CHILDREN AND HEAVY METALS

TRAINING FOR THE HEALTH SECTOR

HEAVY METALS
Nickel, manganese, chromium and cadmium

Children’s Health and the Environment
Training Package for the Health Sector

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LEARNING OBJECTIVES

- To get acquainted with the characteristics of certain heavy metals and to determine their occurrence in the human environment and their significance for health.
- To learn about the sources and routes of children’s exposure, the metals’ fate in the organism and their health effects.
- To inform about the diagnosis and treatment of the health effects of children’s exposure to nickel, manganese, cadmium and chromium.
- To get acquainted with the various means of preventing the adverse health effects of children’s exposure to these compounds.

After this talk, we hope that you will be able to satisfy these four learning objectives.
CHILDREN AND HEAVY METALS
COMPLEX ENVIRONMENT OF CHILDREN AND ADOLESCENTS

HAZARDS
- Physical
- Chemical
- Biological

MEDIA
- Water
- Air
- Food
- Soil
- Objects

SETTINGS
- Rural and urban
- Home
- School
- Playground
- Field
- Street
- Workplace

ACTIVITIES
- Learning
- Working
- Eating
- Drinking
- Sleeping
- Breathing
- Smoking
- Doing sports
- Playing
- “Testing”
- Scavenging

SUSCEPTIBILITY
- Critical windows, timing
- Age
- Nutritional status
- Poverty

OUTCOME EFFECTS
- good or bad?
- Organs
- Systems
- Functions
- Development
- Survival

In this summary slide, we see the complexity of the issues related to children’s environmental health. Hazards (physical, chemical, biological – in many cases favoured by social factors) are introduced into environmental media (water, air, food, soil, objects and toys) with variable efficiency in different settings (urban and rural: home, school, field, playground, street and workplace). A child’s activities bring him or her into contact with these hazards.

<<READ SLIDE>>

Depending upon the individual susceptibility of the child based upon age, general health and social supports, the exposure may cause harm ranging from subtle changes in function to death.

Children’s environmental health is the field which synthesizes these complexities and attempts to make fundamental changes to improve children’s environments and prevent environmental illnesses.
CHILDREN AND HEAVY METALS

WHY CHILDREN?

Children are more vulnerable than adults

- Developing organism
- Increased absorption
- Immature detoxifying capacity
- Greater exposure by body weight
- Windows of susceptibility to environmental threats (from preconception to the first 2–3 years of life)

CHILDREN AND HEAVY METALS

WHY CHILDREN?

Environmental exposure to heavy metals occurs in many places

- Children living near **industry** (smelters, foundries, power plants, waste incineration and ore mines) or **toxic waste sites** may be exposed through air, dust (both outdoor and indoor), water and food

- Canned food may be contaminated with heavy metals leaching from the cans

Cadmium, chromium and zinc are used for pigments, chromium is also used in leather tanning. Copper and chromium compounds, along with arsenic, are ingredients in wood preservatives, and when the treated wood is eventually discarded, the toxic metals re-enter the air, soil, and water. (Cheryl Simon Silver & Dale S. Rothman: Toxic and Health: The potential long-term effects of industrial activity. World Resources Institute, 1995, pp 7-8)
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WHY CHILDREN?

The effects of environmental exposure:

- May be cumulative and intergenerational
- In early life may appear in adulthood or in the next generation
- May lead to long-term consequences or disability
- Depend on: toxicity, dose, timing and magnitude of exposure
- Are exacerbated by poor socioeconomic circumstances (poverty, malnutrition, urbanization, degraded environments, stressful living conditions, etc.)

Because of children’s dynamic and continuous process of growth and development, the effects of environmental threats may be cumulative (e.g. in some instances children may be exposed repeatedly to toxicants or radiations and their effects continue to accumulate). Childhood exposure may affect health in adulthood, or the health of the next generations (i.e. effects are intergenerational, as is the case with children born to mothers who were exposed to lead in their childhood). Exposure may have long-term consequences and produce permanent disability.

The importance of the TIMING of exposure has to be recognized. Dose refers to the quantity of a chemical, whereas type/amount refers to frequency of exposure.

In the poorer regions, the adverse effects are further exacerbated or magnified by poverty, malnutrition and stress (such as is experienced in refugee camps, or areas affected by drought, tornadoes or floods,…or in areas of war or conflict).
CHILDREN AND HEAVY METALS

HEAVY METALS

The most important (most widely spread and toxic) heavy metals – from the viewpoint of environment and health:

- Lead (see separate module)
- Mercury (see separate module)
- Nickel
- Manganese
- Chromium
- Cadmium

Most metals exert their biologoci effects through enzyme ligand binding and for many metals, excretion can be hastened by chelation therapy with agents such as dimer capsuuccinic acid (DMSA, succimer), dimercaptol (BAL) or ethylene-diamine-tetraacetic acid (EDTA). Beyond these generalizations, however, metal toxicology is as varied as the metals themselves. (Frumkin H and Melius J: Toxins. In: Occupational Health ed by B.S. Levy and D.H. Wegman, 4th edition, Lippincot Williams & Wilkins, Philadelphia, 2000, pp. 315-316)

Out of the many kinds of heavy metals occurring in the environment, on the basis of their distribution and toxic properties, these 6 ones have been chosen to illustrate their impact on the health of children. For lead and mercury, separate modules are available, so this module deals only with the 4 remaining metals: nickel, manganese, chromium and cadmium. Arsenic could also be a candidate but it is not listed as a heavy metal. Exposure to beryllium, a toxic heavy metal, occurs in occupational settings rather than as an environmental risk factor affecting children.
CHILDREN AND HEAVY METALS

NICKEL – OCCURRENCE

• White magnetic hard metal used in alloys with copper, chromium, iron and zinc.

• Widely used in industry:
  
  fuel production, electroplating, pigments, ceramics, 
batteries, food production, making jewellery, valves, 
magnets, heat exchangers, medical prostheses, coins, 
household appliances etc.
CHILDREN AND HEAVY METALS

NICKEL – ROUTES AND SOURCES OF EXPOSURE

Inhalation
• Smoking as well as environmental tobacco smoke
• Industrial emission (power plants fuelled by peat, coal, natural gas and oil, mining, steel production and municipal waste incineration)
• Motor vehicles (from petrol and abrasion of the cars' metal parts)

Ingestion (about 99% of the estimated daily intake for nonsmokers)
• Natural food sources: cocoa, tea, nuts, soybean, oats
• In polluted waters: oysters and salmon may accumulate nickel
• Certain vegetables: peas, beans, cabbage, spinach, lettuce
• Elevated levels in drinking-water (from taps and fittings)

Skin
• Metallic coins, jewellery

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NICKEL – FATE IN THE ORGANISM

Absorption
- Soluble ions may be directly absorbed from the lungs or the gastrointestinal tract (1–5%) or through the skin (50–70%)
- Insoluble ions may be phagocytosed by cells lining the respiratory tract

Transport
- By blood, bound to alpha-macroglobulin
- Goes through the placenta

Excretion
- Faeces (90%), urine, saliva, sweat

Accumulation
- Kidney, lungs, liver, brain (for lipophilic nickel compounds)
CHILDREN AND HEAVY METALS

NICKEL – HEALTH EFFECTS

Acute poisoning
• Nickel sulfate or nickel carbonyl: death due to cardiac arrest, pneumonia or brain haemorrhage

Allergies (most common health effects)
• Contact dermatitis (from jewellery, white gold, wristwatches, metal clothing fasteners, piercing)
• Asthma

Adverse pregnancy outcomes (occupational exposure)
• Spontaneous abortion
• Congenital structural malformations
• Chromosomal aberrations

Cancer (occupational inhalation exposure)
• lung, larynx, nose and pharynx

If considered useful, you can use the following references to give examples of the health effects of Nickel.
• “Sensitization to industrial chemical allergens in bronchial asthma in children in environmental pollution” (DuevaLA, Mizernitskii IuL.: Med Tr Prom Ekol. 1997;(2):41-5.
Forty one children with bronchial asthma varying in severity, who live in ecologically hazardous industrial areas were examined. A high incidence of sensibilization to industrial chemical allergens like nickel, chromium and manganese was found.

• “Metal allergy in north Norwegian school children and its relationship with ear piercings and atopy” (Dotterud LK, Falk ES: Contact Dermatitis. 1994 Nov;31(5):308-13.)


• „Nickel and cobalt hypersensitivity reaction before and after orthodontic therapy in children” (Saglam AM, Baysal V, Ceylan AM: J Contemp Dent Pract. 2004 Nov 15;5(4):79-90.)
**Children and Heavy Metals**

**Nickel – Diagnosis and Treatment**

*Diagnosis of acute exposure*
- Urine sample: above 5 μg/dl nickel

*Treatment of acute poisoning*
- Chelating agents: DDC (diethyldithiocarbamate) or disulfiram
- Penicillamin

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NICKEL – PREVENTION OF EXPOSURE

Regulations

WHO
• Nickel compounds are human carcinogens (IARC 1)
• Nickel (metal) is a possible human carcinogen (IARC 2B)
• Drinking-water maximum guideline value (1993): 0.02 mg/l
• Air pollution unit risk: $3.8 \times 10^{-4}$ per 1 $\mu$g/m$^3$ (lifetime)

European Union
• Directive 94/27/EEC on restricting the use of nickel in jewellery, wristwatches, clothing etc.: entered into force 2001
• Drinking-water limit value: 0.02 mg/l (weekly average concentration)
• Air: Directive 2004/107/EC: intensive monitoring and follow-up needed above 20 ng/m$^3$

US Environmental Protection Agency
• Health advisories for children’s water intake exceeding 1 mg/l (for 1- to 10-day intake) or 0.5 mg/l (for longer term)

Ref.:


PINCHE Draft Report, WP 6, pp.88-89, 2005
CHILDREN AND HEAVY METALS

NICKEL – PREVENTION OF EXPOSURE

**Education**

- Warn the public about the widespread use of nickel in jewellery
- Alert people with sensitivity to avoid prolonged contact on the skin and to avoid using nickel-containing stainless steel cookware

Ref.:


*PINCHE Draft Report, WP 6, pp.88-89, 2005*
CHILDREN AND HEAVY METALS

MANGANESE – OCCURRENCE

• Essential human nutrient: recommended daily intake 0.14 mg/kg (US Environmental Protection Agency)

• Organic and inorganic (seven species, valences from 1 to 7) forms

• Very hard and brittle metal widely used in industry: constituent of steel alloys, battery production, glass and ceramics production

• Manganese oxides (permanganates) are used as disinfectants and for bleaching, metal cleaning, flower preservation etc.

• Organic manganese compounds are petrol and fuel oil additives (methylcyclopentadienyl manganese tricarbonyl, MMT)
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MANGANESE – SOURCES OF EXPOSURE

Inhalation
• Industrial emission (80%)
• Combustion of fossil fuels (20%)
• Motor vehicles (from petrol containing MMT as an antiknock compound)

Ingestion
• Natural food sources: nuts, almonds, whole barley, rye, tea, wheat, pecans, leafy green vegetables
• Elevated levels in drinking-water
MANGANESE – FATE IN THE ORGANISM

**Absorption**
- Absorption from the gastrointestinal tract (3–5%) is highly regulated by homeostatic mechanisms, although these may be less developed in children. Iron deficiency and low protein intake increase absorption and high dietary calcium and phosphate decrease it.
- Absorption from the respiratory tract is 100% and opens a direct route to the central nervous system, avoiding the hepatic first-pass clearance.

**Transport**
- By blood, bound to plasma proteins (including beta-1-globulin-transmanganine and transferrin) and within the erythrocytes.
- Goes through the placenta and to breast-milk.

**Excretion**
- Faeces (primary biliary), urine (minimal)

**Accumulation**
- Liver, bones, pancreas, kidney, central nervous system

Source: www.cdc.gov
CHILDREN AND HEAVY METALS

MANGANESE – HEALTH EFFECTS

**Acute poisoning**
- Metal fume fever or manganese pneumonitis (fever, cough, congestion and malaise)
- Liver damage

**Chronic and long-term effects**
- Neurotoxicity (manganism: tremor, clumsiness, cogwheel rigidity, mask-like facies). Infants, children and menstruating women are at greater risk (greater transport into the central nervous system, lower threshold of effect and greater retention of manganese in the brain)
- Chronic respiratory tract inflammation

**Adverse reproductive effects**
- Stillbirths, birth defects (cleft lip, heart defects, imperforate anus, deafness)

Studies performed in Šibenik (Croatia), a town with 31,000 inhabitants, focussed on adverse health effects of emissions from a manganese alloy plant. In a study sponsored by the US EPA, special emphasis was placed on the respiratory effects of environmental exposure to manganese. Results of all studies were presented in Šaric’s report “Biological Effects of Manganese” (EPA -600/1-78-001., Research Triangle Park, US EPA, 1978). Parts of the studies were published as individual papers. A three-year follow-up study showed higher incidence of acute bronchitis and pneumonia in the area heavily contaminated with emissions from the manganese alloy plant. (The manganese concentration was 10-50 times higher than the normal urban concentration of 10-30 ng/m³). Two further studies were carried out among school-children where the acute respiratory morbidity was somewhat higher in the polluted than in the control town. Within the polluted town, however, children living in different distances from the plant did not differ significantly in their respiratory morbidity, but a slight increase of forced expiratory volumes was observed as one moved further away from the plant.
MANGANESE – DIAGNOSIS AND TREATMENT

Diagnosis of acute exposure
• Blood reference values are: 4–15 μg/l (whole blood)
  0.9–2.9 μg/l (serum)
• Urine reference value is below 10 μg/l
• Breast-milk, measured concentrations: 7–120 μg/l

Treatment of acute poisoning
• Chelating agents: CaNa₂EDTA

Treatment of excess manganese exposure including chelation therapy: CaNa₂EDTA increases the urinary excretion and may provide clinical improvement in select cases of severe manganese intoxication.

CHILDREN AND HEAVY METALS

MANGANESE – PREVENTION OF EXPOSURE

Regulations

WHO
• Air pollution guideline value: 0.15 μg/m³ (annual average)
• Drinking-water health-based guideline value: 0.5 mg/l, based on consumers’ complaints: 0.1 mg/l

European Union
• Drinking-water health-based limit value: 0.05 mg/l

US Environmental Protection Agency
• Reference concentration in ambient air: 0.05 μg/m³ (based on changes in neuropsychological functioning)
• Drinking-water health-based limit value: 0.05 mg/l

Risk communication
• Use of MMT in petrol should be limited or prohibited
CHROMIUM – OCCURRENCE

- Essential human nutrient: recommended daily intake: 50–200 μg (adults), 20–60 μg (infants)
- The three most common forms:
  - metallic (Cr⁰) – does not exist naturally
  - trivalent (Cr³⁺) – nutrient, limited solubility
  - hexavalent (Cr⁶⁺) – water soluble, highly toxic
- Widely used in industry due to its anticorrosive property:
  - metal surface plating, leather tanning,
  - glassware cleaning, textile production
CHILDREN AND HEAVY METALS

CHROMIUM – SOURCES OF EXPOSURE

Inhalation
• Industrial emission (fossil fuel combustion, steel production)

Ingestion
• Natural food sources: green beans, broccoli, seafood, cereals
• Elevated levels in drinking-water
• House dust in contaminated areas

Skin
• Chromium plating
• Dust
CHILDREN AND HEAVY METALS

CHROMIUM – FATE IN THE ORGANISM

Absorption
• After inhalation: elemental (Cr⁰) and trivalent chromium (Cr³⁺) are poorly absorbed; the hexavalent form (Cr⁶⁺) is well absorbed
• After ingestion: only 2% of the Cr³⁺ salts and up to 50% of Cr⁶⁺ compounds are absorbed. A large proportion of the ingested Cr⁶⁺ is converted to the less soluble Cr³⁺
• After dermal contact: only Cr⁶⁺ is well absorbed

Transport
• By blood
• Cr⁶⁺ goes through the placenta and into breast-milk

Excretion
• Urine (80%), bile, sweat

Accumulation: no

Ref.: WHO Regional Office for Europe: Air Quality Guidelines for Europe. 2nd ed. WHO Regional Publications, European Series No. 91, 2000.
CHILDREN AND HEAVY METALS

CHROMIUM – HEALTH EFFECTS OF Cr⁺⁶

**Acute poisoning**
- By ingestion: nausea, vomiting, haematemesis, acute renal failure
- By inhalation: acute pneumonitis, runny nose, sneezing, nosebleeds
- By skin contact: irritation, contact dermatitis, eczema

**Allergies (most common health effects)**
- Contact dermatitis, frank eczema

**Reproductive toxicity**
- Low birth weight
- Birth defects
- Disturbed spermatogenesis

**Cancer (Cr⁺⁶ is a human carcinogen, IARC 1)**
- Lung
Diagnosis of acute exposure

- Blood reference value is 0.052–0.156 μg/l (serum)
- Urine concentration is typically 0–40 μg/l
- Breast-milk, average concentration: about 0.3 ppb

Treatment of acute poisoning

- Chelating agents: not available (not needed)
- Vitamin C
CHILDREN AND HEAVY METALS

CHROMIUM – PREVENTION OF EXPOSURE

Regulations

WHO

• Air pollution lifetime risk of 1 μg/m³ for lung cancer is 4 x 10⁻² (Cr⁶⁺)
• Drinking-water provisional guideline value: 0.05 mg/l (total Cr)

US Environmental Protection Agency

• Drinking-water limit value: 0.1 mg/l (total Cr)

European Union

• Drinking-water limit value: 0.05 mg/l (total Cr)
• Directive 2002/95/EC requires the substitution of Cr⁶⁺ (among others) in new electrical and electronic equipment marketed from 1 July 2006

Risk communication

• Excess daily doses of chromium from dietary supplements should be avoided, particularly for children
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CADMIUM – OCCURRENCE

• Pure cadmium ores are relatively rare; they are mostly contained in zinc and lead ores
• Cadmium is widely used in industry:
  electroplating, production of steel, plastics, batteries, fertilizers, pigments, ceramics and textiles
• Solubility: Cd(CH3COO)2, CdCl2 and CdSO4 are water soluble, whereas CdO and CdS are not
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CADMIUM – SOURCES OF EXPOSURE

Inhalation
• Smoking and environmental tobacco smoke
• Industrial emission (waste incineration etc.)

Ingestion (main route of exposure)
• Food (internal organs of animals such as kidney; tins of sardines etc.)
• Elevated levels in drinking-water (impurities in the zinc of galvanized pipes and solders and metal fittings)

Relevant reading:
„Factors affecting lead, cadmium , and arsenic levels in house dust in a smelter town in eastern Germany” (Environ res. 1999Jul;81(1):32-44.)
CHILDREN AND HEAVY METALS

CADMIUM – FATE IN THE ORGANISM

Absorption
• Depends on the solubility of the cadmium compounds
• The fraction absorbed from the intestines is 6–10 % (poor calcium and iron supply increases absorption)

Transport
• By blood to the liver and then bound to metallothionein → transport to the kidneys
• A small fraction gets through the placenta, most of the amount is retained

Excretion
• Stool and (small fraction of the absorbed dose) in urine

Accumulation
• Kidneys (biological half-life: 10–35 years), liver
CHILDREN AND HEAVY METALS

CADMIUM – HEALTH EFFECTS

**Acute toxicity**
- **Inhalation:** acute pneumonia
- **Ingestion:** nausea, vomiting, abdominal cramps, diarrhoea, liver and/or kidney lesions

**Chronic toxicity**
- **Inhalation:** lung cancer (human carcinogen, IARC Group 1), prostate cancer
- **Ingestion:** (based on lesions of the tubular function of the kidney)
  - proteinuria ($\beta_2$-microglobulin)
  - decreased reabsorption of Ca and phosphorus → osteoporosis and osteomalacia → bone fractures, bone-aches (itai-itai disease)
  - hypertension
  - humoral immune response impairment

Relevant readings:
Diagnosis of acute exposure

- Blood: good indicator of recent exposure
  - Reference values: 0.3–1.2 μg/l for nonsmokers (whole blood)
  - 1.4 μg/l for smokers (whole blood)
  - 0.1–0.3 μg/l (serum)
- Urine: N-acetyl-β-D-glucose-aminidase (NAG) is a sensitive marker of functional lesions of the kidneys
- Faeces: exposure is well reflected by the amount of cadmium in the stool

Treatment

- **Acute toxicity**: chelating agents (EDTA)
- **Chronic toxicity**: calcium and vitamin D

EDTA = ethylenediaminetetraacetic acid
The property of EDTA is its ability to chelate or complex metal ions in 1:1 metal-to-EDTA complexes.
CHILDREN AND HEAVY METALS

CADMIUM – PREVENTION OF EXPOSURE

Regulations

World Health Organisation

- Air pollution guideline value: 5 ng/m³ (per year)
- Drinking-water guideline value: 3 µg/l

European Union

- Air pollution limit value: 5 ng/m³ (per year)
- Drinking-water limit value: 5 µg/l
- Food: Commission Regulation EC/466/2001 specifies the maximum permissible levels of cadmium in various food items
- Directives 2002/95/EC and 2002/96/EC restrict the use of cadmium in electronic substances and regulate the recovery and recycling of these devices as waste

Ref: PINCHE Report, WP 6, chapter Cadmium, 2005; accessed at: www.pinche.hvdgm.nl
WHO: “The cadmium body burden of the general population in some parts of Europe cannot be further increased without endangering renal function. [It is important] to prevent any further increase of cadmium in agricultural soils likely to increase the dietary intake of future generations.”

(Air quality guidelines for Europe. 2nd ed. Copenhagen, WHO Regional Office for Europe, 2000 (WHO Regional Publications, European Series, No. 91).
Health and environment professionals have a critical role to play in maintaining and stimulating changes that will restore and protect children’s environmental health. Although the human genome project is very important and scientifically exciting, we all know that genes express themselves within an environment and understanding gene–environment interactions is what will keep our children healthy. So, as we look to our political and personal lives to support sustainable development, we can look to our practices for ways to enhance the environmental health of our patients.

All of us can do something. At the one-to-one patient level we can include environmental etiologies in our differential diagnoses and in our preventive advice. We can be dissatisfied with the diagnosis of “idiopathic” and look hard for potential environmental causes of disease and disability.

We can publish sentinel cases and develop and write up community-based interventions. We can educate our patients, families, colleagues and students didactically.

Finally, we must all become vigorous advocates for the environmental health of our children and future generations. It is not enough to be an informed citizen, we need to write letters and articles, testify at hearings, approach our elected officials with educational and positive messages, avoiding “scares” and “alarmism”, but provide evidence for action and clear proposals for remedial and preventive activities.

And, we must all recognize that as professionals with an understanding of both health and the environment, we are powerful role models. Our choices will be noticed: they should be thoughtful and sustainable.

To expand your information on children’s environmental health, please go to the website of TEACH (Toxicity and Exposure Assessment for Children’s Health), a database that contains over 1400 references to the scientific literature in this field: cfpub.epa.gov/teach/
I end with this beautiful reminder to us from a child in India. We must recognize the risks to our children and assume our responsibilities for preventing them, because we hold our future in our hands — and it is our children.

Thank you.
CHILDREN AND HEAVY METALS

Sources of further information


• Air quality guidelines for Europe. 2nd ed. Copenhagen, WHO Regional Office for Europe, 2000 (WHO Regional Publications, European Series, No. 91).
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