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NITRO AND AMINE AROMATIC DERIVATIVES

Set of compounds possessing one or more ($-NH_2$) or ($-NO_2$) groups on simple or complex aromatic hydrocarbon structures: benzene, toluene, xylene, naphthalene, anthracene…

Very reactive and toxic (carcinogenic, irritant and sensitizing, methemoglobin-forming), widely used especially in occupational settings.

Used in the manufacture of food dyes (tartrazine) and industrial dyes, azo dyes, paints, varnishes, plastics, rubber, explosives (TNT), solvents in chemistry… PPDA is associated in the Middle East and India with henna (to intensify coloration).

- **Amino derivatives**

Monocyclic: Aniline, o-toluidine, acetanilide

Polycyclic: Benzidine, xenylamine, β-naphthylamine, diaminodiphenylmethane = methylene dianiline (MDA), methylene bis orthochloroaniline (MBOCA or MOCA)

- **Physicochemical properties**

Solids or liquids, liposoluble, unpleasant odor, poorly volatile [except aniline and homologues], easily adsorbed on environmental supports: walls, machines, surfaces, and work clothes.

Some products oxidize in light: benzidine and aniline (brown coloration).

Pyrolysis releases caustic gases (nitrous vapors, ammonia) and toxic gases (CO, HCN).

- **Nitro derivatives**

Benzene derivatives: nitrobenzene
Toluene derivatives: nitrotoluene
Phenol derivatives: nitrophenol

Physicochemical properties: oily volatile liquids (nitrobenzene) or solids (DNT, TNT), poorly or not water-soluble, highly liposoluble (+++ skin, CNS). High affinity for proteins → sensitization reactions.

- **Toxicokinetics**

Absorption

- **Cutaneous:** +++ in occupational settings, enhanced by sweating and organic solvents (nitrobenzene, DNT, TNT, aniline)

- **Pulmonary:** minor due to low volatility (≈80% absorbed for nitrobenzene)
- **Digestive:** ingestion of dust or contaminated hands

Distribution

Rapid and wide distribution via blood, especially to adipose tissue.
Most amines cross the placental barrier.

Elimination

Water-soluble metabolites are excreted in urine as sulfate and glucuronide conjugates.
Some eliminated in feces.
A variable fraction is excreted unchanged.

- **Metabolism (Phase I reactions)**

Amino derivatives

- N-acetylation (hepatic N-acetyltransferase, genetic polymorphism):
  - Fast acetylators: N-acetylation + aromatic hydroxylation
  - Slow acetylators: aromatic hydroxylation
- N-hydroxylation: CYP450, catalases, peroxidases
- Aromatic oxidation: CYP450

Nitro derivatives

- Nitroreduction: via glutathione reductase (RBCs and liver) → nitrites
- Followed by oxidation via CYP450
- Nitrobenzene half-life ≈ 1 week
- TNT metabolites give orange/red urine

- **Phase II reactions**

Sulfation and glucuronidation

Note: Nitrobenzene and aniline produce the same final metabolite (p-aminophenol) via phenylhydroxylamine.

- **Mechanisms of toxic action**

1. Hematotoxicity

- Methemoglobinemia ($Fe^{2+} \rightarrow Fe^{3+}$)
- Aplastic anemia: TNT, some hair dyes

2. Hepatotoxicity

- Free radicals production, membrane peroxidation (+++ TNT)
- Toxic derivatives: nitrobenzene, dinitrobenzene, MDA

3. Nephrotoxicity

- Polycystic kidneys: diphenylamine
- Tubular necrosis: p-phenylenediamine
- GSH conjugation toxicity

4. Cardiotoxicity

- Toxic myocarditis (PPDA)
- Cardiomyopathy (MDA)

5. Immunotoxicity

Autoantibodies, irritation, sensitization (+++ hair dyes)

6. Reprotoxicity

Animal studies:

- Testicular atrophy (DNT)
- Inhibition of spermatogenesis

7. Mutagenesis

- Cross placenta
- Fetal methemoglobinemia
- Congenital malformations

8. Carcinogenesis

- Some aromatic amines are procarcinogens
- Group 1 (IARC): β-naphthylamine, benzidine

- **Acute and chronic toxicity**

Mostly chronic occupational exposure

- Skin: dermatitis, eczema, urticaria
- Respiratory: asthma, rhinitis
- Blood: aplastic anemia (TNT)
- General: fatigue, headache, nausea
- PPDA: rhabdomyolysis

Reprotoxicity: crosses placenta, miscarriages, infertility

- **Treatment**
- Decontamination (skin, clothing removal)
- Oxygen therapy
- Antidote: methylene blue, vitamin C, N-acetylcysteine
- Blood transfusion if severe

- **Analysis**

1. Exposure markers

Detection of toxic substance

- **Aniline:** distillation + bromine → white precipitate
- Mauveine reaction → purple color
- **Nitrobenzene:** almond odor, must be reduced to aniline

Urinary metabolites

p-aminophenol detection: (interference with paracetamol)

- Qualitative: blue coloration
- Quantitative: violet coloration

2. Effect markers

- Methemoglobinemia (<2%)
- Sulfhemoglobin
- Heinz bodies
- Hemoglobin adducts
- DNA adducts
- Hematuria
- Urinary cytology

3. Medical tests

Kidney function, skin exam, cyanosis