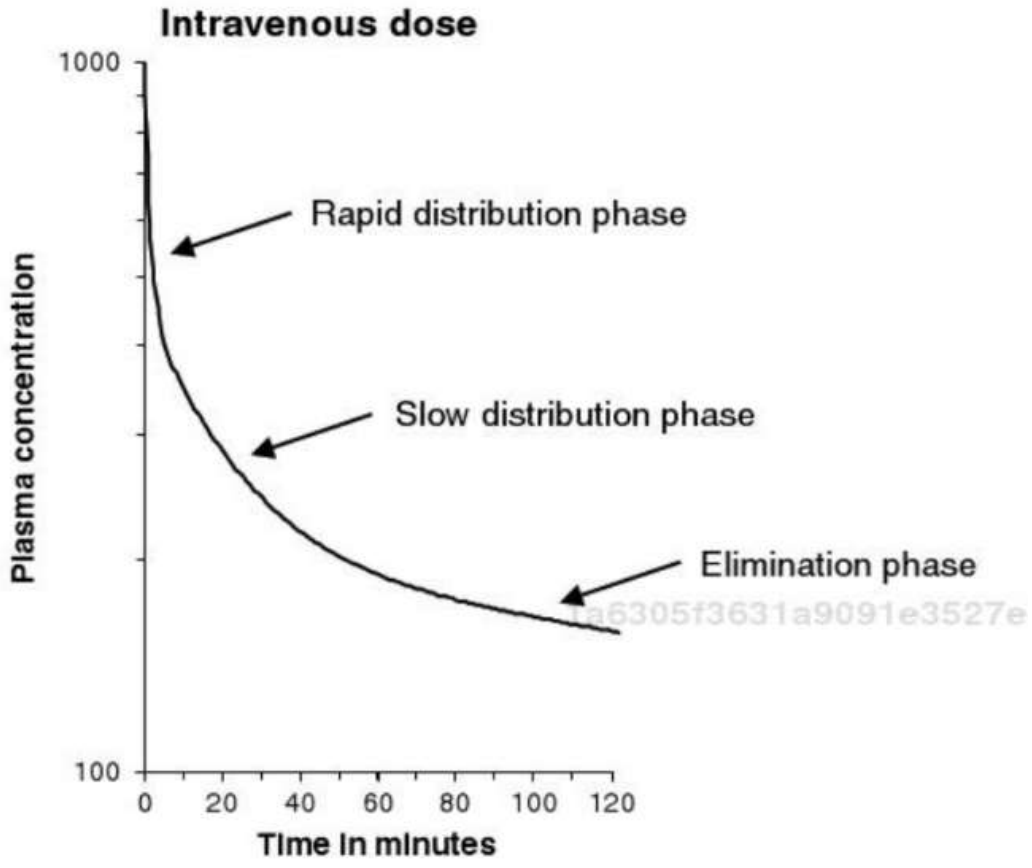


Figure 3.5 *The influence of the rate of absorption of a chemical on the plasma concentration–time curve. A relatively flat low profile is obtained when the rate of absorption is less than the rate of elimination, and this pattern is normally seen with transdermal absorption*

Toxicokinetic

- Distribution
  - Reversible transfer of chemical between general circulation and body tissue
  - Depends on
    - Rate of distribution
      - Ability to cross cell membrane e.g. ability to cross blood brain barrier
      - Tissue blood flow
    - Extent of distribution
      - Affinity of blood/plasma e.g. ability of some chemical to bind with albumin



Toxicokinetic

- Metabolism
  - Biotransformation (Usually Liver)
- Elimination
  - Elimination rate – Half life
  - What determine the rate
    - Capacity & ability of the organ (Liver, Kidney, Lung)
    - Extent of distribution
  - Clearance = rate of elimination/plasma concentration

Risk Asessment

Toxicologic risk assessment

1. Hazard identification

- Population at risk.
- Adverse health effects.

2. Dose-response assessment

- Epidemiological and experimental dose-response data.
- “critical” dose-response relationship.
- Quantitative expression of the dose-response relationship.

3. Exposure assessment

- Past, present and future exposure levels.

4. Risk characterization

- Estimate incidence of adverse health effects, in the pop predicted from the dose-response assessment (Step 2) as applied to the exposure assessment (Step 3).

Management

- At presentation
  - History from all reliable source (patients, family,co-workers)
  - Physical examination
  - Lab investigation for suspected toxin

History Taking

- History is the most valuable tool.
- In some patient (comatose, drowsy, atered conciousness), family, friends, relative,1st medical personel on scene should be questioned.
- All suspected possible toxins should not be missed
- When possible, patient's house and workplace should be examined (not only for toxins but also other things like recrational drugs, empty medicine container or suicide note)

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- If in doubt, extra information can be obtained from
  - Poison Control Centres (Pusat Racun Negara)
  - Material safety Data Sheet (available in almost industrial plant)

O·P·I **MATERIAL SAFETY DATA SHEET** Page 1 of 7 **MSDS-137**

Prepared to OSHA, ACC, ANSI, NOHSC, WHMIS & 2001/58 EC Standards | MSDS Revision: 1.0 | MSDS Revision Date: 02/01/2007

1. PRODUCT IDENTIFICATION

1.1 Product Name: **AXXIUM CLEAR SCULPTING GEL**

1.2 Chemical Name: **METHACRYLATE MIXTURE**

1.3 Synonyms: **NA**

1.4 Trade Names: **NA**

1.5 Product Use: **PROFESSIONAL USE ONLY**

1.6 Manufacturer's Name: **OPI PRODUCTS, INC.**

1.7 Manufacturer's Address: **13034 SATICOY STREET, NO. HOLLYWOOD, CA 91605 USA**

1.8 Emergency Phone: **CHEMTREC: +1 (703) 527-3887 / +1 (800) 424-9300**

1.9 Business Phone: **+1 (818) 759-2400 / +1 (800)-341-9999**

2. HAZARD IDENTIFICATION

2.1 Hazard Identification: **This product is classified as a hazardous substance but not as dangerous goods according to the classification criteria of NOHSC and ADG Code (Australia).**

2.2 Routes of Entry: Inhalation: **YES** Absorption: **YES** Ingestion: **YES**

2.3 Effects of Exposure:

Poison Information And Consultation Service

Monday - Friday

8.10 am - 5.10 pm : +604-657 0099

5.10 pm - 10.00 pm : +012-430 9499

Saturday, Sunday and public holidays :
8.10 am - 5.10 pm : +6012-430 9499

Physical examination

- Starts with the examination of vital signs (GCs, BP, HR etc).
- Then check for signs suggesting of toxicity
- Ingested/absorbed toxin –look for systemic manifestation
- Corrosive toxin –check for GI tract
- Skin contact- acute cutaneus syndrome (blister,rashes, pain)
- Inhalated toxin
  - Water soluble (eg ammonia ,Chlorine) –upper airways symptoms
  - Less water soluble (phosgene)- look for lower airway symptoms
- In some cases of toxicity (especially chronic esposure to toxin), the altered conciousness can be due to other causes like hepatic enchelopathy, Wernicke encelopathy and hypoglycemia.

Labaratory testing

- Can be qualitative or quantitative
- Currently, lack of standard readily available test to identify all the toxins
- Measurement of toxin blood level can help in maanagement

Management (not sure if all done in Malaysia setting)

- Stabilization
  - Maintain airway, breathing, circulation
  - Pt without pulse, BP requird resuscitation
  - Mechanical ventilation might be needed depending on cases
  - IV fluids

- Topical Decontamination
  - Any body surface (plus eyes) that are exposed to toxin is flushed with large amount of saline or water
  - Contaminated clothing, ewellery, accessories should be removed
- Acticated charcoal (in suspected oral toxicity)
  - Should be given as early as possible
  - Has not been proven to reduce mortality/morbididy
- Chelating agent-in metal toxicicty cases

Chelaating Drug	Metal
Deferoxamine	Iron
Dimercaprol	Antimony Arsenic Bismuth mercury
Edate Ca disodium	Cobalt, lead, zinc
Penicillamine	Arsenic, cooper,Lead
Succimer	Arsenic

- Dialysis
  - common in ethylene glycol, lithium,methanol,and salicylates poisoning
  - Less effective if
    - Toxin is large/charged molecule
    - Bound strongly to protein
    - Has large volume of distribution
- Intentional use of toxin need psychiatric evaluation

Examples

Farmers and Farm Personnel

Potential exposures to toxicants resulting from:

- Fertilizer use
- Equipment use
- The use of pesticides and fumigants
- Animal confinement facilities
- Silo

Exposures	Descriptions
Anhydrous ammonia fertilizer	• Odor warning threshold = 53ppm = provide margin of safety. • 400 ppm = irritation of eyes, nose, throat. • 700ppm = immediate eye injury.. • 2500 to 4500 ppm for 30 minutes = lethal. • 5000 pm = rapidly fatal. • Upper airway edema → cyanosis and asphyxiation • Chr sequelae = bronchiolitis obliterans and chr cystic bronchiectasis.
Farm equipment	• Oral siphoning of gasoline with a rubber hose → ingestion and aspiration. • Aspiration of hydrocarbon incl gasoline → severe lung injury, • Welding hazards → inhalation of metal fumes, ozone, NO2, CO2.
Animal confinement	• Oxygen depletion near surface of the manure. • Direct exposure to methane and CO2. • Respi problems = organic toxic dust syndrome, acute and chr bronchitis, occupational asthma, COPD, hypersensitivity pneumonitis.
Toxicity of pesticides	• Very large exposures from ingestion, dermal contact, and inhalation. • Large oral exposures → N&V, diarrhea, pulm edema, cardiac arrhythmias. • Dermal exposure → chemical burns (painful parasthesias, m stiffness).

Doctors, nurses and dentists

Potential toxic exposures	Pathophysiology
Mercury	• Mercury combines easily with metals eg gold, silver, and tin to form alloys called amalgams → used in dental fillings. • Exposure to mercury vapor occurs from instruments that mix amalgam (mechanical amalgamators), sterilizing instruments contaminated with amalgam, and handling, storing, or cleaning mercury or amalgam. • Elemental mercury used in Cantor tubes, thermometers, and sphygmomanometers. • Acute elemental mercury inhalation = local pulmonary toxicity. • Low-level chr exposure = CNS effects eg weakness, fatigue, anorexia, GI disturbances. • Blood or urine mercury levels.
Waste anaesthetic gases	• Leaking gas delivery systems, scavenger system. • Route = inhalation. • Toxic effects: Nitrous oxide peripheral neuropathy, halothane, hepatitis.

General Principals

- Elimination
- Subsitution
- Isolation
- Engineering control
- Admin Control
- PPE
- Legislation