Occupational exposure to chemicals.
Toxic and genotoxic effects
Lead and mercury case study

J. Volf
2012
Prologue

• Every year, 168,000 EU citizens die from work-related accidents or diseases and 7 million are injured in accidents, notes the resolution, which was drafted by Karima Delli (Greens/EFA, FR) and adopted with 371 votes in favour, 47 against and 15 abstentions. (EU December 2011)

Source:
Contents

• Occupational chemical hazard identification/assessment
  – Elementary basis of the toxicology (repetition)
• Exposure assessment in occupational/industrial toxicology
• Occupational Health Risk assessment
• Prevention on occupational poisoning
• Ethical aspects of the occupational risk analysis
• Exercise – solvents, Case study II, Lead
• Case study III Mercury
This Lesson Outcomes

• Knowledge/information
  – Toxicology repetition
  – About occupational safety program UN
  – The basics occupational/industrial toxicology
  – About occupational exposure standards and measurements
  – About representative chemical substances

• Skills
  – Recognize the characteristic smell of some industrial solvents
  – Use several information sources of MAC

• Attitudes
  – Ethical aspects occupational exposure to chemicals as a part of occupational medicine.
  – Ethical aspects of epidemiological study in occupational medicine
Why we are talking about occupational exposure to chemicals?

• MD’s role for patients/clients
  – Have to be able recognize the etiology of diseases – occupational risk
  – Participated on prevention
• The MD’s role in consultation for employ, employer, trade unions
  – Use nature authority for health benefits, wellbeing
MD and occupational exposure to chemicals

• GP – symptoms, syndromes of suspect poisoning /intoxications
  – Rare but exists
  – Occupational anamnesis
  – Preventive examination of employ

• Specialist
  – Communication with all field of medicine
  – Special diagnosis and treatment of professional poisoning
The repetition of toxicology
History

• Phillip von Hohenheim (1493–1541) was an alchemist, physician, astrologer etc.

• ‘father of toxicology’. Of course, most of us know him as “Paracelsus”,

• A title that he took late in his life that means, “equal to or greater than Celsus”, who was a Roman from the first century known for his tract on medicine

• “All things are poison and nothing is without poison, only the dose permits something not to be poisonous.”
What is a toxin?

τοξικόν toxikon

This term refers to toxic substances that are **produced naturally** (nature origin)
What is toxic?

This term relates to poisonous or deadly effects on the body
What is a toxicants?

This term refers to toxic substances that are produced by or are a by-product of human made activities.
What is toxicology?

1st

The study of the nature, effects, and detection of poisons and the treatment of poisoning.
What is toxicology?

Toxicology is a branch of medicine, biology, chemistry and some others (e.g. pharmacology, genetic, law) concerned with the study of the adverse effects of chemicals on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people.

See more: http://en.wikipedia.org/wiki/Toxicology
Toxico kinetics (pharmacokinetics)

– what the body does with the substance (absorption, distribution, biotransformation, excretion)

Clearance – measure of the body´s ability to eliminate a substance

Bioavailability – the rate and extent to which a substance becomes available to target place

Age- or gender- related dependency of kinetics
Toxicodynamics (pharmacodynamics)

-what the substance does to the body (effects and mechanisms of actions):

Stochastic or non-stochastic effect (threshold)

Organ-specific toxic effect

Acute – sub-chronic – chronic effect

Delayed effect: mutagenic, carcinogenic, teratogenic, allergenic
The toxicological paradigm

![Flowchart showing the relationship between Toxicokinetics and Toxicodynamics, including Exposure, Internal Dose, Biologically Effective Dose, Early Biological Effects, Altered Structure/Function, Disease, Susceptibility Factors, Exposition Assessment, and Risk Assessment.]
Xenobiotic metabolism

• Phase I: oxidation, reduction, hydrolysis

• Phase II: conjugation

• Biotransformation via intestinal micro-flora: reduction, de-conjugation
Factors influencing xenobiotic metabolism
Susceptibility factors

Induction of expression of the enzyme protein (upregulation)

Repression of the expression of the enzyme protein (downregulation)

Direct activation of the enzymatic function

Direct inhibition of the enzymatic function
Free radicals

• Chemical entities with one or more unpaired electrons.

• Biological effects:
  • Reaction with virtually all molecules in living cells
  • Cytotoxic and genotoxic effects
  • Damage of cellular membranes,
  • Interaction with proteins,
  • Interaction with lipids (lipid per oxidation)

• The degree of damage will depend on the balance between radical formation and radical inactivation
Genomics

- **Gene sequencing**, which applies various biochemical and bioinformatics tools to study the DNA of organisms.
- **Genotype analysis** that looks at genetic variation between individuals and in populations.
- **Epigenetics** that studies reversible changes in gene function that can be passed from parent to child.
- **Transcriptomics** (or gene expression profiling) is the study of mRNA—the intermediary step between genes and proteins that indicates genes that are active (as opposed to dormant or silent).
- **Proteomics** is the study of proteomes, which are collections of proteins. Proteins carry out the functions encoded by genes.
- **Metabolomics** is the study of the products of biological processes. Such products change in response to such things as nutrition, stress, and disease states.
Processes in the toxicology of cancerogenetic substances
## Chemical carcinogens

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotoxic</strong>: Direct</td>
<td>Alkylating agents</td>
</tr>
<tr>
<td></td>
<td>PAHs, Aromatic amines, nitroarenes, mycotoxins</td>
</tr>
<tr>
<td></td>
<td><strong>Indirect</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Inorganic carcinogens</td>
<td>Ni, Cr, Cd, As</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epigenetic</strong> (nongenotoxic):</td>
<td></td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>Mitogens, proliferating agents</td>
</tr>
<tr>
<td>Solid bodies, fibres</td>
<td>Asbestos</td>
</tr>
<tr>
<td>Tumor promoters</td>
<td>TCDD, DDT</td>
</tr>
<tr>
<td>Hormones</td>
<td>Estradiol, DES</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>Azathioprine, cyclosporin A</td>
</tr>
<tr>
<td>Peroxisome proliferators</td>
<td>Phthalates, clofibrate</td>
</tr>
</tbody>
</table>
The control questions I

- What is a difference between toxic and toxicant?
- What is a toxicodynamic?
- What is a toxicokinetic?
- What is initiating faze in cancer development?
Occupational/industrial toxicology/hygiene

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What is occupational toxicology?

- Occupational /industrial toxicology includes the effects of industrial/occupational toxicants on health of employ.
- Theory: „Exposure healthy employee to known concentration of the known substances„,
- The field combines both regulation, research, and risk assessment.
The algorithm of an industrial hygiene

• Health hazard recognition.
• Health hazard evaluation.
• Health hazard control.
• Employee education and training.
• Audit of the program’s effectiveness and update of the program for continuous improvement.

Source and more: 
Risk Assessment in occupational medicine

• Standard and transparent process haw to move from data to information
• Legal duty for employer
• A tool of the occupational diseases, and poisons prevention
The risk-based industrial hygiene assessment

- Type of hazard (chemical, physical, and biological)
- Toxicity
- Quantity in use
- Duration of use
- Past monitoring data
- Established occupational exposure models
How to assess the risks in your workplace?

1. Identify the hazards
2. Decide who might be harmed and how
3. Evaluate the risks and decide on precautions
4. Record your findings and implement them
5. Review your assessment and update if necessary
Occupational exposure
Occupational exposure

• The exposure to potentially harmful chemical, physical, or biological agents that occurs as a result of one's occupation.
  – Medical aspects
  – Legal aspects

Occupational exposure

• Not only **doses** makes difference between „toxicologiests“.(mg.m⁻³ vs µg. m⁻³)

• Differences exist in **exposure scenario** (8hours vs.24 hours, only in the adulthood)

• Exposure assessment (limits TLVs, OEL,MAC) Can be individualy gague. Personal protecting equipment.

• Optionality ? (USA principles?)
Occupational exposure routes

• Inhalation
  – Dust (partly p.o. exposure)
    • Particles
    • Fibres
  – Aerosols (mist, fog)
  – Vapours
  – Gaseous

• Cutaneos /skin absorption
The particles fractions as defined in EN481 (1993)

- **inhalable fraction** (the mass fraction of particles which can be inhaled by nose or mouth); since there are no experimental data on inhalable fraction of particles with an aerodynamic diameter of > 100 μm, particles > 100 μm are not included in the inhalable convention,

- **thoracic fraction** (the mass fraction of particles that passes the larynx); the median value of the particle size is 11.64 μm with a geometric standard deviation (GSD) of 1.5 μm. It has been shown that 50 % of the particles in air with an aerodynamic diameter of 10 μm belong to the thoracic fraction,

- **respirable fraction** (the mass fraction of particles that reaches the alveoli); the median value is 4.25 μm with a GSD of 1.5 μm. It has been shown that 50 % of the particles with an aerodynamic diameter of 4 μm belong to the respirable fraction.
Exposure characters

Cyclic

Random

Intermittent

Concentrated

Continuous

Source: Thomas Kensler, PhD, Bloomberg School of Public Health
Maximum Allowable Concentration (MAC)

- The maximum exposure to a biologically active physical or chemical agent that is allowed during an 8-hour period (a workday) in a population of workers, or during a 24-hour period in the general population, which does not appear to cause appreciable harm, whether immediate or delayed for any period, in the target population. (From Lewis Dictionary of Toxicology, 1st ed)
The threshold limit value (TLV)

- is a level to which it is believed a worker can be exposed day after day for a working lifetime without adverse health effects. Strictly speaking, TLV is a reserved term of the American Conference of Governmental Industrial Hygienists (ACGIH).
- TLVs, along with biological exposure indices (BEIs), are published annually by the ACGIH.

See [http://www.acgih.org/home.htm](http://www.acgih.org/home.htm)
TLV („gold“ standard)

- Time weighted average (TLV-TWA): average exposure on the basis of a 8h/day, 40h/week work schedule
- Short-term exposure limit (TLV-STEL): spot exposure for a duration of 15 minutes, that cannot be repeated more than 4 times per day
- Ceiling limit (TLV-C): absolute exposure limit that should not be exceeded at any time
Guidance for Interpreting the Carcinogenicity Notation (US)

Carcinogenicity

• Goal to synthesize information to be useful to practicing industrial hygienist
• 5 category system that evolves to reflect advances in science
• Exposures to carcinogens should be kept to a minimum – For A1 agents with a TLV® and for A2 and A3 agents exposure by all routes should be controlled
• For agents with no designation – no human or animal data available to assign
The example of regulation

Occupational exposure assessment
The exposure measurement strategy I

• Qualitative (What)
  – technology assessment and
  – literature review
  – Qualitative analysis of occupational environment

• Quantitative (How much, many)
  – Assessment of the potential employee exposures
  – Observance of OEL, MACs, TLVs, PEL
Overview of the Exposure Assessment Strategy
Checklist for Employee Exposure Monitoring

Item

1. Is there a toxic or hazardous material in the workplace that can be released into the workplace air? Yes... No...

2. If "yes", have you made a written determination for each toxic material that states whether any employee may be exposed to airborne concentrations of each material? Yes... No..

3. If "yes" to 2, does the written determination include at least the following:

   a. Any information, observations, or calculations that would indicate employee exposure? Yes... No..

   b. If employees are exposed to toxic material, statement that exposure is at or above the action level? Yes... No..

   c. Any employee complaints of symptoms attributable to exposures? Yes... No..

   d. Date of determination, work being performed, location within the worksite, names and social security numbers of employees possibly exposed? Yes... No..

   e. Any concentration measurements (area or personal) taken? Yes... No..

   f. Any comments from medical examinations that may point to possible exposures? Yes... No..
4. Is there any reasonable possibility of any employee being exposed above the action level according to the written determination? Yes.... No....

5. If "yes", have you measured the exposure of the employee(s) most likely to have the greatest exposure (maximum risk employees)? Yes.... No....

6. If "no", have you repeated Step 2 and succeeding steps each time there has been a change in production, process, or control measures that could result in an increase in airborne concentrations of any material in Step 2? Yes.... No....

7. If any exposure measurement indicates exposure above the action level, have you:
   a. Identified all employees so exposed? Yes.... No....
   b. Sampled those employees so identified? Yes.... No....
   c. Classified all employees according to noncompliance exposure, possible overexposure, or compliance exposure? Yes.... No....
8. Have you taken the following actions, depending on employee classification:
   a. Resampled employees with noncompliance exposures within 1 month and decided whether controls are to be instituted?
   b. Resampled employees with possible overexposures within 2 months and recategorized them if appropriate?
   c. Resampled employees with compliance exposures every 2 months (or if changes occurred in the operation) and reclassified them if appropriate?

9. Have employees with exposures exceeding Federal standards been informed?

10. Have all employee exposure measurements been properly recorded and filed?

11. Have you instituted appropriate controls for those exposed employees needing them?
The exposure tactics

• Air concentration
  – Personal air sampling
    • Active
    • Passive
  – Area air sampling (active, passive)
  – Wipe sampling
  – Biological exposure test (urine, blood, alveolar air
    • Direct
    • Indirect
NIOSH recommended employee exposure determination and measurement strategy. Each individual substance health standard should be consulted for detailed requirements. AL = action level; PEL = permissible exposure limit.
Personal sampling

Working area/stationary measurements

- Results can be used for exposure limits comparison only with time activities patterns record (TLW, PEL) usually 8 hour shifts
- Simple
- Cheaper
- Less representative for individual exposure
- Norm regulate the statistics or results
Biological monitoring/analyses

- Biological exposure indices (BEI)
- Biological exposure tests CZE (BET)
- Cytogenetic analysis:
  - Biomarker of exposure to gene-toxic carcinogens
  - Biomarker of early adverse effect (reversible)
The BEI® – Definition

• Biological monitoring … entails measurement of the concentration of a chemical determinant in the biological media of the exposed and is an indicator of the uptake of the substance.

• The BEI® determinant can be the chemical itself; one or more metabolites; or a characteristic reversible biochemical change induced by the chemical.

Guidance for Interpreting the BEI® Notation

- Refers to existence of a Biological Exposure Index (BEI®) for the agent
- Biomonitoring serves as a complement to exposure assessment by air sampling
- Most BEIs® based on direct correlation to TLV® (conc. of determinant at TLV® exposure)
- BEIs® used as guidelines in evaluation of potential hazards
<table>
<thead>
<tr>
<th>Látka</th>
<th>Ukazatel</th>
<th>Limitní hodnoty</th>
<th>Doba odběru</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anilin</td>
<td>p-Aminofenol</td>
<td>50 mg/g kreatininu</td>
<td>52 μmol/mmol kreatininu</td>
</tr>
<tr>
<td>Arsen a arsenovodík</td>
<td>Arsen</td>
<td>0,05 mg/g kreatininu</td>
<td>0,075 μmol/mmol kreatininu</td>
</tr>
<tr>
<td>Benzen</td>
<td>S-Fenylmerkapturová kyselina</td>
<td>0,05 mg/g kreatininu</td>
<td>0,024 μmol/mmol kreatininu</td>
</tr>
<tr>
<td>Dimethylformamid</td>
<td>N-Methylformamid</td>
<td>15 mg/l</td>
<td>0,25 mmol/l</td>
</tr>
<tr>
<td>Ethylenbenzen</td>
<td>Mandlová kyselina</td>
<td>1500 mg/g kreatininu</td>
<td>1100 μmol/mmol kreatininu</td>
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<tr>
<td>Ethylen glykolmono butylether</td>
<td>Butoxyoctová kyselina</td>
<td>100 mg/l</td>
<td>0,76 mmol/l</td>
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<tr>
<td>Ethylen glykolmono butyletheracetát</td>
<td>Butoxyoctová kyselina</td>
<td>100 mg/l</td>
<td>0,76 mmol/l</td>
</tr>
<tr>
<td>Ethylen glykolmono ethylether</td>
<td>Ethoxyoctová kyselina</td>
<td>50 mg/l</td>
<td>0,48 mmol/l</td>
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<tr>
<td>Ethylen glykolmono ethyletheracetát</td>
<td>Ethoxyoctová kyselina</td>
<td>50 mg/l</td>
<td>0,48 mmol/l</td>
</tr>
<tr>
<td>Fenol</td>
<td>Fenol</td>
<td>300 mg/g kreatininu</td>
<td>360 μmol/mmol kreatininu</td>
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<tr>
<td>Fluoridy</td>
<td>Fluorid</td>
<td>10 mg/g kreatininu</td>
<td>60 μmol/mmol kreatininu</td>
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<tr>
<td>Fural</td>
<td>Pyroslizová kyselina</td>
<td>200 mg/g kreatininu</td>
<td>200 μmol/mmol kreatininu</td>
</tr>
<tr>
<td>Chrom (VI) sloučeniny</td>
<td>Celkový chrom</td>
<td>0,030 mg/g kreatininu</td>
<td>0,065 μmol/mmol kreatininu</td>
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<tr>
<td>Kadmium</td>
<td>Kadmium</td>
<td>0,005 mg/g kreatininu</td>
<td>0,005 μmol/mmol kreatininu</td>
</tr>
<tr>
<td>Methanol</td>
<td>Methanol</td>
<td>15 mg/l</td>
<td>0,47 mmol/l</td>
</tr>
<tr>
<td>Nikl</td>
<td>Nikl</td>
<td>0,04 mg/g kreatininu</td>
<td>0,077 μmol/mmol kreatininu</td>
</tr>
<tr>
<td>Nitrobenzen</td>
<td>p-Nitrofenol</td>
<td>5 mg/g kreatininu</td>
<td>4 μmol/mmol kreatininu</td>
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## BET II

<table>
<thead>
<tr>
<th>Látka v krvi</th>
<th>Ukazatel</th>
<th>Limity</th>
<th>Doba odběru</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anilin</td>
<td>Methemoglobin</td>
<td>1,5 % hemoglobinu</td>
<td>Konec směny</td>
</tr>
<tr>
<td>Kadmium</td>
<td>Kadmium</td>
<td>0,005 mg/l</td>
<td>Nerozhoduje</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0,045 μmol/l</td>
<td></td>
</tr>
<tr>
<td>Inhibitory cholinesterazy a</td>
<td>Aktivita cholinesterazy a</td>
<td>pokles o 20% z hodnoty před započetím praci</td>
<td>Konec směny</td>
</tr>
<tr>
<td>acetylcholinesterazy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrobenzen</td>
<td>Methemoglobin</td>
<td>1,5 % hemoglobinu</td>
<td>Konec směny</td>
</tr>
<tr>
<td>Oxid uhelnatý</td>
<td>Karbonylhemoglobin</td>
<td>5 % hemoglobinu</td>
<td>Konec směny</td>
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<tr>
<td>Olovo</td>
<td>Plumbaemie</td>
<td>0,4 mg/l</td>
<td>Nerozhoduje</td>
</tr>
<tr>
<td>Polychlorované bifenyly</td>
<td>Polychlorované bifenyly</td>
<td>0,05 mg/l</td>
<td>Nerozhoduje</td>
</tr>
</tbody>
</table>
Chromosomal aberrations and cancer risk

Three epidemiologic studies:

Nordic countries - Italy - Czech Republic

found a significant association between the number of chromosomal aberrations in population and the risk of cancer

Elimination or reduction of occupational exposure is therefore very important to prevent occupationally-related neoplasms

Source: Prof. Černá presentation 2012
1. What inform MD result from biological exposure indicators/tests?
2. What are differences between work area and personal sampling?
3. Why and when we use cytogenetic analyses?
4. Do you know any tests used in gonotoxicology?
Ethical aspects in the occupational/industrial toxicology
Specific occupational medicine „schism“ to serve

• Employer
  – Be protected against health problems
    • occupational diseases occurrence
  – Give information
    • about technology
    • hazard substance,
    • concentrations in the occupational environment
    • etc

• Employee
  – Is a client (or patient)
  – Has a right be protected
  – Has a right to know
  – Has a right to work
  – Has a duty to give information, samples participate preventive and periodical medical examination
Occupational medical doctor

- Have to protect candidates or workers against discrimination, social and health risk
- Prevent the poisoning, occupational disease
- Have to be „fair“ to employer
- In any case protect medical secret – health status and susceptibility of worker
- Decide …..APTUS(A)
Ars medici/evidence based medicine

http://www.rozmanitosti.eu/zbozi
Preventive measurements in industrial/occupational
Preventive measurements

- Legal tools (convention, acts, agreements)
  - Some hazards substances are prohibit
  - Some work (job) are prohibit for women
- Technology
  - Without hazard substances
  - Sealing (close technology)
  - Ventilation
- Organisation
  - Brakes
  - PPE
- Promotion
World

• UN

• ILO International Labor Organization/Office (1919/1946)
  http://www.ilo.org/global/lang--en/index.htm#a3

• WHO
Introduce

- International Programme on Chemical Safety
- IPCS WHO

Assess Risks, Build the Evidence, Set Standards, Articulate Policy, Build Capacity for Action.

Source: WHO Geneva
USA

- American Conference of Governmental Industrial Hygienists (1938 /1946)
- [http://www.acgih.org/home.htm](http://www.acgih.org/home.htm)
- Threshold Limit Values (1941)
- OSHA
EU Occupational health agency
OSHA EU

REACH

REACH is the European Community Regulation on chemicals and their safe use (EC 1907/2006). It deals with the Registration, Evaluation, Authorisation and Restriction of Chemical substances. The law entered into force on 1 June 2007.

Carcinogens and Mutagens at work EU


EU statistics

EU Directives OSH

• **Exposure to chemical agents and chemical safety - OSH directives**
  
  • **Directive 2009/161/EU - indicative occupational exposure limit values**
  
  • **Directive 2009/148/EC - exposure to asbestos at work**
    – of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work (Text with EEA relevance)
  
  • **Directive 2006/15/EC - indicative occupational exposure limit values**
  
  • **Directive 2004/37/EC - carcinogens or mutagens at work**
    – of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) Directive 89/391/EEC)
  
  • **Directive 2000/39/EC - indicative occupational exposure limit values**
    – of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work.
  
  • **Directive 98/24/EC - risks related to chemical agents at work**
    – of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC)
  
  • **Directive 91/322/EEC - indicative limit values**
Information sources

- Books
- Journals
- D bases
- Poison (Toxicological) Control Centres
- Toxicological information centres and Phone lines (call centres)
Information data sources

Toxicological Databases (free)II

- http://ull.chemistry.uakron.edu/erd/index.html
- http://potency.berkeley.edu/cpdb.html
- http://www.epa.gov/ecotox
- http://ace.ace.orst.edu/info/extoxnet
- http://www.epa.gov/gap-db/gapdb.htm
- http://www.state.nj.us/health/eoh/rtkweb/rtkhsfs.htm
- http://193.51.164.11/cgi/ihound/chem/ih_chem_frames.html
- http://www.cdc.gov/niosh/ipcs/icstart.html
Toxicological Databases (free) II

- http://www.inchem.org
- http://www.cdc.gov/niosh/idlh/idlh-1.html
- http://www.cdc.gov/niosh/npg/pgdstart.html
- http://ntp.niehs.nih.gov/
- http://www.cdc.gov/niosh/pel88/npelname.html
- http://solvdb.ncms.org/index.html
- http://www.uvp5.univ-paris5.fr/teletox/
Poison centres

- Czech poison centre  Phone: 224 91 92 93
  

[http://www.who.int/gho/phe/chemical_safety/phe_poison_centres_20110701.xls](http://www.who.int/gho/phe/chemical_safety/phe_poison_centres_20110701.xls)
Source of an additional information

International Labor Organization (ILO) Chemical Control

- Occupational exposure to chemicals toxic and genotoxic Toolkit see:
Control questions III

1. Do you know effective preventive measure on occupational toxicology?
2. Do you know the name of international and important national agencies for occupational medicine/industrial hygiene or occupational health and safety?
3. What do you know about poisons centre?
Exercises
Olfactory sens

- Is very important tool in any medicine
- It is more important in industrial toxicology
- Olfactometrie is common use methodology

**Task** use the nose for recognise the chemical substance – solvent

- CAVE! Protect your olfactory sens with „good smell practice“
The solution

Will be given after the exercise
Exercise

• There is a set of samples
  – A
  – B
  – C
  – D
  – E
Case studies

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Important occupational hazardous chemical substances

- Lead
- Mercury
- Cadmium
- Industrial solvents
Lead

- [http://www.ila-lead.org/lead-information/lead-the-facts](http://www.ila-lead.org/lead-information/lead-the-facts)
Lead

**Occupational exposure**: battery manufacturing, lead smelters

**Acute toxicity of inorganic lead:**
Intestinal colics, nausea, constipation, diarrhea, abdominal pain, capillary spasm, irritation, encephalopathy, ataxia

**Chronic toxicity of inorganic lead:**
Affect hematopoetic system (micro-or normocyte anemia based on the interaction with hemoglobin synthesis in bone marrow). GIT (abdominal pain, constipation, diarrhea),

**Organic lead**: Central and peripheral nervous system (loss of concentration, impaired memory, in children negative impact on intelligence)

Source: Prof. Černá presentation 2012
Lead (cont.)

Kidney (nephropathy)
Cardiovascular effect (?)
Reproduction, carcinogenicity
The big age dependent toxic effects!!!!
CAVE! Small children. (parents clothes)

Plumbemia BLL 10 μg/dL

Therapy: BAL, EDTA

More: http://www.websters-dictionary-online.com
## Correlation between blood lead level and effects

<table>
<thead>
<tr>
<th>B-Pb µg/l</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150</td>
<td>Inhibition of δ-aminolevulinic acid dehydratase</td>
</tr>
<tr>
<td>100-200</td>
<td>Impaired intellectual and cognitive development of children</td>
</tr>
<tr>
<td>200-600</td>
<td>Increased erythrocyte protoporphyrin conc.</td>
</tr>
<tr>
<td>&gt;400</td>
<td>Increased urinary coproporphyrin and δ-ALA concentration</td>
</tr>
<tr>
<td>500-600</td>
<td>Chronic encephalopathy in children</td>
</tr>
<tr>
<td>&gt;800</td>
<td>Chronic encephalopathy in adults</td>
</tr>
<tr>
<td>600-800</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>700-1000</td>
<td>Impaired renal function</td>
</tr>
<tr>
<td>800-3000</td>
<td>Acute lead encephalopathy</td>
</tr>
</tbody>
</table>

Source: Prof. Černá presentation 2012
Mercury

- http://www.biomedcentral.com/content/pdf/1471-227X-10-7.pdf
Mercury

Elemental mercury vapour.

Acute toxicity: inhalation - rare, pneumonia, emphysema, orally – GIT problems

Chronic: akrodyinia, nephrotic syndrome, gingivitis, tremor mercurialise, erethism, polyneuropathy

Mercury salts:

Acute: Orally erosive effect, hemorrhagic vomiting, renal damage

Chronic (see vapour)

Methyl mercury:

Acute: CNS effect; paresthesia, ataxia, loss of sensation, difficulties with speaking and hearing.

Chronic: similar to acute

Teratogenic, mutagenic, carcinogenic effects
Cadmium

• Very long biological half-life (10 – 30 y)

• Occupational exposure to Cd dust or aerosols

• Inhalation exposure – 40 to 50 % of inhaled Cd is absorbed

• Absorption from GIT is about 2 – 8 % (higher resorption in women)

• Albumin-bound Cd – liver - metallothionein

• Cd does not cross substantially the placenta barrier

• Renal cortex is the target organ

Source: Prof. Černá presentation 2012
Cadmium – adverse health effects

Carcinogen for human (Class 1 according to IARC)
Kidney dysfunction (proteinuria, increased excretion of albumins, globulins, $\beta_2$-microglobulins
Osteoporosis, interference with calcium metabolism
Itai-Itai disease (osteomalacia)
Hypertension??

Source: Prof. Černá presentation 2012
Aromatic hydrocarbons
Benzene, toluene, xylene

Benzene:

According to ILO convention in 1972, the use of benzene is prohibited if suitable substitute products are available.

Inhalation is dominant route of human exposure.

Occupational exposure: petrochemical industry, petrol station.

Environmental exposure: ambient air, indoor air, smoking.

Source: Prof. Černá presentation 2012
Benzene – kinetics and health effects

• Inhalation and dermal absorption,

• Because of lipophilic character the highest level is in organs with the high lipid amount

• Acute toxicity:
  • **Mild form** - dizziness, excitation, euphoria, headache, nausea, vomiting
  • **Severe form** – visual disturbance, shallow and rapid pulse, breathlessness, profound CNS depression, loss of consciousness, collapse

Source: Prof. Černá presentation 2012
Benzene – chronic and delayed effects

• **Hematopoetic disorders:**
  - Erythroid system: aplastic anemia, erythroblastic myelosis, acute erythremia
  - Leukopoetic system: leukopenia, leukemia, lymphocytosis
  - Thrombopoetic system: thrombocytopenia

• **Carcinogenicity** (leukemia)

• **Immunotoxicity**

Source: Prof. Černá presentation 2012
Toluene

Emissions of motor vehicles, mineral-oil industry, industrial use as solvent etc.

Inhalation, dermal absorption

**Acute and chronic toxicity:**

- Euphoria, irritation, narcotic effect
- Pseudoneurasthenic syndrome (mental lability, sleep disturbance, chronic fatigue)
- Psychoorganic syndrome (changes in mental performance, loss of personality)

Reproductive toxicity

Source: Prof. Černá presentation 2012
Halogenated hydrocarbons

Use:

Lipophilic compounds, mostly used as solvents: dichloromethane, trichloroethylene, trichloroethane (chloroform), tetrachloroethylene (perchlorethylene).

Vinyl chloride = monomeric constituent for PVC

Kinetics: inhalation absorption, extensive biotransformation

Source: Prof. Černá presentation 2012
Halogenated hydrocarbons

Adverse health effects:
Irritation, anesthetic effect, depressive effects on CNS
Damage to parenchymal organs (liver, kidney)
Mutagenicity, potential carcinogenicity
Reproductive and developmental toxicity

Source: Prof. Černá presentation 2012
Organophosphate insecticides

Large and well-defined class of pesticides

The toxicity is the result of excessive stimulation of cholinergic nerves based on the ability to inhibit acetylcholinesterase.

Rapid hydrolysation of acetylcholin at the postganglionic membrane of the synapse.

Organophosphates bind more tightly to the enzymes active site that does acetylcholine.

Accumulation of acetylcholine at the receptor

Source: Prof. Černá presentation 2012
Organophosphate insecticides

Symptoms of toxicity result from cholinesterase inhibition:
Headache, giddiness, nervousness, blurred vision, weakness, nausea, cramps, diarrhea.

Sweating, miosis, vomiting, cyanosis, convulsions, coma, cardiac arrhythmia, respiratory failure.

Delayed neuropathy

Therapy: atropine

Source: Prof. Černá presentation 2012
The end