Outline

1. A little history
2. Determinants and mechanisms of toxicity
   + examples based (own) epidemiological research and on (anecdotal) experience of “Clinic for occupational and environmental diseases” UZ Leuven
1. Some history
Agricola – De Re Metallica

Book VI (Hoover, p.214):

- some [illnesses] affect the joints, others attack the lungs, some the eyes, and finally some are fatal to men

“we should always devote more care to maintaining our health […] than to making profits” (Book VI, Hoover translation, p.214)
De Morbis quibus obnoxii sunt Metallorum Fossores

Diseases to which miners of metals are exposed

De Morbis Artificum CAPUT PRIMUM

Varia et multiplex morborum seges, quam non raro artifices quidam extrema sui pernicie ex iis artibus quas exercent, pro lucro referunt, ex duabus praecipue causis, ut reor, progerminat; quam prior, ac potissima, est prava materiae conditio quam tractant, quae noxios halitus ac tenues particulae humanae naturae infensas exspirans, particulares morbos invehit

Various and manifold is the harvest of diseases reaped by certain workers from the crafts and trades that they pursue; all the profit that they get is fatal injury to their health. That crop germinates mostly, I think, from two causes. The first and most potent is the harmful character of the materials that they handle, for these emit noxious vapours and very fine particles imimical to human beings and induce particular diseases.
De Morbis Artificum
CAPUT PRIMUM

Not only the miners in mines are severely punished by metallic pests, but many others too whose work is near the mines invite serious injury, I mean all the metal workers who shovel, smelt, cast and refine.

Also those living close to the mines are affected by metal exhalations that obscure the vital spirits … and alter the natural economy of the body.

2. Determinants and mechanisms of toxicity of metals
<table>
<thead>
<tr>
<th>Group Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinides</td>
</tr>
<tr>
<td>Alkali Metal</td>
</tr>
</tbody>
</table>

### Atomic Weight

<table>
<thead>
<tr>
<th>Element</th>
<th>Atomic Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1.0079</td>
</tr>
<tr>
<td>He</td>
<td>4.0030</td>
</tr>
<tr>
<td>Li</td>
<td>6.941</td>
</tr>
<tr>
<td>Be</td>
<td>9.0122</td>
</tr>
<tr>
<td>Na</td>
<td>22.989</td>
</tr>
<tr>
<td>Mg</td>
<td>24.305</td>
</tr>
<tr>
<td>K</td>
<td>39.098</td>
</tr>
<tr>
<td>Ca</td>
<td>40.078</td>
</tr>
<tr>
<td>Sc</td>
<td>44.958</td>
</tr>
<tr>
<td>Ti</td>
<td>47.88</td>
</tr>
<tr>
<td>V</td>
<td>50.941</td>
</tr>
<tr>
<td>Cr</td>
<td>52.000</td>
</tr>
<tr>
<td>Mn</td>
<td>54.938</td>
</tr>
<tr>
<td>Fe</td>
<td>55.845</td>
</tr>
<tr>
<td>Co</td>
<td>58.933</td>
</tr>
<tr>
<td>Ni</td>
<td>58.693</td>
</tr>
<tr>
<td>Cu</td>
<td>63.546</td>
</tr>
<tr>
<td>Zn</td>
<td>65.39</td>
</tr>
<tr>
<td>Ga</td>
<td>70.922</td>
</tr>
<tr>
<td>Ge</td>
<td>72.61</td>
</tr>
<tr>
<td>As</td>
<td>74.921</td>
</tr>
<tr>
<td>Se</td>
<td>78.96</td>
</tr>
<tr>
<td>Br</td>
<td>79.904</td>
</tr>
<tr>
<td>Kr</td>
<td>83.80</td>
</tr>
<tr>
<td>Rb</td>
<td>85.408</td>
</tr>
<tr>
<td>Sr</td>
<td>87.62</td>
</tr>
<tr>
<td>Y</td>
<td>88.906</td>
</tr>
<tr>
<td>Zr</td>
<td>91.224</td>
</tr>
<tr>
<td>Nb</td>
<td>92.906</td>
</tr>
<tr>
<td>Mo</td>
<td>95.94</td>
</tr>
<tr>
<td>Tc</td>
<td>98.79</td>
</tr>
<tr>
<td>Ru</td>
<td>101.07</td>
</tr>
<tr>
<td>Rh</td>
<td>102.91</td>
</tr>
<tr>
<td>Pd</td>
<td>106.42</td>
</tr>
<tr>
<td>Ag</td>
<td>107.87</td>
</tr>
<tr>
<td>Cd</td>
<td>112.41</td>
</tr>
<tr>
<td>In</td>
<td>114.82</td>
</tr>
<tr>
<td>Sn</td>
<td>118.71</td>
</tr>
<tr>
<td>Sb</td>
<td>121.79</td>
</tr>
<tr>
<td>Te</td>
<td>127.60</td>
</tr>
<tr>
<td>I</td>
<td>126.90</td>
</tr>
<tr>
<td>Xe</td>
<td>131.29</td>
</tr>
<tr>
<td>Cs</td>
<td>132.91</td>
</tr>
<tr>
<td>Ba</td>
<td>137.33</td>
</tr>
<tr>
<td>La</td>
<td>138.90</td>
</tr>
<tr>
<td>Ce</td>
<td>140.12</td>
</tr>
<tr>
<td>Pr</td>
<td>140.91</td>
</tr>
<tr>
<td>Nd</td>
<td>144.24</td>
</tr>
<tr>
<td>Pm</td>
<td>144.93</td>
</tr>
<tr>
<td>Sm</td>
<td>150.36</td>
</tr>
<tr>
<td>Eu</td>
<td>151.97</td>
</tr>
<tr>
<td>Gd</td>
<td>157.25</td>
</tr>
<tr>
<td>Tb</td>
<td>158.93</td>
</tr>
<tr>
<td>Dy</td>
<td>162.5</td>
</tr>
<tr>
<td>Ho</td>
<td>164.93</td>
</tr>
<tr>
<td>Er</td>
<td>167.26</td>
</tr>
<tr>
<td>Tm</td>
<td>168.93</td>
</tr>
<tr>
<td>Yb</td>
<td>173.04</td>
</tr>
<tr>
<td>Lu</td>
<td>174.97</td>
</tr>
</tbody>
</table>

### Source of information

Nordberg GF, Fowler BA and Nordberg M. (Editors)

**Handbook on the Toxicology of Metals**

4th edition. 2015


ISBN 978-0-12-398292-6 (Volume I)
ISBN 978-0-12-398293-3 (Volume II)
Health effects of metals

• Many metals are “essential”
  Fe, Cu, Co, Zn, Mn, Mo, ...
  ➢ deficiencies lead to disease
  ➢ excesses lead to disease
• Some metals are non-essential
  Pb, Cd, Hg, As, Sn, U, ...
  ➢ low levels of exposure may lead to disease

“Heavy” metals
Biological effects of metals

Binding with ligands

- **transport** (transferrin, ferritin, albumin, ceruloplasmin)
- **accumulation** (metallothionein)

- binding with functional groups (-SH) on enzymes
- binding with tissue proteins: antigenicity
- interactions with DNA: mutagenicity
Fe\(^{2+}/Fe^{3+}\), Cu\(^{1+}/Cu^{2+}\), Co\(^{2+}/Co^{3+}\)

- catalysis of biological **redox** reactions:
  - cytochromes (Fe), catalase (Fe), superoxide dismutase (Cu, Zn, Mn), xanthine oxidase (Mo, Fe)
- production of **toxic metabolites of oxygen**

\[
\begin{align*}
\text{Fe} & \quad \text{O}_2^- + \text{H}_2\text{O}_2 & \rightarrow & \text{O}_2 + \text{OH}^- + \text{OH}^-
\end{align*}
\]

**Ability to change oxidation state**

**metal speciation**

- dose
- exposure conditions
- host factors

**biological effects**
Metal speciation

- Metallic (valence 0)
  - Pure metal
  - Alloys
- Ionic (generally +)
  - Oxides
  - Salts
  - Complexes
  - ...
- Organometallic compounds

Metal speciation

physico-chemical properties

solubility
bioavailability

toxicokinetics

+ size！
nanomaterials

dose
exposure conditions
host factors

biological effects
Metal speciation

- Influences type of exposure
  - e.g. gaseous forms of metals
    
    \[ \text{Hg}^\circ, \text{AsH}_3, \text{Ni(CO)}_4 \rightarrow \text{rapid respiratory uptake and systemic distribution} \]

Metal speciation

- Influences cellular bioavailability
  - e.g. degree of oxidation of Cr
    - \( \text{Cr}^{\text{III}} \): “non toxic, non allergenic, non carcinogenic”
    - \( \text{Cr}^{\text{VI}} \): toxic, allergenic, carcinogenic
Sialkot (Pakistan)
• children (♂, 10-14y)
  • 104 working
  • 75 schoolchildren
  ➢ Questionnaire
  ➢ Pulmonary function
  ➢ Urine: 20 metals

8-OHdG (reflects oxidative DNA damage)

• More reported asthma & cough in working children
• No differences in lung function
• Concentrations of stainless steel-related metals much higher in working children
  ➢ Cr-U (μL/L)  GM [25th-75th percentile]
    Schoolchildren:  0.7 [0.4-1.1]
    Working children: 23 [8.3-59]
    (BEI for adults = 25 μg/L)
Speciation and the toxicity of Hg

- The human toxicity of Hg-compounds is highly dependent on the species of Hg
  - Hg° (metallic)
  - Hg ions (Hg⁺ or Hg⁺⁺): HgCl₂, HgI₂, Hg(NO₃)₂, ...
  - organic Hg:
    - Hg(CH)₃, Hg(CH₃)₂, ...
    - Long chain Hg (insecticides, fungicides, bactericides, …)

Clarkson et al. NEJM 2003, 349, 1731-7

Toxicity of Hg

- Acute poisoning
  - ingestion (salts): G-I, kidney, shock
  - inhalation (Hg°): chemical pneumonitis
  - (parenteral Hg°: little toxicity)
Toxicity of Hg

- Chronic exposure (inhalation of Hg°):
  - CNS: tremor, personality changes, psychomotor performance,
  - PNS: sensorimotor polyneuropathy
  - discrete renal changes
  - gingivitis
  - eye: mercurialentis, colour vision
  - immune dysfunction
  - teratogenic
Toxicity of Hg

- Chronic exposure (ingestion of CH$_3$Hg):
  - CNS: toxicity for CNS (cerebellum)
  - Teratogenic & neuropsychological development
  - Cardiovascular effects??*

* no: Mozaffarian et al. NEJM 2011, 364; 1116-25

Lauwerys et al. Human Toxicology, 1987, 6, 253-6

- Baby, 3 month, African origin
  - renal tubular dysfunction (Fanconi) + cataract
  - screening for heavy metals:
    - Hg-B 1.9 μg/100 ml (NI < 1)
    - Hg-U 274 μg/g creat. (NI < 25)
  - in mother
    - Hg-B 9.1 μg/100 ml - Hg-U 784 μg/ml

- skin-lightening soap (Hgl$_2$) during pregnancy
  - NYC (EHP, 5 Oct 2010), UK (BMJ, 23 Nov 2010 ), ...
Potential health consequences of applying mercury-containing skin-lightening creams during pregnancy and lactation periods

Iman Al-Saleh
Environmental Health Program, Research Center, King Faisal Specialist Hospital and Research Centre, P.O. Box 3554, Riyadh 11211, Saudi Arabia

ARTICLE INFO
Article history:
Received 20 January 2016
Received in revised form 9 March 2016
Accepted 10 March 2016

Keywords:
Mercury
Skin-lightening creams
Women
Reproductive toxicity
Pregnancy
Lactation

ABSTRACT
Many studies have highlighted the widespread use of skin-lightening creams containing mercury by women during and after pregnancy to remove dark spots. Women, especially pregnant and lactating mothers using these products are at risk of mercury poisoning because sometimes it has no clinical symptoms, particularly during early exposure. Studies have shown that prenatal and postnatal mercury exposure can cause permanent neurological damage in children. Furthermore, mercury can cause women infertility and birth defects. Even though several studies have examined the reproductive and/or developmental consequences of gestational and lactational mercury exposure from fish consumption and/or dental amalgam, no studies have assessed the possible effects of the long-term use of mercury-containing skin-lightening products by women of childbearing age on their pregnancy outcome and children’s health. This commentary aims to collate information on the popular use of mercury-containing skin-lightening creams and sheds the light to the readers about the limitations of the available data on its impact during a prenatal and/or postnatal period. There is an urgent need to assess the adverse health effects of applying these products during pregnancy or lactation on child growth and development through birth cohort studies. Until data from these studies are available, women should be advised not to use topical skin-lightening creams during pregnancy and lactation.

Skin-lightening products are sold in different forms, including soaps and creams; the soap is usually marketed as “antiseptic soap” (Glahder et al., 1999; UNEP, 2008). The use of skin-lightening creams has become a common practice among women for cosmetics purposes (Olumide et al., 2008; Adawe and Oberg, 2013). The creams are extensively promoted online, by the media, and sometimes even by dermatologic clinics. Their use has been popular for decades among women throughout the world, mainly in Africa and Asia. Having a light skin or fair complexion has become an aspiration for many people around the world, and the use of skin-lightening creams has become an increasingly popular cosmetic practice in other parts of the world (Blay, 2011; Ladizinski et al., 2011; Dlova et al., 2015) despite several published studies on their adverse health effects after extended application. According
their adverse health effects after extended application. According to a 2015 report by global industry analysts covering major geographic regions such as the USA, Japan, Europe, Asia-Pacific (China, India, and “Rest of Asia-Pacific”), and “Rest of World” (http://www.researchandmarkets.com/reports/1056077), the market for skin-lightening creams is projected to reach US$23.0 billion by 2020.

Mercury is added to creams because of its ability to inhibit the pigment melanin (Engler, 2005). The hypothesis is that mercury may replace the copper required for tyrosinase activity and thereby inactivate the enzyme, leading to the whitening action (Denton et al., 1952). Inorganic mercury is used in these creams because the skin easily absorbs it (Palmer et al., 2000). Organic forms such as phenyl mercuric acetate are sometimes used as cosmetic preservatives, and inorganic forms, such as ammoniated mercury, are the active ingredients in skin-lightening creams (Marzulli and Brown, 1972).
Case

- Man, 57 y, D. R. Congo, politician
- “Fear of being poisoned”

NI: 29.11.2010 - 11.01.2011

<table>
<thead>
<tr>
<th>Hg-B</th>
<th>67 μg/L</th>
<th>43 μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hg-U</td>
<td>26 μg/g creat.</td>
<td>25 μg/g creat.</td>
</tr>
</tbody>
</table>

Harada et al. Sci Tot Environ 2001, 269, 183-7

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Company (city)</th>
<th>Country</th>
<th>Total mercury (μg/mL)</th>
<th>Mercury ionic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top</td>
<td>NI (ND)</td>
<td>Spain</td>
<td>7.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Jumbo</td>
<td>Jumbo (ND)</td>
<td>UK</td>
<td>6.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Jaribu</td>
<td>Anglo Fabrics Ltd (Bolton)</td>
<td>England</td>
<td>6.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Rico</td>
<td>Rico Skin Care Ltd UND</td>
<td>UK</td>
<td>6.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Miki</td>
<td>C &amp; C International Ltd (ND)</td>
<td>UK</td>
<td>5.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Shabba</td>
<td>Paramount Manufacturing Co (ND)</td>
<td>England</td>
<td>2.1</td>
<td>0.47</td>
</tr>
<tr>
<td>Movate</td>
<td>Melzo (Milan)</td>
<td>Italy</td>
<td>7.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Dorot</td>
<td>Cassons &amp; Co Ltd (Nairobi)</td>
<td>Kenya</td>
<td>0.18 x 10⁻³</td>
<td>0.41 x 10⁻⁴</td>
</tr>
<tr>
<td>Neko</td>
<td>Obei Chemical Industries Ltd (Nairobi)</td>
<td>Kenya</td>
<td>2.3 x 10⁻³</td>
<td>5.3 x 10⁻⁴</td>
</tr>
<tr>
<td>Gesa</td>
<td>East Africa Industries Ltd (Nairobi)</td>
<td>Kenya</td>
<td>0.08 x 10⁻³</td>
<td>2.0 x 10⁻⁴</td>
</tr>
<tr>
<td>A sepso</td>
<td>East Africa Industries Ltd (Nairobi)</td>
<td>Kenya</td>
<td>0.11 x 10⁻³</td>
<td>0.25 x 10⁻⁴</td>
</tr>
<tr>
<td>Choice</td>
<td>NI (ND)</td>
<td>NI</td>
<td>0.34 x 10⁻³</td>
<td>0.78 x 10⁻⁴</td>
</tr>
<tr>
<td>Cassons</td>
<td>NI (ND)</td>
<td>NI</td>
<td>0.34 x 10⁻³</td>
<td>0.78 x 10⁻⁴</td>
</tr>
</tbody>
</table>
Mekako Soap

Product Description

Mekako is famous brand in ethica people. It's function of this soap is mysterious. Day and
by used, you can found your skin changed perfect. That's you want Langa for even in
dreams.

There are 3 mekako soap from 3 suppliers on Alibaba.com.

Product Details

Quick Details

Type: Toilet Soap

Environment: No

Specifications

We supply mekako soap, please contact us.

We posted mekako soap...
Lead, Mercury, and Arsenic in US- and Indian-Manufactured Ayurvedic Medicines Sold via the Internet

Robert B. Saper, MD, MPH
Russell S. Phillips, MD
Anusha Sehgal, MD (Ayurveda)
Naduz Khoury, MPH
Roger B. Davis, ScD
Janet Paquin, PhD
Venkatesh Thrupul, PhD
Stefanos N. Kalos, MD, MPH

Ayurveda is a traditional medical system used by a majority of India’s 1.1 billion population. Ayurveda is also used worldwide by the South Asian diaspora and others. However, since 1978 more than 80 cases of lead poisoning associated with Ayurvedic medicine use have been reported worldwide. Ayurvedic medicines are divided into 2 major types: herbal and rasa shastra. Rasa shastra is an ancient practice of deliberately combining herbs with metals (eg, mercury, lead, iron, zinc), minerals (eg, mica), and gems (eg, pear). Rasa shastra experts claim that these medicines, if properly prepared and administered, are safe and therapeutic.

Context: Lead, mercury, and arsenic have been detected in a substantial proportion of Indian-manufactured traditional Ayurvedic medicines. Metals may be present due to the practice of rasa shastra (combining herbs with metals, minerals, and gems). Whether toxic metals are present in both US- and Indian-manufactured Ayurvedic medicines is unknown.

Objectives: To determine the prevalence of Ayurvedic medicines available via the Internet containing detectable lead, mercury, or arsenic and to compare the prevalence of toxic metals in US- vs Indian-manufactured medicines and between rasa shastra and non-rasa shastra medicines.

Design: A search using 5 Internet search engines and the search terms Ayurveda and Ayurvedic medicine identified 25 Web sites offering traditional Ayurvedic herbs, formulas, or ingredients commonly used in Ayurveda, indicated for oral use, and available for sale. From 673 identified products, 210 Ayurvedic medicines were randomly selected for purchase in August-October 2005. Country of manufacturer/Web site supplier, rasa shastra status, and claims of Good Manufacturing Practices were recorded. Metal concentrations were measured using x-ray fluorescence spectroscopy.

Main Outcome Measures: Prevalence of medicines with detectable toxic metals in the entire sample and stratified by country of manufacture and rasa shastra status.

Results: One hundred ninety-three of the 230 requested medicines were received and analyzed. The prevalence of metal-containing products was 20.7% (95% confidence interval 19.2%, 22.2%). The prevalence of metals in US-manufactured products was 21.8% (95% CI, 19.4% to 24.2%) compared with 19.9% (95% CI, 11.3% to 30.1%) in Indian products (P = .86). Rasa shastra compared with non-rasa shastra medicines had a greater prevalence of metals (40.6% vs 17.1%; P < .001) and higher median concentrations of lead (11.5 μg/g vs 7.0 μg/g; P = .03) and mercury (20,600 μg/g vs 34.5 μg/g; P = .04). Among the metal-containing products, 99% were sold by US Web sites and 75% claimed Good Manufacturing Practices. All metal-containing products exceeded 1 or more standards for acceptable daily intake of toxic metals.

Conclusion: One-fifth of both US-manufactured and Indian-manufactured Ayurvedic medicines purchased via the Internet contain detectable lead, mercury, or arsenic.
Hg & the “personal” environment

• dental amalgams
  • no evidence for significant toxicity resulting from placement of dental amalgams or from their presence (except rare instances of Hg allergy)
  • probably safer not to place amalgam fillings during pregnancy [precautionary principle]

Hg & the domestic environment

• Broken thermometers (500 mg Hg) & other medical devices
• Broken compact fluorescent lamps (CFL, “energy saving light bulbs”): 5 mg Hg
  • http://www.epa.gov/cfl/cflcleanup.html
  • http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_124.pdf [SCHER 18.05.2010]: “human health risk for adults unlikely”, children ?
• Nance et al. Human health risks from mercury exposure from broken compact fluorescent lamps (CFLs). Regul Toxicol Pharmacol 2012, 62, 542-52
Hg & the domestic environment

- Cultural or religious use of Hg
- Hg brought home from work, incl. dental offices
- “cottage industry” (reclaiming of silver and gold from ore or from old amalgams)

Acrodynia in a 2 y old child

Case (2008, UZ Leuven):
- Child 2 y
- Acrodynia (erythema, scaling), no other symptoms
- Hg-U: 15 μg/g creatinine (NI < 5)
- Detailed exposure history: no obvious exposure to mercury source, but family moved into newly built house; baby slept in small bedroom in freshly laid concrete floor without cover.
- Hypothesis: emission of Hg from cement?
Hg in cement?

M. De Ceulaer, Thesis Master of Safety, 2012

• Concentration of Hg in cement (n=6):
  • median 410 μg/kg [<LOD - 4166 μg/kg]

• Concentration of Hg in air samples (n=35), after placing concrete floor:
  • median 131 ng/m³ (<LOD - 273 ng/m³)

Hg in the general environment

A The Global Cycle of Mercury
Hg in the general environment

Clarkson et al. NEJM 2003, 349, 1731-7

Hg in the general environment

Clarkson et al. NEJM 2003, 349, 1731-7
Hg & the general environment

- Minamata disease (1950s → 1960 → )
- effluent from factory + biotransformation by marine organisms → consumption of fish contaminated by CH$_3$Hg

Larson HJ. *Lancet*, 2013, October 10

The Minamata Convention on Mercury: risk in perspective

On Oct 10, 2013, a document is to be signed in Kumamoto, Japan that will not only be historic in its ambitions, but also a memorial to local history where the first case of Minamata disease was identified in 1956.

Minamata disease is caused by mercury poisoning and results in severe neurological damage. In the first identified case of the debilitating disease in Minamata city, mercury poisoning was traced to chemical waste, which had been dumped into the nearby sea by the Chisso Corporation. The waste led to accumulated mercury poisoning of fish, and consequent devastating effects including severe neurological disorders for thousands who had consumed the fish as their main food source. More than 900 died due to mercury-related poisoning and others lived with long-term disabling conditions.
Dose (concentration x time)

- determines degree of damage
  - *e.g.* Cd
- high/acute exposure → pulmonary oedema
- moderate/chronic exposure
  → emphysema
  → lung cancer
  → kidney damage
  → bone damage
Cd and osteoporosis

- Itai-Itai disease (high environmental exposure)
- Also at lower exposures?

Study

- Company producing radiators and convectors
- Discovery of high cadmium exposure in relation to soldering process

➢ Cross-sectional study: effect of Cd exposure on bone mineral density?
Solder: Ag (20-50 %), Cu (10-40 %), Cd (15-30 %)
The start of non-ferro industry in Flanders
Incidence of total cancer

![Graph showing the incidence of total cancer with low and high exposure groups.](image)


Incidence of lung cancer

![Graph showing the incidence of lung cancer with low and high exposure groups.](image)

Exposure conditions

- exposure to other agents
e.g. inhaled Cobalt compounds

  - Co alone → asthma, but no interstitial lung disease
  - Co with tungsten carbide (WC) = “hard metal”
    - Hard metal Lung Disease, “Cobalt Lung” ¹
    - Lung cancer (IARC2A) ²

² IARC Vol 86, 2006
Cobalt (e- donor) + Tungsten Carbide (e- carrier) → Active oxygen species!


Hard metal
Diamond tooling

Diamond polishing with diamond-cobalt disks
**Thermal spraying of hard metal**

*Hard facing*

- **F-24 y-NS**
- Diamond polisher
- TLC 49% pred
- DLco 27% pred

Images showing an x-ray and CT scans from 1986 and 1991, highlighting the progression of lung conditions.

Images of workers engaged in hard facing tasks, demonstrating the process of thermal spraying of hard metal.
Case 13-09-2006

Hard Metal Lung – Cobalt Lung

Giant cell Interstitial Pneumonia (GIP)

Multinucleated “cannibalistic” giant macrophages

Courtesy E.K. Verbeken
Toxicity of Pb

• “LOW” CHRONIC DOSE
  • household paint decay (indoor dust)
  • leaded gasoline (soil contamination)
  • lead smelters (soil contamination)
  • drinking water (pipes + soft acidic water)
  • food
  • ceramic glazing
  • cosmetics and folk medicines
Neurobehavioral effects of low levels of Pb

Needleman et al. (NEJM 1979;300:689-95)

- 7 y old children
- dentin Pb > 20 ppm vs < 10 ppm
  - lower IQ
  - ↓ speech & language processing
  - ↓ attention
- controlling for confounders
- no history of clinical Pb poisoning
Neurobehavioral effects of low levels of Pb

Needleman et al. (NEJM 1990;322:83-88)

- follow-up 132/270 children studied 1975-78
- dentin Pb > 20 ppm vs < 10 ppm
  - drop-out from high school: O.R. 7.4
  - reading disability: O.R. 5.8
  - lower class standing
  - more absenteeism & minor delinquency
  - poorer vocabulary & hand-eye coordination
Neurobehavioral effects of low levels of Pb

Baghurst et al. (NEJM 1992;327:1279-84)

- Port Pirie cohort study (Australia)
- 494 children 0 - 7y
- Pb-B
  - mother antenataly + delivery
  - umbilical cord, 6 mo, 15 mo, 2 y, annually
- inverse correlation between Pb-B and IQ
  - from 10 μg/dl to 30 μg/dl: IQ - 4.4-5.3 points
Neurobehavioral effects of low levels of Pb

Canfield et al. (NEJM 2003;348:1517-26)
- 172 children 6 mo - 5 y
- Pb-B
  - 6, 12, 18, 24, 36, 48, 60 mo
  - Stanford-Binet Intelligence Scale at 3 and 5 y
- inverse correlation between Pb-B and IQ
  - increase of 10 μg/dl (average): IQ -4.6 points
  - even if Pb-B < 10 μg/dl (n=101): IQ -7.4 points for average lifetime 1 to 10 μg/dl
  - adjusted for maternal IQ, quality of home environment, etc

---

Mass Lead Intoxication from Informal Used Lead-Acid Battery Recycling in Dakar, Senegal

Pascal Haefliger,1 Monique Mathieu-Noff,2 Stephanie Locciro,1 Cheikh Ndiaye,2 Malang Coly,3 Amadou Diouf,4 Absa Lam Faye,4 Aminata Sow,5 Joanna Tempowski,1 Jenny Pronczuk,1 Antonio Pedro Filipe Junior,3 Roberto Bertolli,1 and Maria Neira1

1Department of Public Health and Environment, World Health Organization, Geneva, Switzerland; 2Centre Anti-Poison, CHRU Lille, Lille, France; 3Senegal Country Office, World Health Organization, Dakar, Senegal; 4Centre Anti-Poison, Dakar, Senegal; 5Hôpital de Pikine, Pikine, Dakar, Senegal

BACKGROUND AND OBJECTIVES: Between November 2007 and March 2008, 18 children died from a rapidly progressive central nervous system disease of unexplained origin in a community involved in the recycling of used lead-acid batteries (ULAB) in the suburbs of Dakar, Senegal. We investigated the cause of these deaths.

METHODS: Because autopsies were not possible, the investigation centered on clinical and laboratory assessments performed on 32 siblings of deceased children and 23 mothers and on 18 children and 8 adults living in the same area, complemented by environmental health investigations.

RESULTS: All 81 individuals investigated were poisoned with lead, some of them severely. The blood lead level of the 50 children tested ranged from 39.8 to 613.9 μg/dL with a mean of 129.5 μg/dL. Seventeen children showed severe neurologic features of toxicity. Holmes and soil in surrounding areas were heavily contaminated with lead (indoors, up to 14,000 mg/kg; outdoors, up to 302,000 mg/kg) as a result of informal ULAB recycling.

CONCLUSIONS: Our investigations revealed a mass lead intoxication that occurred through inhalation and ingestion of soil and dust heavily contaminated with lead as a result of informal and unsafe ULAB recycling. Circumstantial evidence suggested that most or all of the 18 deaths were due to encephalopathy resulting from severe lead intoxication. Findings also suggest that most inhabitants of the contaminated area, estimated at 950, are also likely to be poisoned. This highlights the severe health risks posed by informal ULAB recycling, in particular in developing countries, and emphasizes the need to strengthen national and international efforts to address this global public health problem.


Selection of study participants. All siblings of the 18 deceased children and all of the siblings’ mothers (exact number unknown) were invited by the local health authorities to participate in the study. A total of 32 siblings and 23 siblings’ mothers agreed to participate. A second group of 18 children and 8 adults was selected with the assistance of local community leaders using the following selection criteria: They were not related to the deceased children, they were living in the NGagne Diaw neighborhood, and their age and sex had to be equally distributed. It was not possible to match study groups. All study participants or their representatives gave written consent to participate in the study. The study was approved by the Senegalese national ethics committee.

We considered all 18 children from the NGagne Diaw neighborhood who died from a rapidly progressive central nervous system disease of unexplained origin between November 2007 and March 2008 to be possible victims of lead intoxication.
Pb and pre-eclampsia in Kinshasa

Kinshasa: pre-eclampsia

- Highly prevalent
- Season-dependent:
  - 6% in rainy season
  - 13% in dry season

Higher exposure to metal-contaminated dust?

Elongi et al. Under review
Occupational allergic asthma

Metallic agents

- **platinum** (complex salts)
- **cobalt** (hard metal, diamond tools, pigments, …)
- **chromium** (stainless steel, electroplating, cement, pigments, …)
- **nickel**
- [aluminium: “potroom asthma”]
- other
Case

- Male, 51 y, referred (29/01/2002) by occupational physician
- Smoker (~30 packyears) until 4 mo ago
- No previous respiratory disease
- Worker, since 32 y, in metal refining plant
  - ~ 22 y Selenium
  - ~ 5 y “various”
  - ~ 5 y Indium
  - Since early 2001: development of production of “very pure cobalt”

Case

- During holiday abroad (09/2001): “bronchitis” R/ antibiotics + sick leave for 1 wk
- Upon work resumption:
  - First day: cough & dyspnea +++
  - After 2 days: local hospital (6 days)
    - No infection, no atopy
    - Chest x-ray: no signs of ILD
    - Severe “asthmatic bronchitis”: FEV$_1$ 41% pred.
    - R/ oral corticosteroids, then asthma therapy
- Sick leave until end of 2001:
  - 20/12/2001: FEV$_1$ 63% pred.
Case

• 01/2002: resumed work, mainly administrative tasks, but still occasional contact with cobalt laboratory
  • Work-related dyspnea
  • Nonspecific bronchial hyperresponsiveness
  • Reduced exercise tolerance

Case

29/01/2002

• Clinical examination: no abnormalities

• Pulmonary function:
  • FVC 4.36 L 100%
  • FEV₁ 2.67 L 76% (+5% after β₂)
  • TLC 6.84 L 100%
  • DLco 7.5 U 75%
  • Kco 1.18 U 81%

04/02/2002

• Histamine PC₂₀ 0.64 mg/mL (nl > 8 mg/mL)
Case

- Occupational asthma caused by cobalt?

Specific bronchial provocation with

\[ \text{CoCl}_2 \text{ 0.01\% administered by nebulizer} \]

= 0.1 mg CoCl\(_2\).\(6\)H\(_2\)O mg/mL

= 0.4 mmol/L

= 0.024 mg Co\(^{++}\)/mL

**Day 1**

- 30 min NaCl 0.9%

- Histamine PC\(_{20}\) 1.81 mg/ml
Day 2

CoCl₂ 0.01%

Day 3

CoCl₂ 0.01%
Day 4

CoCl₂ 0.01%

15 min

FEV₁ (% start)

Day 5

histamine PC₂₀
0.56 mg/ml

Urinary cobalt

24 h collections
(8 am – 8 am)

Co-U (µg/g creat)

-27
1
2
3
4

day
male, 48 y, floorer
allergic contact dermatitis to cement ($Cr^VI$)

male, 48 y, floorer
allergic contact dermatitis to cement (CrVI)


Chronic Beryllium lung Disease
(CBD, Berylliosis)

• Be used in (light) alloys (aerospace, electronics, dental, …), ceramics, nuclear weapons, …
  ➢ granulomatous lung disease (≈ sarcoidosis)
• cellular (type IV) immune response to Be
  ➢ diagnosis: Be Lymphocyte Proliferation Test
    ex vivo incubation of lymphocytes with Be salt
    if proliferation (SI > 3): proof of sensitization to Be
• HLA-DPβ1 glu69 confers high susceptibility
84 sarcoidosis patients with possible exposure to Be were re-evaluated for Be exposure (1997-2005; Borstel, Freiburg, Tel Aviv)
- detailed occupational history
- 2 Be-LPT with blood lymphocytes

34 diagnosed with CBD

**TABLE 2** Workplaces and occupational settings with beryllium exposure identified by occupational case history

<table>
<thead>
<tr>
<th>Occupational beryllium exposure</th>
<th>CBD</th>
<th>Exposed sensitised healthy</th>
<th>Exposed nonsensitised healthy</th>
<th>Sarcoïdosis exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals</td>
<td>34</td>
<td>7</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Dental technician/dentist</td>
<td>13</td>
<td>1 (1/0)</td>
<td>4 (4/0)</td>
<td>10 (6; 4)</td>
</tr>
<tr>
<td>Engine development/mechanics/ automobile industry</td>
<td>2 (1/1)</td>
<td>2 (2/0)</td>
<td>1 (1/0)</td>
<td>7 (7/0)</td>
</tr>
<tr>
<td>Brass alloys, beryllium-containing alloys&lt;sup&gt;*&lt;/sup&gt;</td>
<td>4 (4/0)</td>
<td>1 (1/0)</td>
<td>14 (8/6)</td>
<td></td>
</tr>
<tr>
<td>Metallurgic factory</td>
<td>2 (1/1)</td>
<td></td>
<td>4 (1/3)</td>
<td></td>
</tr>
<tr>
<td>Aircraft production and maintenance</td>
<td>3 (2/1)</td>
<td></td>
<td>2 (2/0)</td>
<td></td>
</tr>
<tr>
<td>Nonsparking tools</td>
<td>1 (1/0)</td>
<td></td>
<td>1 (1/0)</td>
<td></td>
</tr>
<tr>
<td>Radiation shielding</td>
<td>1 (0/1)</td>
<td>1 (1/0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Military vehicle armour</td>
<td>2 (1/1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescent lamps</td>
<td>2 (1/1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microelectronics/electrical relays</td>
<td>1 (1/0)</td>
<td>1 (1/0)</td>
<td>8 (6/2)</td>
<td></td>
</tr>
<tr>
<td>Chemical industry&lt;sup&gt;+&lt;/sup&gt;</td>
<td>1 (1/0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engraving of gems</td>
<td>1 (1/0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ore mining</td>
<td>1 (1/0)</td>
<td></td>
<td>1 (1/0)</td>
<td></td>
</tr>
<tr>
<td>Grinding of optical lenses for precision instruments</td>
<td>1 (1/0)</td>
<td>1 (1/0)</td>
<td>2 (2/0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as total n (patients in Germany/patients in Israel). CBD: chronic beryllium disease. <sup>*</sup> galvanic industry, ship yards, metal processing; <sup>+</sup> additive to glass, ceramics, plastics/catalyst; <sup>+</sup> i.e. contaminated garments.
Sarcoidosis and exposures?

• Sarcoidosis is a diagnosis of exclusion!
• always evaluate the possibility of an exogenous cause
  ➢ silica
  ➢ talc
  ➢ beryllium (Be-LPT)
  ➢ other metals (Al, Zr, Cr, Co, …)
  ➢ “inorganic particles” (WTC)
  ➢ atypical mycobacteria


Contrary to this drawing, there is no simple test. The suspicion and the determination of work-relatedness depend primarily on a careful occupational history

From LEVY BS, WEGMAN DH. Occupational health (3d ed), p.60
When you find one case of occupational disease, there are likely more around ...

In occupational medicine, n is nearly always >1

Modified From LEVY BS, WEGMAN DH. Occupational health (3rd ed), p.60

Thank you for your attention

ben.nemery@kuleuven.be