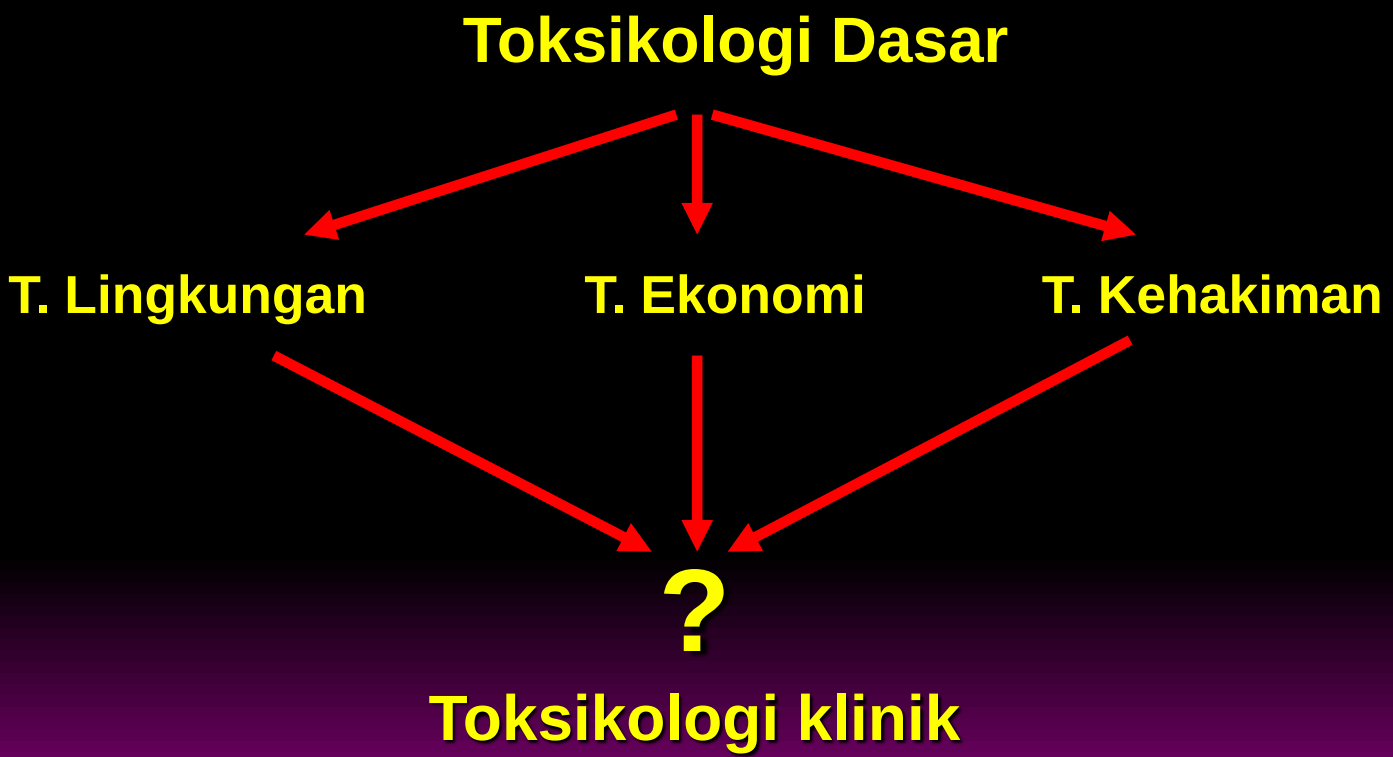
Toksikologi Klinik

Fathiyah Safithri

- Ilmu yang mempelajari aksi berbahaya zat kimia atas sistem biologis, yang bertujuan untuk diagnosis, penyembuhan dan mengurangi resiko bahaya pada pasien atau korban keracunan

Arti Penting

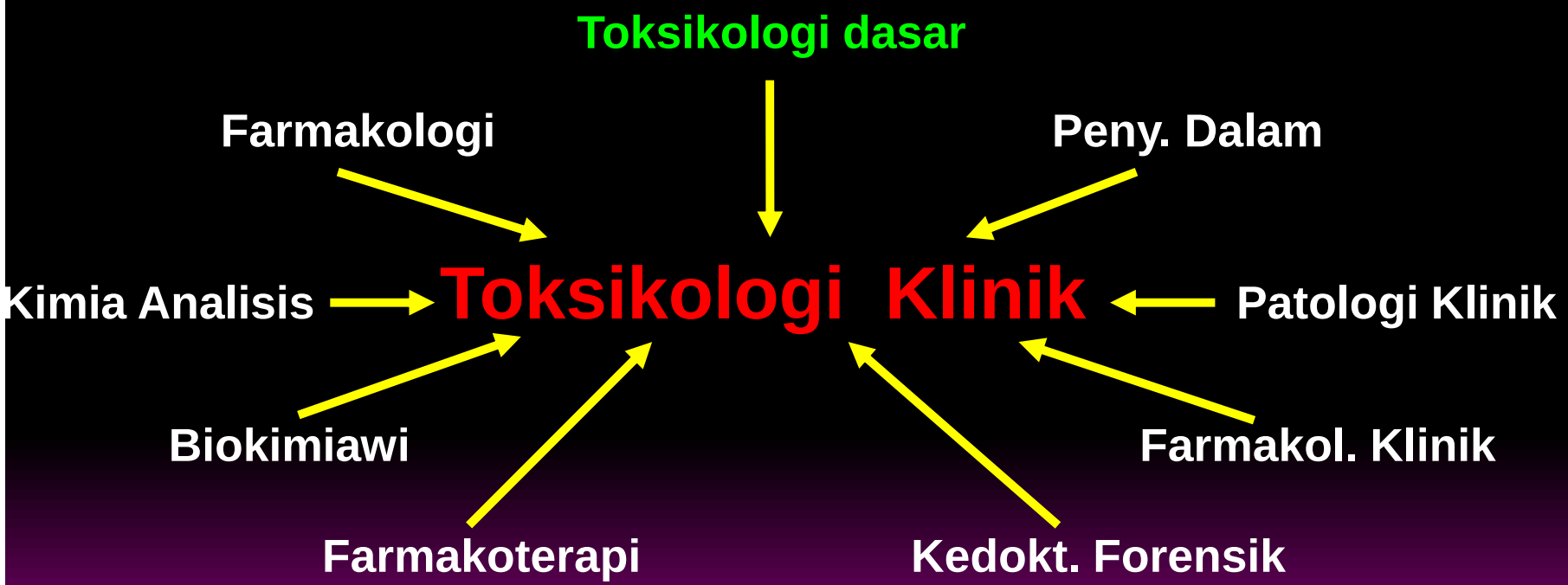
Ruang Lingkup



- Toksikologi lingkungan : pemejanan thd px scr tdk sengaja, krn senyawa yg mrpkn suatu polutan. Co. Pasien dtg ke rs krn makan kangkung (krn area tanam, akibat pestisida yg mencemari sungai yg t'tanam kangkung)
- Toksikologi Ekonomi : Pemejanan disengaja u/ mendapat nilai ekonomi yg lebih. mis zat pewarna pakaian digunakan pd makanan u/ pewarna u/ menambah nilai ekonomi. (geplak yg b'warna cerah, formalin)

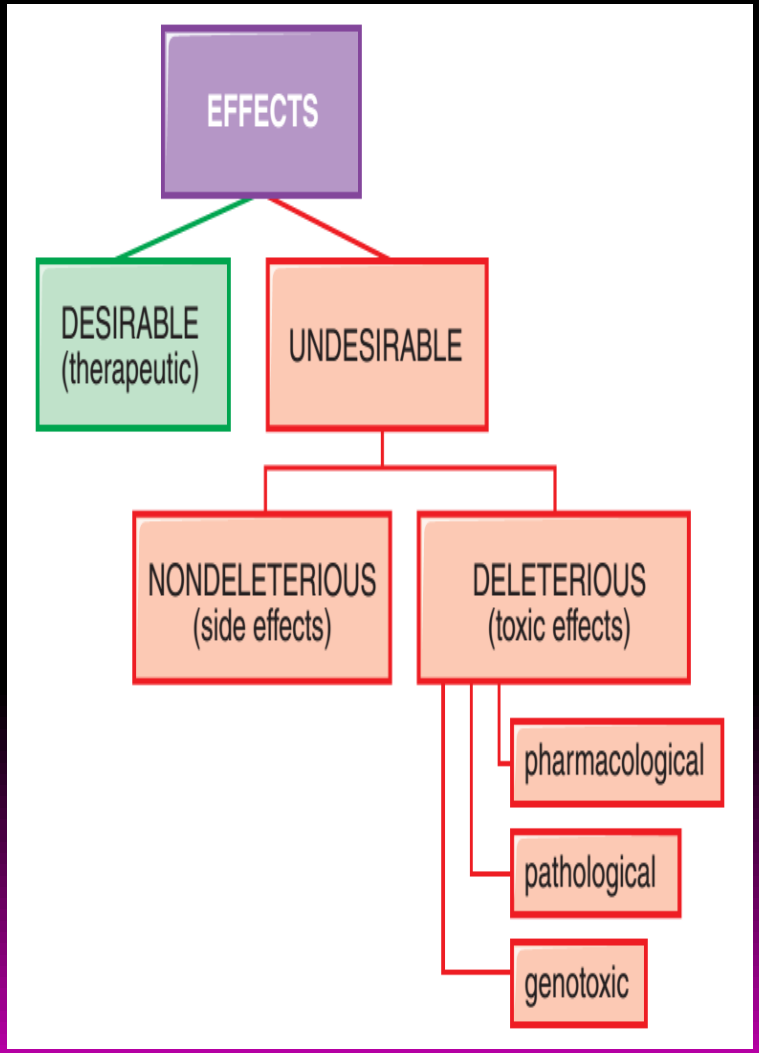
- Toksikologi Kehakiman : Bila sudah merambah ke urusan yg berwajib, melanggar aturan dan menimbulkan masalah.
- Bs suatu kasus hy masuk dl 1 lingkup ilmu toksikologi, tp 1 kasus masuk 2 lingkup atau bahkan 3 lingkup tsb.
- Co. Kangkung tercemar, saat masak di+ bahan yg memperparah (zat tambahan), keracunan, dan dilaporkan ke polisi.

Hubungannya Dengan Ilmu Lain



Toksikologi Klinik

- Setiap obat pd dasarnya dpt bersifat toksik
- Pd dose-dependent reaction, efek toksik obat dpt diklasifikasikan sbg
  - farmakologis
  - patologis
  - genotoksik
- Insiden dan keseriusan toksisitas tgt pada : konsentrasi obat dlm tubuh dan durasi paparan



Pharmacological toxicity

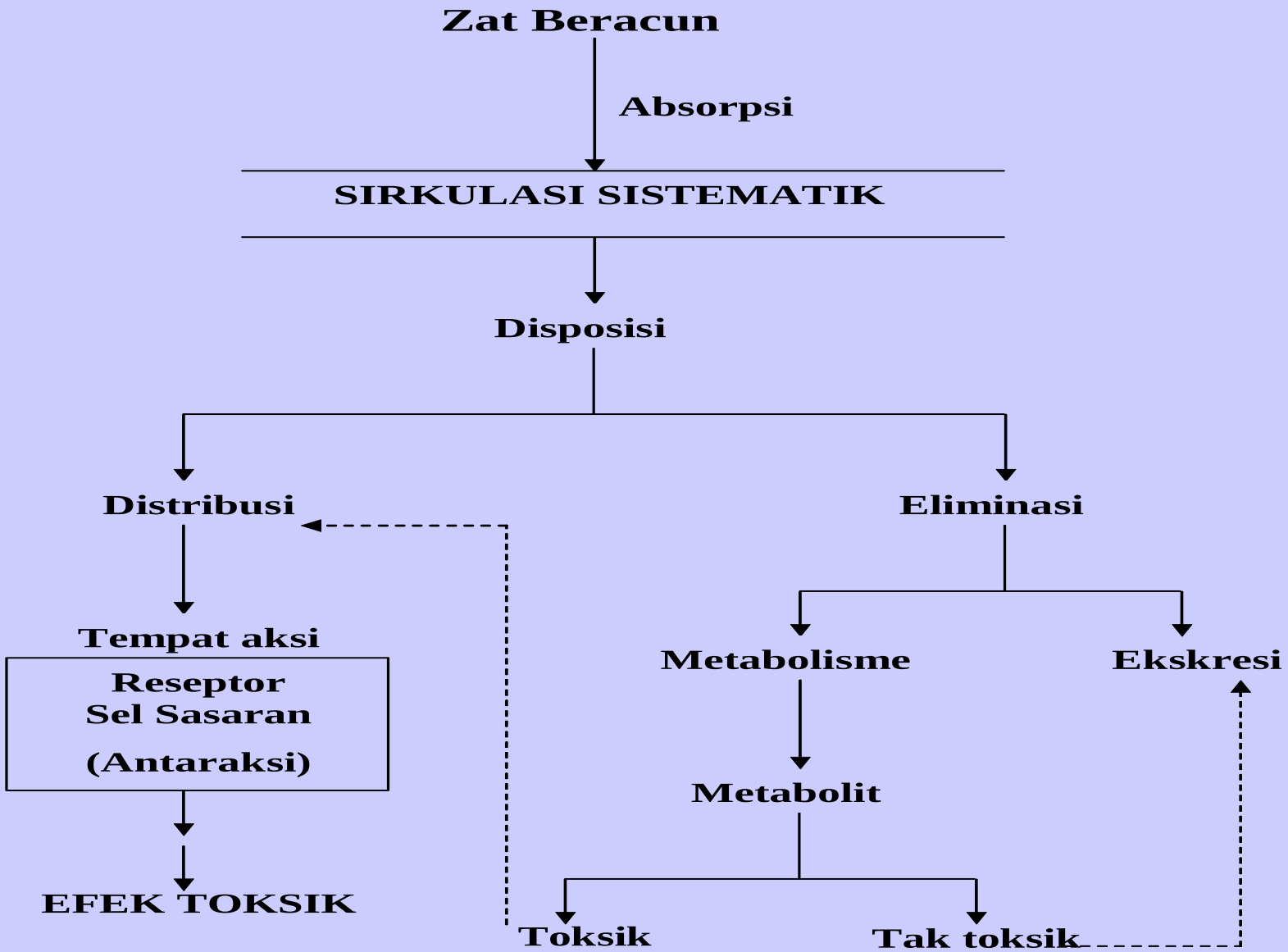
Tergantung dosis

- Barbiturat : ansiolitik-sedasi-somnolen-koma
- Nifedipin : derajat hipotensi tgt dosis

Tergantung lama paparan

- Antipsikotik : tardive dyskinesia tgt lama paparan

TOKSIKOKINETIKA RACUN



- **Toksisitas obat tergantung :**

a. Karakteristik absorbsi – koefisien partisi tinggi dan derajat ionisasi rendah → mudah diabsorbsi

b. Karakteristik distribusi :

- Tergantung aliran darah
- Akumulasi organ tubuh tertentu (efek toksik dan terapi tergantung akumulasi ini)
- Ikatan obat dengan protein plasma → mengurangi efektivitas/toksisitas

c. Karakteristik Metabolisme

Bbrp bahan kimia bersifat racun karena ia mengalami biotransformasi menjadi bahan kimia dengan efek toksik lebih besar (metabolit reaktif)

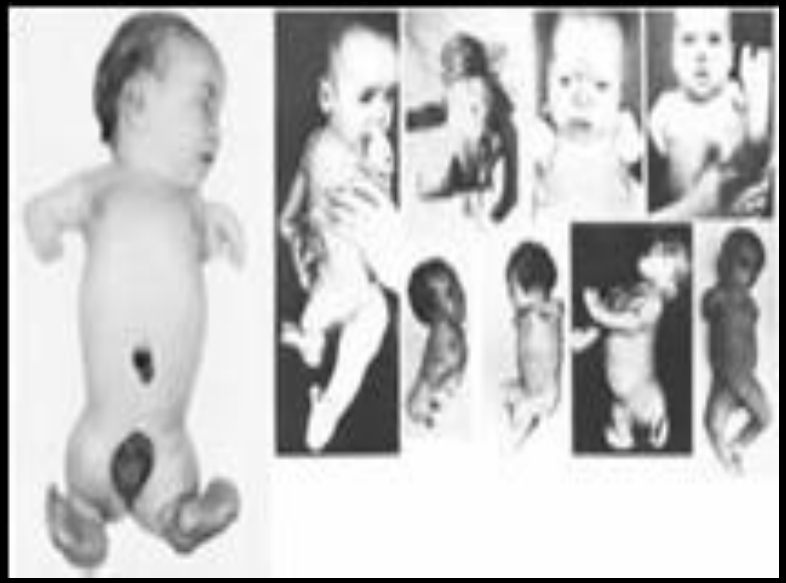
- Mis :
  - ✓ metanol→ formic acid (highly toksik metabolite) dg bantuan enz alcohol dehydrogenase. Ethanol dpt menghambat perubahan tsb
  - ✓ Acetaminophen → electrophilic metabolite. Metabolit ini didetoksifikasi oleh glutathione. Jk glutathionenya habis / tdk mencukupi →metabolit reaktif tsb berikatan dengan essensial macromolekul constituent dari hepatosit → cell death. N-acetylcysteine menjaga konsentrasi glutathione.

- Karakteristik ekskresi :
  - Alat ekskresi terpenting : hati & ginjal
  - Obat dianggap benda asing, tubuh mengubah → bentuk yang bisa diekskresi (lebih larut air, lebih polar)
  - Metabolit yang terbentuk → tidak aktif & toksisitasnya berkurang
  - Ekskresi dalam bentuk utuh / asalnya atau metabolit
  - Keracunan – diuresis bermanfaat bila – obat di ekskresi lewat urin dalam bentuk aktif

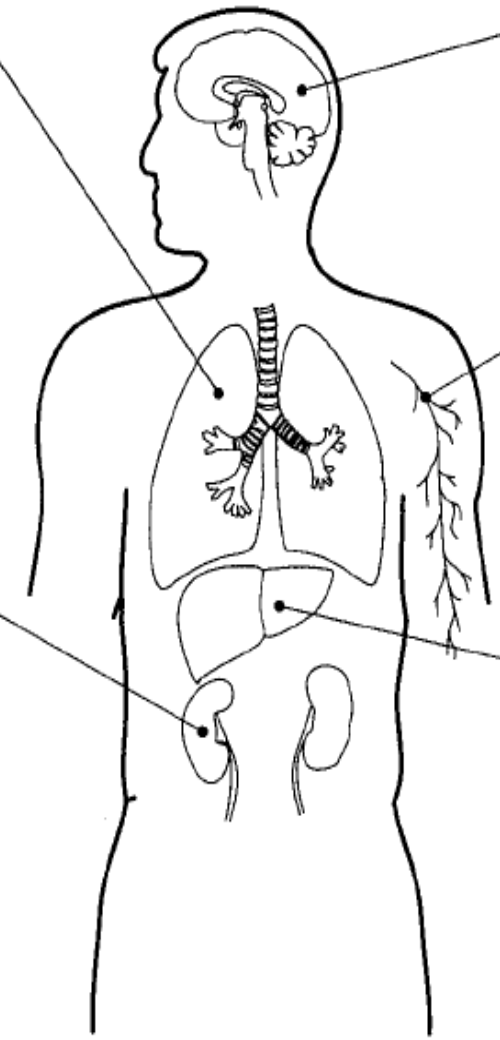
Contoh Penemuan Keracunan

- 1895 : Tumor VU pada pekerja pabrik anilin.
- 1950 : Talidomid (digunakan untuk sedatif)
  Toksisitas akut : rendah
  Kronis : Cacat Fokomelia
- 1960 : Metil merkuri dalam ikan
  Penyakit Paralisis - Kematian

Thalidomide (1962)



Organ Toxicity of Selected Chemicals



Pulmonary Toxicants

Drugs	Chemicals
Amiodarone	Asbestos
Bleomycin	Beryllium
Busulfan	Cadmium oxide
Cyclophosphamide	Chlorine gas
Methotrexate	Nitrogen dioxide
	Ozone
	Paraquat
	Phosgene
	Silica
	Sulfur dioxide

Renal Toxicants

Drugs	Chemicals
Cephalexin	Chloroform
Cephalothin	Citrinin
Cisplatin	Hexachlorobutadiene
Cyclosporine A	Mercuric chloride
Gentamicin	
Ifosfamide	
NSAIDs	
Streptozocin	

Central Neurotoxicants

Drugs	Chemicals
Cocaine	Lead
Ethambutol	Mercury
Quinine	Methanol
	Organochlorine insecticides

Peripheral Neurotoxicants

Drugs	Chemicals
Doxorubicin	Acrylamide
Isoniazid	Carbon disulfide
Nitrofurantoin	Lead
	n-Hexane

Hepatotoxicants

Drugs	Chemicals
Acetaminophen	Allyl formate
Chlorpromazine	Beryllium
Estrogens	Carbon tetrachloride
Ethanol	Vinylidene chloride
Halothane	
Isoniazid	
Nitrofurantoin	
Phenylbutazone	
Urethane	
6-Mercaptopurine	

Characteristics of Toxicity of Metals

Metal	Selected features of toxicity
Arsenic	
Inorganic	Diarrhea, hyperkeratosis, garlic breath, Mees' lines on fingernails
Arsine gas	Hemolysis
Beryllium	Pneumonitis, chronic granulomatous disease, contact dermatitis
Cadmium	Pneumonitis, emphysema, kidney damage
Iron	Gastric irritation, liver damage
Lead	Peripheral and central neurotoxicity, kidney damage, anemia
Mercury	Pneumonitis, neuropsychiatric toxicity (excitability, emotional instability, depression, insomnia), motor dysfunction (tremors)
Elemental	
Organic	Sensory neuropathy (dysarthia, paresthesia, constriction of visual field, loss of taste, hearing, smell), motor dysfunction (tremors)
Inorganic	Kidney damage, irritation of oral cavity and gastrointestinal tract

Examples of Toxic Food Additives and Contaminants

Agent	Type	Source and Effects
Nitrate, nitrite	Preservative	Present in vegetables; form carcinogenic nitrosamines
Sulfites	Preservative	Antioxidants used to reduce spoilage; can produce allergic reactions, especially in asthmatics
Tartrazine	Food color	Can cause urticaria in sensitive individuals
Botulinum toxin	Contaminant	Produced by *Clostridium botulinum* in improperly canned vegetables; nausea, vomiting, diarrhea, paralysis
Salmonella	Contaminant	Improper processing of food allows *Salmonella* from intestinal tract to survive; the most common cause of gastroenteritis
Aflatoxins	Contaminant (mycotoxin)	Produced by *Aspergillus flavus,* especially grains, corn, and peanuts; carcinogenic and hepatotoxic
Ochratoxin, citrinin	Contaminant (mycotoxin)	Produced by *Penicillium* strains; nephropathy (endemic Balkan nephropathy)
Polybrominated biphenyls (PBBs)	Contaminant	Fire retardant inadvertently substituted for feed supplement in Michigan; livestock loss, undetermined effect on human health

Toxicity of Selected Solvents

Solvent	Uses	Effect and Mechanism
Aliphatic solvents		
Chloroform	Drug purification	Hepatic centrilobular necrosis, likely from reactive metabolites
Trichloroethylene	Degreasing, dry cleaning	Sensitizes the myocardium to epinephrine, interferes with alcohol metabolism
Methylene chloride	Degreasing, paint stripping, aerosol propellant	Metabolized to CO, resulting in formation of carboxyhemoglobin
Hexane, methyl n-butyl ketone	Wood glue, plastics manufacturing	Polyneuropathy from their metabolite, 2,5-hexanedione
Aromatic solvents		
Benzene	Petroleum product, adhesives and coatings	Leukemia, aplastic anemia, likely from reactive intermediates
Toluene	Adhesives	Cerebellar degeneration with repeated high-dose exposure (glue sniffing)

Toxicity of Selected Pesticides

Class and Examples	Effect and Mechanism
Organochlorine insecticides	Neuronal hyperactivity; convulsions; impaired vision, concentration, and memory
DDT, chlordane, aldrin, heptachlor	Altered membrane permeability to Na^+, K^+
	Block repolarization by inhibiting Na^+, K^+-ATPase
	Block GABA-stimulated chloride uptake
Organophosphate insecticides	Bronchoconstriction and secretion, muscular weakness or paralysis, CNS depression, including respiratory centers
Bromophos, chlorpyrifos, parathion, malathion, diazinon	Inhibition of acetylcholinesterase (reversible or irreversible)
Carbamate insecticides	Same as organophosphate insecticides
Carbaryl	Inhibition of acetylcholinesterase (reversible)
Pyrethrin and pyrethroid insecticides	Neuronal hyperactivity, incoordination, tremors with hyperthermia, seizures
Pyrethrin I, II; fenvalerate, permethrin	Delayed inactivation of channels in excitable tissues, causing repetitive firing and at high doses, depolarization
	Block GABA-stimulated chloride uptake
Chlorophenoxy herbicides	Muscle weakness, aching, and tenderness; hypotonia
2,4-D; 2,4,5-T	
Bipyridyl herbicides	Delayed respiratory distress, fibrosis, and atelectasis
Paraquat, diquat	Gastrointestinal, liver, and kidney toxicity
	Formation of reactive oxygen species
Rodenticides	Block tricarboxylic acid cycle (fluoroacetates)
Compound 1080, warfarin, strychnine	Prevent blood clotting
	Induce seizures

ATPase, adenosine triphosphatase; GABA, γ-aminobutyric acid; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid

IMMUNE-RELATED DRUG EFFECTS

Table 7.5 Drugs known to produce systemic lupus erythematosus

Practolol	(β-adrenergic receptor blocker)
Chlorpromazine	(antipsychotic)
Hydralazine	(antihypertensive)
Isoniazide	(antibacterial agent)
Diphenylhydantoin	(anticonvulsant)
Ethosuximide	(anticonvulsant)

Perbedaan respon toksik, idiosinkrasi dan allergi

Table 7.3 Distinguishing characteristics of toxic, idiosyncratic, and allergic responses to drugs

	Toxic response	*Idiosyncratic response*	*Allergic response*
Occurrence			
Incidence in population	In all subjects, if dose high enough	Only in genetically abnormal subjects	Varies widely
Incidence among drugs	All drugs	Few drugs	Many drugs
Circumstance	Prior exposure unnecessary	Prior exposure unnecessary	Prior exposure essential
Dose–response relationship	Dose related	Dose related	Independent of dose; erratic relationship
Mechanism	Drug–receptor interaction	Drug–receptor interaction	Through antigen–antibody reaction; specific antibody formed in response to first dose of antigen
Effect produced	Determined by drug–receptor interaction; depends on eliciting drug	Determined by drug–receptor interaction; depends on eliciting drug	Independent of eliciting drug; determined by mediators released by antigen–antibody complex
Effect antagonized	By specific antagonists	By specific antagonists	By antihistamines, epinephrine, or anti-inflammatory steroids, such as cortisone

Apa beda ES, efek merugikan dan efek toksik ?

- Obat dpt menimbulkan efek yg tidak diinginkan yg berkaitan dgn dosis yg diberikan :
- 1. efek samping (*side effect*)
- 2. efek merugikan (*adverse effect*)
- 3. efek toksik (*toxic effect*)

Side effect

- Efek yang tidak berbahaya atau merugikan
- Mis : mulut kering atau sedasi karena antihistamin
- Efek dpt ditoleransi, obat brmanfaat utk pengobatan

Adverse effect

- efek yang merugikan dan berbahaya
- Mis : diare terus menerus, muntah, gangguan SSP yg menyebabkan bingung, kerusakan organ krn konsumsi obat jangka panjang

Toxic effect

- Efek yg sangat berbahaya/mengancam kehidupan
- Pemberian obat dihentikan/diberi terapi supportif/antidotumnya

Differential diagnosis of Poisoning Based Physiologic State

Stimulated	Depressed
Sympathetics	Sympatholytics
Sympathomimetics	α_1-Adrenergic antagonists
Ergot alkaloids	α_2-Adrenergic agonists
Methylxanthines	ACE inhibitors
Monoamine oxidase inhibitors	Angiotensin receptor blockers
Thyroid hormones	Antipsychotics
Anticholinergics	β-adrenergic blockers
Antihistamines	Calcium channel blockers
Antiparkinsonian agents	Cardiac glycosides
Antipsychotics	Cyclic antidepressants
Antispasmodics	Cholinergics
Belladonna alkaloids	Acetylcholinesterase inhibitors
Cyclic antidepressants	Muscarinic agonists
Muscle relaxants	Nicotinic agonists
Mushrooms and plants	Opioids
Hallucinogens	Analgesics
Cannabinoids (marijuana)	GI antispasmodics
LSD and analogues	Heroin
Mescaline and analogues	Sedative-hypnotics
Mushrooms	Alcohols
Phencyclidine and analogues	Anticonvulsants
Withdrawal syndromes	Barbiturates
Barbiturates	Benzodiazepines
Benzodiazepines	GABA precursors
Ethanol	Muscle relaxants
Opioids	Other agents
Sedative-hypnotics	GHB Products
Sympatholytics	

SEVERITY OF PHYSIOLOGIC STIMULATION AND DEPRESSION IN POISONING AND DRUG WITHDRAWAL

Physiologic Stimulation	
Grade 1	Anxious, irritable, tremulous; vital signs normal; diaphoresis, flushing or pallor, mydriasis, and hyperreflexia may be present
Grade 2	Agitated; may have confusion or hallucinations but is able to converse and follow commands; vital signs mildly to moderately increased
Grade 3	Delirious; unintelligible speech, uncontrollable motor hyperactivity; moderately to markedly increased vital signs; tachyarrhythmias possible
Grade 4	Coma, seizures, cardiovascular collapse
Physiologic Depression	
Grade 1	Awake, lethargic, or sleeping but arousable by voice or tactile stimulation; able to converse and follow commands; may be confused
Grade 2	Responds to pain but not voice; can vocalize but not converse; spontaneous motor activity present; brainstem reflexes intact
Grade 3	Unresponsive to pain; spontaneous motor activity absent; brainstem reflexes depressed; motor tone, respirations, and temperature decreased
Grade 4	Unresponsive to pain; flaccid paralysis; brainstem reflexes and respirations absent; cardiovascular vital signs decreased

TERATOGENESIS

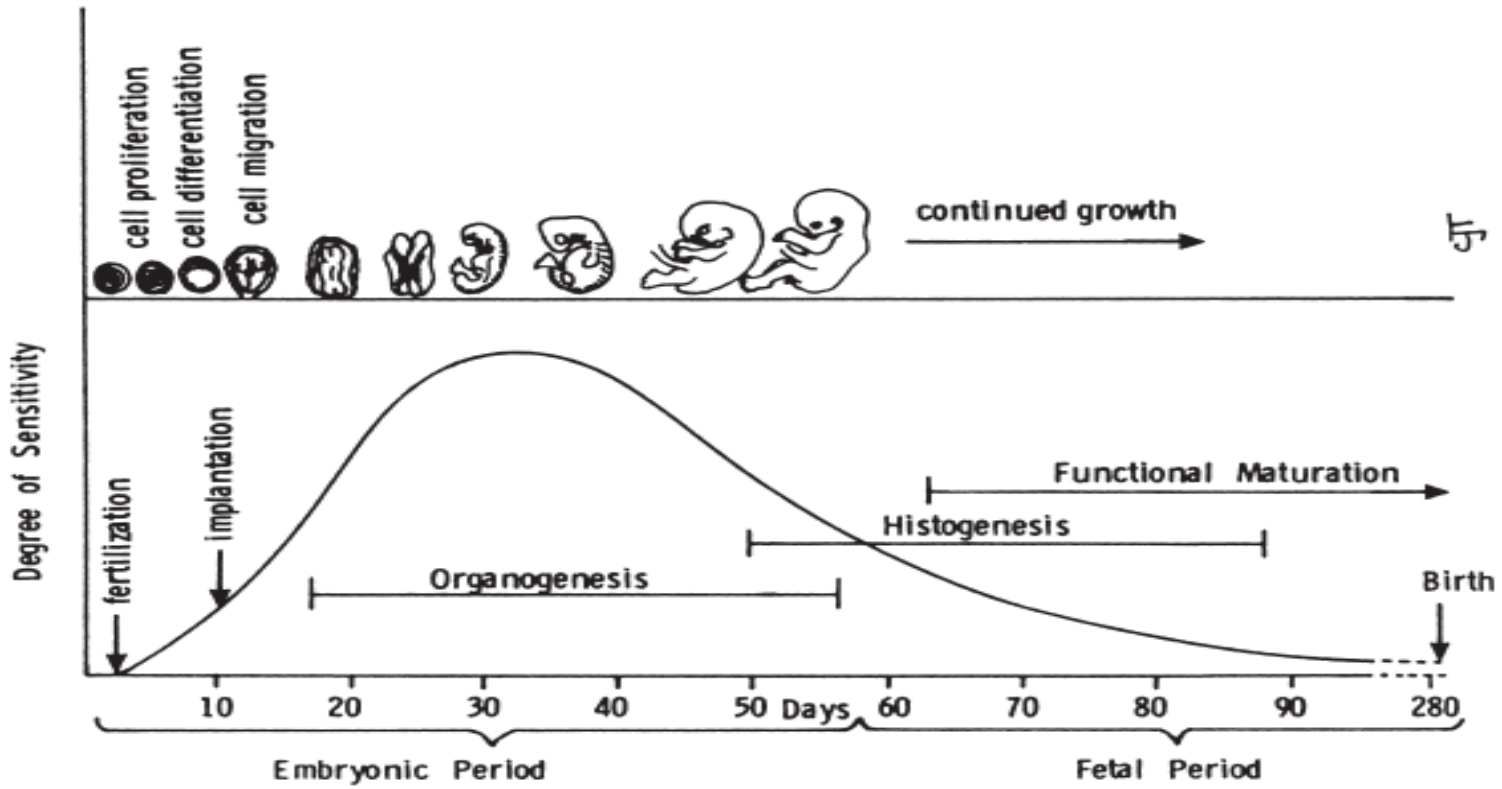
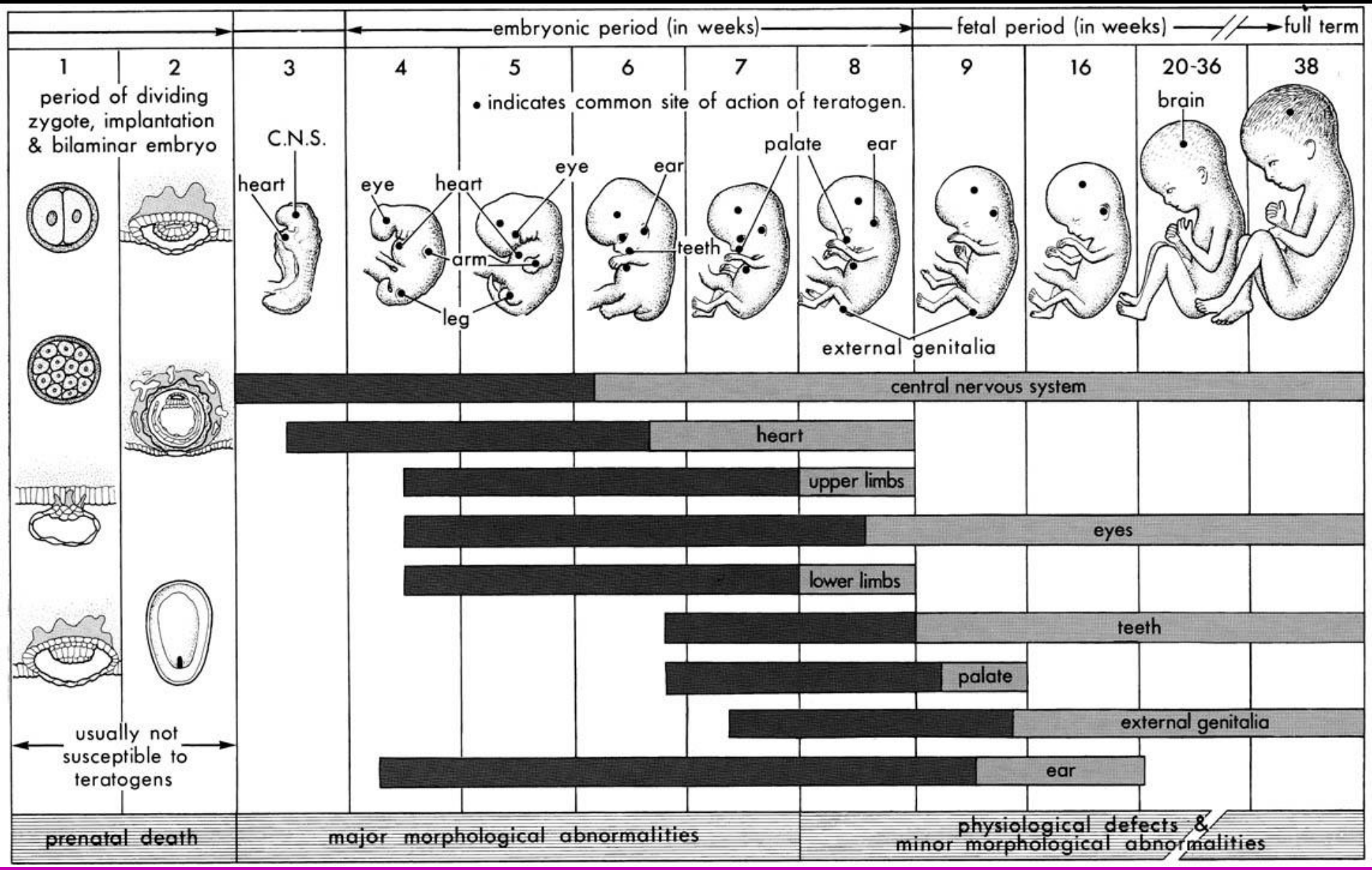


Figure 7.12 The stages of mammalian embryogenesis indicating the periods of greatest susceptibility to teratogens.

Source: J. A. Timbrell (1991), *Principles of Biochemical Toxicology*, 2nd ed. London: Taylor & Francis.


embryonic period (in weeks)
fetal period (in weeks)
full term
1
2
3
4
5
6
7
8
9
16
20-36
38
period of dividing zygote, implantation & bilaminar embryo
• indicates common site of action of teratogen.
C.N.S.
heart
eye
heart
eye
ear
palate
ear
brain
arm
teeth
leg
external genitalia
central nervous system
heart
upper limbs
eyes
lower limbs
teeth
palate
external genitalia
ear
usually not susceptible to teratogens
prenatal death
major morphological abnormalities
physiological defects & minor morphological abnormalities

TERATOGENESIS

Table 7.6 Comparison of maximum periods of teratogenic sensitivity for various organs/systems in humans

Organ/system	*Days following fertilization*
Brain	15–60
Eye	15–40
Genitalia	35–60
Heart	15–40
Limbs	25–35

Note
The period of susceptibility in humans occurs primarily in the first 60 days of pregnancy, at a time when a woman might not be aware of her pregnancy.

Table 10–1 DRUGS THAT SHOULD BE AVOIDED DURING PREGNANCY BECAUSE OF PROVEN OR STRONGLY SUSPECTED TERATOGENICITY*

Drug	Teratogenic Effect
Anticancer/Immunosuppressant Drugs	
Cyclophosphamide	CNS malformation, secondary cancer
Methotrexate	CNS and limb malformations
Antiseizure Drugs	
Carbamazepine	Neural tube defects
Valproic acid	Neural tube defects
Phenytoin	Growth retardation, CNS defects
Sex Hormones	
Androgens (e.g., danazol)	Masculinization of the female fetus
Diethylstilbestrol	Vaginal carcinoma in female offspring
Other Drugs	
Alcohol (in high doses)	Fetal alcohol syndrome, stillbirth, spontaneous abortion, low birth weight, mental retardation
Angiotensin-converting enzyme inhibitors	Renal failure, renal tubular dysgenesis, skull hypoplasia (from exposure during the second and third trimesters)
Antithyroid drugs (propylthiouracil, methimazole)	Goiter and hypothyroidism
Nonsteroidal anti-inflammatory drugs	Premature closure of the ductus arteriosus
Lithium	Ebstein's anomaly (cardiac defects)
Sulfonylurea oral hypoglycemic drugs (e.g., tolbutamide)	Neonatal hypoglycemia
Vitamin A derivatives (isotretinoin, etretinate, megadoses of vitamin A)	Multiple defects (CNS, craniofacial, cardiovascular, others)
Tetracycline	Tooth and bone anomalies
Thalidomide	Shortened limbs, internal organ defects
Warfarin	Skeletal and CNS defects

CNS = central nervous system.

*The absence of a drug from this table does not mean that the drug is not a teratogen; it only means that teratogenicity has not been proved. For most proven teratogens, the risk of a congenital anomaly is only 10%.

Table 7.7 CNS depressants associated with neonatal withdrawal syndrome

Opiates/narcotics
- Methadone
- Heroin
- Codeine
- Pentazocine (Talwin)
- Propoxyphene (Darvon)
- Other narcotics

Other drugs
- Alcohol
- Barbiturates
- Bromine
- Chlordiazepine (Librium)
- Diazepam (Valium)
- Diphenhydramine (Benadryl)
- Ethchlorvynol (Placidyl)

Source: E. L. Abel (ed.) (1996) *Fetal Alcohol Syndrome: From Mechanism to Prevention*. Boca Raton, FL: CRC Press. Reprinted with permission.

Treatment of Drug Overdose

Penatalaksanaan Toksisitas Akut

- Tergantung jenis bahan toksik
- Berdasar jenis terapi :
  - **terapi non spesifik** → terapi supportif utk mendukung fungsi vital
    - ✓Sesak → O2
    - ✓Muntah dan diare → rehidrasi dg infus
    - ✓Hipoglikemi → glukosa
    - ✓Kejang → obat antikonvulsi,
    - ✓Dll
  - **terapi spesifik** → antidotum

IDENTIFIKASI RACUN

Mengenali bahan yang diduga menjadi penyebab keracunan

↓

Penting untuk diagnosis

↓

Jenis/ sifat berbeda

↓

pertolongan / pengobatan berbeda

CARA IDENTIFIKASI :

- wawancara dengan pasien / keluarga atau teman
- identifikasi di tempat kejadian
- pemeriksaan laboratorium
    - ^ sampel biologis
    - ^ pakaian
    - ^ barang-barang disekitar

Sangat penting tahu KAPAN racun ditelan

- memperkirakan kadar racun dlm plasma
- memperkirakan tk keparahan
- dapat tahu racun sudah sampai pada fase apa
- untuk dapat memperkirakan racun sdh mencapai organ apa

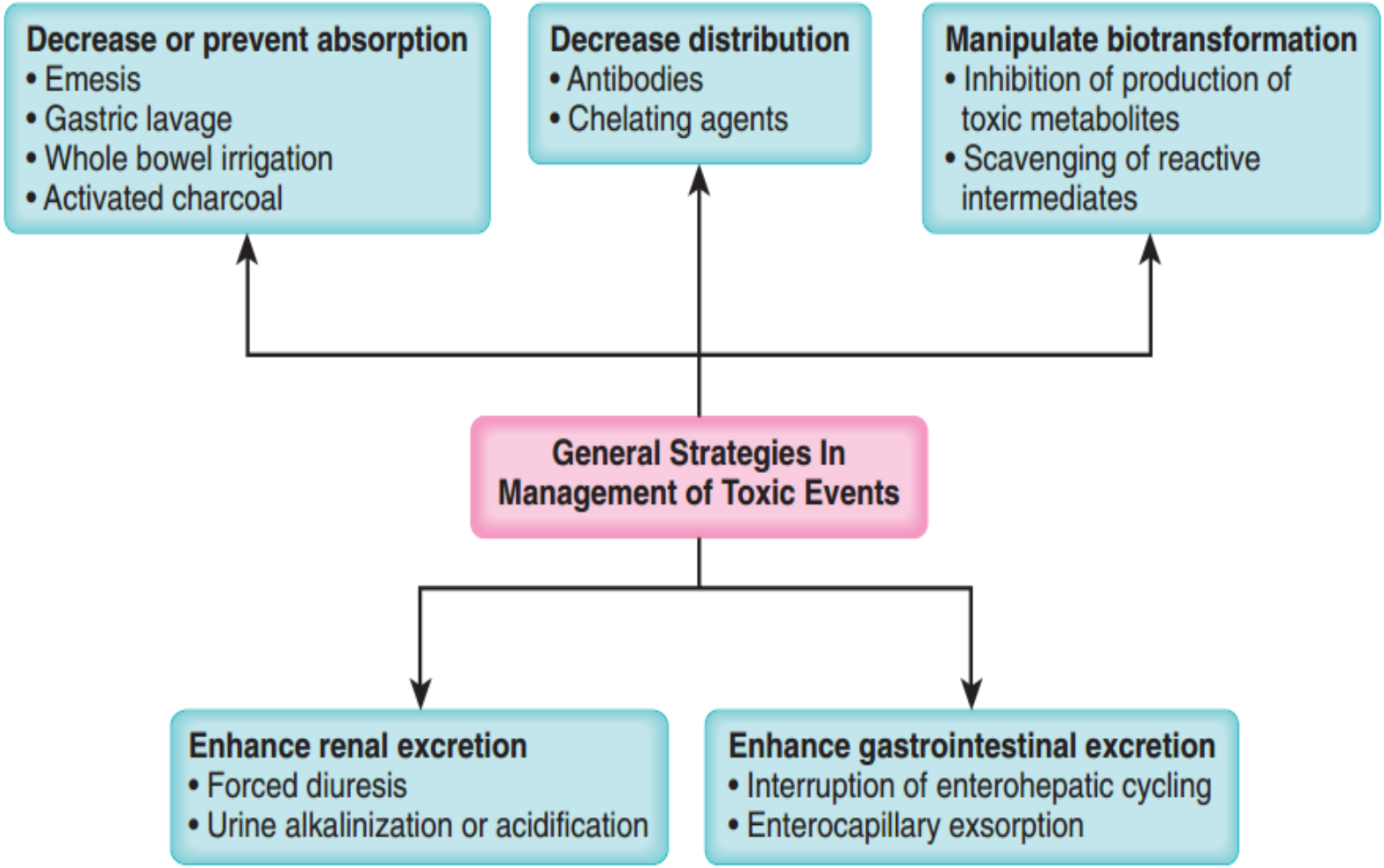


Figure 7-3. General strategies in management of toxic events.

Principal Theraphies

(1) initial decontamination;

= menjaga konsentrasi racun di jaringan yang krusial serendah mungkin dengan cara : **mencegah absorbsi lebih lanjut**

(2) enhance elimination;

= menjaga konsentrasi racun di jaringan yang krusial serendah mungkin dengan cara : **meningkatkan eliminasi**

(3) specific antidotes

= melawan efek farmakologis dan toksikologis pada organ target

Mencegah Absorbsi Toksikan Lebih Lanjut

- Rangsang muntah
- Pemberian Obat Emetik : Ipekak, Apomorfin
- Gastric lavage
- Pemberian Chemical Adsorption
- Pemberian Chemical Inactivation
- Purgation
- Whole-bowel irrigation (WBI) : *polyethylene glycol*

Rangsang muntah

- ✓ Menstimulasi pharynx posterior
- ✓ Indikasi : keracunan bahan kimia per oral, immediate (< 4 jam)
- ✓ Kontraindikasi :
  - pasien menelan bahan korosif spt asam kuat, alkali (drain cleaners) → perforasi lambung dan nekrosis esofagus.
  - Pasien koma / pingsan → aspirasi pada isi lambung
  - Pasien menelan CNS stimulant → precipitate convulsion
  - Pasien menelan petroleum distillate (kerosin, gastolin, atau petroleum based liquid furniture polish)→ pemuntahan hidrokarbonnya → aspirasi → chemical pneumonitis.

Pemberian Obat Emetik

Ipecac

- ✓ bekerja sebagai emetic karena menyebabkan efek iritasi pada enteric tract dan berefek pada chemorecepptor trigger zone (CTZ) pada area postrema medulla.
- ✓ Indikasi : pasien harus sadar dan menelan racun < 60 menit
- ✓ sirup ipekak bisa dibeli tanpa resep, onset 15-30 menit
- ✓ dosis anak 6 bln - 12 th : 15 ml
- ✓ dosis anak > 12th -dewasa : 30 ml
- ✓ emesis tidak boleh diberikan dlm kondisi lambung kosong jd harus dikasih minum air

Pemberian Obat Emetik

Apomorphine

- ✓menstimulasi CTZ , dan memberikan efek emetik
- ✓pemberian : parenteral t.u subcutane ➔bisa diberikan pada pasien yang tdk sadar atau tidak kooperatif
- ✓menginduksikan muntah stlh 3-5 mnit,.

Gastric Lavage

- Cara : memasukkan nasogastrik tube (NGT) ke lambung → mengalirkan air / air hangat / susu / cairan normal salin (NS), atau setengah NS lewat NGT → u/ membuang racun yang belum terserap
- Indikasi : pada pasien sadar, menelan bahan berbahaya dalam wktu < 60 menit
- Kontra indikasi : tidak boleh diberikan rutin dalam managemen pasien keracunan

CHEMICAL ADSORPTION

Actived Charcoal Drugs (ACD)

- permukaan partikel ACD akan menyerap bahan kimia atau obat (racun) → mencegah absorbsi lbh lanjut dan toksisitas
- Bahan kimia yang bisa diserap ; theophiline, fenobarbital, carbamazepine, dapsone, quinine
- Penggunaan bersama dg ipekak atau antidote tertentu →ACD akan menyerap ipekak / antidotenya → me ↓ efek ipekak /antidote
- ACD di usus menghambat enterohepatic cycle toksikan (tricyclic antideppressant dan *gluthimide)* → mempercepat ekskresinya

Arang aktif

Dosis : 1 g / kg BB atau 10 X senyawa yang tertelan, bisa diulang 0,5 – 1 g/kg BB/ 2 - 6 jam

Cara :

a. campur dg 4 – 8 bag air minumkan

b. campur dg katartikanya (jangan diulang

c. bila muntah, ulangi, dosis kecil sering, atau dg nasogastrik, bisa di+antimuntah

d. diulang bila : obat dg distribusi dan ikatan protein-plasma kecil, sekresi lewat hepar &usus, metabolit aktif mengalami resirkulasi

Activated Charcoal *continued*

Shake container throughly.

Pour liquid into container.

Have patient drink full dose.

CHEMICAL INACTIVATION

- Butuh waktu lebih lama dibanding pemberian ACD atau gastric lavage
- Pemberian bahan kimia ini bertujuan : mengubah unsur kimia racun menjadi kurang toxic atau menghambat absorbsi nya lebih lanjut
- Mis :
  - formaldehid + amonia → hexamethylenetetramine
  - Sodium formaldehide sulfoxylate bs mengubah ion merkuri menjadi metallic mercury yang kurang bisa larut
  - Sodium bicarbonate mengubah ion ferrous mjd ferrous carbonate yang absorbsinya jelek

PURGATION / Pemberian Katartik

- meminimalisasi absorbsi dengan cara mempercepat lewatnya toksin melalui GI tract
- Indikasi :
  - ✓ pasien menelan enteric coated tablets
  - ✓ waktu setelah penelanan bhn toksik > 1 jam

Contoh :

- **Sorbitol 70%, dewasa 50 – 100 ml, anak 1 ml / kg BB, paling disukai**
- **magnesium sitrat 10% (1,6 meq/ml), dewasa 100 –150 ml, anak 1ml/ kg BB**
- **magnesium sulfat 10% (0,8 meq/ml), dewasa 150 –250 ml, anak 1-2 ml/ kg BB,** → hati2 pada pasien gagal ginjal **dan penelanan nefrotoksin**
- **natrium sulfat 10% (1,4 meq/ml), dewasa 150 –250 ml, anak 1- 2 ml/ kgBB, hindari natrium pada hipertensi & gagal jantung kronis, katartika dg dasar minyak dilarang**

Whole-bowel irrigation (WBI)

- Dg *polyethylene glycol*
- teknik ini memicu defekasi dan mengeliminasi seluruh isi usus
- dipakai pada kasus keracunan akut oleh tablet sustained release atau tablet enteric coated dan ingestion of iron, lead, zinc.

Meningkatkan Eliminasi

- Obat dan racun → diekskresi melalui urin melalui filtrasi glomerulus dan sekresi aktif tubulus → dpt direabsorbsi kembali ke sirkulasi darah jk obat tsb lipofilik atau melalui aktif mekanisme transport
- REABSORBSI PASIF bisa diubah dg diuretik, perubahan asam basa urine

Penggunaan Diuretik

→ menghambat reabsorbsi dengan menurunkan gradien konsentrasi obat dari sel lumen tubulus

- meningkatkan aliran melewati tubulus
- Diuretik yg bisa dipakai : Furosemide (t'sering) dan osmotic diuretic
- Diuresis paksa hrus hati-hati, trutama utk pasien yang gagal ginjal, gagal jantung, gagal paru/ pulmonary complications

Perubahan pH Urine

- Prinsip : molekul yang tidak terionisasi terabsorbsi jauh lebih cepat daripada molekul polar (yg terionisasi)
- Perubahan dari yg tdk terionisasi mjd terionisasi pada toksicant dpt terjadi akibat perubahan pH pada cairan tubulus → mempercepat eliminasi
- Contoh :

  → Obat asam (mis: fenobarbital dan salisilat) lebih cepat diekskresi pada kondisi urin alkaline daripada urin asam.→Alkalinisasi urin akan mempercepat eliminasi urin terhadap ***chlorpropamide, diflunisal, fluoride, methotrexate,*** **phenobarbital, and salicylate**

  → Obat basa spt amphetamin secara teoritis dpt ditingkatkan ekskresinya dengan acidifikasi urin

Perubahan pH Urine

- Alkalinisasi urin KI : pada kasus fungsi renal compromised atau renal failure
- Acidifikasi urin dpt dilakukan dgn administrasi amonium klorida atau asam askorbat
- Ekskresi obat asam lwt urin secara partikular sensitif thd perubahan pH urin jk pKa-nya antara 3-7,5. Obat basa : antara 7,5-10,5

DIALISIS

- Hemodialisis dan peritoneal dialisis
- Hemodialisis sangat lebih efektif dbndg peritoneal dialisis dan esensial untuk bbrap kasus intoksikasi life threatening, spt metanol, ethylene glycol, salicylate

Table 8.2 Hemodialysis (HD) and hemoperfusion (HP) in drug overdose

Carbamazepine	HP preferred
Ethylene glycol, methanol	HD preferred
Lithium	HP not effective
Theophylline	Both HP and HD effective
Salicylates	HD indicated for acute overdose
Valproic acid	HD preferred

Source: K. R. Olson and B. Roth (1997), *Update on Management of Patient With Poisoning or Drug Overdose*, Northbrook, IL: American College of Chest Physicians. Reprinted with permission.

Antidotum

TOXICANT	ANTIDOTE/TREATMENT
Acetaminophen	N-acetylcysteine
Anticholinesterase, organophosphates	Atropine, pralidoxime
Iron salts	Deferoxamine
Methanol, ethylene glycol (antifreeze)	Ethanol, fomepizole, dialysis, CaEDTA, demercaprol, succimer
Arsenic, mercury, gold	Dimercaprol, succimer
Copper, arsenic, lead, gold	Penicillamine
Antimuscarinic, anticholinergic agents	Physostigmine
Cyanide	Amyl nitrite, sodium nitrite, sodium thiosulfate
Salicylates	Alkalinize urine, dialysis
Heparin	Protamine
Methemoglobinemia	Methylene blue
Opioids	Naloxone

TOXICANT	ANTIDOTE/TREATMENT
Benzodiazepines	Flumazenil
Tricyclic antidepressants	Sodium bicarbonate for QRS prolongation, diazepam or lorazepam for seizures, cardiac monitor for arrhythmias
Warfarin	Vitamin K
Carbon Monoxide	100% O2, hyperbaric O2
Digitalis	Stop dig, normalize K, lidocaine, anti-dig Fab
Beta-blockers	Glucagon
streptokinase	Aminocaproic acid
Theophylline/phenobarbital	Activated charcoal
Cocaine/amphetamines	Supportive, avoid beta-blockers
Lithium	Dialysis

Some Specific Antidotes for Toxic Drugs and Chemicals

Agent	Antidote	Mechanism of Action
Drugs		
Heparin	Protamine	Ionically neutralizes heparin
Acetaminophen	*N*-acetylcysteine	Inactivates toxic metabolite
Narcotics and opioids	Naloxone	Displaces drugs from receptors
Insulin, oral hypoglycemics	Glucose	Reverses glucose depletion
Chemicals		
Methanol	Ethanol	Blocks metabolism to toxic metabolite
Ethylene glycol	Ethanol	Blocks metabolism to toxic metabolite
Botulinum toxin	Antiserum	Immunologically neutralizes toxicant
Cyanide	Sodium nitrate	Forms methemoglobin, which binds cyanide, thus removing it from active pool
	Sodium thiosulfate	Provides a source of sulfur to detoxify cyanide
Organophosphates	Atropine	Displaces acetylcholine from its receptor
	Pralidoxime	Reactivates acetylcholinesterase
Carbon monoxide	Oxygen	Displaces toxicant from hemoglobin
Nitrites	Methylene blue	Reduces methemoglobin to hemoglobin
Arsenic	Dimercaprol	Forms inactive complex with metal
Iron	Deferoxamine	Forms inactive complex with metal
Lead	Calcium disodium edetate	Forms inactive complete with metal
Warfarin	Vitamin K_1	Stimulates coagulation factor synthesis

Organophosphate/Carbamate Poisoning Pathophysiology

- Inhibit the enzyme acetylcholinesterase which breaks down acetylcholine
- acetylcholine accumulates in the parasympathetic NS results in overstimulation & hyperactivity of smooth muscle and glands

Organophosphate Poisoning

MUSCARINIC

- **D**-efecation
- **U**-rination
- **M**-iosis
- **B**-bronchorrea
- **E**-xcitation (muscular)
- **L**-acrimation, salivation

NICOTINIC

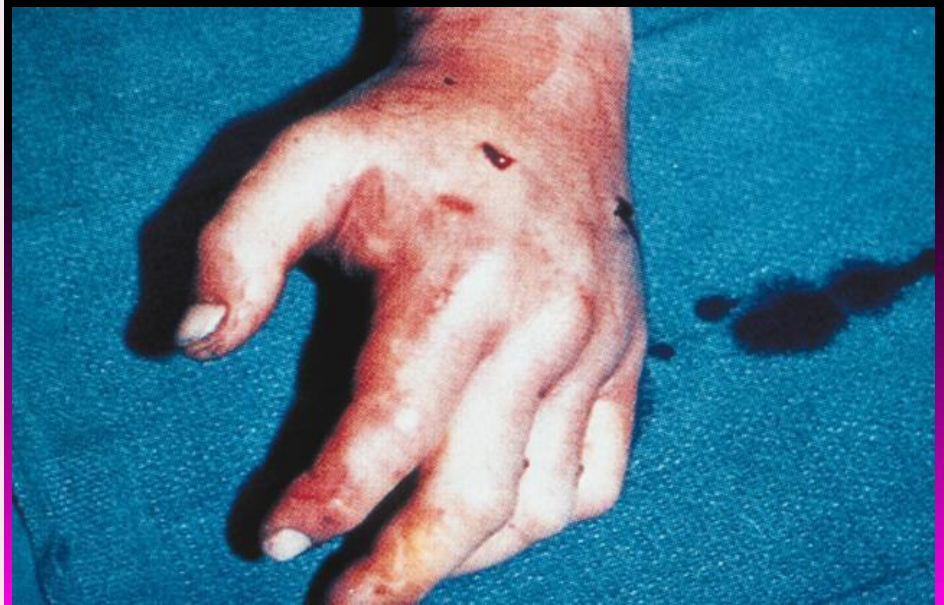
- **M**-uscle weakness
- **T**-achycardia
- **W**-weakness
- **H**-hypertension
- **F**-fasciculations

Anticholinergic
= Atropine
Pralidoxime (2-PAM)
= regenerates acetylcholinesterase

snike bite

Rattlesnake

Cottonmouth (water moccasin)



- Venom bisa menghancurkan protein, komponen lain jaringan, RBC, dan mempengaruhi faktor pembekuan
- infarction dan nekrosis bisa berkembang pada tempat gigitan
- gigitan yg parah bs mjd fatal dlm 6-30 jam (jarang skali ada yang fatal sblm 30 mnit)
- Perkembangan antibodi monoklonal manusia dpt melawan toksin spesifik gigitan ular → hasil terapeutik yang potensial →

SABU : SERUM ANTI BISA ULAR

KESALAHAN YG SERING TERJADI PADA "MANAGEMENT OF POISONING"

- Universal antidote (magnsium oksida , asam tannat) → tidak bermanfaat bahkan merusak .
- Menetralkan zat asam / alkali yang tertelan berakibat - pembebasan panas dan meningkatkan destruksi jaringan. (Melarutkan zat kaustik dan asam lebih baik dengan menggunakan susu / air 15 ml / Kg)
- Induksi muntah dengan menggunakan jari tangan , coper salt , larutan hypertonik -> merusak mulut dan oesophagus

- Penggunaan katartik dengan bahan dasar minyak ->lipid pneumonia .
- Cairan pembilas yang banyak mengandung Na dan fosfat ->gangguan keseimbangan elektrolit .
- Pemberian glukose dalam kadar besar -> menurunkan kadar fosfat dan kalium .
- Pengasaman urin yang kurang hati hati -> meningkatkan kemungkinan gagal ginjal. (destruksi dan ekskresi myoglobin)
- Penggunaan kateter ->merupakan sumber infeksi

Kesalahan :

* *Antidotum universal* (arang roti panggang, magnesium oksida, asam tanat) tidak bermanfaat, merusak
* Sirop ipekak diberikan segera
* Zat asam/alkali kuat tidak boleh dinetralisir, tapi diencerkan.
* Induksi muntah, hati-hati dapat merusak mulut dan esofagus
* Bilas lambung, tak harus dilakukan, pemejanan lebih dari 2 jam tak perlu, cairan pembilas yg banyak mengandung na- trium dan fosfat gangguan keseimbangan elektrolit yg berat
* Stimulan pernafasan & obat analeptik tidak bermanfaat, merusak
* Pengasaman urin gagal ginjal
* Dialisis dan jumlah cairan yang besar menurunkan suhu tubuh & gangguan fungsi kardiovaskular
* Hati-hati dalam mendiagnosis kematian otak overdosis sedatif-hipnotik

Fundamentals of Poisoning Management

Supportive Care

Airway protection
Oxygenation/ventilation
Treatment of arrhythmias
Hemodynamic support
Treatment of seizures
Correction of temperature abnormalities
Correction of metabolic derangements
Prevention of secondary complications

Prevention of Further Poison Absorption

Gastrointestinal decontamination
- Syrup of ipecac–induced emesis
- Gastric lavage
- Activated charcoal
- Whole-bowel irrigation
- Catharsis
- Dilution
- Endoscopic/surgical removal

Decontamination of other sites
- Eye decontamination
- Skin decontamination
- Body cavity evacuation

Enhancement of Poison Elimination

- Multiple-dose activated charcoal
- Diuresis
- Alteration of urinary pH
- Chelation
- Extracorporeal removal
  - Peritoneal dialysis
  - Hemodialysis
  - Hemoperfusion
  - Hemofiltration
  - Plasmapheresis
  - Exchange transfusion
- Hyperbaric oxygenation

Administration of Antidotes

- Neutralization by antibodies
- Neutralization by chemical binding
- Metabolic antagonism
- Physiologic antagonism

Prevention of Reexposure

- Adult education
- Child-proofing
- Notification of regulatory agencies
- Psychiatric referral

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