Introduction to occupational (industrial) toxicology

Occupational diseases and predictive toxicological tests

Gunnar Damgård Nielsen
PhD, Dr Sc (pharm)
National Research Centre for the Working Environment
gdn@nrcwe.dk

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Poison

Toxikon: Greek word for bow (arrow poison)
Toxicum: Roman word for poison
Toxin: English, for a toxic naturally occurring compound.

Toxicology is the science of poison (adverse effects on living systems). Toxicity describes the nature of an adverse effect.

Paracelsus (1493-1541): Dosis sola facit veneum/the dose alone makes a poison.

Worker protection (industrial health) - an interdisciplinary approach

**Occupational medicine** (symptoms, diseases and diagnosis)
(Diseases from dust (asbestos, quartz, cotton), metals (beryllium, cadmium, lead, manganese, mercury) and carcinogenic compounds (benzene, chromates, aromatic amines, and vinyl chloride)

Hippocrates (~400 BC; e.g. metals), Galen (~150 AD; mines and acid mists), Paracelsus (~1500; Monograph on miners disease), Ramazzini (~1700; father of occupational medicine), Pott (~1750; scrotal cancer in young chimney sweeps)

**Occupational hygiene** (exposures assessment and preventive measures) (substitution, enclosure, ventilation, personal sampling)

**Occupational toxicology** (predictive testing) (short-term and long-term animal studies; biological monitoring)

**Epidemiology** (prevalence and incidence)

Development of industrial toxicology

At World War I, about 3000 to 4000 compounds were studied for acute toxicity for chemical warfare purposes, including phosgene (COCl₂) and bis(β-chloroethyl) sulfide).

By the mid-1930s, large chemical companies established toxicological Laboratories, for example, DuPont, Dow and Union Carbide. In the US grants for industrial toxicology were given to US universities, for example, Harvard, University of Pittsburgh, New York University, University of Cincinnati and Johns Hopkins University.

In 1949, the US FDA proposed procedures for 2-year studies in rats and 1-year studies in non-rodents as dogs.

In 1959, the US FDA proposed a protocol for "lifetime" test with rats. The FDA also proposed a protocol for the three-generation reproductive study.

Society of Toxicology (1960) for industrial toxicologists in the US.

Acute toxicity is still an issue in occupational toxicology

Example:
Organophosphate pesticides (acute toxicity and delayed polyneuropathy)

Phosgene (COCl₂), ozone, nitrogen dioxide, causing lung oedema.

CO, H₂S (both blocking of appropriate oxygen supply)

Very high exposures to airway irritants (e.g.Cl₂, CH₃COOH, HCl, dust from World Trade Center) can cause Reactive airways dysfunction syndrome, RADS)

Insecticides  |  Isocyanates for polyurethane  |  Manure: H₂S  |  Alkaline dust
Examples of newer acute studies

- Spray products interfere with lung surfactants
- Sensory irritation
- Organophosphate pesticides
Neuronal Cells

Illustration of a neuron
Anticholinesterase organophosphates (OP): insecticides and chemical warfare agents

Acetylcholinesterase (AChE)

Neuropathy target esterase (NTE)

Can be hydrolysed or may proceed to irreversible inhibition (aging)

AChE: acute toxicity
NTE: delayed neurotoxicity

Tri-ortho-cresyl phosphate: delayed neuropathy

Diseases:
- Adulterated for Jamaica ginger (1920):
- Adulterated cooking oil (many thousands)
- Pilots at risk?

Risk assessment can benefit from predictive toxicology and a relevant exposure assessment

Tri ortho cresyl phosphate in rats
Enlarged dystrophic axons in the terminal (medullary) levels of the gracile fasciculus

Pesticides give rise to public health concern

Both occupational herbicide and occupational insecticide exposure were significantly associated with Parkinson’s disease; 28 cross-sectional studies and 1 cohort study ï exposure assessment were based on exposure-history a) - potential bias: recall bias and past exposure?

Public exposures to pesticides were not associated with any significant health risk (HI << 1) and the cancer risk was negligible (about $10^{-7}$ for infants) b) - potential limitations: only inhalation; high body burden due to dermal uptake and food

Only new prospective studies with appropriate exposure assessments are informative a)

Most occupational diseases are due to repeated exposures.
Occupational exposure routes and classical endpoints. Effects often due to high exposures

Skin and eyes
   a) Local effects (e.g. irritation, necrosis and contact sensitisation)
   b) Systemic effects after skin contact include absorption and internal organ effects

Inhalation
   a) Local effects on the respiratory tract (e.g. irritation, asthma, COPD, pneumoconiosis and cancer)
   b) Systemic effects after absorption (e.g. on the CNS, liver, kidney, cardiovascular system and cancer)

Skin irritation

- Ambient temperature
- Humidity/environment
- Mechanical stress
- Chemicals: Sufactants, Solvents, Acids, Bases, Oxidizing agents
- Radiation

Stratum corneum damages: barrier dysfunction

- Pruritus
- Inflammation

Functio laesa (dysfunction)
- Dolor (pain)
- Tumor (swelling)
- Rubor (redness)
- Calor (heat)

Allergic contact dermatitis

Skin sensitizers

E.g. fragrances, preservatives, rubber chemicals, industrial epoxy resins, acrylates, medicaments, chromates and nickel

Reacts (haptenation) with skin proteins

Activation of the immune system

Danger signal

Skin sensitization

New exposure

Allergic contact dermatitis

Validated in vivo predictive tests

Skin irritation
• Draize rabbit skin test

Allergic contact dermatitis
• Guinea pig maximization test (adjuvant test)
• Buehler occluded patch test (repeated application on guinea pigs)
• Local lymph node assay (application on mouse ears and measurement of proliferation in the local lymph node)


Important occupational lung diseases

1. Asthma
2. Chronic obstructive pulmonary disease
3. Pneumoconioses
4. Cancer in the airways

Hoffmeyer et al. Pneumokoniosen. Pneumologie 2007, 61, 774-797
Work-related asthma (WRA)

- Occupational (de novo) asthma (OA)
  - Caused by sensitizers
  - Irritant induced
- Work-exacerbated (of pre-existing) asthma (WEA)

Occupational asthma (OA) has been defined as a disorder characterized by variable airflow limitation, airway hyperresponsiveness, and airway inflammation due to a particular occupational environment and not to stimuli outside the workplace.

1. Asthma

Illustration af anatomien ved et astmaanfald

Se fx Encyclopædia Britannica.
Sensitizers causing occupational asthma

IgE from proteins (diagnosis from IgE in human serum):

- Experimental animals
- Molds
- Latex gloves
- Wheat flour
- Wood dust

Low molecular weight compounds

For example: acid anhydrides, acrylates, polyisocyanates.

Diagnosis in humans by provocation
Appropriate animal models???

Dykewicz MS. Occupational asthma: current concepts in pathogenesis, diagnosis, and management.
J Allergy Clin Immunol 2009, 123, 519-528.
2. Chronic obstructive pulmonary disease due to emphysema

Emphysematous lung destruction reduces maximum expiratory flow by decreasing the elastic recoil force available to drive air out of the lungs.

Emphysema is characterized by dilatation and destruction of lung tissue beyond the terminal bronchioles.

Smoking
Coal dust
Silica dust

Centrilobular emphysema (CLE)

Smoke induced emphysema

Appropriate models?

3. Pneumoconioses \(^{a,b}\)

Dust induced interstitial lung diseases causing functional changes. Symptoms: breathlessness and cough

Pneumoconioses with prominent interstitial fibrosis (malignant fibrosis)

- Asbestos: asbestosis
- Crystalline silica (SiO\(_2\))\(^*\): silicosis
- Dust from coal mining: coal workers’ pneumoconiosis

\(^*\)

About 300 studies in 2014\(^{c}\): Do we need new studies? If we need new studies, what type of questions should they address, would they be fulfilled by human or animal studies and what type of methods could be used?

a) Hoffmeyer et al. Pneumokoniosen. Pneumologie 2007, 61, 774-797
Silicosis (in general >10-20y of exposure)

Whole lung section with chronic silicosis. Small circumscribed nodules are seen in the upper zone.

Silicotic nodule with a central zone of hyalinised collagen with a whorled appearance and peripheral dust-containing macrophages.

Massive opacity (nodulus) in the right upper zone of the lung.

Hoffmeyer et al. Pneumokoniosen. Pneumologie 2007, 61, 774-797
Results from a rat model:

2 mg quartz (DQ12) were intratracheally instilled. Lungs and bronchoalveolar lavage fluid were collected seven days (7d) following the instillation.

Inflammation 7d after 2 mg DQ12 i.t. administered in rats

Lung from a control rat  Lung from an exposed rat

No validated animal model. Are our models sufficient?
Crystalline silica can induce many different effects

- Pneumoconiosis
- Chronic bronchitis
- Emphysema
- Mineral dust airway disease
- Increase infection (TB)
- Lung cancer
- Autoimmune diseases
- Renal disease

In general, all compounds may induce many different diseases!

Study in the German porcelain industry; NOAEL for decrease in lung function at 0.25 mg/m³

Human lung carcinogens

- Asbestos
- Chrystaline silica (quarts)
- Chromium (VI)
- Cadmium
- Nickel
- Arsenic
- Beryllium
- Tobacco smoke
- Polycyclic aromatic hydrocarbons (e.g. soot and tar)

By far, the majority of carcinogenic compounds have been discovered in long-term animal studies

4. Cancer in the respiratory system. Asbestos, an example of cancer-inducing fibres

Serpentine: Chrysotile (white)

Amphibole: Amosite (brown)

Amphibole: Crocidolite (blue)


Asbestos

**Non-malignant:** pleural plaques (often calcified, in the parietal pleura [lines the chest wall and the surface of the diaphragm])

**Malignant:** mesothelioma (pleura or peritoneum)

**Non-malignant:** asbestosis (peribronchiolar fibrosis/scarring).

**Malignant:** laryngeal cancer and lung cancer.

Se illustrationer af dette via søgning på internettet

Lung cancer  
Mesothelioma
Toxicological approaches to evaluation of fibres (3Ds)

Life-long inhalation studies in mice and rats (dose (D))

Physical/mineralogical properties (e.g. Dimensions (D), durability (D), breakdown products and surface properties)
The purpose of predictive toxicology is to prevent outbreak of diseases. Types of test for toxicity

- Acute toxicity
- Skin, eye and airway irritation, and corrosivity
- Sensitization
- Repeated dose toxicity
- Reproductive toxicity
- Genotoxicity
- Carcinogenicity
Key references


