

Environmental Toxicology

Toxic Effects of Solvents and Vapors

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- Solvents, a class of liquid organic chemicals with variable **lipophilicity** (\uparrow with C no) and **volatility**, small molecular size, and lack of charge.
- Absorption of **inhaled** volatile organic compound occurs in the alveoli, with almost instantaneous equilibration with blood in the pulmonary capillaries.
- Solvents are absorbed readily from the GI tract and **across the skin**.
- Absorbed, metabolized, excreted and accumulated (in adipose tissue)
- Most solvents produce some degree of CNS depression.

- The toxic effects of solvents are both general and specific. Solvent structure, exposure level, frequency and co-exposure, and subject sensitivity will determine the toxic effects.
- Toxic effect may be additive, synergistic, or potentiated.

General Classes of Organic Solvents

- Aliphatic hydrocarbons (n-hexane); many are Halogenated eg. CCl_4 , TCE
- Alcohols (methanol)
- Cyclic hydrocarbons (cyclohexane)
- Amides/amines
- Esters (ethyl acetate)
- Ethers (ethyl ether)
- Ketones (acetone)
- Glycols (ethylene glycol)
- Aromatic hydrocarbons (benzene)
- Aldehydes (acetaldehyde)

Many are in mixtures (thinners), and in many compounds (paints, etc).

Not to mention multiple exposure in our daily life.

Lancet 349:1239-43, 1997

The main determinants of a solvent's inherent toxicity

- the number of carbon atom (lipophilicity \propto CNS depressant; volatility)
- whether it is saturated or has double or triple bonds between adjacent carbon atoms
- its configuration (straight chain, branch chain, or cyclic)
- Whether it is halogenated
- the presence of functional groups
 - ex. Amides/amines-potent sensitizer
 - aldehyde-irritating

- Hydrocarbons that are extensively metabolized tend to be more cytotoxic/mutagenic
- Unsaturated, short chain halocarbon-carcinogens
- The toxicity of solvent within the same class may vary dramatically.
 - Trichloroethane-not carcinogenic
 - Trichloroethylene-carcinogenic
 - 2,4 diaminotoluene-liver tumor
 - 2,6-diaminotoluene-not tumorigenic

General effects

- Hydrocarbons, chlorinated hydrocarbons, alcohols, ethers, esters, and ketones:
- Acute high-level vapor exposure ----> **narcosis and death.**
- Animal analogy is the LC50 (acute inhalation toxicity)
- People will show signs of **CNS disturbance.** While there is variation in signs and symptoms with solvent structure, results are quite similar. Disorientation, euphoria, giddiness, confusion, progressing to unconsciousness, paralysis, convulsion, and death from respiratory or cardiovascular arrest is typically observed.
- The similarity of the narcosis produced by solvents of diverse structure suggests that these effects result from a physical interaction of a solvent with cells of the CNS.

Specific Effects

- Hematotoxicity ---- benzene
- CNS depressant effect ---- alkylbenzenes
- Hepatotoxicity ---- certain chlorinated hydrocarbons
- Ocular toxicity ---- methanol
- Neurotoxicity ---- n-hexane
- Reproductive toxicity ---- ethylene glycol ethers
- Carcinogenicity ---- all chlorinated hydrocarbons, dioxane

Multiple exposure pathways frequently exist

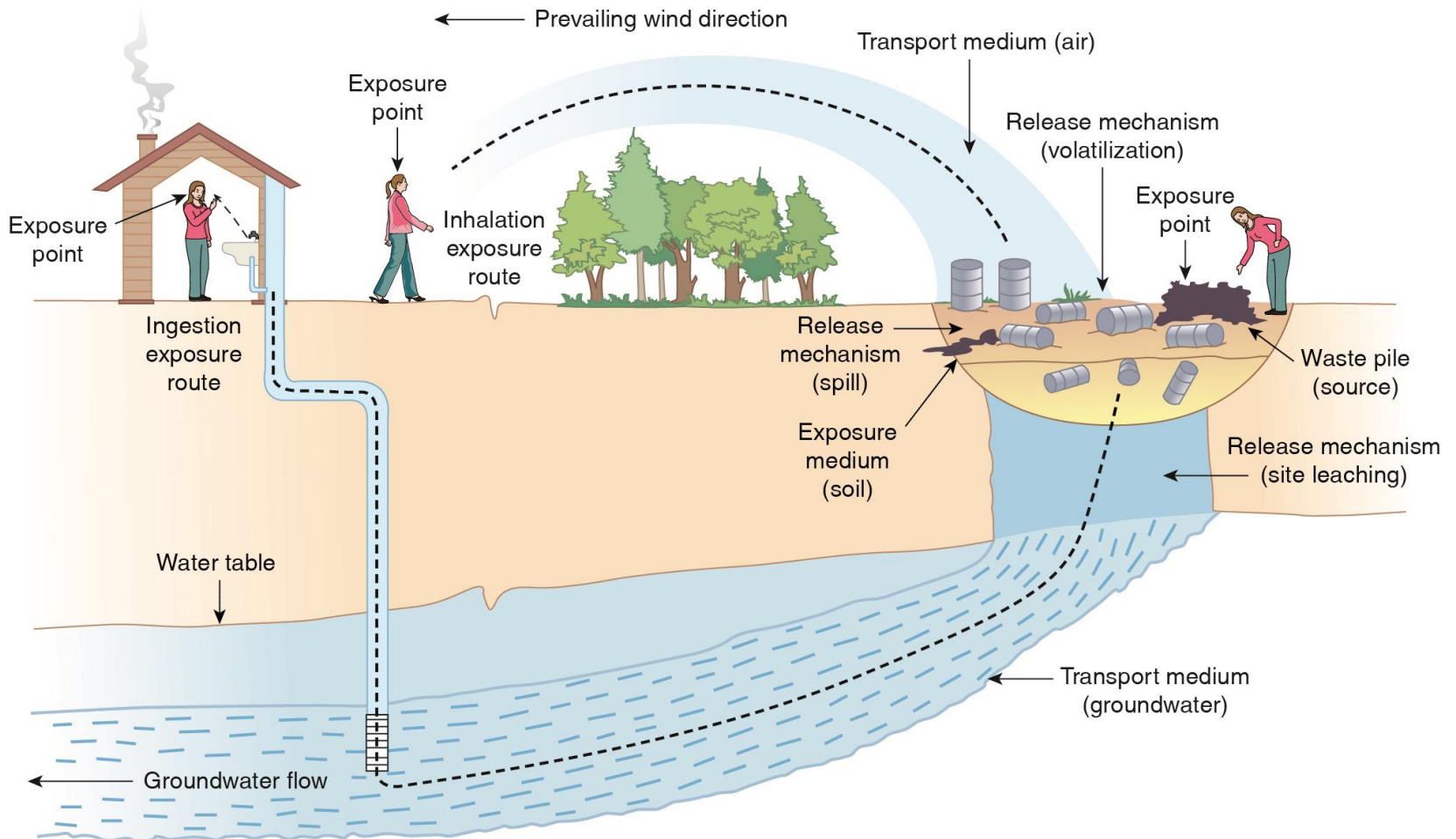


Figure 24-1. Solvent exposure pathways and media. (Adapted from EPA, 1989.)

Sources of exposure

- **Daily activity- workplace, gas station, smoking, household, etc.**
- **Solvent abuse- produce euphoria, delusions, sedation and visual and auditory hallucination**
- **Environmental contamination- major volatile organic solvents (VOCs)**

PEL vs. TLV

- PELs (Permissible exposure limits), established by OSHA (US Occupational Safety and Health Administration), are legally enforceable.
- TLV (Threshold limit values), published by the ACGIH (American Conference of governmental Industrial Hygienists), are more stringent than PELs but don't carry the weight of law.
- TLV is the average conc. for a 8-hr workday or 40-hr workweek, without adverse effect, for working lifetime.
- The STELs (short-term exposure limits) and ceiling values are designed to protect against the acute effects of high level, short-term solvent exposure.

- Biological monitoring: is useful as technological advances are made, because it provides a better measure of exposure than classic industrial hygiene monitoring.
- Solvent-induced toxicity is dependent on:
 - Toxicity of solvent
 - Exposure route
 - Amount or rate of exposure
 - Duration of exposure
 - Individual susceptibility
 - Interaction with other chemicals

Solvent-induced chronic encephalopathy (CSE)

- Nonspecific symptoms (headache, fatigue, sleep disorders) with or without changes in neuropsychological dysfunction
- Type I Symptoms only
- Type 2A Sustained personality or mood change
- Type 2B Impairment in intellectual function
- Type 3 Dementia

Table 24-2

Functions that may be Assessed in a Neuropsychological Evaluation

Psychomotor functions

- Reaction time

- Motor speed and dexterity

- Eye–hand coordination

Sustained attention/concentration and perceptual speed

Verbal and nonverbal memory

- Immediate memory

- Delayed memory

Learning

Visual constructive ability

Conceptual ability

Evaluation of personality and affect

SOURCE: Reproduced from Cranmer (1986), with permission from Elsevier.

Solvent abuse

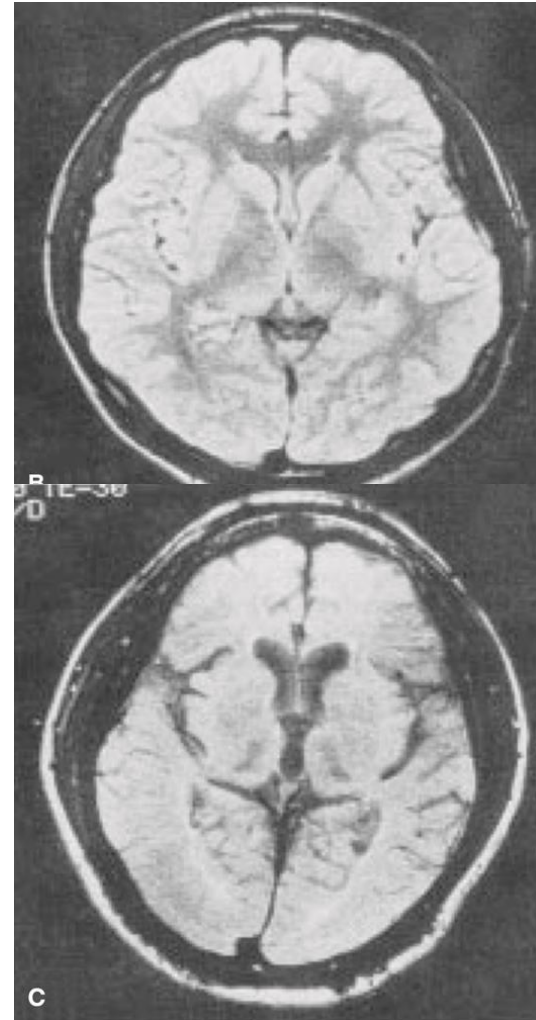
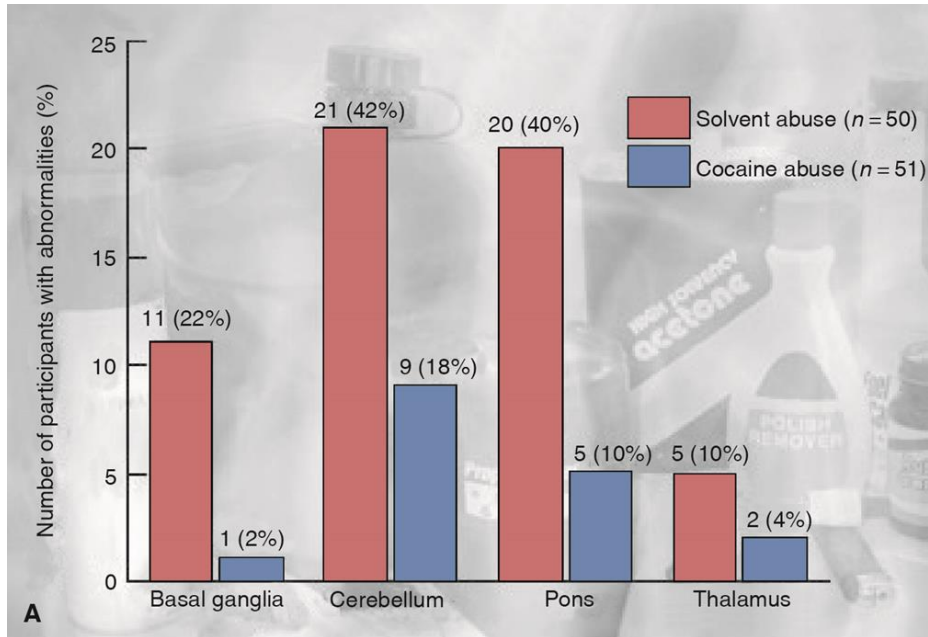


Figure 24-2. (A) *Inhalant and cocaine abusers with subcortical abnormalities, by brain region affected.* (B and C) *Brain damage in a toluene abuser.* (A) Magnetic resonance imaging (MRI) scans of chronic inhalant abusers and chronic cocaine abusers showed more frequent occurrence of abnormalities in the basal ganglia, cerebellum, pons, and thalamus for those who abused solvents. (Methias, 2002.) MRI shows marked atrophy (shrinkage) of brain tissue in a toluene abuser (C) compared with a nonabusing individual (B). Note the smaller size and the larger empty (dark) space within the toluene abuser's brain. The white outer circle in each image is the skull. (Available electronically at <http://www.drugabuse.gov/PDF/RRInhalants.pdf>.) (Courtesy of Neil Rosenberg, MD, as published in *NIDA Research Report Series*, March 2012.)

TABLE 15.1 Some Commonly Abused Inhalants (Part 1)

Compound	Principal uses
Acetone	Nail polish remover, adhesives, general solvent
Aliphatic and aromatic hydrocarbons	Gasoline, white spirits
Bromochlorodifluoromethane (BCF)	Fire extinguishers
n-Butane	Cigarette lighters, bottled fuel gas
Butanone (methyl ethyl ketone, MEK)	Adhesives, general solvent
Carbon tetrachloride	Grain fumigant, laboratory solvent
Chlorodifluoromethane (Halon 122 or Freon 22)	Aerosol propellant
Chloroform	Laboratory solvent
Dichlorodifluoromethane (Halon or Freon 12)	Aerosol propellant, refrigerant
Dichlorotetrafluoroethane (Halon 242 or Freon 114)	Aerosol propellant
Diethyl ether	Laboratory solvent

Source: After Dinwiddie, 1994.

TABLE 15.1 Some Commonly Abused Inhalants (Part 2)

Compound	Principal uses
Enflurane	Anesthetic
Ethyl acetate	Adhesives
Halothane	Anesthetic
n-Hexane	General solvent
Isoflurane	Anesthetic
Methyl isobutyl ketone (MIBK)	General solvent
Nitrous oxide	Anesthetic, whipped cream dispensers
Propane	Bottled fuel gas
Tetrachloroethylene (perchloroethylene)	Dry-cleaning and degreasing agent
Toluene	Adhesives, acrylic paints, paint stripper
Trichloroethane (methylchloroform)	Dry-cleaning and degreasing agent, correction fluid
Trichloroethylene	Dry-cleaning and degreasing agent, chewing gum remover
Trichlorofluoromethane (Halon or Freon 11)	Aerosol propellant, refrigerant
Xylene	Woodwork adhesives, histology clearing agent

Source: After Dinwiddie, 1994.

Environmental Contamination

- Everyone is exposed daily to solvents, evidenced through biomonitoring.
- VOCs in atmospheric conc. is extremely low; yet some are relatively high (toluene, PERC, etc. in industrial area.)
- Solvent contamination in drinking water is a worldwide problem, because all solvents are soluble in water to some extent.
- Water chlorination may contribute to CHCl_3 and trihalomethane formation. Some VOCs may contribute to human exposure (inhalation) through heated running water.
- VOCs in groundwater tend to remain trapped until reaches the surface; microbial degradation happens in certain VOCs.

Toxicokinetics

- Volatility and lipophilicity → govern absorption and deposition
- Relatively low MW and are uncharged → pass freely through membranes by passive diffusion.
- Inhaled VOCs → absorption mainly in alveoli
- High blood:air partition coefficient (PC) favors uptake of VOCs.
- Solvents are well absorbed from the GI tract
- Lipophilic solvents penetrate stratum corneum readily.

Transport and Distribution

- GI: solvents → portal vein → liver (first pass effect, CYP2E1) → arterial circulation; exhaled by lungs through pulmonary circulation

Elimination (fig 24-3)

- Toluene: rapid metabolism and redistribution from brain to body fat
- Acetone: water soluble, limited amounts deposit in brain, great majority in blood and body water → large volume of distribution and relative slow metabolism and exhalation. [Hi blood:air PC and retention in the blood]

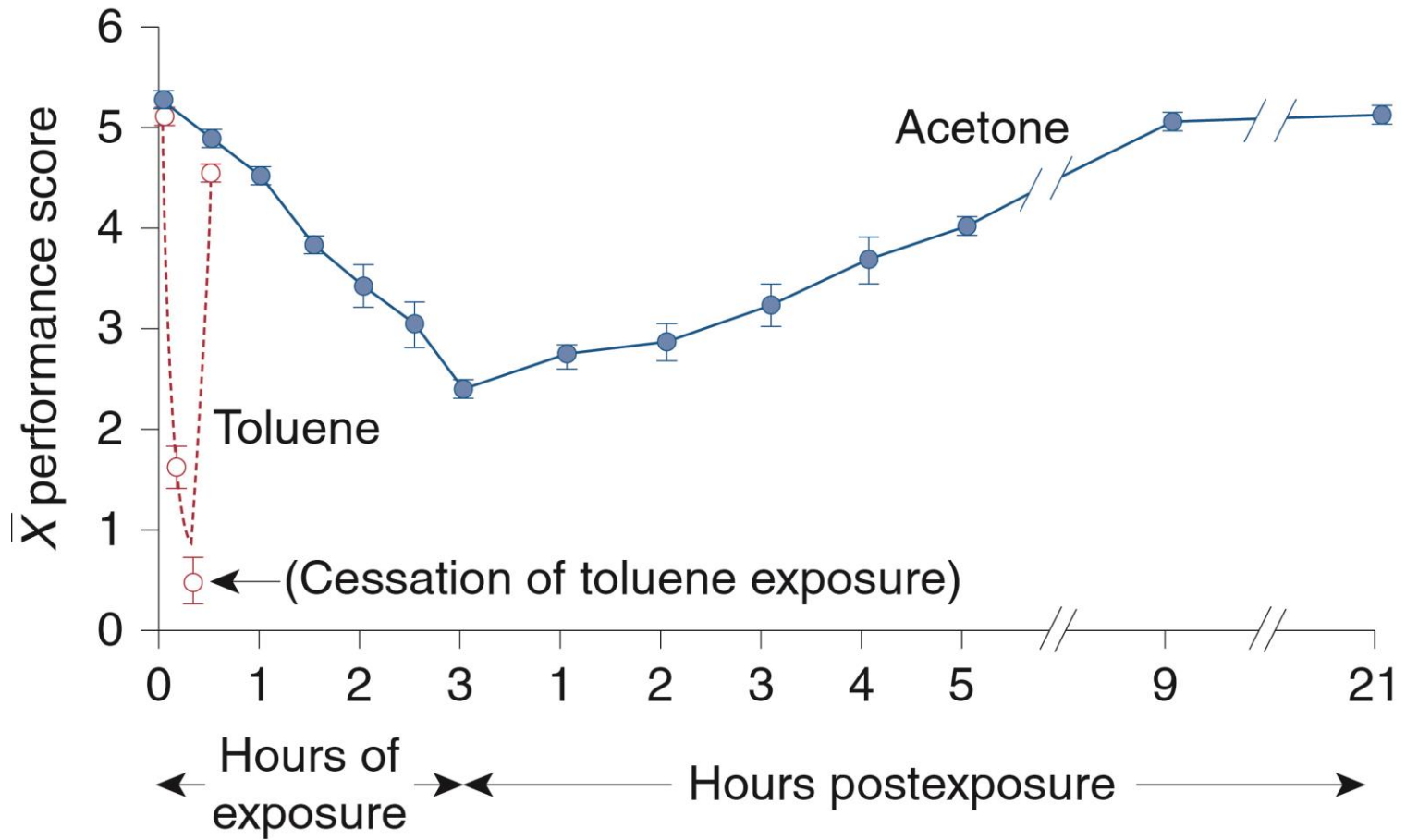


Figure 24-3. Comparison of the induction of and recovery from toluene and acetone narcosis. Rats inhaled 45 mg/L of toluene or acetone for 20 minutes or three hours, respectively. Animal performance/reflexes were monitored periodically as measures of the degree of CNS depression. (Reproduced from Bruckner and Peterson, 1981, with permission from Elsevier.)

Metabolism

- toluene (lipophilic in neuronal membranes) → metabolized to hydroxyl and carboxyl metabolites and excreted [detoxification]
- Benzene → metabolized to epoxide, quinone reactive metabolizes [bioactivation]
- CYPs (2D6, 2C9, 3A4, 1A2, 2C19 and 2E1) play an important role in solve metabolism
- Genetic polymorphism, induction (CYP2E1 induced by ethanol, acetone, pyridazine, chlorzoxazone, isoniazid, etc.) may contribute to CYPs induced toxicity

- CYP2E1, high-affinity, low-capacity isoform; catalyst many solvents (benzene, styrene, CHCl₃, TCE, and vinyl chloride in humans)
- CYP1B1/2, low-affinity, high-capacity isoform
- CYP isoforms exhibit species selectivity (CYP1A1 oxidizes TCE in mice but not in rats), substrate selectivity (CYP2E1 metabolize TCE and benzene, but not toluene), and regioselectivity (CYP1A1; toluene to o-cresol; but not to benzyl alcohol) for solvents.

Potentially Sensitive Populations

Endogenous Factors

Children

- 10-fold children's safety factor
- UDP-GT not mature in infant

Elderly

- CYP2E1 expression doesn't decrease with age
- Age influences the DME of solvents (body fat plays a role)
- Phase II pathways in humans are not altered by aging (in response to increased ROS production with aging)

Gender

- Dist of water- and lipid-soluble solvents can vary substantially between men and women.
- No major sex differences in P450-mediated hepatic metabolism in most mammals.
- UDP-GT activity appears higher in males.
- Women seem to have modestly lower glomerular filtration rates.

Genetics

- Pharmacogenetics exists within different ethnic groups

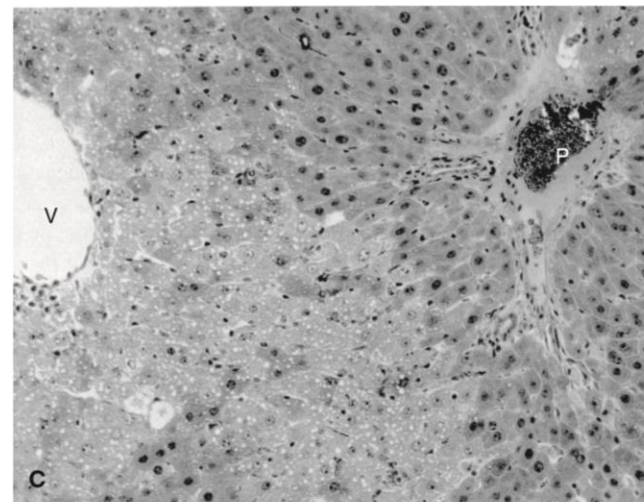
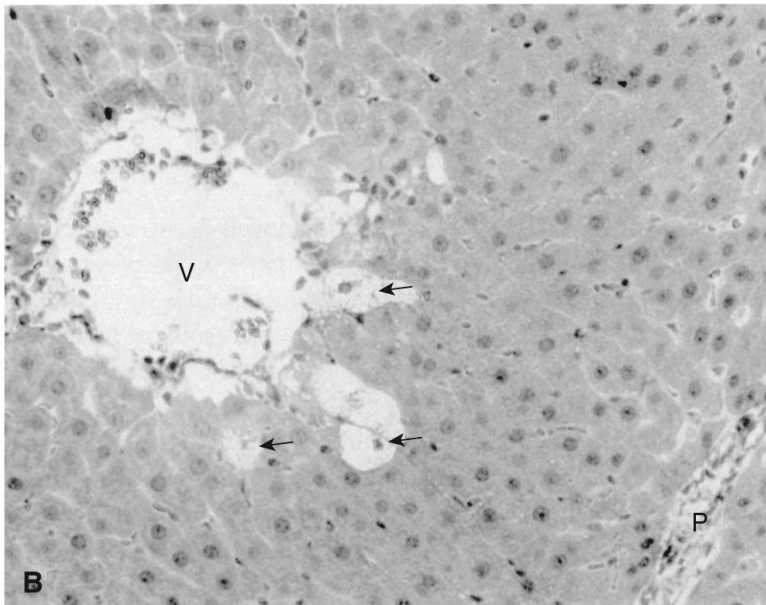
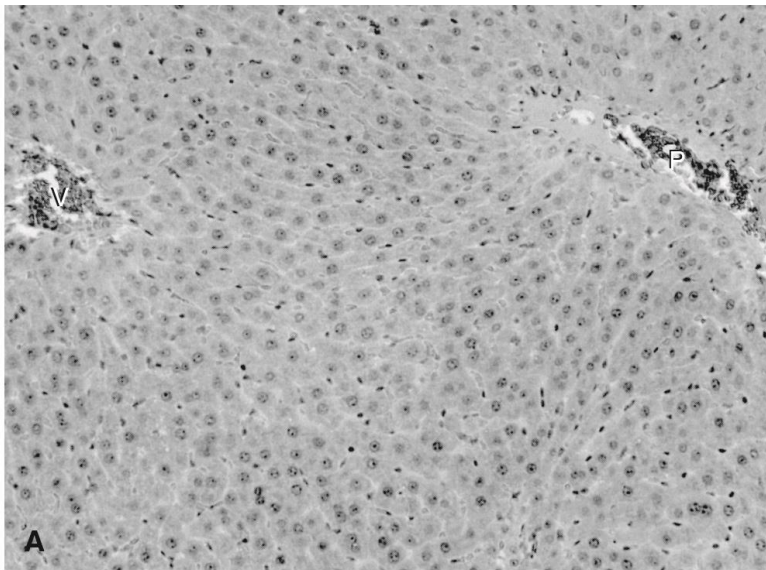


Figure 24-4. *Potentialiation of CCl₄ hepatotoxicity by 2-butanol.* Rats were (A) untreated; (B) given 0.1 mL CCl₄/kg IP; or (C) pretreated with 2-butanol (2.2 mL/kg PO) 16 hours before 0.1 mL/kg CCl₄ IP. Central veins and portal triads are designated V and P, respectively. Occasional hepatocytes (arrows) adjacent to the central vein are vacuolated in "B." Note the demarcation between vacuolated necrotic centrilobular and midzonal cells, and normally appearing periportal cells in "C." Hematoxylin and eosin stain. (A and C) $\times 315$; (B) $\times 480$. (Reproduced from Traiger and Bruckner, 1976, with permission from ASPET.)

P450 inducers

2-butanol induced CYP2E1 and therefore, Induced centrolobular necrosis in liver.
 Many CYP inducers also induce PhII
 Detoxifying enzymes.

Exogenous Factors

P450 Inhibitors

- Grapefruit flavanoids inhibit CYP3A4 → increases certain therapeutic agents metabolized by CYP3A4

Lifestyle

- Exercise, alveolar ventilation rate → VOC uptake
- Dietary, influences absorption and metabolism
- Circadian rhythms: most toxic when given VOC during the initial part of rodent's dark/active cycle (low hepatic GSH levels at this time).

Solvent Mixtures

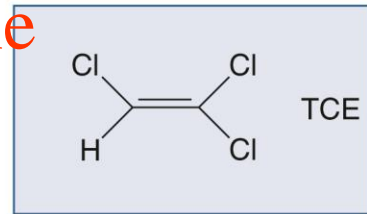
- The most common 4-component VOC mixture is TCE, PCE, 1,1,1-trichloroethane (TRI), and 1,1-dichloroethane.
- Rats + PERC and TRI → suppressed TRI metabolism
- Workers + TCE and PERC → lower urinary TCE metabolites than exposed to TCE alone
- Interaction due to competitive metabolic inhibition; this may protect against cytotoxicity, carcinogenicity of each solvent.
- Conversely, parent VOC increased → enhance neurologic effects

Trichloroethylene (TCE)

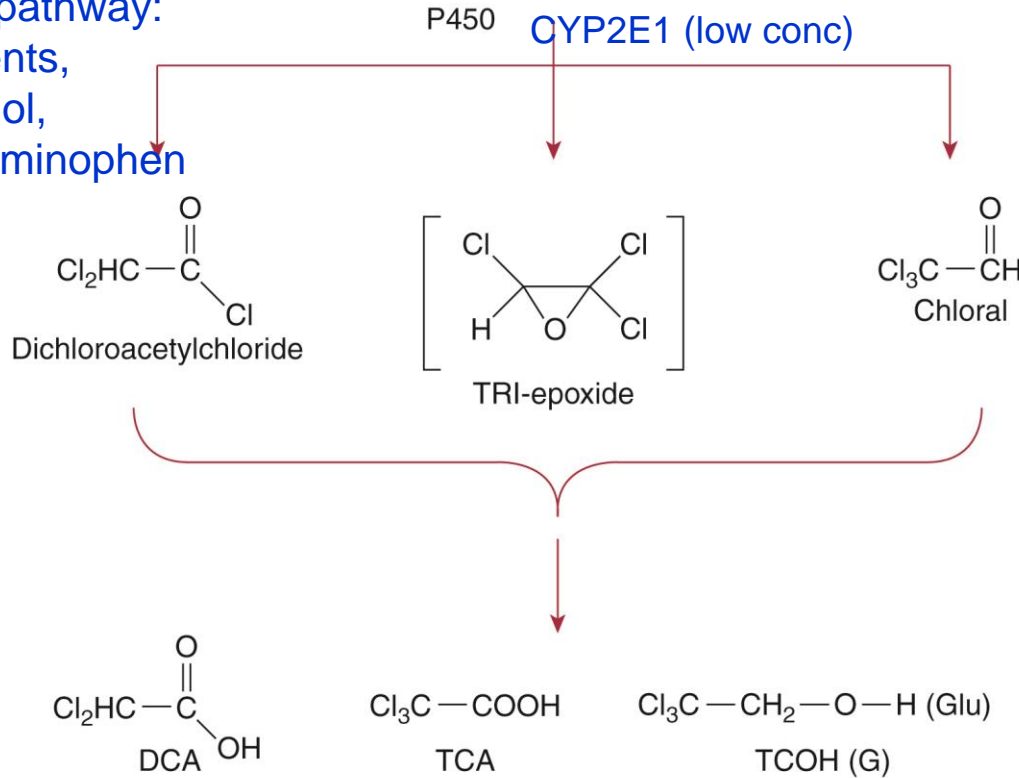
- **Use:** solvent for fats,, in dry cleaning,
- moderate exposure → symptoms similar to alcohol inebriation
- Hi conc. → narcotic effect
- Death occurring after heavy exposure, due to ventricular fibrillation
- Neurotoxicity, immunotoxicity, developmental toxicity, liver toxicity, kidney toxicity, endocrine effects, and cancer
- TCE acts through multiple metabolites and metabolic pathways:
 - CYP450 metabolites include TCA, DCA.
 - GST metabolites include DCVC.
- TCE acts through multiple modes of action.

- CNS depression is due to TCE and TCOH (trichloroethanol).
- Absorption, fast; metabolized mainly in liver;
- CYP catalyzed oxidation Mice >>rats>humans
- very Hi DCA and TCA → hepatocarcinogen in mice
- TCA is a nongenotoxic liver carcinogen in B6C3F1 mice.
- TCA induces PPAR α , (LPO, oxidative DNA damage and transcription factor activation) →DNA replication,, clonal expansion of hepatocytes and suppression of apoptosis,
- PPAR α : human is 10% of that in rodent liver.

Trichloroethylene (TCE)



Some competitors for CYP pathway:
Solvents,
Alcohol,
acetaminophen



(mainly in mice)

TCA: trichloroacetate
TCOH: trichloroethanol

GST →

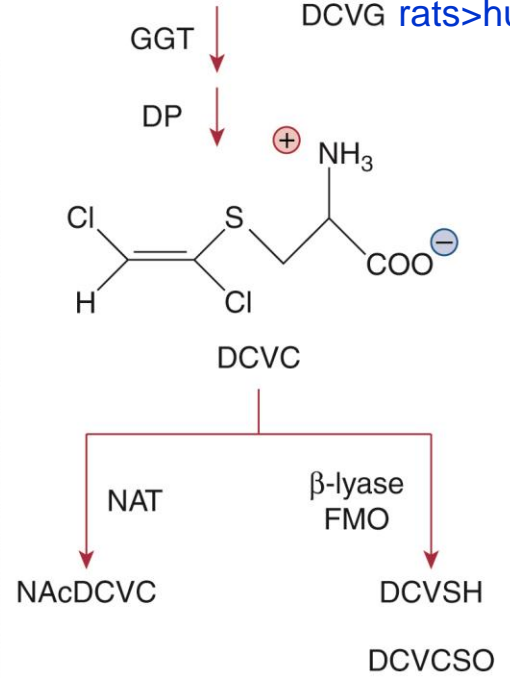
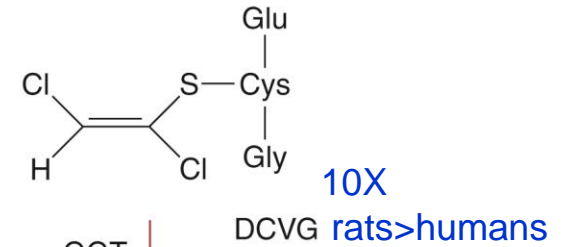


Figure 24-5. General scheme of metabolism for TCE. Abbreviations: β-Lyase, cysteine conjugate β-lyase; DCA, dichloroacetate; DCVC, S-(1,2-dichlorovinyl)-L-cysteine; DCVSH, 1,2-dichlorovinylthiol; DCVCSO, DCVC sulfoxide; DCVG, S-(1,2-dichlorovinyl)glutathione; DP, dipeptidase; FMO, flavin-containing monooxygenase; GGT, γ-glutamyltransferase; GST, GSH S-transferase; P450, cytochrome P450; TCA, trichloroacetate; TCOH, trichloroethanol; TCOG, TCOH glucuronide. (Reproduced from Lash *et al.*, 2005, with permission from Elsevier.)

Kidney tumors

DCVC is bioactivated in proximal tubular cells to reactive thiol S-(1,2-dichlorovinyl)thiol

Liver tumors

Expression of CYP2E1 in the hepatocytes
TCA and DCA

Lung cancer

Chloral hydrate accumulation in Clara cells

Tetrachloroethylene/Perchloroethylene (PERC)

- Widely used for dry-cleaning fabrics and metal degreasing operations
- liver, kidney, and central nervous system (CNS) from acute and chronic inhalation exposure to PERC
- Metabolism: CYP2B in rats; 2B6 in humans
- PERC → PERC oxide → trichloroacetyl chloride → TCA, found in urine
- Human, less susceptible to hepatorenal injury (toxic or carcinogenic) than rodents
- probably carcinogenic to humans

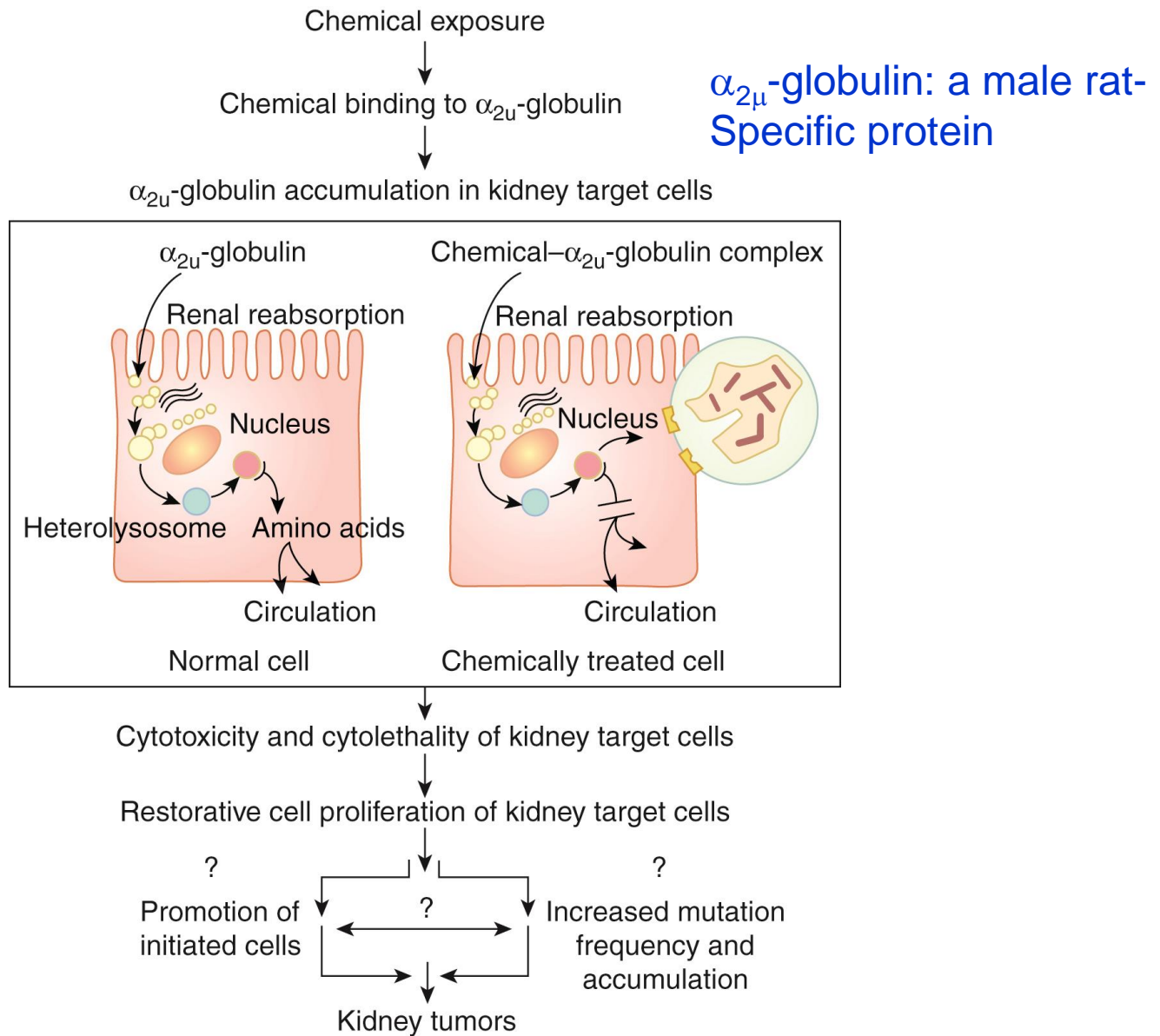


Figure 24-6. Proposed mechanism of solvent-induced kidney cancer in male rats involving α_{2u} -globulin. (Used with permission from Borghoff *et al.*, 1996a.)

1,1,1-Trichloroethane (TRI)

- A metal degreaser, general purpose solvent
- High dose rodent carcinogen; potential human carcinogen
- Efficiently absorbed from lung and GI
- Human absorbs TRI less than that of TCE due to TRI's relatively poor metabolism.

Methylene Chloride (MC)

- Was used to decaffeinate coffee
- Rapidly absorbed and distributed in body
- <5% was exhaled unchanged; 25-34% was exhaled as CO;
- MC (low conc.) → CYP2E1 (hi affinity; low capacity) → formyl chloride (reactive metabolite) → CO
- MC (Hi exposure level) → GSH mediated, GST-T1 (low affinity; high capacity) (genetic polymorphism in humans)

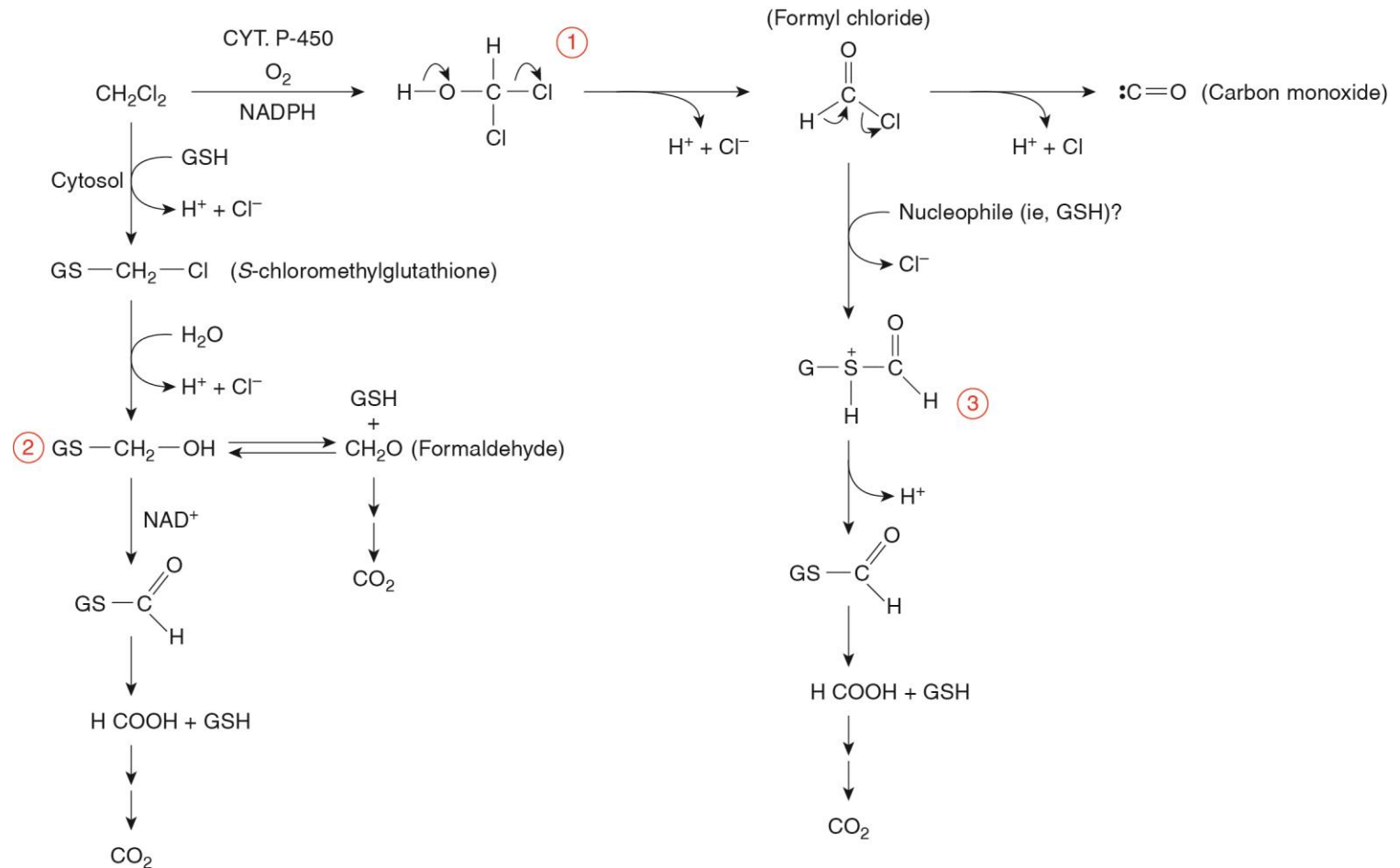
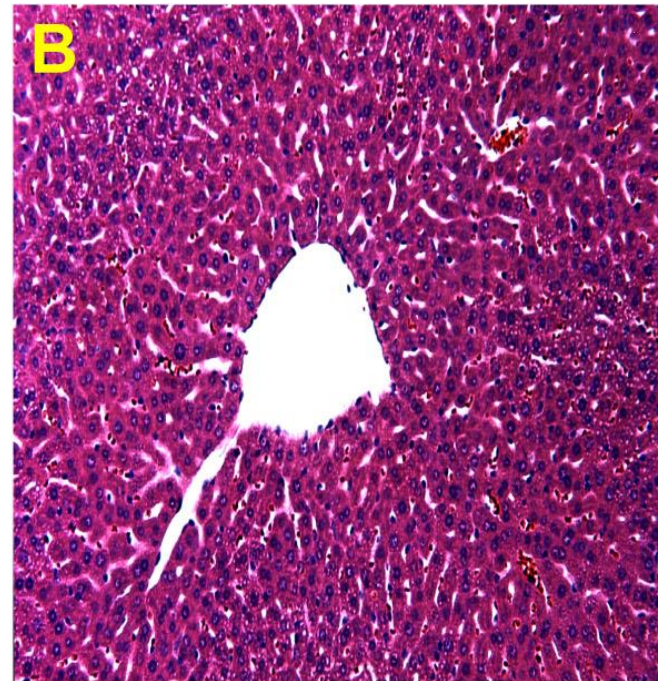
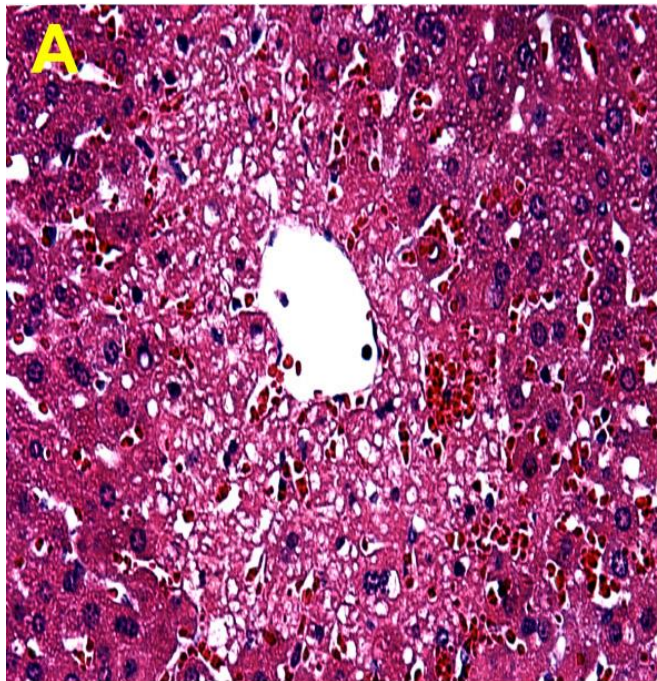
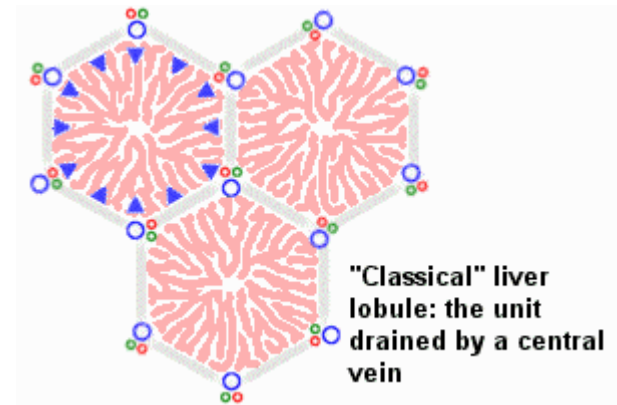
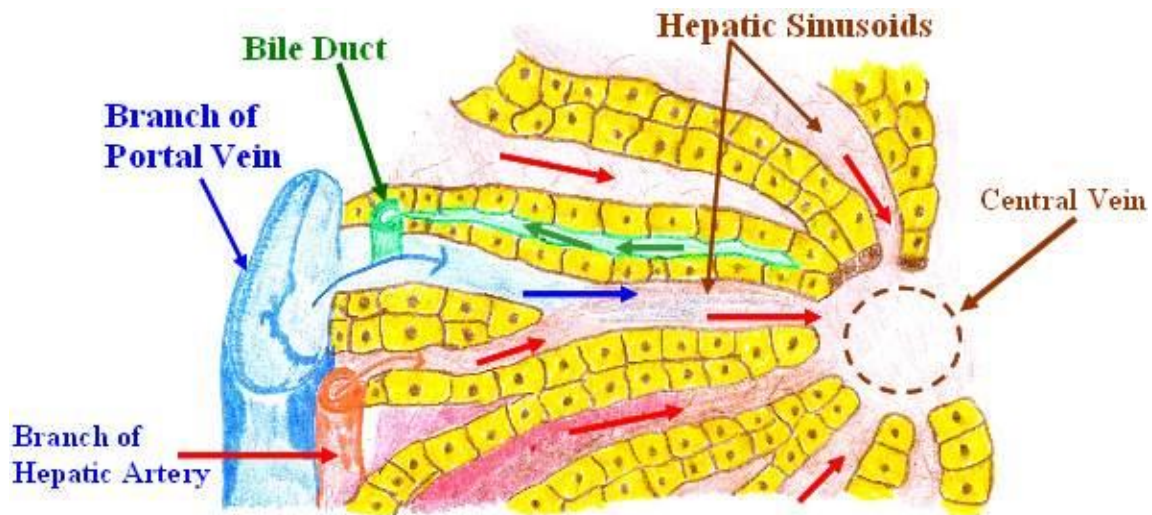


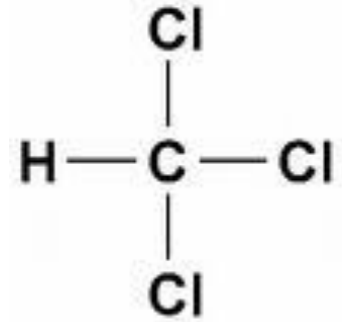
Figure 24-7. Proposed pathways for methylene chloride (CH_2Cl_2) metabolism. (1) Mixed-function oxidase pathway; (2) glutathione transferase pathway; and (3) nucleotide pathway. (Modified from Andersen *et al.*, 1987, with permission from Elsevier.)

Carbon tetrachloride

- Use: solvent, dry cleaning, etc.
- 12-24 hr post exposure can lead to centrilobular necrosis; however, after removing the source of exposure, 14 days later can recover
- is an indirect hepatocarcinogen in mouse
- $\text{CCl}_4 \rightarrow$ reductive dehalogenation to trichloromethyl radical $\text{CCl}_3\bullet \rightarrow$ react with $\text{O}_2 \rightarrow$ trichloromethyl peroxy radical $(\text{CCl}_3 \text{OO}\bullet) \rightarrow$ covalently bind to macromolecules \rightarrow LPO, loss of membrane integrity, leakage of enzymes.
- Perturbation of intracellular calcium homeostasis also an integral part of CCl_4 induced toxicity
- CYP2E1 is responsible for low dose activation in humans.
- CYP2E1 inducers can potentiate CCl_4 hepatotoxicity in lab animals and humans



Chloroform



- Use: solvent, anesthetic agent, etc.
- Exposure: 400 ppm 30 min, without complaint 1000 ppm several min lead to dizziness and GI upset
14,000 ppm can cause narcosis
- Toxicity: acute exposure lead to liver and kidney damage and cardiac arrhythmia
- In animals it is an carcinogen
- Cause centrolobular necrosis
- Phosgene (Cl-CO-Cl) is a postulated toxic metabolite.
- Phosgene is reduced via GSH to HCl, and causes toxicity

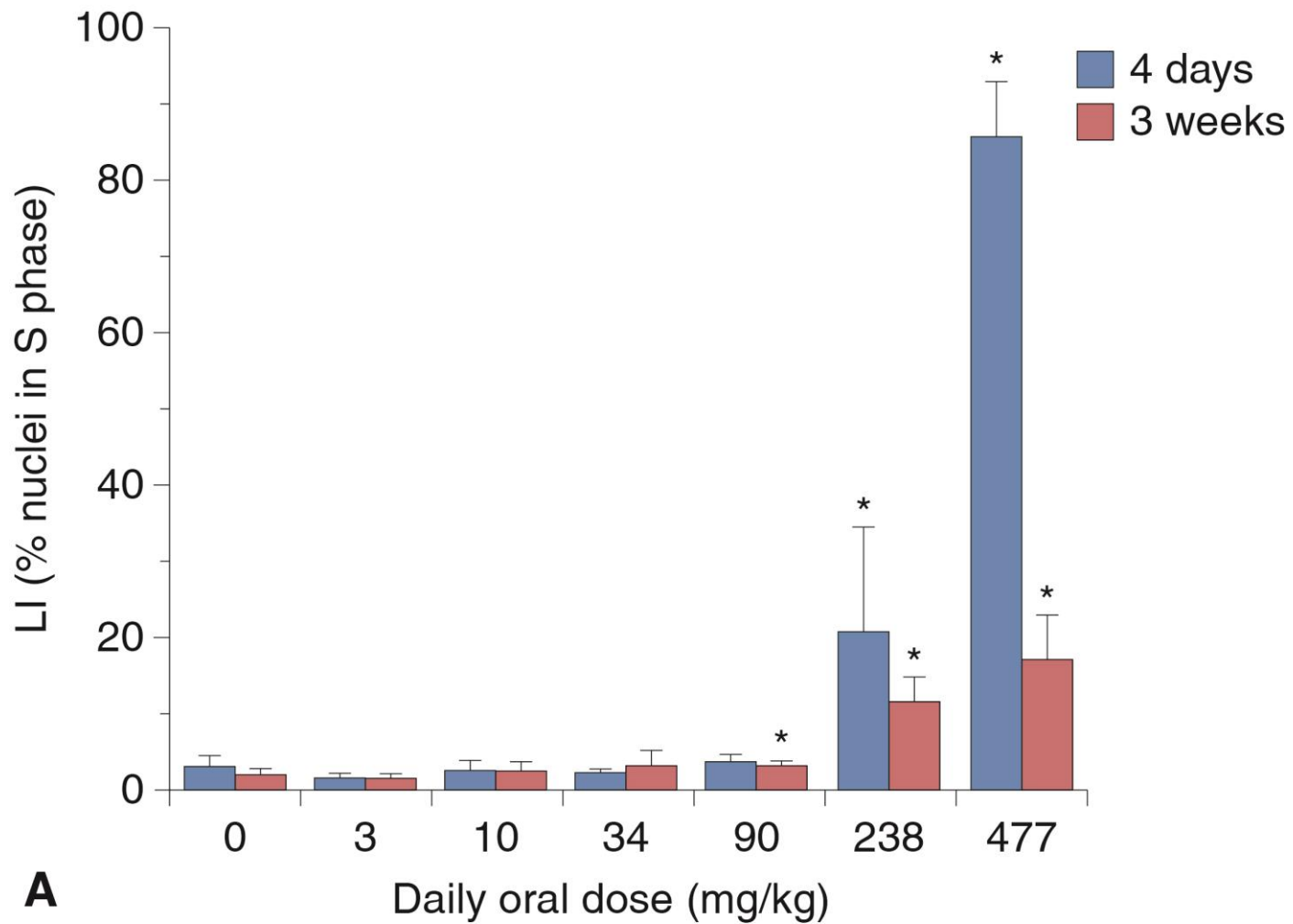


Figure 24-8. Hepatocyte liver LI in female B6C3F1 mice given CHCl₃ orally in corn oil (A) or drinking water (B) for four days or three weeks. The LI is defined as the percent of hepatocyte nuclei positive for 5-bromo-2'-deoxyuridine immunohistochemical staining (ie, percent of cells in the S phase, the period of DNA synthesis during the cell cycle). Values represent the mean \pm SD for five mice. Asterisks (*) denote a significant difference from similarly treated control mice (<0.05). Note that 1800 ppm CHCl₃ in water corresponds to a cumulative uptake of 329 mg/kg per day. (Reproduced with permission from Larson *et al.*, 1994.)

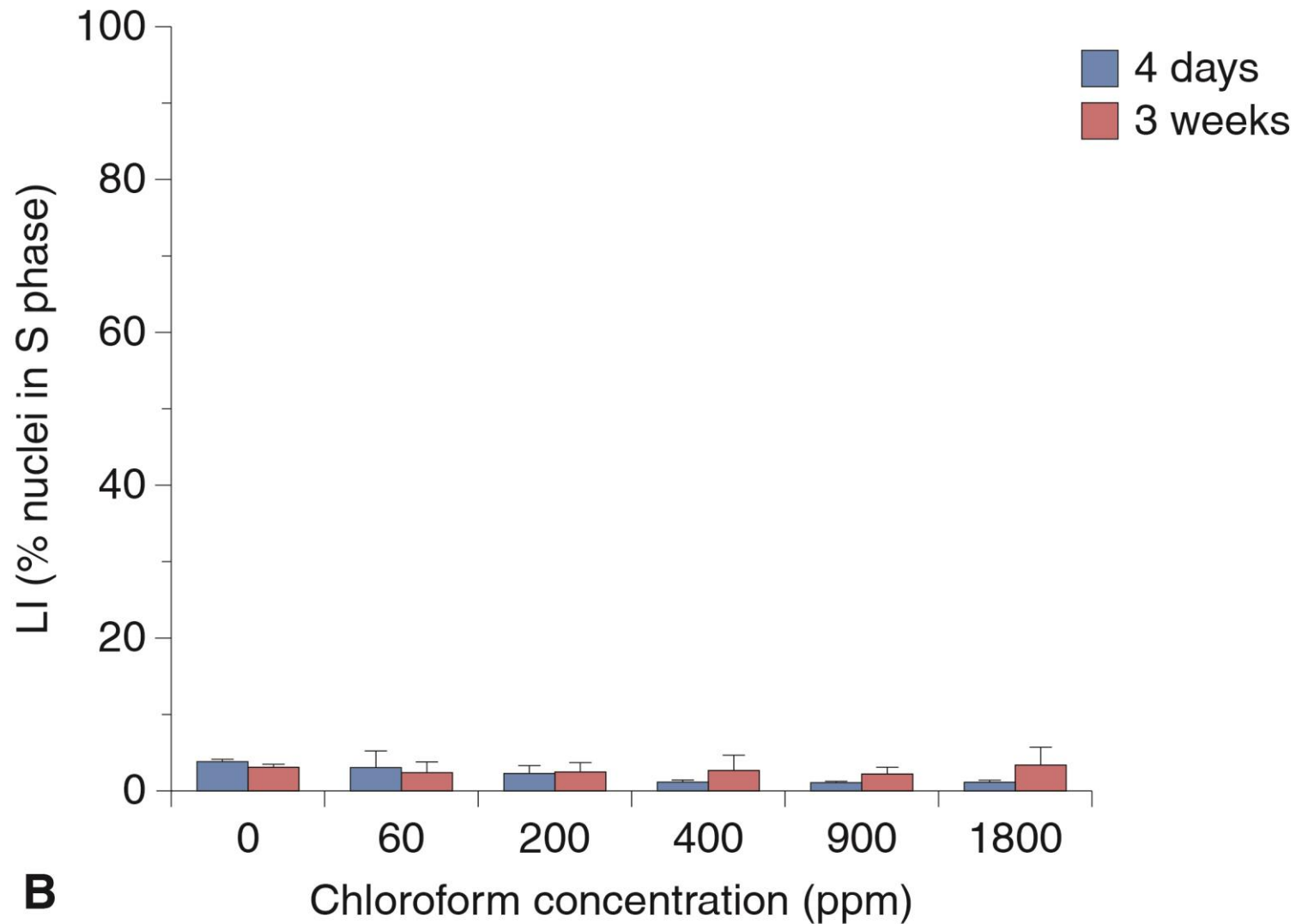


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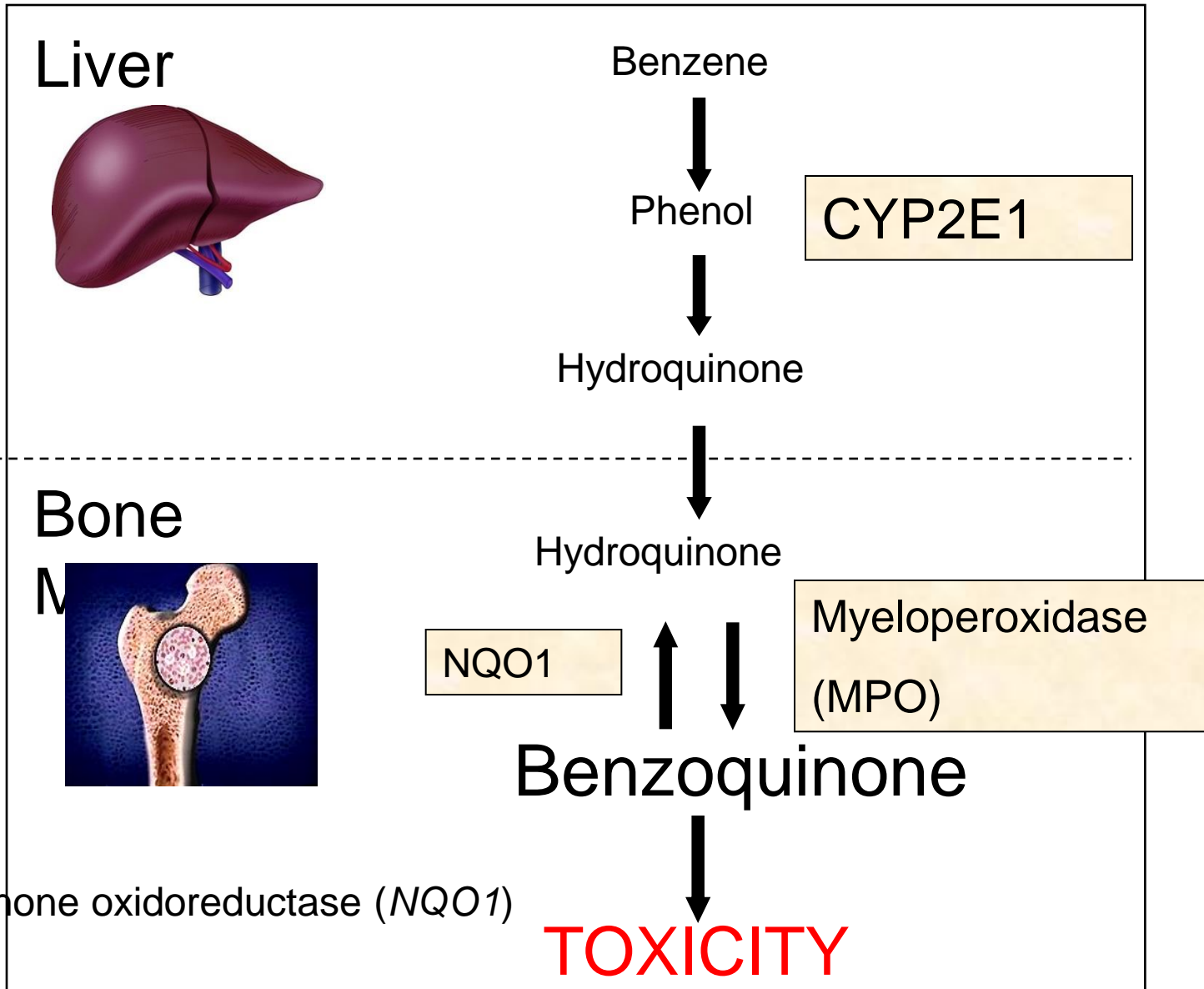
Aromatic Hydrocarbons

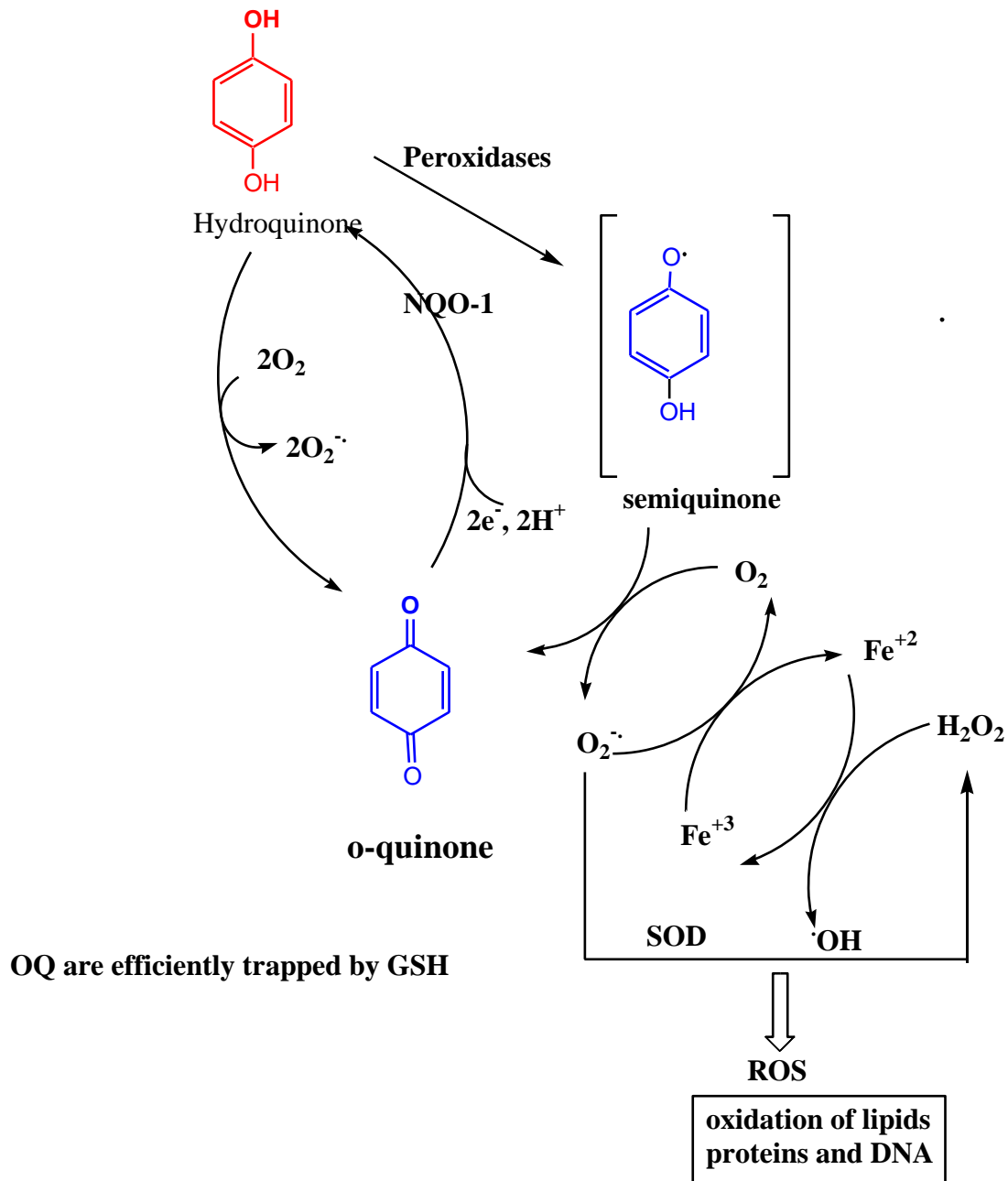
- Benzene, toluene and xylene
- Most common aromatic hydrocarbons found in petroleum
- High volatility
- Low water solubility
- Priority pollutants

Benzene (Aromatic Hydrocarbon)

- Use: solvents, starting material, etc.
- Exposure: inhalation (major in occupational exposure), dermal
- Toxic effect: hematopoietic toxicity, an effect unique to benzene among the simple aromatic hydrocarbons.
- Chronic exposure to low levels in the workplace is associated with blood disorders including aplastic anemia and leukemia.
- Different sensitivity in individuals and animals.

Benzene Metabolism





Myelogenous Hyperplasia in NQO1-/- Mice:



Benzene-Induced Leukemia in NQO1-/- Mice (Hypothetical):

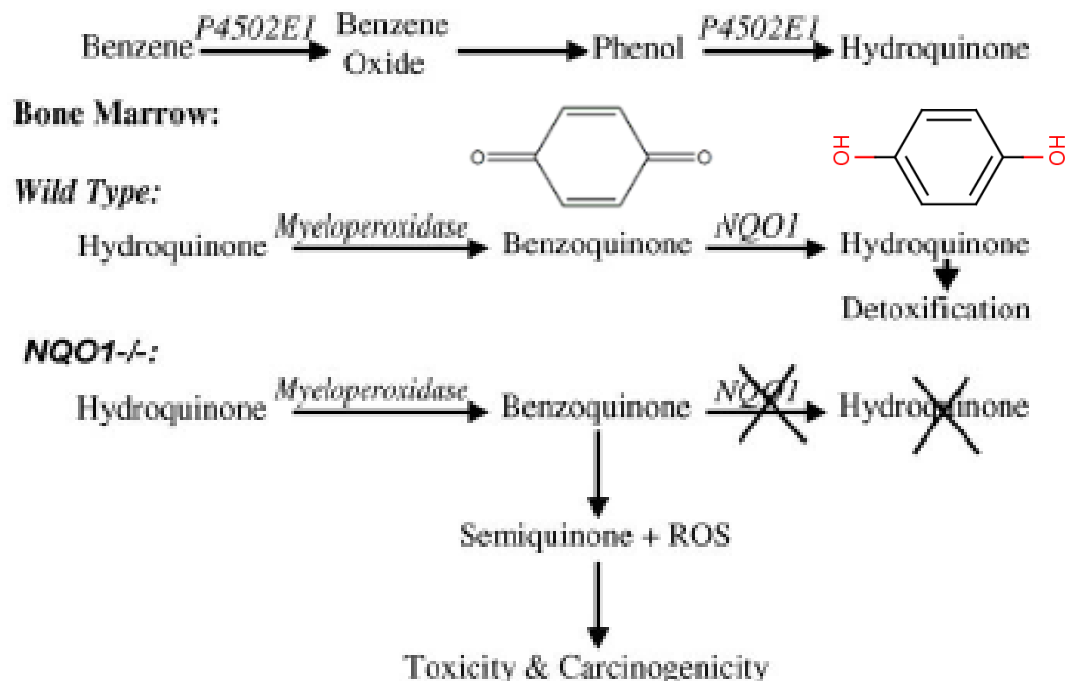


Fig. 5. Model to demonstrate the role of NQO1 in protection against myelogenous hyperplasia and benzene-induced leukemia.

Benzene Toxicity

❖ Mechanism (Chronic)

- Conversion of benzene to reactive metabolite
 - Benzene oxide \Rightarrow Quinones, semiquinones
 - Initial reactions \Rightarrow Liver
 - Final reactions \Rightarrow Bone marrow
- Covalently bind to DNA, RNA and proteins
- ROS

OSHA Standard for Benzene

Time Period

8 hr TWA(Time-Weighed Average)

1937-1940

150 ppm (Benzene in inspired air)

1941-1946

100 ppm

1948-1956

35 ppm

1957-1962

25 ppm

1963-1968

15 ppm

1969-1987

10 ppm

1987-now

1 ppm

Current TLV

0.5 ppm (ACGIH)

(Threshold Limit Value)

(American conference of Governmental Industrial Hygienists)

NIOSH recommendation

0.1 ppm

Air pollution std. for non-cancer effects

0.03 ppm

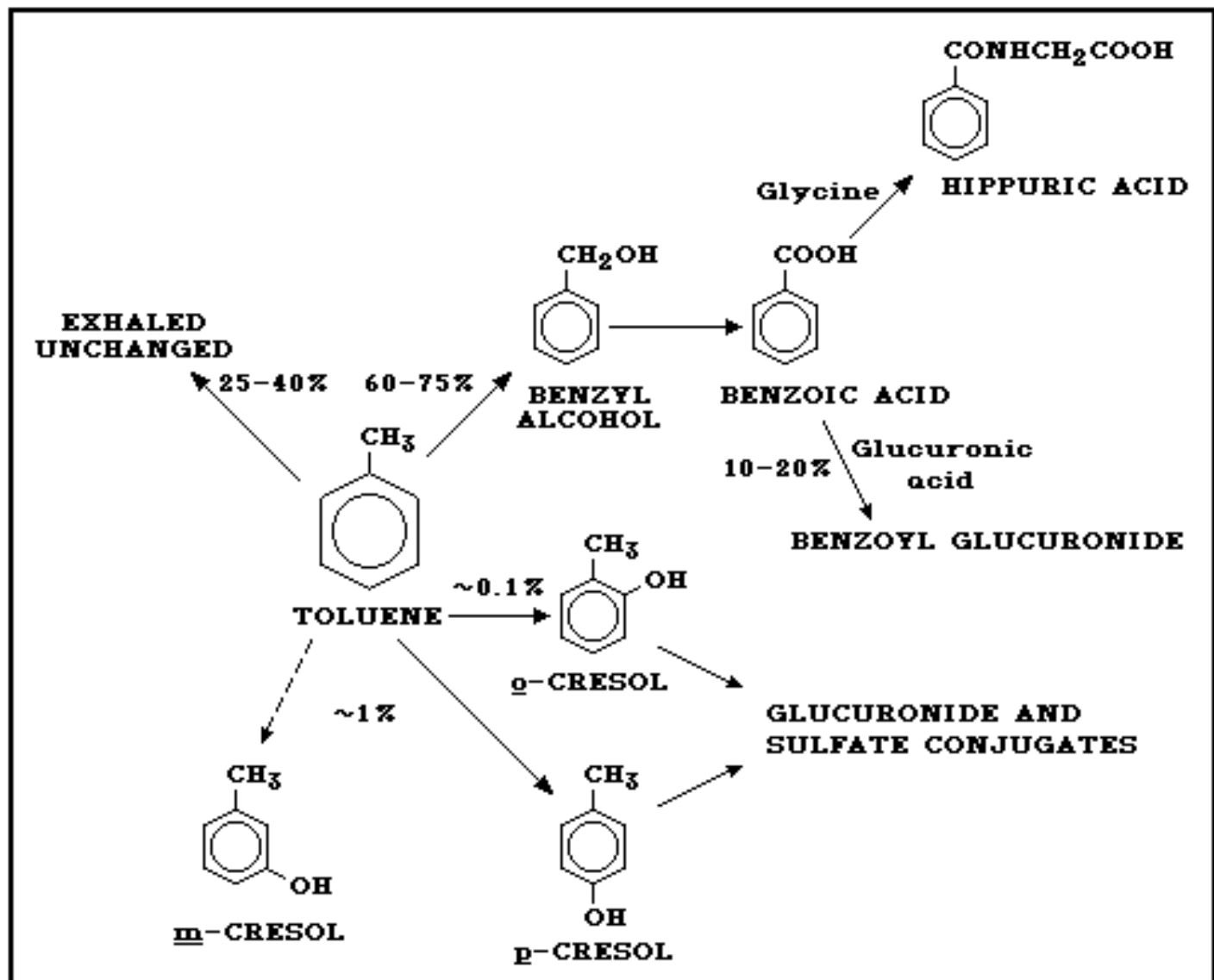
Biomarkers in Chinese Workers

44 controls and 44 workers exposed to high levels of benzene

- **Air monitoring** (5 air samples over 2 weeks)
 - Median benzene exposure (8 hr TWA) - 99 mg/m³ (31 ppm)
- **Biomarkers of Exposure** (1 blood & 1 urine sample)
 - Hb and albumin adducts of benzene oxide & benzoquinone
 - urinary metabolites: unmetabolized benzene, phenol, hydroquinone, catechol, muconic acid
- **Biomarkers of Effect**
 - hematotoxicity (blood cell counts)
 - cytogenetic damage (aneuploidy, translocations)
- **Biomarkers of Susceptibility**
 - P4502E1 and NQO1 (quinone reductase) polymorphisms

Toluene

- Toluene is also called methylbenzene.
- a clear, colourless liquid that is volatile, flammable, and explosive in air.
- is used in:
 - the production of other chemicals;
 - as a solvent carrier in paints, thinners, adhesives, inks, and pharmaceutical products
 - as an additive in cosmetic products.
- Purified toluene usually contains less than 0.01% benzene, but the industrial grade may contain up to 25% benzene.



Metabolism of toluene in human beings and animals.

Toluene and Xylene

❖ **Uses**

- Synthesis of resins, plastics, gasoline additives
- Paints, thinners, glues, cleaning agents

❖ **Exposure**

- Low level
- Industrial workers, gas station attendants

❖ **Toluene more lipophilic than benzene**

Toluene and Xylene Toxicity

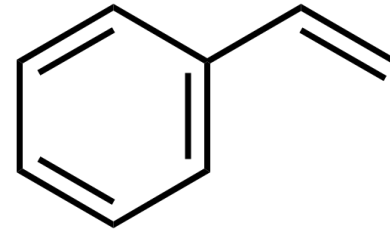
❖ Acute

- Central nervous system
 - Depression, narcosis
- Gastrointestinal disturbances

❖ Chronic

- Impaired cognition, reaction times
- Hearing loss

Styrene



- Used to produce synthetic rubber, latex, reinforced plastics
- Source include tobacco smoke, auto exhaust, and emission from building
- possibly **carcinogenic** to humans
- possibly **reproductive** and **developmental** toxicity

Aliphatic Alcohols

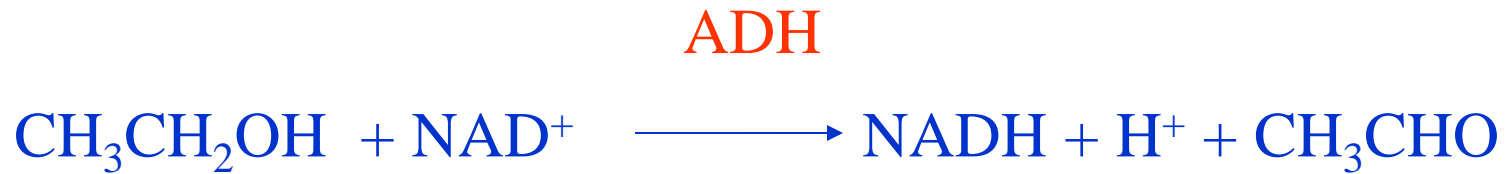
Ethyl Alcohol (Ethanol)

- Use: solvent, drink (social drink), etc.
- Target organ: CNS, blood, fetal alcohol syndrome, liver

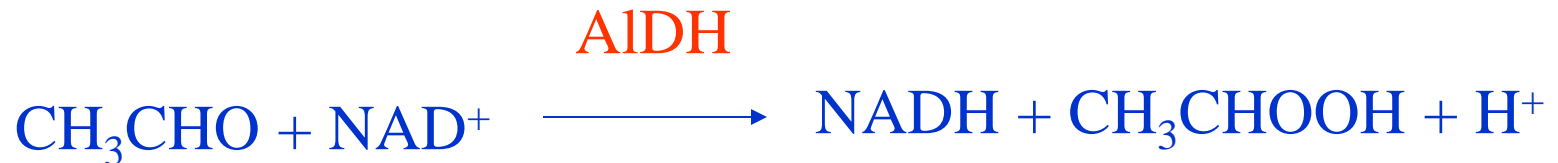
Aliphatic Alcohols

Ethyl Alcohol (Ethanol)

- Ethyl alcohol
 - Solvent, intoxicating beverage
 - Occupational exposure minor
 - Toxic effects
 - CNS depression
 - Disrupt cell membrane
 - Block NMDA receptors
 - Fetal alcohol syndrome
 - Hepatotoxic
 - Metabolism to acetaldehyde
 - ROS
 - Malnutrition



Acetaldehyde



K_m for ethanol 8-10 mM (CYP2E1)

0.2-2 mM (ADH)

EtOH is not toxic at mM levels

Large doses will deprive the GSH in organs.

Much EtOH toxicity in liver may be due to acetaldehyde.

Polymorphism of ADH & ALDH

- Asians-ADH1*2 variant (rapidly metabolize)
50% ALDH2*2 (inactive)
- USA-ADH1*1 (inactive)
- Hispanics –low levels of ADH1*2 ALDH2*2

Alcoholism vs acetaldehyde-related cancer

Alcohol and Cell Injury

- Cellular Effects of EtOH:
 - Induction of cytochrome P-450
 - Fluidization of cellular membranes
 - Alteration in signal transduction pathways
 - Production of free radicals
 - Alteration of cytoskeleton and mitochondrial function

Alcoholic Steatosis

- Pathogenesis:

- Excess NADH produced by EtOH dehydrogenase and acetaldehyde dehydrogenase leads to shunting of substrates away from catabolism to lipid biosynthesis
- Impaired mitochondrial oxidation of lipid
- Impaired assembly and secretion of lipoproteins
- Increased peripheral catabolism of fat

Alcoholic Hepatitis

- Pathogenesis:
 - Causes of steatosis
 - Induction of inflammatory response
 - Direct toxic effect of EtOH and/or metabolites
 - EtOH-induced release of bacterial endotoxin from gut
 - Kupffer cell activation with cytokine release (TNF- α , IL-1, IL-6, etc.)
 - Neutrophil influx in response to cytokines
 - Collagen deposition by hepatic stellate (Ito) cells

Table 24-3

Possible Mechanisms of Ethanol Carcinogenicity

Congeners: additives and contaminants in alcoholic beverages influence carcinogenicity

CYP2E1 induction by ethanol increases metabolic activation of procarcinogens

Ethanol acts as a solvent for carcinogens, enhancing their absorption into tissues of the upper GI tract. Ethanol affects the actions of certain hormones on hormone-sensitive tissues

Immune function is suppressed by alcohol

Absorption and bioavailability of nutrients are reduced by alcohol

SOURCE: Adapted with permission from Ahmed (1995).

Methanol

Use: solvent, propellant, fuel, moonshine whisky, etc.

- Toxicity: species specificity
- rodent relatively resistant (no more than narcosis)
- neurotoxin
- primate, most vulnerable (due to slower conversion of formate to CO_2 via tetrahydrofolate;
- this step, rat \gg 2.5 X in humans) blindness (formate inhibits cytochrome oxidase, and optic nerve cells are low in this enzyme.
- Therefore, optic nerve cells are prone to formate induced toxicity.)

Methanol intoxication

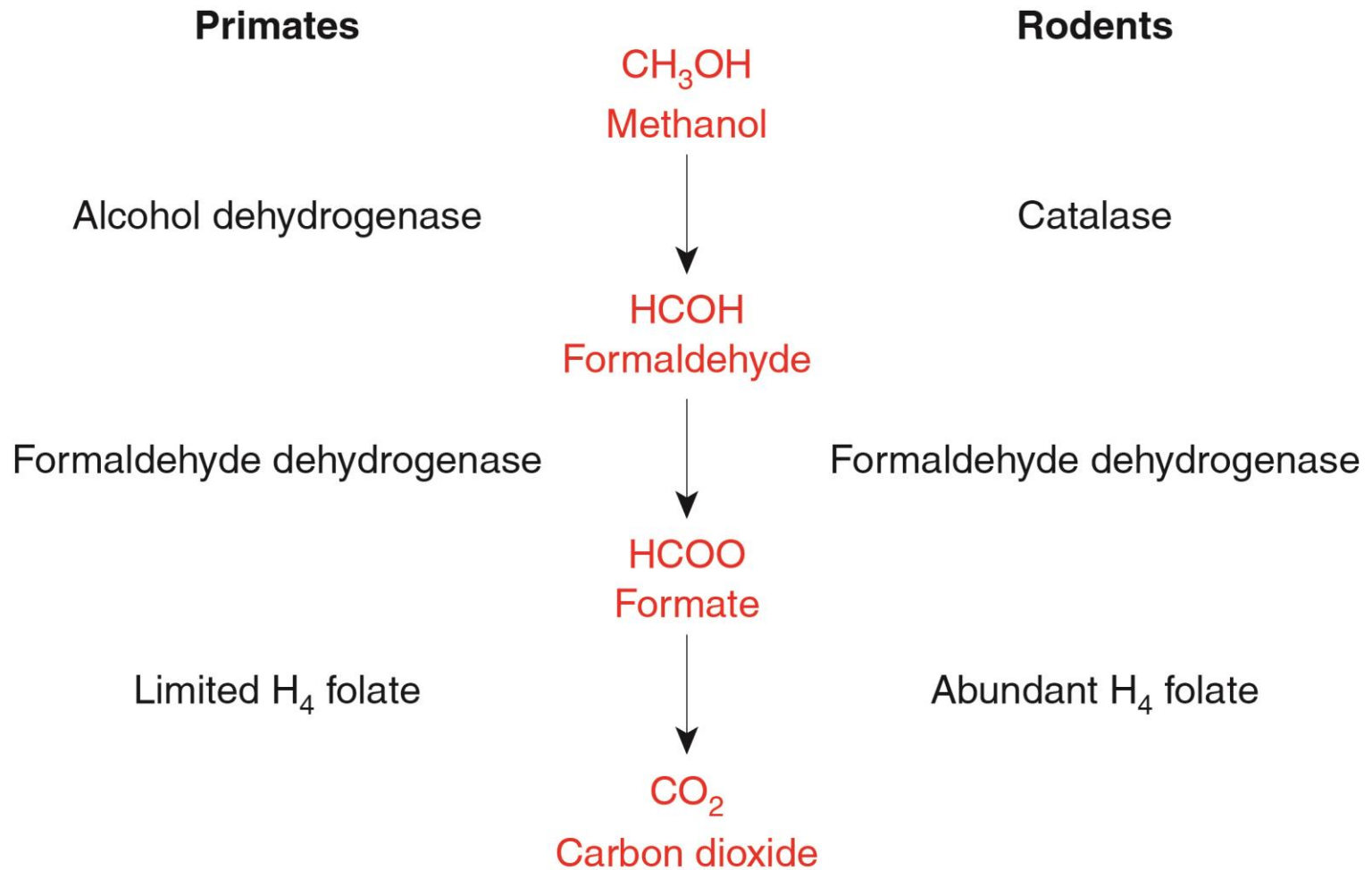
- Neurologic symptoms:
 - headache
 - dizziness
 - amnesia
 - restlessness
 - acute mania
 - lethargy
 - confusion
 - coma
 - convulsions

OPHTHALMOLOGIC TOXICITY

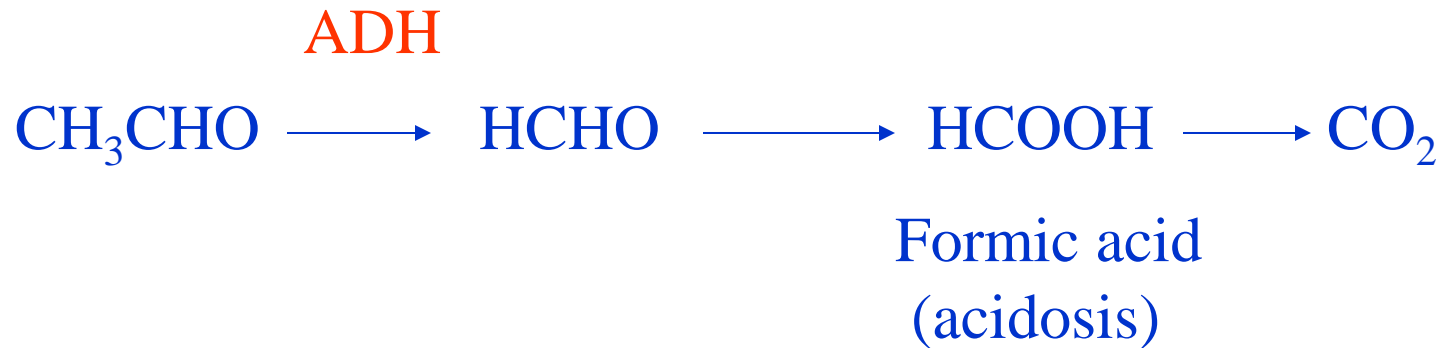
- blurred vision
- eye pain
- partial or complete loss of vision
- visual hallucinations (bright lights, snowstorm, dancing spots, flashes)

OPHTHALMOLOGIC TOXICITY

- Occur when serum pH drops below 7.2
- Low pH → intracellular concentration of formate↑
- Improvement of vision with correction of acidosis, because formate moves out of the cell
- Formate is an inhibitor of cytochrome oxidase, which could inhibit ATP formation in the optic nerve leading to a stasis of axoplasmic flow, axonal swelling, optic disc edema and finally loss of visual function



• **FIGURE 24-10. Scheme for the metabolism of methanol.**



Thus, ethanol, competitive inhibitor of ADH;
4-methylpyrazole, a ADH inhibitor; and sodium bicarbonate,
to correct acidosis; have been successfully employed
in methanol toxicity.

Ethylene Glycol (Glycol)

(1,2-dihydroxyethane)

Use: heat exchanger, antifreeze formulation,
hydraulic fluid, etc.

- Toxicity: p.o., human is more vulnerable than rodent in toxicity
can lead to kidney damage in human

EG--ADH--> glycolaldehyde, and further to
glycolic acid (lead to acidosis) -----> oxalate
(cause renal toxicity)

Thus, 4-methylpyrazole, a ADH inhibitor, can
serve as an antidote for Ethylene Glycol
induced toxicity. (the same as methaol)

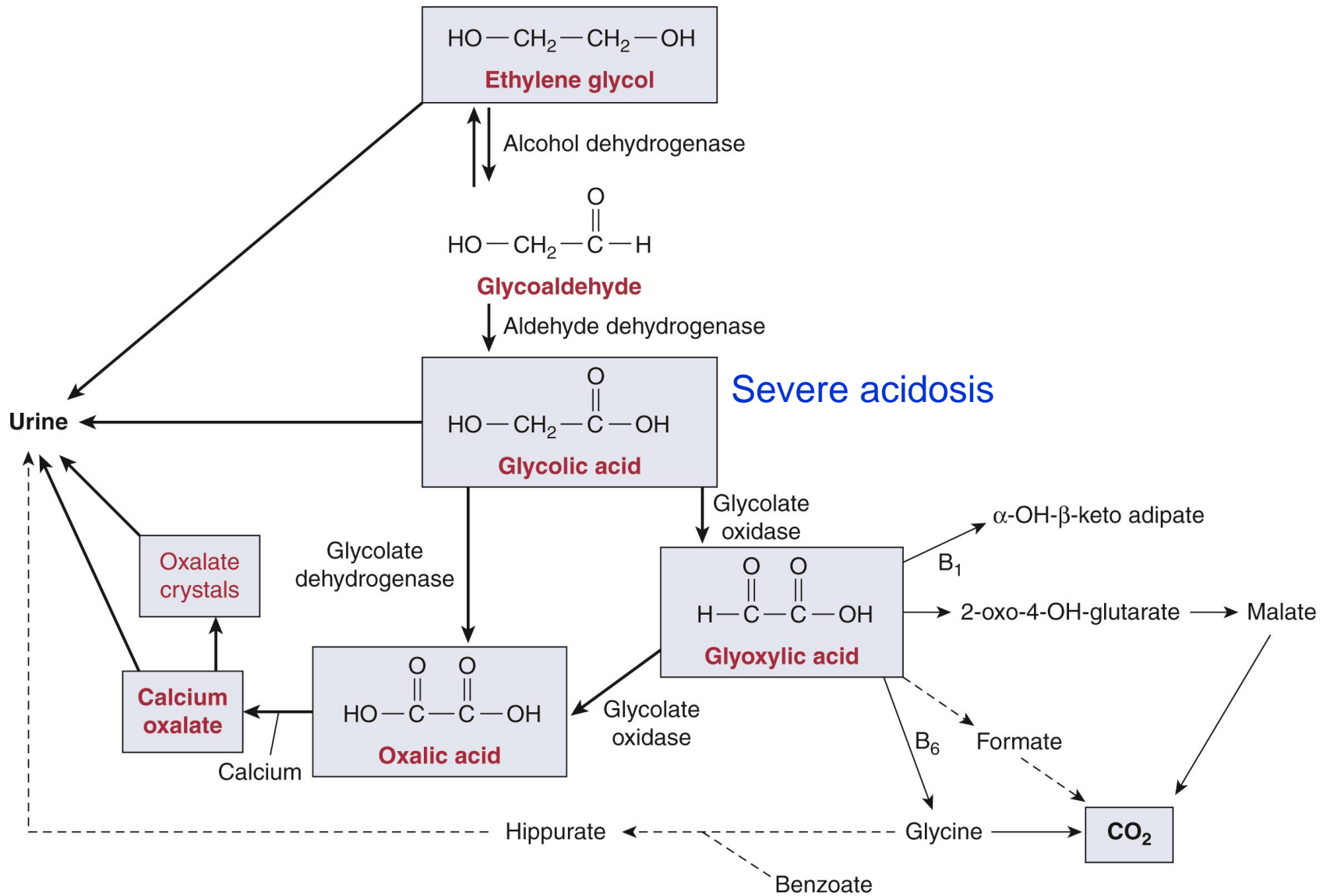


Fig. 24-11 Metabolic scheme for ethylene glycol in animals.

Diethylene Glycol (DEG)

- Elixir Sulfanilamide accident, lead to 105 death, in US in 1937
- DEG-contaminated propylene glycol or glycerin in pharmaceutical preparations has caused many fatalities.
- LD50 is 1.34 ml/kg, and renal failure is the hallmark findings in these cases
- DEG/EG, well absorbed from the GI, distributed well in body water and organs
- Metabolized by ADH and ALDH, the identity of the cause of renal toxicity is yet to be identified.
- ADH inhibitors can be used as the antidote for DEG

Sulfanilamide Disaster

sulfonamide antibacterial agent

FDA Consumer magazine

June 1981 Issue

Taste of Raspberries, Taste of Death The 1937 Elixir Sulfanilamide Incident

By the 1930s it was widely recognized that the Food and Drugs Act of 1906 was obsolete, but bitter disagreement arose as to what should replace it. By 1937 most of the arguments had been resolved but Congressional action was stalled. Then came a shocking development--the deaths of more than 100 people after using a drug that was clearly unsafe. The incident hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products.

Propylene Glycol (PG)

- PG is listed as a GRAS, it is widely used in cosmetics, processed food and tobacco products.
- Low acute and chronic toxicity
- Readily absorbed from GI, distributed throughout total body water
- PG → ADH → lactaldehyde (55%) → lactic acid (acidosis, following large PG, rare) → lactate (gluconeogenesis, detoxified);
- 45% excreted unchanged in urine. Short $T_{1/2}$, 2-4 hr in human;
- Dipropylene glycol and tripropylene glycol have low toxic potential just like the structural similar PG.

Glycol Ethers

- Solvent for surface coating, vanishes, latex painting
- mainly metabolized to alkoxyacetic acids
 - 2-Methoxyethanol (ME) $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$
 - 2-Ethoxyethanol (2-EE)
 - 2-Butoxyethanol (2-BE)
- Toxic metabolite, methoxyacetic acid (MAA)
- Increase progesterone production

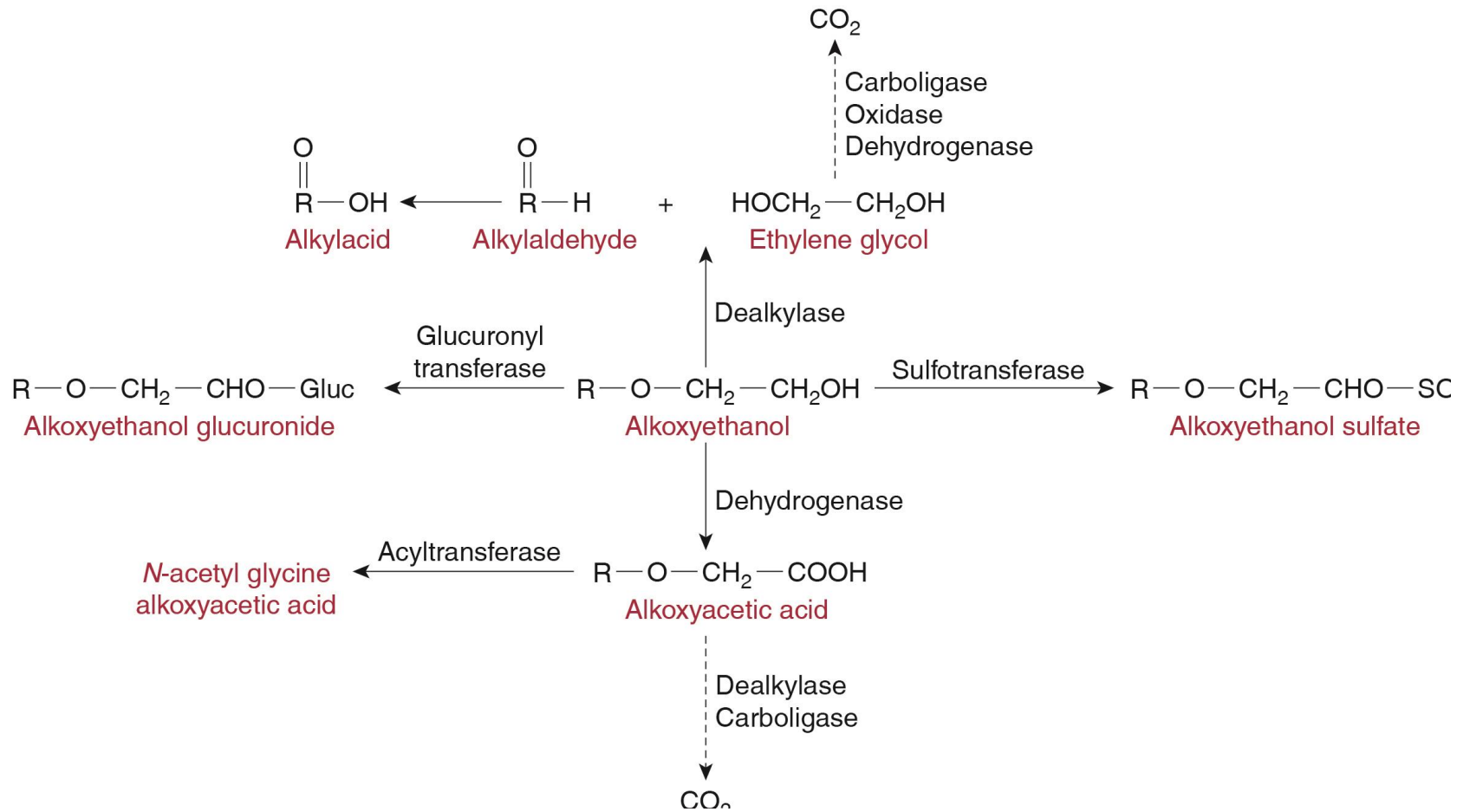
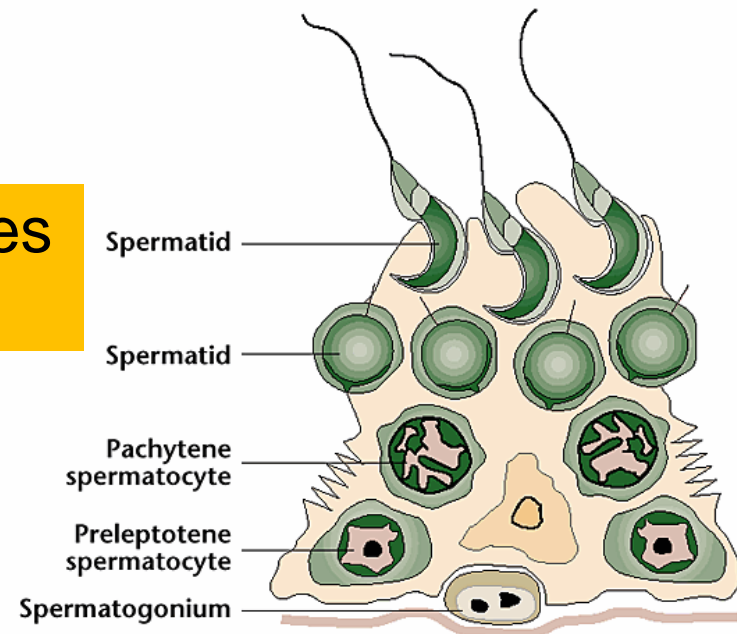


Figure 24-12 Metabolism of glycol ethers.

Glycol ether

- Reproductive toxicity
 - Female :spontaneous abortion, menstrual disturbance, and subfertility
 - Increased progesterone production
 - Male: spermatotoxicity (<10 ppm)
 - seminiferous tubule atrophy

-induction of apoptosis in spermatocytes
- affects Sertoli cells



Glycol ether

- **Developmental toxicity**
malformations –cleft lip, neural tube defect
-possibly by altering embryonic pH
- **Hematotoxicity**
2-BE butyl Hemolytic to RBC (Female is more sensitive , thrombosis, less efficient in elimination)
- **Immunotoxicity**
2-methoxyacetaldehyde as ultimate toxicant
Reduced and splenic thymus weight
Deplete immature thymocyte
- **Carcinogenicity**
Kidney and liver tumors

Methyl tertiary-butyl ether (MTBE)

- Oxygenator in fuel additive (15%)
- groundwater contamination

In animals cancer bioassay

- lymphomas and leukemias
- Kidney and testicular tumors
- Liver adenoma

Table 24-4**Summary Results of MTBE Cancer Bioassays**

AUTHORS	ANIMAL STRAIN/SPECIES	EXPOSURE ROUTE	POSITIVE RESULTS
Chun <i>et al.</i> (1992)	Fischer 344 rats	Inhalation	Kidney and testicular tumors (males)
Burleigh-Flayer <i>et al.</i> (1992)	CD-1 mice	Inhalation	Liver adenomas (females)
Belpoggi <i>et al.</i> (1995)	Sprague–Dawley rats	Oral	Testicular tumors (males) Leukemia + lymphoma (females)

Carbon disulfide CS₂

- Production of rayon fiber, cellophane and CCl₄
- Metabolite of dithiocarbamate and disulfiram
- Neurotoxicity
 - Enhance noise-induced hearing loss
 - Encephalopathy
 - Axonal degeneration
 - Covalent protein cross-linking with neurofilament
- Cardiovascular disease
 - Elevation of blood cholesterol
 - Atherosclerosis
- Reproductive effects
 - decreased sperm count and menstrual disturbances

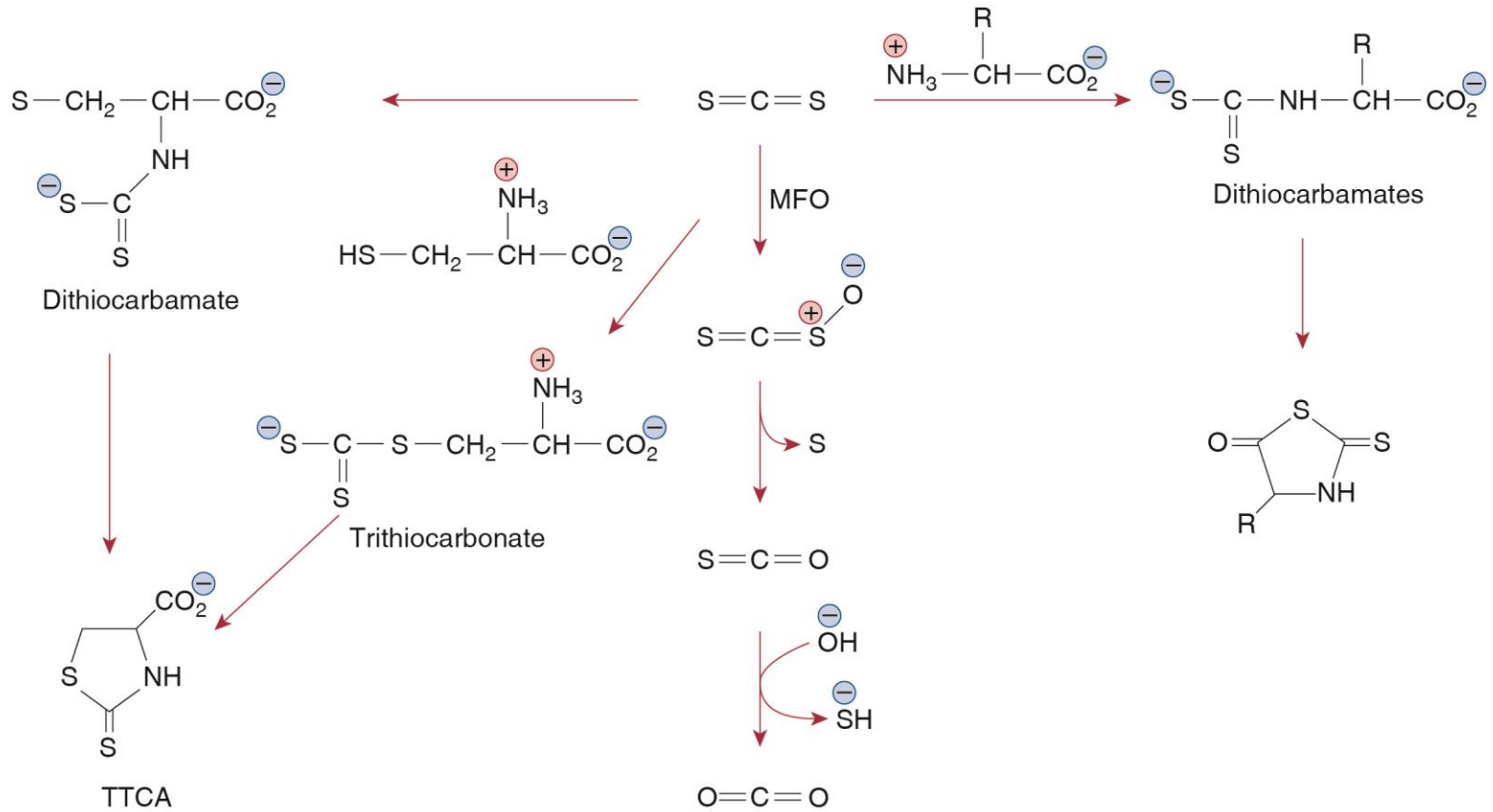
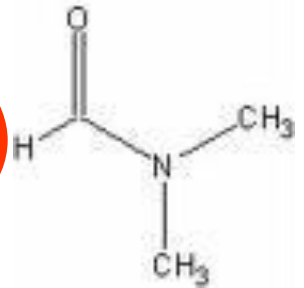


Figure 24-13 Metabolism of carbon disulfide.

DMF (Dimethylformamide)



- Use: solvent; in the production of acrylic resins and leathers
- 10 ppm--permissible exposure limit
- Liver damage; in unprotected worker, skin absorption is more important than inhalation.
- HBV carrier or increased BMI had synergistic effects with DMF in causing liver abnormalities (abnormal LFTs and clinical chronic liver diseases).