GENERAL TOXICOLOGY

TOXICOLOGY

POISON → * CHARACTERISTIC
* ACTION OF DAMAGE
* CLINICAL SIGN
* THERAPEUTIC MANNER

SUBSTANCE → INDIVIDUAL

PHYSIOLOGY
PATOLOGY
→ LIFEABILITY

DAMAGE OF ACTIONS

LOCAL
DAMAGEOF LOCAL CEL
(SKIN, MUCOUS)
LOCAL PAIN
S/ SYSTEMIC
TOXEMIA

SYSTHEMIC
ABSORPTION → CIRCULATION →
ORGAN → S/SPESIFIC
CYANIDA → RESPIRATION
INSECTISIDE → CNS
STRYCHNIN →.SPINAL CHORD

KINETIC OF POISON

ABSORBTION : → DEPEND ON :

- FAT SOLUBELITY
- PARTICLE SIZE
- BROAD OF SURFACE ABSORBTION
- CONTACT MANNER
- BLOOD CIRCULATION

PLACE OF ABSORBTION

- SKIN
- RESPIRATION
- G.I. TRACT

DISTRIBUTION :

$$Vd = \frac{\text{DOSE}}{\text{PLASMA CONCENTRATION}}$$

- RATE OF DETOXIFICATION
- CHARACTERISTIC PIOSON
- PROTEIN TISSUE / PLASMA BINDING

EXCRETION :

- FAECES
- URINE
- BILE
- LUNG
- THE MILK ECT.

MECHANISM OF DETOXIFICATION

FASE I :

* OXIDATION→ MAO, COMT
* REDUCTION → ENZIM MIKROSOMAL
  - DECHLORINATION
  - DEHALOGENATION
* HYDROLISIS
* HYDRATION

FASE II :

* SULFATION → SULFOTRANSFERASE
* GLUCORONIDATION →GLUKOROSIL TRNSFERASE
* CONYUGATION → AS.GLUKORONAT
* ACETYLATION →
* METYLATION →

FACTORS TO INFLUENCE FOR ACTION OF POISON

1. DIFFERENCE OT THE SPESIES

   CAT → SENSITIF PHENOL & ORGANOCHLORIN

   → MORPHIN (STIMULATION)
2. AGE → DETOXIFIKASI AND EXCRETION
3. CHARACTERISTIC OF POISON → INSECTISIDE, LOGAM BERAT, GAS
4. DOSE OF POISON
5. CONTACT MANNER (LOKAL. SISTEMATIK)
6. CUMULATIVE EFFECT (DTT,GLIKOSIDA)
7. CONDITION (RESISTENSI) & SEX

POISONING PROCESS

- ACUTE → 24 HOURS
- SUBCHRONIC→ REPEATE UNTIL 90 DAYS
- CRONIC→ Up than 6 mounth

EFFECT AND ACTION OF POISON

1. LIVER AND REN DAMAGE
   - CCL4
   - SULFONAMIDE, ANAESTHETIC
   - INSECTISIDE

2. BONE MARROW DAMAGE
   - CHLORAMPHENICOL
   - INSECTISIDE, POISON OF THE SNAKE

3. BLOOD CEL DAMAGE
   - SULFONAMIDE, CHLORAMPHENICOLE
   - ICHTYOTOXIN, INSECTISIDE

4. NEURON CEL DAMAGE
   - AMINOGLYCOSIDE, POISON OF THE SNAKE, FROG POISON, INSECTISIDE.

5. TERATOGENIC EFFECT
6. MAIN DRUGS EFFECT TO BE MORE
7. WRONG IN DRUG APPLICATION
8. HYPERSENSITIF REACTION
9. ENZYM DAMAGE
   - INSECTISIDE, METAL POISON

PATOLOGIC MOLEKULER CHANGE

1. Congestive
2. Degeneration
3. Necrosis
4. Apoptosis

PENANGANAN KERACUNAN :

PRINSIP : HENTIKAN KONTAK RACUN → PENDERITA

- **RACUN KONTAK (ASAM/BASA KUAT) →KULIT / MUKOSA → CUCI AIR BERSIH**
- **RACUN GAS → UDARA SEGAR (OXIGEN)**
- **RACUN LAMBUNG → TERGANTUNG KEJADIAN**

BELUM TERABSORBSI → DIRANGSANG VOMIT → (OBAT EMETIKA):
APOMORFIN : 0,1-0,3 mg/kgbb/sc

STUPOR
RACUN KOROSIF → **EMETIKA KONTRAINDIKASI**
RACUN TERABSORBSI

- **BILA TIDAK BERHASIL → CEGAH ABSORBSI RACUN :**
  - *** SUSU + KAOLIN**
  - *** ADSORBEN (NORIT + AKTIVATED CARCOAL)**

- **TELAH TERABSORBSI → ANTAGONIS SPESIFIK**
  - **- INSEKTISIDA ORGANOFOSFAT, CARBAMAT → ATROPIN SULFAT**
  - **- ARSEN, MERKURI, TIMAH HITAM,CHROMAT → DIMERCAPROL (BAL)**
  - **- CUPRUM, MERKURI →PENICILINAMIN**
  - **- MORFIN →NALOXON**
  - **- BISA ULAR → ANTIVENIN**

DRUG TOXICITY TEST

A. PRACLINIC TOXICITY TEST :

1. GENERAL TOXICITY TEST

a. Acute toxicity test

b. Subacute toxicity test

c. Chronic toxicity

2. SPECIFIC TOXICITY TEST :

a. Teratogenic Test

b. Carcinogenic Test

c. Mutagenic Test

B. CLINIC TOXICITY TEST →

4 FASE

- ‘All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.’- Paracelus (16th century physician-alchemist)

- ‘A poison is any substance or matter which, when applied to the body outwardly, or in any way introduced into it, can destroy life by its own inherent qualities, without acting mechanically, and irrespective of temperature.’

- Toxicology is the science that deals with the amount of an agent that causes an adverse action in some living system.

- Acute poisoning accounts for 10-20% of hospital admission for general medicine.

Factors influencing toxicity:

1. Absorption

- oral
- sublingual
- injection (I.V., I.P., subcut, I.A.)
- pulmonary
- topical

2. Distribution

- binding – plasma proteins, tissue (liver, bone, fat)

3. Metabolism

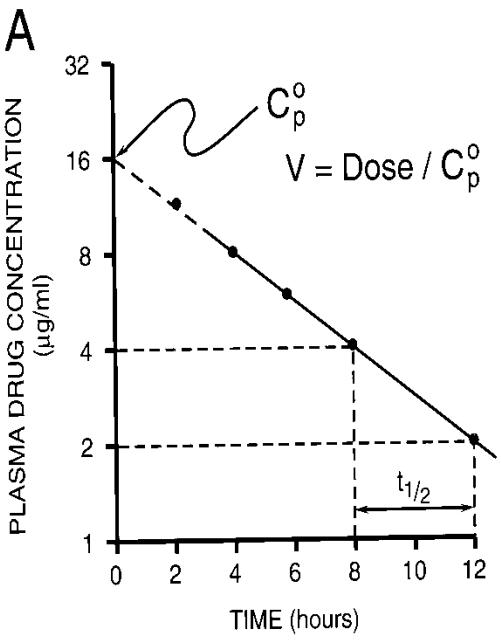
- Mainly liver (some in GI tract, kidneys, lungs)
- Phase I – introduce or expose a functional group on the parent compound – losing pharmacological effect
- Phase II – produces polar conjugates – generally inactive and easily excreted in urine and/or faeces

4. excretion

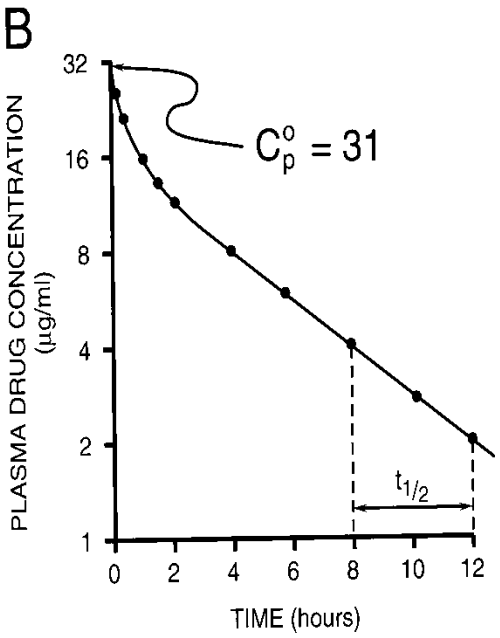
Factors influencing toxicity:

All these factors determine the drug/toxin bioavailability

plasma concentration – time curves



Drug eliminated from a single compartment by a first order process
half life ~ 4hrs



If sample before 2 hrs, reveals drug elimination is a multiexponential process

Factors influencing toxicity:

a steady-state concentration will be achieved when a drug is administered at a constant rate

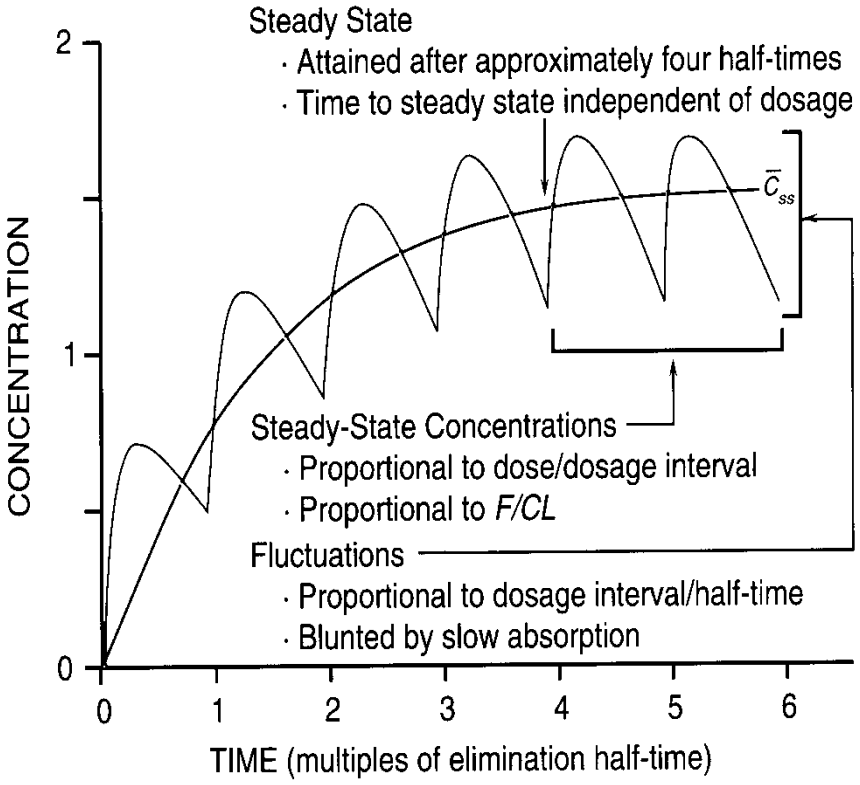


Figure 1–5. Fundamental pharmacokinetic relationships for repeated administration of drugs.

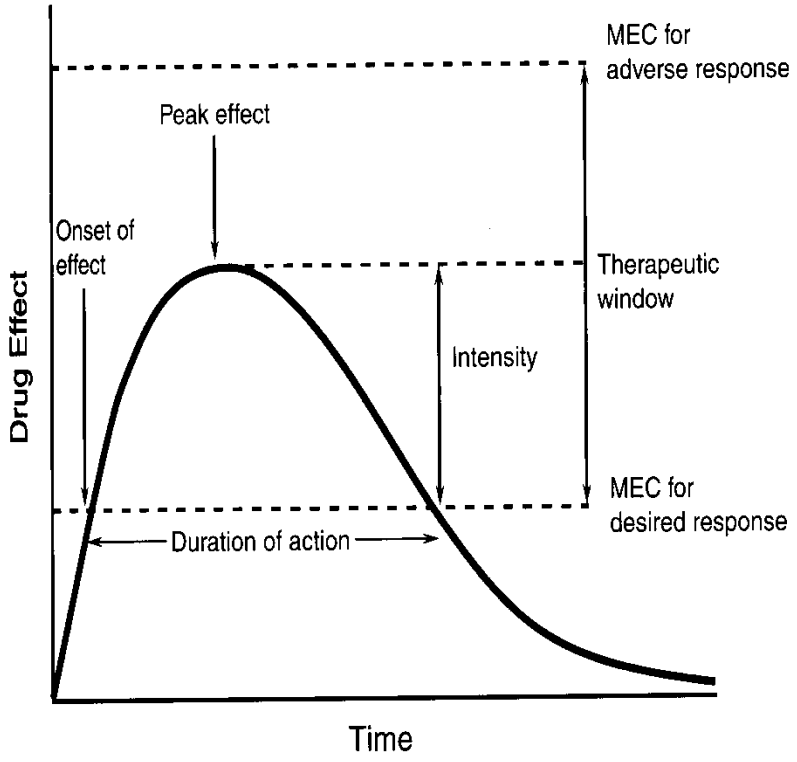
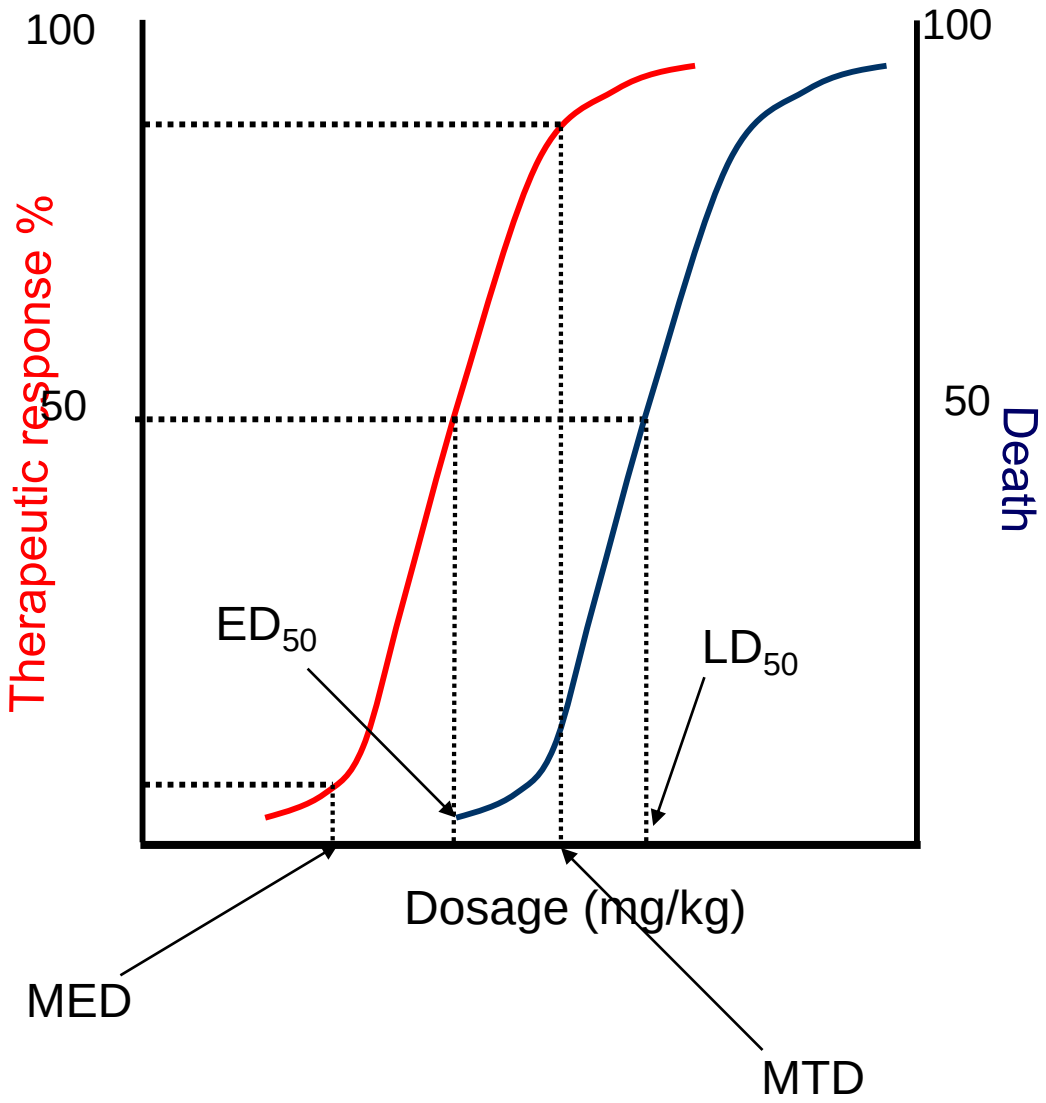


Figure 1–6. Temporal characteristics of drug effect and relationship to the therapeutic window.

•drug absorption 10x as rapid as elimination

•can have the same relationship for cumulative toxicity



ED_{50}- dose which will be therapeutically effective in 50% of animals (median effective dose)

LD_{50}- dose which will, on average, kill 50% of animals in a population

MED- minimum effective dose (the least dose that is likely to be effective).
Also called toxic dose-low(TDL)

MTD- maximum tolerated dose (or minimum toxic dose) (more than this will produce signs of toxicity).
Also called highest nontoxic dose (HNTD)

Other terms:

Therapeutic Index (TI) = $\frac{LD_{50}}{ED_{50}}$ - indicates relative safety of drug

Therapeutically: MTD

$\frac{}{MED}$ - how many times can I overdose safely?

For: barbiturate anaesthesia – 3-4

benzodiazepines >20

ie: represents a therapeutic window

Standard Safety Margin (SSM) = $\frac{LD_1}{ED_{99}}$ – more conservative estimate than TI

LD_1 – dose required to kill 1%

ED_{99} – dose therapeutically effective in 99%

Principle causes of drug toxicity/side effects

a. the predictable

b. the less predictable

c. the unpredictable

a. the predictable

- excessive action at a primary site (overdosage)
  e.g. anaesthetics, warfarin

- non-selectivity: *acting at unrelated sites* (more likely with overdosage)
  e.g. chlorpromazine

- incomplete selective toxicity: *acts against the host as well as the target organism or cell*
  e.g. protein synthesis inhibitors, antimicrobials, antifungals

- tolerance (dependence & abuse potential)
  e.g. opioids, benzodiazepines

- unavoidable side-effects
  e.g. immunosuppression by corticosteroids – opportunistic infections

a. the predictable

Pharmacokinectic Drug interactions:

•absorption
e.g. gastric emptying, gut motility — alcohol and laxatives

•distribution
e.g. displacement from plasma proteins — aspirin and warfarin

•metabolism
e.g. increased by enzyme induction — barbiturates and steroids

excretion
e.g. increased renal clearance — diurectics

a. the predictable

•age

- most drugs tested on young to middle-aged volunteers

-causing problems such as:

-drug clearance mechanisms (renal and hepatic) are limited in newborns

-clearance is reduced in elderly (increasing half life)

reduction in lean body mass, serum albumin, total body water.
increased body fat
declined renal function
reduced hepatic blood flow
reduced activities of cytochrome P450 enzymes

•gender

- a relative increase of body fat in females

b. the less predictable

Genetic susceptibility (including species and strain differences

e.g. polymorphism in NAT2 in the liver (N-acetyltransferase2).

- metabolises about 16 common drugs (procainamide, hydralazine)
- 15 alleles (some with reduced or absent catalytic activity)

c. the unpredictable

untoward adverse reactions

- drug allergies and anaphylactic reactions
  e.g. penicillin

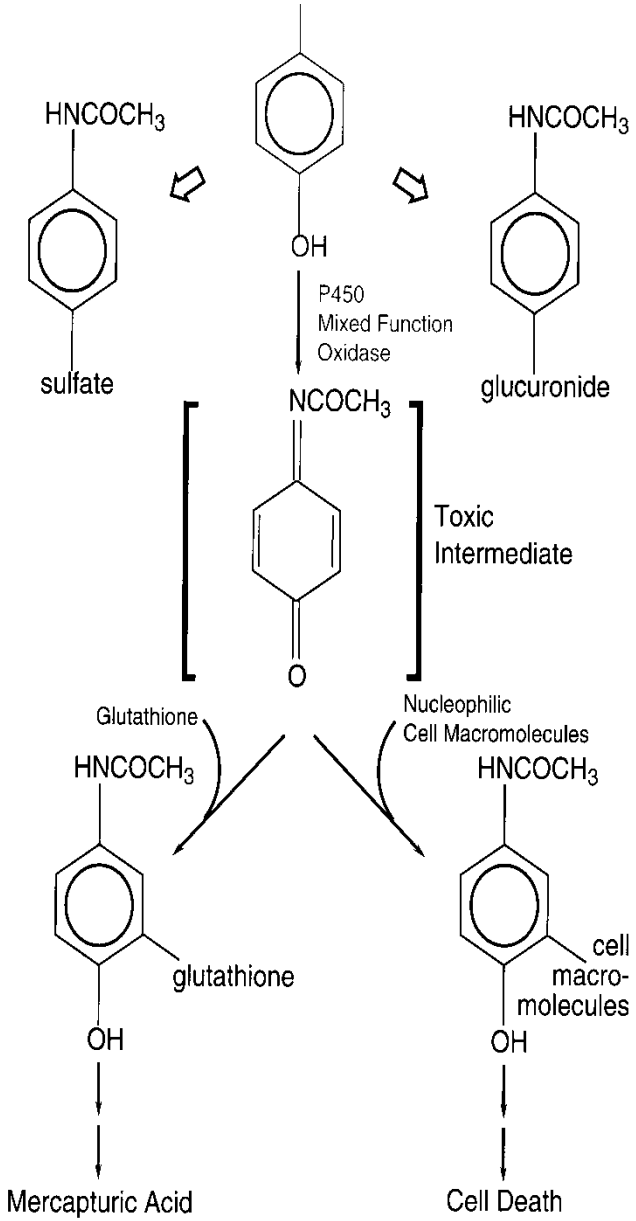
Chemical forms that produce toxicity

The parent drug is often the cause of toxic effects

However, toxic effects may result from metabolites:

For example: paracetamol

4th most common cause of death following self-poisoining in UK in 1989



Induction of microsomal enzymes

A number of drugs such as ethanol and carbamazepine, increase the activity of microsomal oxidase and conjugating systems when administered repeatedly.

For example: phenobarbitone significantly increases phase I microsomal oxidases

Phase I metabolism causes accumulation of toxic metabolites of paracetamol

General mechanisms of toxin-induced cell damage

- Mostly caused by toxic metabolites

e.g. by being able to form covalent bonds

- Toxicity normally by cell necrosis

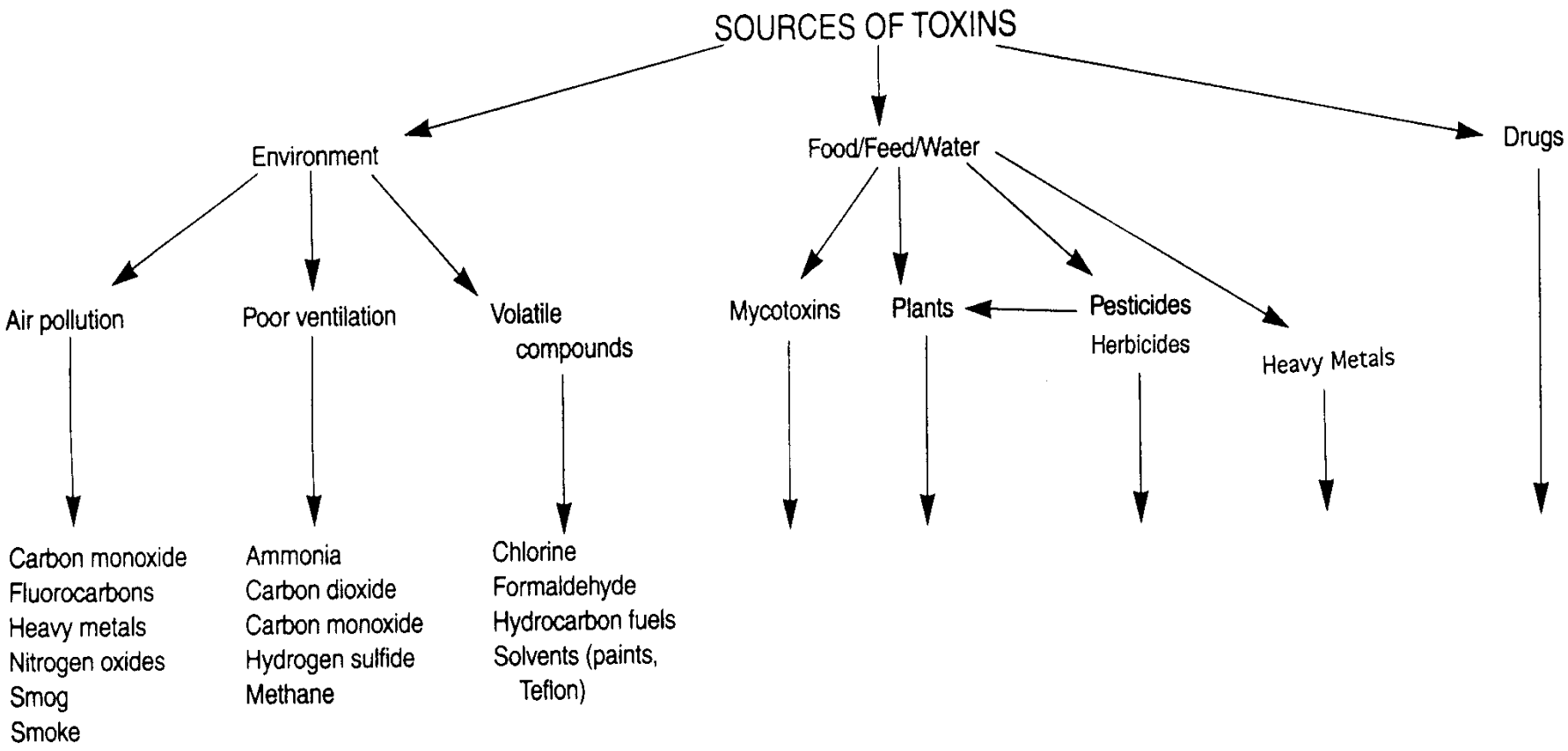
Hepatotoxicity

- Toxicity usually manifested as hepatitis
- Examples include: paracetamol, halothane, chlorpromazine

Nephrotoxicity

- Commonly seen with NSAIDs and ACEIs (acute renal failure)

Normally a result of their pharmacological action in patients whose underlying disease renal function is dependent on PG or angII biosynthesis


SOURCES OF TOXINS
Environment
Food/Feed/Water
Drugs
Air pollution
Poor ventilation
Volatile compounds
Mycotoxins
Plants
Pesticides
Herbicides
Heavy Metals
Carbon monoxide
Fluorocarbons
Heavy metals
Nitrogen oxides
Smog
Smoke
Ammonia
Carbon dioxide
Carbon monoxide
Hydrogen sulfide
Methane
Chlorine
Formaldehyde
Hydrocarbon fuels
Solvents (paints, Teflon)

Examples:

Mineral or Inorganic Poisons:

- metals, metalloids and non-metals

e.g. lead, mercury, arsenic, phosphorus, sulphur

- salts of metals and non-metals

e.g. copper sulphate, arsenious oxide, zinc phosphide

- acids and alkalis

Organic Poisons:

- pesticides

e.g. fungicides, herbicides and insecticides

- plants

e.g. oxalic acid – rhubarb, aflatoxins – ground nut meal

- drugs

e.g. barbiturates, ketamine, opiates, phenothiazines, atropine

Mineral or Inorganic Poisons:

- metals, metalloids and non-metals

metal	source	symptoms
lead		
inorganic	oil paint, batteries	ataxia, diarrhoea, convulsions
organic	petrol	hairloss, joint swelling, anaemia
barium	rat poison	salivation, sweating, muscular cramps, convulsions
thallium	photographic	salivation, diarrhoea, muscular cramps

Organic Poisons:

plants

source	active principles	symptoms
nuts	aflatoxins (B1, B2)	anaphylactic shock, ataxia, blindness, jaundice
rhubarb	oxalic acid (in leaf)	nausea, vomiting, convulsions
oak (acorns)	tannins	ataxia, salivation, flatulence
solanum family (deadly nightshade, potato, tomato)	glycoalkaloids atropine scopolamine (hyoscine)	salivation, convulsions, blindness

Organic Poisons:

drugs

drug	use	Mechanism/symptom
barbiturates	sedation, general anaesthesia	enhancement of $GABA_A$ receptor function respiratory paralysis
ketamine	dissociative anaesthesia	NMDA receptor antagonist increased incranial pressure
phenothiazines e.g. chlorpromazine	neuroleptic	D_2 receptor antagonist jaundice

Assessing the patient:

ABC

First ensure that:

- the Airway is clear
- the patient is Breathing adequately
- the Circulation is not compromised

If the patient is alert and stable, take a history:

1. Full details of how many and what type of substance has been taken

2. Who the drugs belong to and the source

3. Why?

4. Details of past medical history

e.g. history of asthma, jaundice, drug abuse, head injury, epilepsy, CV problems and previous psychiatric history

Clinical examination

- a standard clinical examination has to be carried out on every poisoned patient

looking for needle marks/evidence of self-harm.

- the patient's weight often critical for determining if toxicity is likely given dose ingested

e.g. the N-acetylcysteine dose for paracetamol poisoning
(paracetamol produces glutathione (GSH) depletion and new GSH depends on supply of cysteine)

Clinical examination – conscious patient

The Glasgow Coma Scale (GCS) is most frequently used in the assessment of the degree of impaired consciousness

TABLE 1.1 The Glasgow Coma Scale

	Score
Eye opening:	
Spontaneously	4
To speech	3
To pain	2
None	1
Best verbal response:	
Orientated	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor responses:	
Obeys commands	6
Localisation to pain	5
Normal flexion to pain	4
Spastic flexion	3
Extension to pain	2
None	1
Max score = 15; Min score = 3	

Beware patients feigning unconsciousness

Clinical examination – unconscious patient

Diagnosis depends on exclusion of other causes of coma

e.g. meningitis, intracranial bleeds, hypoglycaemia, diabetic ketoacidosis

Clinical feature	Possible cause
pinpoint pupils, reduced respiratory rate	opioids (iv if needle tracks) cholinesterase inhibitors (increased salivation) clonidine phenothiazines
dilated pupils, reduced respiratory rate	benzodiazepines
dilated pupils, tachycardia	tricyclics (dry mouth, warm peripheries) amphetamines, ecstasy, cocaine
abdominal cramps, tachycardia, diarrhoea, restlessness	Withdrawal from: alcohol, benzodiazepines, opioids