Appendix D. Chemicals Known to Cause Local and Systemic Effects

Chemicals Causing Local Effects

Note: The lists provided here are for illustrative purposes, and are not intended to be comprehensive.

Eye Effects Chemical properties/considerations relevant to eye effects include:

- Acidity
- Basicity/alkalinity
- Chemical burns (isocyanates, mustards)
- Interaction with proteins (metal salt deposition, quinones, etc.)
- Mechanical abrasions
- Solvent effects
- Surfactancy

Toxicity/irritation/corrosion to the Skin Irritation Consider:

- Acidity
- Basicity/alkalinity
- Chemical burns
- Lipophilicity
- Mechanical abrasions
- Solvent effects
- Surfactancy

Dermal/Contact Sensitization Consider:

- Electrophilic or nucleophilic groups that could haptenize protein through covalent modification, for example: Aldehydes, ketone, codicils, quinones, other conjugated, unsaturated functional groups, epoxy groups.
- Structural similarities to classes of contact allergens (parent chemical) or impurities belonging to known classes of contact allergens, for example: Antibiotics, Chlorinated antiseptics, Dyes (azo, amine), Formaldehyde releasers, Mercurials, Metals (nickel, chromium, cobalt), Natural products (plant rosins, balsams), and Preservatives.

Photo-toxicity and Photosensitization Consider:

- Chemical structures that are UV absorbing (such as highly conjugated aromatics), for example: Furocoumarins, Polycyclic aromatics, and Porphyrins.
- Structural similarity to systemic agents that cause photoreactions, for example: Non-steroidal anti-inflammatory agents, Sulfonamides, and Tetracyclines.

Local Toxicity to the Gastrointestinal Mucosa Consider:

- Local effects in the G.I. tract will be mediated by solubility, irritation, corrosivity, and local metabolism.
- For irritant and corrosive effects, consider the factors elaborated above for eye and skin.
- For metabolic activation, consider the factors elaborated upon below.

Toxicity to the Respiratory System Consider:

- Irritants that may cause asthma, a disease characterized by (1) airway obstruction that is reversible, (2) airway inflammation, and (3) airway hyperresponsiveness. Classes of compounds that can cause asthma include: Aldehydes, Anhydrides, Isocyanates, and Metals.
- Irritant materials may cause upper airway reactivity (e.g., bronchitis)

- Water soluble, reactive materials (e.g., formaldehyde) may cause nasal or upper airway toxicity an/or irritation
- Particulates and fibers of a particle size that results in deep lung deposition may potentially cause chronic lung injury. Such injury is mediated by inflammatory responses, lung overload, and sustained cell turnover. Examples include: Fibers with a certain length to width ratio (e.g., asbestos), and Particulate dusts (silica, clays, talcs).
- Other classes of respiratory toxicants include: Ammonia and volatile, basic amines, Isocyanates, Metal carbides, Metal oxides, Metal dusts and fumes, Nitrogen oxides, Surfactants, and Transition metals, arsenic, beryllium.

Chemicals Causing Systemic Effects

Systemic Toxicity Mediated by Intrinsic Chemical Reactivity or Biotransformation to Reactive Toxicants
Systemic organ toxicity is frequently mediated by the presence of reactive functional groups (whether present in the parent compound or introduced via biotransformation). Reactive compounds or metabolites may exert toxic effects by modification of cellular macromolecules (structural and functional cellular proteins, DNA). This can result in destruction or dysfunction of the target molecules. In addition, covalent modification of target molecules which are covalently modified may render them "foreign" or antigenic (capable of eliciting an immune response). DNA-reactive chemicals have genotoxic potential.

Toxicity Caused by Electrophiles Structural "Red flags" for chemicals containing electrophilic centers include:

- Acyl halides
- Aryl halides
- Azides, – and S-mustards
- Epoxides, strained rings (e.g., sultones)
- Nitroso groups
- Polarized, conjugated double bonds (e.g., quinones, a, ß unsaturated ketones, esters, nitriles)

Functional groups which undergo metabolism to electrophilic centers include:

- Alkyl esters of sulfonic or phosphonic acids
- Aromatic compounds with functional groups that can yield benzylic, aryl carbonium or Nitronium ions
- Aromatic nitro, azo or amine groups
- Conjugated aromatics that undergo epoxidation

Toxicity Caused by Free Radical Formation Compounds which can accept or lose electrons can mediate free radical formation through redox cycling. Structural "Red flags" include:

- Aminophenols
- Catechols, quinines, hydroquinones
- Metal complexes (iron and chromium)
- Peroxides
- Phenothiazines
- Polycyclic aromatics

Systemic Toxicity Associated with Receptor-Mediated Mechanisms Some compounds exert toxicity through substitution for known or unknown tissue receptor ligands. Classes of compounds that could exert toxicity though such mechanisms include:

- Environmental estrogens (putative hormone receptor ligands)
- Fibrates, phthalates (peroxisome proliferator receptor agonists)
- Polychlorinated aromatics (Ah receptor ligands)
- Retinoids (retinoic acid receptor ligands)

Target Organ and Functional Toxicity
Toxicity to the Liver As the primary organ of biotransformation, the liver is susceptible to toxicity mediated by chemical reactivity, as described above. Other agents with toxicity to the liver include:

- Chlorinated hydrocarbons
- Metals, etc.

Toxicity to the Kidney Classes of compounds that are potential nephrotoxins include:

- Amines
- Certain classes of systemic drugs
- Halogenated aliphatic hydrocarbons
- Heavy metals
- Herbicides
- Insoluble salts that precipitate in the kidney (e.g., calcium complexes)
- Mycotoxins
- Organic solvents

Toxicity to the Respiratory System Effects of inhaled respiratory toxicants were addressed above.

Neurotoxicity Chemicals/Classes of compounds which may manifest neurotoxicity include:

- Acids and thioacids
- Arylamide and related substances
- Acrylamides
- Alcohols
- Aliphatic halogenated hydrocarbons
- Alkanes
- Aromatic hydrocarbons
- Carbon disulfide and organic sulfur -containing compounds
- Carbon monoxide
- Catecholamines
- Certain classes of systemic drugs
- Chlorinated solvents
- Cyanide
- Cyclic halogenated hydrocarbons
- Environmental estrogens
- Ethylene oxide
- Gamma-diketones
- Inorganic nitrogenous compounds
- Isocyanates
- Ketones
- Lead
- Mercury compounds
- Metals and metalloids other than mercury and lead
- Nitriles
- Organic nitrogens
- Organophosphates and Organophosphorus compounds
- Organotins
- Certain Pesticides
- Phenols and related substances
- Phosphorus
- Protein cross-linking agents
- Psychoactive drugs
- Pyridines (e.g., MPTP)

Immunotoxicity (Immunosuppression / Autoimmunity) Classes of compounds which may manifest immunotoxicity include:

- Heavy metals
- Organic solvents
- Certain Pesticides
- Polyhalogenated aromatic hydrocarbons

Genetic Toxicity Classes of compounds that manifest genetic toxicity are often electrophilic agents capable of modifying DNA. Such agents may act as gene mutagens, clastogens or aneugens. These are compounds that can insert themselves into DNA. Other examples are free radical generators or chemicals that induce oxidative damage may also act as gene mutagens, clastogens or aneugens. Chemicals with mutagenic structural alerts include:

- Acrylates and methacrylates
- Aliphatic or aromatic nitro groups
- Aliphatic or aromatic epoxides
- Alkyl hydrazines
- Alkyl esters of phosphonic or sulfonic acids
- Alkyl aldehydes
- Aromatic ring N-oxides
- Aromatic azo groups
- Aromatic and aliphatic aziridynyl derivatives
- Aromatic alkyl amino or dialkyl amino groups
- Aromatic and aliphatic substituted alkyl halides
- Aromatic amines and N-hydroesters of aromatic amines
- Carbamates
- Chloramines
- Halomethanes
- Monohaloalkanes
- Multiple-ring systems
- N-methylol derivatives
- Nitrogen and sulfur mustards
- Nitroso compounds
- Propiolactones and propiosultones
- Vinyls and vinyl sulfones

Reproductive Toxicity Classes of compounds which may manifest reproductive toxicity include:

- Alcohols
- Alkylating agents
- Chlorinated hydrocarbons
- Certain Fungicides
- Certain Herbicides
- Hydrazines
- Certain Insecticides
- Metals and trace elements
- Nonylphenols
- Plastic monomers
- Solvents (e.g., glycol ethers, benzene, xylenes)
- Steroids or steroid receptor ligands

Developmental Toxicity Classes of compounds which may manifest developmental toxicity include:

- Acrylates
- Androgenic chemicals
- Anilines

- Boron containing compounds
- Chelators
- Chlorobiphenyls
- Compounds which have potential for mutagenicity and oncogenicity
- Epoxides
- Lead
- Lithium
- Mercury
- Nitrogen Heterocyclic compounds
- Phthalates
- Retinoids
- Salicylates
- Short-chain branched carboxylic acid (e.g., valproic acid)
- Small benzenes
- Synthetic steroids (e.g., diethylstibesterol)
- Triazines
- Vinyl groups

Blood Toxicity Classes of compounds which may manifest developmental toxicity include:

- Simple aromatic amines and azo dyes that undergo azo reduction to release aromatic amines