Occupational toxicology – Part 5

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SITE SPECIFIC TOXICITIES

A. Immunotoxicity
B. Haematotoxicity
C. Pulmonotoxicity
D. Cardiotoxicity
E. Hepatotoxicity
F. NEPHROTOXICITY
G. NEUROTOXICITY
H. REPRODUCTIVE TOXICITY
I. DERMATOTOXICITY

F. NEPHROTOXICITY:

The diagnosis of renal disease of occupational origin is rarely considered clinically, and the etiology of renal failure in such cases is seldom fully elucidated. The true incidence of renal failure secondary to occupational exposure is unknown. Serial measurement of urea/creatinine is inadequate, because the test result does not become abnormal until significant renal damage has occurred.

Newer tests of renal (tubular) injury:

– high molecular weight proteinuria (albuminuria, ferritin).
– low molecular weight proteinuria (β-2 microglobulin, retinol-binding protein).

The predictive value of the above has however not been validated.

Renal disease associated with occupational exposure:

1. Acute renal failure – urine sediment = acute tubular necrosis.
2. Chronic renal disease associated with chronic interstitial nephritis.

The kidneys are especially vulnerable to occupational exposure because they handle 20% of cardiac output:

– Glomerular filtration = 125 mL/min (180 L/day).
– Filtrate largely gets reabsorbed in the proximal tubuli, with concentration and acidification occurring in the distal tubuli.
– Toxins are therefore highly concentrated and may exist in ionic forms (filtrate pH changes).

Acute renal dysfunction:

Symptoms: acute tubular necrosis (acute renal failure) acute interstitial nephritis, proteinuria and haematuria.

Causes of acute renal disease:

– Heavy metals e.g. cadmium, mercury, chromium, vanadium.
– Organic solvents e.g. halogenated hydrocarbons (carbon tetrachloride), non-halogenated hydrocarbons (dioxane, toluene, ethylene glycol, phenol, dinitro-o-cresol, phenol, pentachlorophenol).
– Pesticides (carbaryl, organic mercurials).
– Arsine gas.
– Yellow phosphorus.

Chronic renal dysfunction:

Prototypic renal disease associated with environmental exposure is Balkan endemic nephropathy (BAN), identified in the late 1950s. BEN is an interstitial nephropathy associated with urinary tract tumours. Papillary transitional cell cancer is seen in 30–40% of patients with BEN.

Causes of chronic renal disease:

– Lead: chronic renal insufficiency with hypertension and gout in children, interstitial fibrosis, 1–2 g proteinuria, nephrosclerosis.
– Cadmium (substantial accumulation in smokers): Fanconi's syndrome, nephrolithiasis, hypercalcuria/hyperphosphaturia.
– Mercury: nephrotic syndrome.
– Beryllium: systemic granulomatosis, hypercalcuria, hyperuricemia.
– Silicosis: glomerulonephritis.
– Organic solvents: membranous nephropathy.
– Carbon disulphide: accelerated atherosclerosis.

EXCLUDE analgesic and 'herbal'/botanical nephropathy, e.g. aristolochic acid.

End-stage renal dysfunction due to agents that alter renal metabolism (Xenobiotic substances):

– Some individual susceptibility higher after toxic exposure.
– Reduced threshold for appearance of overt renal damage after exposure to subtoxic doses of a second substance.
– Prior exposure to chemicals capable of inducing enzyme synthesis (P450).

E.g. acute renal failure in an alcoholic after subtoxic dose exposure to halogenated hydrocarbons.

G. NEUROTOXICITY:

The blood-brain barrier is selectively permeable but metals, gases and solvents can still penetrate sufficiently to cause damage. Each of the neuraxis regions (brain, spinal cord, peripheral nerves and muscles) react differently to toxic injury. Within any given region, different cell populations also react differently = 'selective vulnerability'. Depending on the location and type of neuronal dysfunction, toxicity may culminate in a wide spectrum of symptoms and signs.

Disorder presentation can be very diverse – possible syndromes (or combinations):

headache, pain, cognitive and psychiatric disturbances, visual changes, seizures, ataxia, tremors, rigidity, weakness and sensory loss.

The extent and severity of neurological deficits is difficult to assess.

General principles:

1. A clear dose-toxicity relationship exists in the majority of neurotoxic exposures: neurological symptoms appear only after a cumulative exposure reaches a threshold level.
2. Individual susceptibility varies over a limited range, but idiosyncratic reactions are rare.
3. Toxins typically cause non-focal or symmetric neurological syndromes (most useful finding).
4. There is usually a strong temporal relationship between exposure and onset of symptoms.
5. Some recovery is typically possible after removal from the exposure (despite limited regeneration capability of nervous system).
6. Multiple neurological syndromes are possible from a single toxin e.g. lead.
7. ALWAYS exclude other neurological disease.

Agents associated with toxic polyneuropathies:

1. *Mostly sensory or sensorimotor polyneuropathy (little or no weakness):*
   – acrylamide.
   – metals: arsenic, mercury, thallium.
   – carbon disulphide.
   – ethylene oxide.

– methyl bromide.
– polychlorinated biphenyls (PCB).
– thallium.

2. *Predominantly motor polyneuropathy or sensorimotor polyneuropathy (significant weakness):*
– Metals: lead, arsenic, mercury.
– hexacarbons: n-hexane, methyl-n-butyl ketone.
– organophosphates.

3. *'Purely' sensory neuropathy (disabling sensory loss with no weakness):*
– pyridoxine abuse.
– cis-platinum.

4. *Cranial neuropathy:*
– trichloroethylene (trigeminal neuropathy)
– thallium.

5. *Predominantly autonomic dysfunction:*
– acrylamide.
– n-hexane (glue-sniffers).
– thallium.
– Vacor (PNU).

6. *Possible association with neuropathies (mostly anecdotal):*
– methyl methcrylate.
– dioxin.
– carbon monoxide.
– benzene.
– pyrethrins.

Neurotoxic syndromes:

1. Acute encephalopathy: various toxins at sufficient doses.
2. Chronic encephalopathy: various toxins at chronic / low-doses.
3. Parkinsonism: manganese, CO, methanol.
4. Motor neuron disease: lead, manganese.
5. Myeloneuropathy: nitrous oxide, organophosphates, n-hexane.
6. Polyneuropathy – weakness: acrylamide, arsenic, mercury, thallium, PCB, methyl bromide, ethylene oxide, carbon disulphide.
7. Polyneuropathy + weakness: lead, arsenic, mercury, hexacarbons (n-hexane, MBK), organophosphates.
8. 'Purely' sensory neuropathy: pyridoxine abuse, cis-platinum.
9. Cranial neuropathy: trichloroethylene (trigeminal neuropathy), thallium.
10. Prominent autonomic dysfunction: acrylamide, n-hexane, thallium, vacor (PNU).

H. REPRODUCTIVE TOXICITY:

Only a few substances have been shown to have strong associations with adverse reproductive outcomes in humans. A large number of agents are, however, suspect based on animal literature and toxicological assessment.

Adverse reproductive effects are not only very stressful for affected families, but the social burden of these adverse health outcomes, including high medical costs for compromised infants, increased use of advance technology to achieve conception and to monitor the pregnancy, can be huge.

Reproductive effects have a relative short latency between exposure and clinical event as compared to the long latency for cancer. If workers and the community are protected from exposures that are harmful to reproduction or the foetus, they will usually also be protected from other health effects associated with these exposures.

Adverse reproductive outcomes associated with exposures: Female
– infertility 8–12%.
– spontaneous abortion 10–20%.
– birth weight <2500 g 4–7%.
– preterm ≤ 37 weeks 14–18%.
– stillbirth 2–4%.
– infant death 1%.
– birth defects (throughout 1 year of life) 2–5%.
– chromosomal abnormalities in live births 0.2%.
– menstrual disorders.

Adverse reproductive outcomes associated with exposures: Male
– azoospermia 1%.
– oligospermia.
– teratospermia.
– asthenospermia.
– decreased libido.
– impotence.
– testicular atrophy.
– infertility 8–12%.
– chromosomal anomalies.
– severe mental retardation.

Agents associated with adverse human reproductive or developmental effects:
– anaesthetic gases e.g. nitrous oxide, halothane, ethane (reduced fertility, spontaneous abortion, birth defects).
– anti-neoplastic drugs (spontaneous abortion, birth defects).
– arsenic (spontaneous abortion, low birth weight).
– carbon disulphide (spontaneous abortion, menstrual disorders, oligospermia, asthenospermia, teratospermia).
– carbon monoxide (spontaneous abortion, low birth weight).
– cadmium (decreased fertility).
– DDT (menstrual disorders, detected in semen of infertile men).
– dioxins (menstrual disorders, spontaneous abortion, birth defects).
– electromagnetic fields (EMF) (spontaneous abortion, childhood cancer).
– ethylene glycol ethers (spontaneous abortion, oligospermia).
– ethylene oxide (spontaneous abortion).
– lead (infertility, spontaneous abortion, preterm, neurological defects, oligospermia, teratospermia, asthenospermia).
– mercury (menstrual disorders, spontaneous abortion, low birth weight, CNS malformation, cerebral palsy, decreased libido, impotence).
– physical stress (preterm, low birth weight, spontaneous abortion).
– PCBs (low birth weight, hyperpigmentation, menstrual disorders).
– ionizing radiation (infertility, menstrual disorders, spontaneous abortion, birth defects, childhood cancer, oligospermia).
– microwave radiation (oligospermia, asthenospermia).
– organic solvents e.g. perchloroethylene, methylene chloride, toluene, xylene, glycol ethers (menstrual disorders, spontaneous abortion, birth defects).
– tobacco smoke – cadmium, nicotine, carbon dioxide, polyaromatic hydrocarbons (PAHs) (foetal loss, low birth weight).
– video display terminals (VDT) (spontaneous abortion, birth defects).
– ethanol (azoospermia, testicular atrophy).
– boron (oligospermia).
– carbaryl (teratospermia).
– chloroprene (asthenospermia, teratospermia, decreased libido).
– excessive heat (oligospermia).
– manganese (decreased libido, impotence).
– vinyl chloride (decreased libido, impotence).
– estrogens (oligospermia).

I. DERMATOTOXICITY:

Factors contributing to skin irritation:

1. *Factors related to the substance:*

1.1. Chemical nature of the substance:
• pH.
• solubility in water and fats.
• detergent action.

1.2. Physical state:
• gas.
• volatile liquid.

- heavy liquid.
- semi-solid.
- solid.

1.3. Concentration:
- amount.
- contact with skin.

2. *Host factors:*
- surface area affected.
- region of skin.
- length of exposure.
- presence or absence of occlusion.
- dryness/sweating.
- pigmentation.
- presence of hair.
- sebaceous activity.
- concurrent and pre-existing skin disease.
- pruritogenic threshold.

3. *General host factors:*
- sex.
- age.
- race.
- genetic background.

4. *Environmental factors:*

4.1. Temperature.
- heat.
- cold.

4.2. Humidity and moisture
- friction.
- pressure.
- occlusion.
- lacerations.

Clinical presentation:

Contact dermatitis:

Irritant contact dermatitis:
- Immediate reactions.
- Delayed reactions (89%).

Phototoxic reactions: coal tar, dyes, furocoumarins (psoralen).

Cutaneous irritations:

1. Hydrofluoric acid burns.
2. Cement burns.
3. Fibrous glass dermatitis.
4. Pigmentary changes.
   - Melanosis.
   - Leukodermia (hydroquinone).
5. Allergic contact dermatitis: Immunologically mediated (type IV).

Contact urticaria:

1. Non-allergic contact urticaria.
2. Allergic contact urticaria.

Biological causes:

1. Bacterial disease:
   - Staphylococcal and streptococcal infections: furunculosis, paronychia.
   - Cutaneous TBC – Typical mycobacterial infections.
   - Atypical mycobacterial infections.
   - Tularemia.
   - Brucellosis.
   - Anthrax.
   - Erysipeloid.
2. Viral disease:
   - Herpes simplex.
   - Viral warts.
   - Orf (contagious Erythema).
3. Fungal infection:
   - Candida.
   - Dermatophytes.
   - Coccidiodomycosis.
   - Sporotrichosis.
   - Blastomycosis.
   - Chromomycosis.

Parasytic disease:

1. Protozoa:
   - Cutaneous leishmaniasis.
   - Helminths: swimmer's itch, larva migrans.
2. Arthropods:
   - Scabies.
   - Lyme disease.

Physical causes:

1. Mechanical trauma:
   - Intermittent friction of low intensity: lichenification of the skin.
   - Greater and prolonged pressure: corns, calluses.
2. Heat:
   - Burns.
   - Miliaria.
   - Intertrigo.
3. Cold:
   - Frostbite.
   - Chilblains (perniosis).
4. Vibration syndrome.
5. Ionizing radiation:
   - Acute radiodermatitis: single accidental exposure to 1000 Roentgens (R) or more.
   - Chronic radiodermatitis: smaller dose exposures over a daily or weekly period of 300-800 R or a total dose of 5000-6000 R over a longer period.

Occupational acne:

1. Oil acne (folliculitis): oil, heavy tar, coal tar pitch exposure.
2. Acne cosmetica.
3. Acne mechanica: local pressure, friction, rubbing, squeezing and stretching.
4. Tropical acne (in hot moist climates).
5. Chloracne (rare).

Skin cancer: UV (ultraviolet) light, polycyclic aromatic hydrocarbons, arsenic, ionizing radiation, trauma e.g. burn scars.

CONCLUSION

Toxicological risk assessment:

Steps in risk assessment:

Step 1: Hazard identification
– Population exposed/at risk.
– Adverse health effects.

Step 2: Dose-response relationship (DRR)
– Collect data on effects of hazardous substances.
– Identification of a 'critical' DRR.
– Quantitative expression of the DRR.

Step 3: Exposure assessment
– Estimation of past, present and future exposure levels
– Actual doses received.

Step 4: Risk characterization
– Incidence of adverse health effects in population at risk predicted by the DRR (Step 2) as applied to the exposure assessment (Step 3).

Uncertainties inherent to the toxicological risk assessment:

1. Human data is frequently lacking.
2. Human data is limited due to the inability to detect low-incidence effects.
3. Animal data is often of uncertain relevance to humans.
4. The mechanisms of action for effects are poorly understood.
5. The exposure of the population at risk may not be quantifiable or calculation of doses may not be possible.

Reference:

LaDou J. Occupational & Environmental Medicine. 2nd ed. United States of America: McGraw-Hill; 1997.