

Toxicity of Chemical and Physical Agents

Exposure • metabolism • molecular injury • susceptibility

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Learning outcomes

- Explain why toxicity depends on dose, route, duration, and host susceptibility.
- Trace xenobiotics from environmental compartments to absorption, tissue distribution, metabolism, storage, and elimination.
- Distinguish detoxification from bioactivation and explain phase I, phase II, and CYP450 roles.
- Apply the framework to source-described toxic exposures and recognize the limits of population exposure thresholds.

Toxicology: What does the discipline study?

Agents and exposure

- Distribution of poisons within a living organism
- Chemical agents including drugs and pollutants
- Physical hazards such as radiation and heat

Biologic consequences

- Molecular and cellular mechanisms of injury
- Organ-specific functional and structural effects
- Variation among exposed persons

Toxicology connects exposure, fate, mechanism and organism-level response.

Chemical and physical hazards are related, not identical

Chemical agent

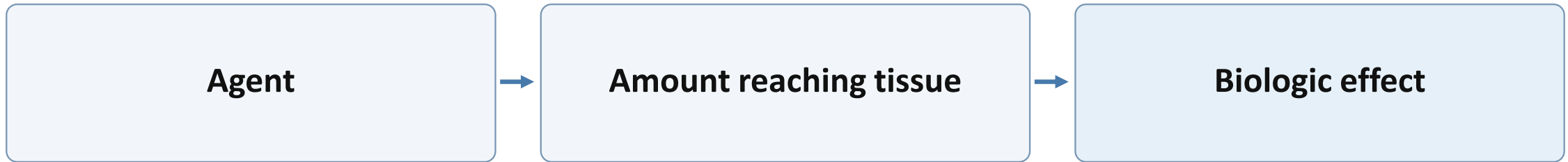
- Enters by skin, lung or gastrointestinal tract
- May be redistributed, biotransformed or stored
- A metabolite may be more toxic than the original compound

Physical agent

- Transfers energy or disturbs tissue homeostasis
- Includes heat and ionizing radiation
- Magnitude, duration and vulnerable tissue affect injury

The shared theme is exposure → biologic response; Metabolic activation is mainly a chemical-agent concept.

A poison is defined by exposure, not by name alone



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- The concept of poison is fundamentally quantitative: A substance may be useful at one exposure and harmful at another.
 - Dose cannot be interpreted without exposure duration, route, target tissue, and susceptibility.
 - Therapeutic chemicals illustrate the narrow or broad separation between benefit and harm.

Dose does not equal delivered tissue dose

Administered or encountered

- Amount in air, water, food or on skin
- Initial route of contact
- Duration and pattern of exposure

Biologically available

- Fraction absorbed and distributed
- Extent of metabolic conversion
- Concentration and persistence at sensitive sites

The tissue dose is influenced by toxicokinetics, not just the external concentration.

Why population “safe levels” have limitations

- Permissible exposures support comparison of populations and risk estimation.
- Age, genetic predisposition and organ sensitivities modify the effect of the same exposure.
- Mixed pollutants may interact, so a single-agent threshold cannot describe every combination.
- A regulatory cutoff does not prove that every individual below it is unharmed.

Four sources of interindividual variation

Age

Developmental and age-associated physiology can change susceptibility.

Genetics

Enzyme polymorphisms alter toxicant metabolism.

Tissue state

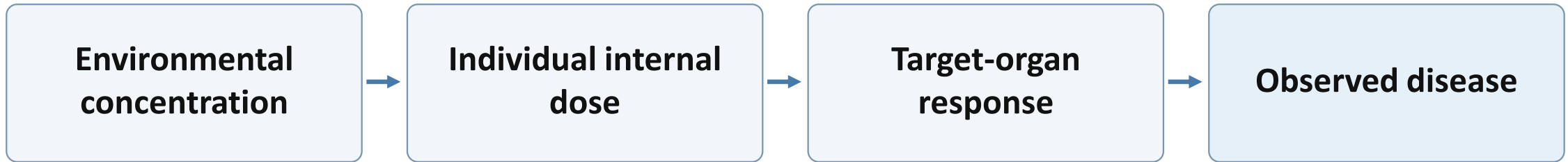
Different organs and individuals have different vulnerabilities.

Co-exposure

Drugs, environmental chemicals and mixed pollutants can modify effects.

The same nominal environmental exposure does not imply the same biologic outcome.

From pollutant exposure to disease risk

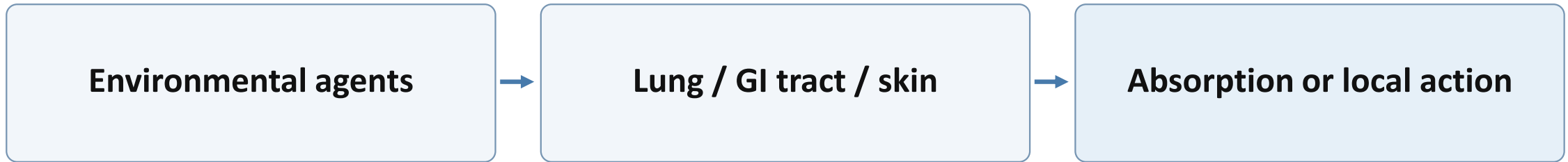


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- External measurements are surrogates for biologically effective exposure.
 - Modifiers can act at uptake, metabolism, distribution or cellular repair.
 - Risk estimates describe populations; Diagnosis requires patient-specific evidence.

Xenobiotics are exogenous chemicals

- Xenobiotics enter the body from the air, water, food and soil.
- The term includes pollutants, solvents, drugs and other externally derived chemicals.
- A xenobiotic is not automatically toxic: Dose, chemical identity and biologic handling determine harm.
- The Robbins exposure schema follows environmental source → uptake → tissue fate.

Three portals of xenobiotic entry



- Airborne agents reach the body through respiration.
- Chemicals in food or water may be absorbed through the gastrointestinal tract.
- Skin contact provides a separate absorption pathway; Portal and physicochemical properties both matter.

Route of entry can predict initial tissue exposure

At the portal

- Local airway epithelial injury after inhalation
- GI mucosal contact after ingestion
- Cutaneous injury following skin contact

After absorption

- Blood carries agent to distant tissues
- Systemic toxicity may follow any portal
- Metabolism can alter the active species

Portal toxicity and systemic toxicity are not mutually exclusive.

Inhalation: Direct contact and systemic uptake

- Pollutants in inspired air contact conducting airways and potentially alveoli.
- Local toxicity depends on the identity and properties of the inhaled substance.
- Absorbed agents may travel through the bloodstream to organs beyond the lung.
- The outdoor-air examples later in this chapter illustrate local oxidant injury and systemic asphyxiation.

Ingestion: The gastrointestinal entry route

- Contaminated food and water can deliver xenobiotics to the GI tract.
- Some agents act at the contact site; Others enter the blood and act remotely.
- The fate of absorbed material depends on distribution, metabolic conversion and excretion.
- Chemical identity matters more than the route alone when anticipating target-organ injury.

Skin contact: A distinct pathway of absorption

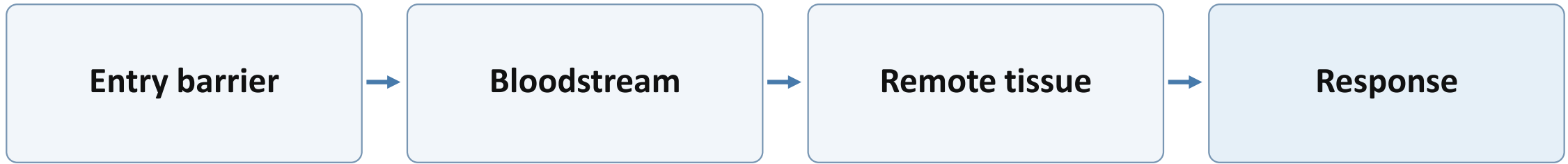
- Direct cutaneous exposure can cause injury at the site of contact.
- Some chemicals cross the skin barrier and enter systemic circulation.
- Lipid-soluble chemicals may traverse cellular membranes readily.
- When evaluating exposure, document which surface contacted the agent, not merely the agent name.

Comparison of environmental entry routes

Entry route	Typical environmental source	First contacted tissue
Inhalation	Airborne gases or particles	Respiratory tract
Ingestion	Contaminated water or food	Gastrointestinal mucosa
Skin contact	Chemicals on exposed surfaces	Skin / cutaneous barrier

Regardless of route, absorbed xenobiotics may produce remote systemic effects.

Systemic distribution begins after absorption

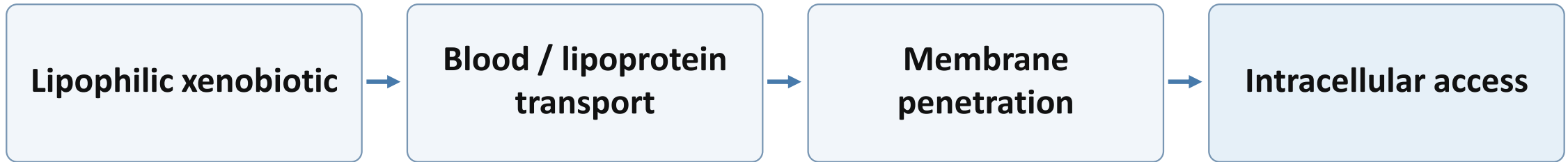


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- A chemical may act locally before—or without—appreciable systemic distribution.
 - Bloodborne agents can reach multiple organs with different sensitivities.
 - Subsequent storage, conversion and elimination alter the intensity and duration of exposure.

Lipid solubility changes xenobiotic behavior

- Many solvents and drugs are lipophilic.
- Lipophilicity facilitates transport in blood associated with lipoproteins.
- It also favors movement across cell membranes into intracellular compartments.
- Thus distribution is a chemical-property-dependent process rather than simple uniform mixing.

Why lipophilic substances readily reach cells



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- The lipid-rich plasma membrane permits entry of many lipophilic compounds.
 - Transport into a cell does not itself establish that the compound is toxic.
 - Biotransformation after entry may detoxify the compound or form damaging metabolites.

Distribution is not the same as accumulation

- The bloodstream distributes a xenobiotic among tissues.
- Some agents persist in reservoirs such as bone, adipose tissue and brain.
- Others are excreted or converted into metabolites that are more readily eliminated.
- Tissue retention and organ sensitivity jointly influence the pattern of disease.

Possible destinations of an absorbed xenobiotic

Local action

Biologic effect at the entry site

Remote action

Effect after vascular transport

Storage

Retention in bone, fat, brain or other tissues

Elimination

Excretion unchanged or after conversion

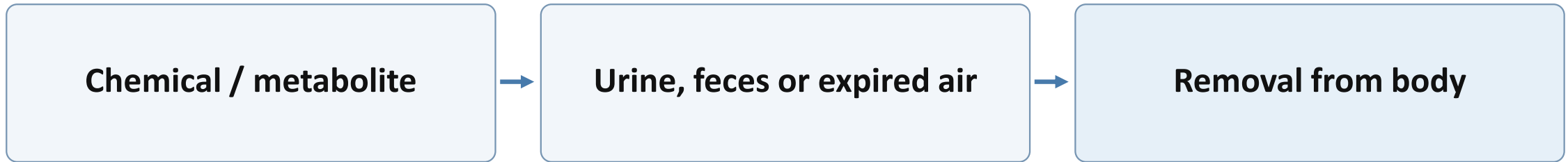
These are competing or sequential fates—not necessarily mutually exclusive.

Storage sites cited

Potential reservoir	Pathology interpretation
Bone	A possible compartment for persistent material
Adipose tissue	A relevant reservoir for some lipid-soluble agents
Brain	A site where accumulation may matter to neural function
Other tissues	Storage depends on the agent and tissue chemistry

The source gives illustrative reservoirs, not a fixed destination for every xenobiotic.

Exit routes of chemicals and metabolites



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- Some agents are eliminated by renal or gastrointestinal routes.
 - Other compounds leave the body in expired air.
 - Biotransformation often increases water solubility and facilitates excretion.

Persistence and excretion are different endpoints

Retention

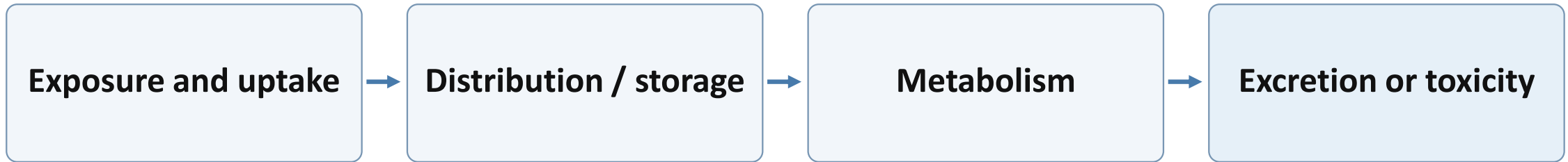
- Agent remains within an organ or tissue compartment
- Toxicity can persist while biologically active material remains
- Storage does not guarantee injury; Identity and target matter

Clearance

- Unchanged compound or metabolite leaves the body
- Water solubility often promotes excretion
- Removal can terminate or limit tissue exposure

Compare chemical half-life and tissue vulnerability conceptually; The supplied core excerpt gives no numerical half-lives.

Integrated xenobiotic disposition

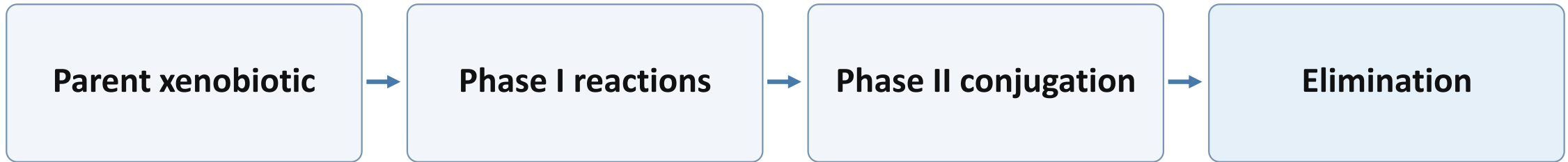


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- The same absorbed agent may partition into storage, be biotransformed, or reach sensitive organs.
 - Metabolic conversion is a branching point: Detoxification and activation have opposite consequences.
 - An exposure history is incomplete without some understanding of disposition.

Biotransformation can protect or injure

- Many xenobiotics are converted to inactive, water-soluble products.
- Some metabolic pathways instead generate chemically reactive intermediates.
- The original chemical and its metabolites may have different biologic properties.
- Therefore, metabolic enzyme activity can either decrease or increase toxicity.

The two-phase metabolism concept



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- Phase I commonly involves oxidation, reduction or hydrolysis.
 - Phase II introduces or conjugates groups, often increasing water solubility.
 - This scheme is a major pattern, not a compulsory sequence for every chemical.

Phase I: Three reaction classes

Reaction	Core chemical change	Source context
Oxidation	Oxidative chemical transformation	Often CYP-catalyzed
Reduction	Chemical reduction	One form of phase I conversion
Hydrolysis	Bond cleavage through reaction with water	Another form of phase I conversion

Phase I does not guarantee detoxification: The metabolite may be reactive.

Phase I is not always a safety mechanism

- Phase I products may be less harmful, unchanged in hazard, or more reactive.
- CYP450 catalyzes many phase I processes.
- Formation of a toxic intermediate is called metabolic activation or bioactivation.
- This explains why a parent compound can become injurious only after enzyme-mediated conversion.

Phase II: Conjugation pathways in the source

Reaction	Principle
Glucuronidation	Addition of a glucuronide-containing group
Sulfation	Sulfate conjugation
Methylation	Transfer of a methyl group
Glutathione (GSH) conjugation	Conjugation involving the antioxidant GSH

These reactions commonly favor water-soluble products; Pathways depend on substrate.

Water solubility helps eliminate xenobiotics

- Phase II metabolism commonly yields products that are more water-soluble.
- Water-soluble chemicals are more readily eliminated from the body.
- Successful detoxification depends on forming a product that lacks harmful reactivity.
- A conjugate should not automatically be described as nontoxic without knowing the specific agent.

Detoxification versus metabolic activation

Detoxification

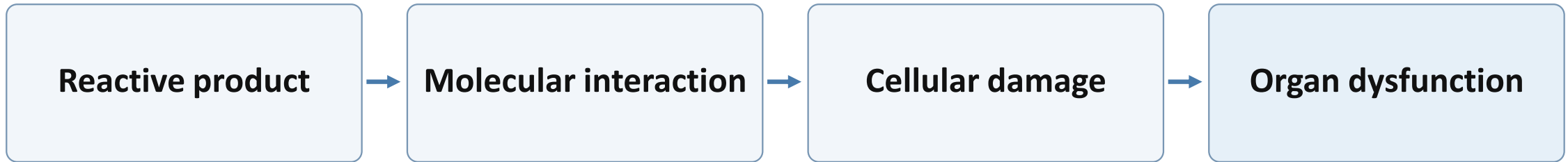
- Parent xenobiotic undergoes metabolic conversion
- Nontoxic product forms
- Elimination limits ongoing exposure

Activation

- Metabolism creates a reactive intermediate
- Cellular molecules become targets
- Damage may outstrip cellular repair

These opposing branches form the core of the textbook's xenobiotic-metabolism model.

Reactive metabolite to tissue injury



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- Reactive products may affect enzymes, receptors, membranes or DNA.
 - The type of molecular target influences the pattern of pathology.
 - Cellular repair may prevent a damaging interaction from becoming overt disease.

Principal molecular targets

Proteins / enzymes

Disrupted molecular function

Receptors

Altered cellular response

Membranes

Impaired cell-compartment integrity

DNA

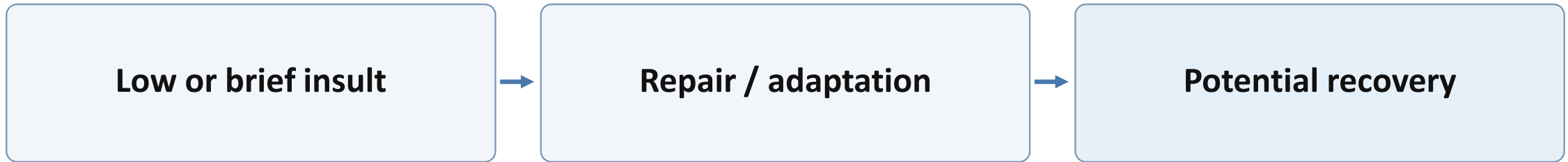
Genetic injury and possible long-term sequelae

Robbins explicitly names these cellular components as targets of reactive metabolites.

Cellular repair determines whether injury persists

- Molecular damage does not inevitably cause irreversible tissue injury.
- Cells possess mechanisms to repair damaged molecules and structures.
- When the burden of damage exceeds repair capacity, toxicity emerges.
- Persistent damage can produce short-term or long-term adverse outcomes.

Injury severity: Dose and duration matter



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- Robbins Chapter 2 contrasts reversible injury after limited exposure with cell death after more severe or prolonged insults.
 - Sensitivity also depends on cell type, metabolic state and adaptability.
 - The diagram is conceptual: No universal exposure boundary exists between reversible and irreversible damage.

Reversible injury versus cell death

Reversible injury

- Lesser or shorter toxic insult
- Cell dysfunction may recover after the agent is removed
- Repair capacity remains adequate

Irreversible injury

- Severe or sustained insult
- Essential cell components fail
- Cell death and tissue damage may follow

A single agent can cause either outcome at different exposure intensities.

Toxicants can damage several systems at once

- The same stimulus can affect mitochondria, membranes, DNA and protein machinery.
- Multiple pathways may interact rather than act independently.
- This is why microscopic patterns of toxic injury may not reveal a single causal mechanism.
- Interpret organ pathology together with agent exposure and biochemistry.

Cytochrome P450 is the major phase I catalyst

- The CYP450 system is a large family of heme-containing enzymes.
- Individual CYP enzymes have preferred, but not exclusive, substrate specificities.
- They participate in metabolism of solvents, chemicals, alcohol and numerous drugs.
- CYP-mediated conversion may detoxify chemicals or generate injurious metabolites.

Where CYP enzymes are expressed

Liver

- Hepatocytes are a major site of CYP expression
- Many enzymes localize to endoplasmic reticulum
- Hepatic metabolism shapes systemic chemical disposition

Extrahepatic tissues

- Skin, lung and GI mucosa also contain CYP enzymes
- Local metabolism can occur near an entry surface
- Both detoxification and activation are possible

Tissue location affects where enzymatic products are generated.

Hepatic and extrahepatic metabolism

Hepatocytes

- High CYP expression
- Major organ for metabolism of absorbed compounds
- Can be a target of CYP-dependent toxic products

Other organs

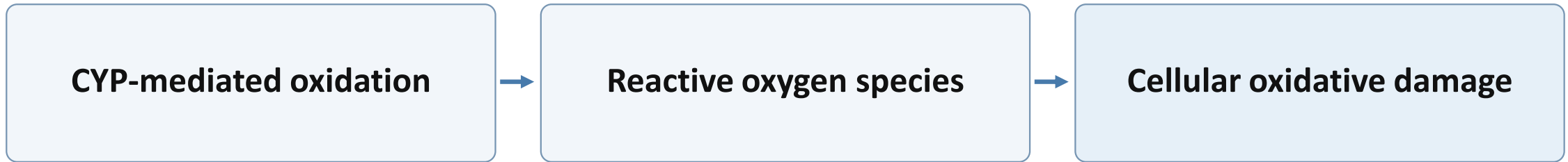
- Skin, lung and gastrointestinal mucosa express CYPs
- Metabolism can occur near the portal of exposure
- Local activation can make an exposed tissue vulnerable

Do not assume all xenobiotic metabolism is restricted to the liver.

CYP enzymes are heme-dependent catalysts

- The family contains many distinct CYP isoenzymes with varied substrate preferences.
- They perform chemical transformations central to phase I handling of xenobiotics.
- CYP activity depends on the particular enzyme and the encountered substrate.
- Consequently, naming “CYP450” alone is insufficient to predict a chemical’s precise fate.

CYP catalysis also produces ROS



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- Reactive oxygen species can arise as by-products of CYP metabolism.
 - Oxidative injury can accompany either otherwise protective or activating conversions.
 - ROS to broader mechanisms of cell injury discussed in Chapter 2.

The CYP paradox: Protection and bioactivation

- Metabolism commonly terminates activity and helps excrete chemicals.
- Less commonly, CYP conversion increases chemical reactivity and toxic potential.
- The damaging agent may therefore be a metabolite rather than the environmental parent.
- Mechanistic attribution should identify the reactive species when established.

Why CYP activity varies across individuals

- Genetic polymorphisms in specific CYP genes produce one source of variation.
- Environmental chemical exposures and medications can modify CYP abundance or activity.
- Smoking, alcohol and hormones are among factors associated with induction.
- Fasting and starvation may decrease CYP activity.

Modifiers of CYP activity in the Robbins text

Genotype

Polymorphisms in specific CYP genes

Chemical exposure

Environmental substances and medications

Behavior / physiology

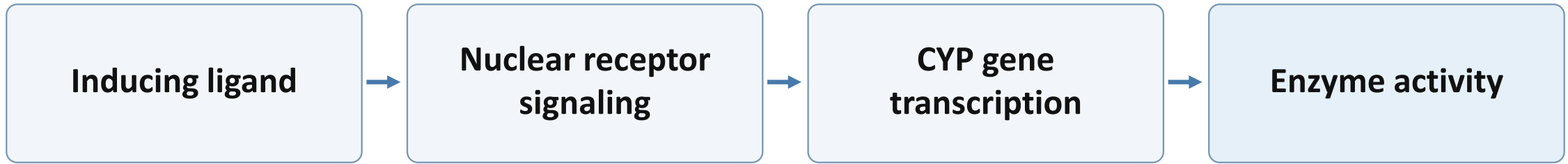
Smoking, alcohol, hormonal influences

Nutritional state

Fasting or starvation may reduce activity

Consequences are substrate-dependent: Altered activity may increase clearance or bioactivation.

CYP induction is transcriptionally regulated



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- Inducing chemicals bind regulatory receptors described in the source.
 - Activated receptors help recruit transcriptional machinery to CYP regulatory regions.
 - The impact on toxicity depends on which CYP and metabolic route are affected.

Nuclear receptors regulate CYP transcription

- Chemical exposure can activate nuclear-receptor-mediated transcription.
- Receptor partners, including retinoid X receptor (RXR), in this regulatory network.
- Transcriptional complexes bind CYP gene regulatory sequences.
- Different receptor systems should not be assumed to share identical binding partners or transcriptional mechanisms.

Receptors named in xenobiotic enzyme regulation

Source-listed regulator	Abbreviation
Aryl hydrocarbon receptor	AhR
Peroxisome proliferator-activated receptors	PPARs
Constitutive androstane receptor	CAR
Pregnane X receptor	PXR

These regulators link chemical exposure to xenobiotic-metabolizing gene expression.

Enzyme induction has two possible outcomes

When a metabolite is harmless

- Greater conversion can enhance elimination
- Parent-compound exposure may decrease
- Detoxifying pathway can dominate

When a metabolite is reactive

- Greater conversion can increase activation
- Cellular injury may become more likely
- Total outcome also depends on competing pathways

Induction is not synonymous with protection or toxicity; Identify the substrate and product.

Illustrative CYP substrates

Therapeutic agents

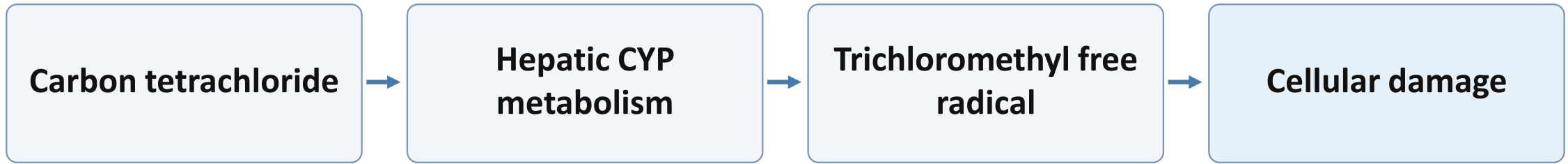
- Acetaminophen
- Barbiturates
- Warfarin and anticonvulsants

Other exposures

- Alcohol
- Carbon tetrachloride
- Benzo[a]pyrene in cigarette smoke

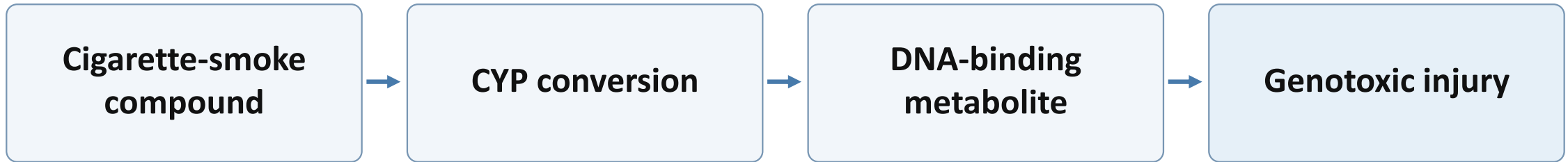
Different substrates need not share the same CYP enzyme or injury pattern.

Carbon tetrachloride: Bioactivation example



- CCl_4 to illustrate generation of a toxic radical by hepatic metabolism.
- The parent xenobiotic becomes hazardous through a reactive intermediate.
- This is a classic mechanistic contrast with phase II-mediated detoxification.

Benzo[a]pyrene: A genotoxic activation example



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- Benzo[a]pyrene is an example of a procarcinogen that requires metabolic activation.
 - The activated product can bind DNA in lung tissue.
 - Genotoxic effects illustrate a potential long-term consequence of xenobiotic metabolism.

Acetaminophen: Competing metabolic fates

Predominant conjugation pathway

- Glucuronidation and sulfation
- Products eliminated in urine
- Detoxification predominates at therapeutic exposures

Minor CYP-dependent pathway

- CYP metabolism generates NAPQI
- NAPQI is reactive and potentially hepatotoxic
- Normal GSH conjugation limits exposure

These are parallel metabolic fates; The proportion entering reactive pathways matters.

GSH determines the outcome of NAPQI exposure

GSH is sufficient

- Reactive NAPQI is conjugated
- Inactivation reduces chemical reactivity
- Hepatocyte injury is limited

GSH becomes depleted

- Unconjugated NAPQI accumulates
- Protein binding and mitochondrial dysfunction
- Oxidant injury and centrilobular necrosis

The critical fork is reactive metabolite formation relative to available detoxification.

Acetaminophen: Morphology follows chemistry

- The Robbins example links excessive NAPQI to centrilobular hepatocellular necrosis.
- Severe injury can progress from hepatocyte damage to acute liver failure.
- The named molecular mechanisms include protein binding and GSH depletion.
- This is an application of the general parent-compound → metabolite → target-organ sequence.

Ozone and carbon monoxide: Two toxicity patterns

Ground-level ozone

- Oxidant exposure at the respiratory surface
- ROS-associated epithelial damage
- Airway inflammation and reduced lung function

Carbon monoxide

- Absorbed systemically after inhalation
- Formation of carboxyhemoglobin
- Impaired oxygen transport and tissue hypoxia

Adjacent chapter examples contrast local chemical oxidant injury with systemic oxygen deprivation.

Physical agents: Interpret the kind of energy

- Robbins explicitly extends toxicology to radiation and heat.
- The later chapter separates mechanical, thermal, electrical and ionizing-radiation injury.
- Unlike xenobiotic metabolism, the primary exposure variable may be deposited energy or temperature disturbance.
- Each physical-agent category has separate mechanisms and is addressed in its own indexed unit.

Chemical versus physical injury: Conceptual comparison

Question	Chemical agents	Physical agents
Primary exposure	Compound or reactive metabolite	Energy, force or thermal stress
Internal disposition	Absorption, distribution and metabolism	Energy transfer / physical tissue effect
Important modifier	Bioactivation, retention, host enzymes	Magnitude, duration, tissue vulnerability
Shared final outcome	Cellular dysfunction, injury or death	Cellular dysfunction, injury or death

Conceptual overview, not a diagnostic classification.

Case study: Inhaled compound with distant effects

HYPOTHETICAL TEACHING SCENARIO

A worker inhales a chemical vapor and later develops dysfunction in an organ other than the lung.

What two steps are needed to explain a remote target-organ effect?

Pulmonary absorption followed by vascular distribution.

Chemical transformation may additionally create an active metabolite, but remote injury need not require bioactivation.

Case study: Identical exposure, different response

HYPOTHETICAL TEACHING SCENARIO

Two individuals encounter the same nominal exposure; Only one develops clinically evident injury.

Which host-related factors could explain this difference?

Differences in age, genetics, tissue sensitivity, concurrent exposure, or metabolic enzyme activity.

Exposure equivalence does not prove equivalent internal dose or organ-level sensitivity.

Case study: The parent molecule appears inert

HYPOTHETICAL TEACHING SCENARIO

A chemical becomes hazardous only after conversion by hepatic enzymes.

Which metabolic process explains the new toxicity?

Bioactivation, commonly through a phase I/CYP-catalyzed pathway.

The reactive metabolite—not necessarily the original molecule—may interact with membranes, proteins or DNA.

Case study: Excessive analgesic exposure

HYPOTHETICAL TEACHING SCENARIO

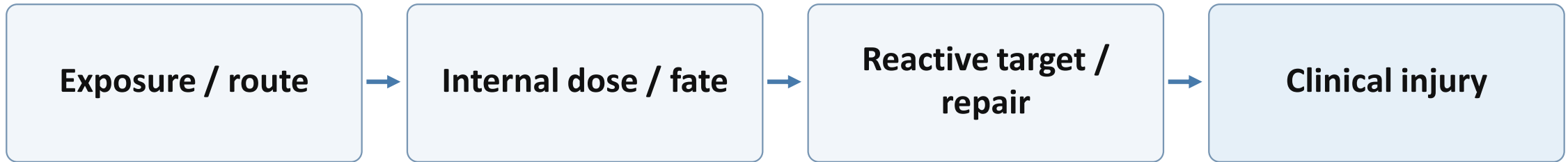
A hypothetical patient with excessive acetaminophen ingestion develops hepatocellular necrosis.

Which competing processes explain the injury?

CYP-mediated NAPQI formation, inadequate GSH conjugation, and reactive metabolite injury.

The later Robbins drug section identifies these processes and the centrilobular morphology.

Synthesis: How to reason through any toxic exposure



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- Specify the agent and exposure history before interpreting the pathology.
 - Identify whether clearance, storage or enzyme-dependent activation dominates.
 - Integrate the affected molecular target, tissue susceptibility and observed injury.

Five principles to retain

- Dose and exposure pattern determine whether a chemical behaves as a poison.
- Xenobiotics enter through lung, GI tract or skin and may act locally or systemically.
- Metabolism can detoxify or activate; Phase I and phase II are not universally protective steps.
- CYP450 enzyme variability and receptor-mediated regulation modify susceptibility.
- Cellular repair, tissue vulnerabilities and time determine whether injury resolves or persists.

Core source and contextual readings

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. 2026. Chapter 9, “Toxicity of Chemical and Physical Agents,” pp. 371–372.
- Chapter 9, Fig. 9.3: exposure to pollutants; Fig. 9.4: xenobiotic metabolism.
- Related applied examples in Chapter 9: outdoor air pollution, acetaminophen injury, and injury by physical agents.
- General cellular injury context: Chapter 2, “Mechanisms of Cell Injury.”