<<NOTE TO USER:  Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation in the space indicated.>>

<<NOTE TO USER:  This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation.  These slides cover many facets of the problem.  Present only those slides that apply most directly to the local situation in the region.  Please replace the examples, data, pictures and case studies with ones that are relevant to your situation.>>

<<NOTE TO USER: This slide set discusses routes of exposure, adverse health effects and case studies from environmental exposure to heavy metals, other than lead and mercury, please go to the modules on lead and mercury for more information on those. Please refer to other modules (e.g. water, neurodevelopment, biomonitoring, environmental and developmental origins of disease) for complementary information>>
The scope of this module is to provide an overview of the public health impact, adverse health effects, epidemiology, mechanism of action and prevention of heavy metals (other than lead and mercury) toxicity in children.

**LEARNING OBJECTIVES**

- To define the spectrum of heavy metals (others than lead and mercury) with adverse effects on human health
- To describe the epidemiology of adverse effects of heavy metals (Arsenic, Cadmium, Copper and Thallium) in children
- To describe sources and routes of exposure of children to those heavy metals
- To understand the mechanism and illustrate the clinical effects of heavy metals’ toxicity
- To discuss the strategy of prevention of heavy metals' adverse effects
Children and heavy metals

WHY HEAVY METALS?

WHO 10 chemicals of major public health concern including heavy metals

- Air pollution
- Arsenic
- Asbestos
- Benzene
- Cadmium
- Dioxin and dioxin-like substances
- Inadequate or excess fluoride
- Lead
- Mercury
- Highly hazardous pesticides

Chemicals are part of our daily life. All living and inanimate matter is made up of chemicals and virtually every manufactured product involves the use of chemicals. Many chemicals can, when properly used, significantly contribute to the improvement of our quality of life, health and well-being. But other chemicals are highly hazardous and can negatively affect our health and environment when improperly managed. WHO compiled a list of the 10 major chemicals of concern, which includes many heavy metals:

- Air pollution
- Arsenic
- Asbestos
- Benzene
- Cadmium
- Dioxin and dioxin-like substances
- Inadequate or excess fluoride
- Lead
- Mercury
- Highly hazardous pesticides

Notes from:

The "periodic table" or Mendeleev's table, organizes chemical elements according to their atomic number, electron configuration and valence numbers. This table illustrates the groups of elements.

The main heavy metals are listed below, with their atomic numbers, symbols and names:

4 - Beryllium (Be)  
13 - Aluminum (Al)  
24 - Chrome (Cr)  
25 - Manganese (Mn)  
26 - Iron (Fe)  
27 - Cobalt (Co)  
28 - Nickel (Ni)  
29 - Copper (Cu)  
30 - Zinc (Zn)  
33 - Arsenic (As)  
34 - Selenium (Se)  
42 - Molybdenum (Mo)  
47 - Silver (Ag)  
48 - Cadmium (Ca)  
50 - Tin (Sn)  
51 - Antimony (Sb)  
60 - Mercury (Hg)  
80 - Mercury (Hg)  
81 - Thallium (Tl)  
82 - Lead (Plumbum, Pb)

Motivations for controlling heavy metal concentrations in gas streams are diverse. Some of them are dangerous to health or to the environment (e.g. Hg, Cd, As, Pb, Cr), some may cause corrosion (e.g. Zn, Pb), some are harmful in other ways (e.g. arsenic may pollute catalysts). Within the European community, the 13 elements of highest concern are As, Cd, Co, Cr, Cu, Hg, Mn, Ni, Pb, Sn, and Tl, the emissions of which are regulated in waste incinerators. Some of these elements are actually necessary for humans in minute amounts (Co, Cu, Cr, Ni) while others are carcinogenic or toxic, affecting, among others, the central nervous system (Hg, Pb, As), the kidneys or liver (Hg, Pb, Cd, Cu) or skin, bones, or teeth (Ni, Cd, Cu, Cr).[^1]

Heavy metal pollution can arise from many sources but most commonly arises from the purification of metals, e.g., the smelting of...
copper and the preparation of nuclear fuels. Electroplating is the primary source of chromium and cadmium. Through precipitation of their compounds or by ion exchange into soils and mud, heavy metal pollutants can localize and lay dormant. Unlike organic pollutants, heavy metals do not decay and thus pose a different kind of challenge for remediation. Currently, plants or microorganisms are tentatively used to remove some heavy metals such as mercury. Plants which exhibit hyper accumulation can be used to remove heavy metals from soils by concentrating them in their bio matter. Some treatment of mining tailings has occurred where the vegetation is then incinerated to recover the heavy metals.

In medical usage, heavy metals are loosely defined and include all toxic metals irrespective of their atomic weight: "heavy metal poisoning" can possibly include excessive amounts of iron, manganese, aluminum, mercury, or beryllium (the fourth lightest element) or such a semimetal as arsenic. This definition excludes bismuth, the heaviest of approximately stable elements, because of its low toxicity.

Refs:
• Malkoç S et al. Street dust pollution of some metals along Eskisehir urban roads, Turkey. Available at bildiri.anadolu.edu.tr/papers/bildirimakale/3492_b353n54.pdf – accessed 22 September 2011
• Zevenhoven, Kilpinen. Trace elements. Alkali metals. 2001. 8-27

Image from www.webelements.com – used with copyright permission
In medicine, heavy metals are often not well defined and include all toxic metals (including lighter ones): "heavy metal poisoning" can possibly include excessive amounts of iron, manganese, aluminum, mercury, or beryllium (the fourth lightest element) or such a semimetal as arsenic. This definition excludes bismuth, the heaviest of approximately stable elements, because of its low toxicity.

There are various definitions used for heavy metals. Many are based on specific gravity. This slide states several of these definitions.

Refs:
- US Environmental Protection Agency (EPA). EPA’s Terms of Environment. U.S. Environmental Protection

Other ways to define heavy metals are based on atomic weight. This slide shows examples of these definitions.

Refs:
• Streit B. Lexikon der Okotoxikologie. VCH, Weinheim. 1994.

Some heavy metals have essential roles for human health. Listed in this slide are several examples of health attributes of heavy metals, including:

- **Copper** – is an integral part of numerous enzymes including ferro-oxidase (ceruloplasmin), cytochrome – c – oxidase, superoxide dismutase and others. It plays a role in iron metabolism, melanin synthesis and central nervous system function. The adult body contains 50-120 mg of copper. High concentrations are found in liver, brain, heart, spleen and kidneys.

- **Selenium** – is a component of the enzyme glutathione peroxidase, which protects protein, cell membranes, lipids and nucleic acids from oxidant molecules.

- **Chromium** – potentiates the action of insulin in patients with impaired glucose tolerance. The suggested intake (in adults) is 50-200 micrograms/day.

Some of these elements are necessary for humans in minute amounts (Co, Cu, Cr, Ni), while others are carcinogenic or toxic, affecting, among others, the central nervous system (Hg, Pb, As), the kidneys or liver (Hg, Pb, Cd, Cu) or skin, bones, or teeth (Ni, Cd, Cu, Cr).

Heavy metal pollution can arise from many sources but often arises from metal purification processes, such as the smelting of copper and the preparation of nuclear fuels. Electroplating is the primary source of chromium and cadmium. Through precipitation of their compounds or by ion exchange into soils and mud, heavy metal pollutants can localize and lay dormant. Unlike organic pollutants, heavy metals do not decay and thus pose a different kind of challenge for remediation. Currently, plants or microorganisms are tentatively used to remove some heavy metals such as mercury. Plants which exhibit hyper accumulation can be used to remove heavy metals from soils by concentrating them in their bio matter. Some treatment of mining tailings has occurred where the vegetation is then incinerated to recover the heavy metals.

Ref:
Gold injections have been used to treat rheumatoid arthritis since the 1930s. The injections are given each week at first, although the frequency may be decreased as the gold becomes effective. Gold injections can be continued for life if they are helpful. Side-effects can occur, affecting the blood and the kidneys, and regular blood and urine tests are used to check for any abnormalities. Skin irritation may sometimes occur. Gold tablets were introduced at one point but are very rarely used because they are not as effective as the injections.

Arsenic trioxide was approved by the US Food and Drug Administration as an orphan drug for the secondary treatment of acute promyelocytic leukemia.

**Refs:**
- Arthritis Research Campaign. UK. Available at www.arc.org – accessed June 2010
Children and heavy metals

SELECTED HEAVY METALS AND ISSUES

1. Arsenic
2. Cadmium
3. Copper
4. Thallium
5. Controversies about issues associated with exposure to heavy metals

This slide lists the heavy metals and related issues discussed in this module.

<<NOTE TO USER: Please change this slide if you are only presenting selected components of this library of slides.>>
Elemental arsenic is a naturally-occurring silver-gray solid metalloid. The element (zero valence) form, which rarely exists in nature and has low solubility, is seldom a cause of human toxicity. The other forms of arsenic and their toxicity are discussed in the following slides.

Ref:
Main sources of arsenic include:

<<READ SLIDE>>

Refs:


In 2009 the Center for Food Safety (CFS) and the Institute for Agriculture and Trade Policy (IATP) filed a petition with the Food and Drug Administration (FDA) calling for the immediate withdrawal of approvals for all animal drug applications for arsenic-containing compounds used in animal feed. These additives are commonly used in poultry production to induce faster weight gain and create the appearance of a healthy color in meat from chickens, turkeys and hogs. The petition was supported by a coalition of food and farm groups around the country.

Arsenic-containing compounds have been approved additives to animal feed since the 1940s and are currently used in chicken, turkey and swine production. Most arsenic-containing animal feed additives are not used to treat sickness. Instead, arsenicals are generally approved for "increased weight gain, improved feed efficiency, and improved pigmentation." The European Union has never approved the use of arsenicals in animal feed, acknowledging the lack of science supporting health or safety standards for such uses.

In 2009 U.S. Representative Steve Torah of New York announced legislation calling for a ban on the use of the arsenical compound roxarsone in poultry feed. His bill, the "Poison-Free Poultry Act of 2009," would prohibit all uses of roxarsone as a food additive in poultry. The groups applauded the bill, but maintained that it did not go far enough. Their petition not only calls for a ban on roxarsone, but also on Arsanilic acid, Nitarsone, and Carbarsone, commonly used compounds which contain arsenicals.

Chromated copper arsenate-treated wood can be hazardous to human health because arsenic is classified as a known carcinogen. Exposure to arsenic can cause cancer of the lung, bladder, skin, kidney, prostate, and nasal passage. Data released in November 2003 by the US Environmental Protection Agency show that 90 percent of children repeatedly exposed to arsenic-treated wood face a greater than one-in-one million risk of cancer. One-in-one million is the US Environmental Protection Agency's historic threshold of concern about the carcinogenic effects of toxic chemicals. Arsenic exposure can also lead to nerve damage, dizziness, and numbness. Arsenic has been linked to immune diseases, cardiovascular disease, diabetes, and changes in hormone function. Lung and bladder cancer are the two health effects most often related to exposure to chromated copper arsenate-treated wood.

Chromated copper arsenate-treated wood can be found virtually anywhere outdoor lumber is being utilized. Due to the increased risk to children, the uses currently receiving the most attention are play sets, decks, and picnic tables. Arsenic can leach to the surface of the treated wood, becoming accessible for absorption through exposed hands and skin touching the wood surface and, especially in the case of children, ingestion through normal hand-to-mouth behavior. The arsenic can also leach into the ground surrounding the location of the treated wood, providing yet another exposure pathway for children in the area.

In March 2003, US Environmental Protection Agency finalized a voluntary agreement with preservative manufacturers to ban the production of chromated copper arsenate-treated wood for most residential uses as of December 31, 2003. However, the ban does not prohibit the sale of chromated copper arsenate-treated wood produced prior to December 31, 2003, nor does the measure address existing structures. With regard to retail sales, a warning label must be displayed in locations where chromated copper arsenate-treated wood is sold. The US Environmental Protection Agency has also removed chromated copper arsenate from its list of approved chemical pesticides.

The Consumer Product Safety Commission (CPSC) is also involved in the regulation of arsenic-treated wood. The Consumer Product Safety Commission has officially stated that there is an increased lifetime risk of developing lung or bladder cancer from exposure to arsenic for the individual who plays on chromated copper arsenate-treated wood play sets during early childhood. However, in November 2003, Consumer Product Safety Commission declined to ban the use of chromated copper arsenate-treated wood in playground equipment citing the US Environmental Protection Agency -industry voluntary agreement to phase out the manufacture of chromated copper arsenate-treated wood.

Arsenic Trioxide was approved by the US Food and Drug Administration as an orphan drug for the secondary treatment of acute promyelocytic leukemia.
Refs:
•National Center for Healthy Housing. Available at www.nchh.org/Home.aspx - accessed 22 September 2011

Picture: WHO
This slide presents the source of arsenic exposure in three countries.

<<READ SLIDE>>

Refs:
This slide presents data on prenatal arsenic exposure in relation to parental smoking.

Ref:

While the harmful health effects of carbon monoxide, nicotine, tar, irritants and other noxious gases that are present in tobacco smoke are well known, those due to heavy metals and other toxic mineral elements in tobacco smoke are not sufficiently emphasized. Tobacco smoking influences the concentrations of several elements in some organs. This review summarizes the known effects of some trace elements and other biochemically important elements (Al, As, Cd, Cr, Cu, Pb, Mn, Hg, Ni, Po-210, Se, and Zn) which are linked with smoking. Cigarette smoking may be a substantial source of intake of these hazardous elements not only to the smoker but also, through passive smoking, to nonsmokers. The adverse health effects of these toxic elements on the fetus through maternal smoking, and on infants through parental smoking, are of special concern.
The toxicity of arsenic depends on its chemical composition and valency, arsine gas being the most toxic form.

Please note the information on this slide comes mostly from adult exposure data.

*Ref.*

Hemolysis from arsine inhalation may result in intra-renal deposition of hemoglobin and debris of lysed erythrocytes leading to renal tubular damage and renal failure, as well as hypoxia.

Refs:
This slide and the following 3 slides describe the toxicokinetics of arsenic in the body, at four stages, using the acronym ADME:
A - Absorption
D - Distribution
M - Metabolism
E - Excretion

**ARSENIC - ABSORPTION**

- Inorganic arsenic (As$^{3+}$) 80-90% absorbed from intestine
- Organic arsenic (seafood) poorly absorbed from intestine - considered not toxic in children
- Arsine gas – by inhalation
- Skin - As$^{3+}$ high absorption (lipid soluble)

**Ref:**
Distribution of arsenic, once absorbed, in the human tissues is uneven, with higher affinity and higher concentrations in some tissues.

*Note:* Mees' lines are white bands traversing the nail.
Arsenic undergoes transformation in the body from the pentavalent (As$^{5+}$), less toxic form, which is well absorbed, to the trivalent (As$^{3+}$), more toxic form.

Ref:

Figure kindly provided by Steven G. Gilbert, PhD, DABT. Credit: The Institute of Neurotoxicology and Neurological Disorders / Toxipedia. Used with permission. Available at www.toxipedia.org – further educational resources available at www.toxipedia.org/display/toxipedia/Teaching+Resources
Arsenic is excreted mainly by the kidneys. Renal tubules can convert As\(^{5+}\) (Arsenate) to the more toxic As\(^{3+}\) (Arsenite).

Prenatal exposure to arsenic, through placental transfer, can cause marked damage to the fetus.

Ref:
Acute arsenic toxicity has multi-organ system manifestations: gastrointestinal, muscular, cardiac and neurological symptoms.

<<READ SLIDE>>
Children and heavy metals

PEDIATRIC ARSENIC INGESTION CASE

❖ Pediatric case of acute arsenic ingestion treated initially with dimercaprol (BAL) and D-penicillamine (DP), and later with dimercaptosuccinic acid (DMSA)

❖ 22-month-old girl ingested 1 oz 2.27% sodium arsenate.

❖ Immediate vomiting and diarrhea.

❖ Presented with a blood pressure of 96/72 mm Hg, pulse 160 beats/min, respirations 22 breaths/min. Pale and lethargic.

Cullen et al, 1995

Acute arsenic toxicity is rare, with no pediatric cases of acute arsenic poisoning in the recent literature. We report a pediatric case of acute arsenic ingestion treated initially with dimercaprol (BAL) and D-penicillamine (DP), and later with dimercaptosuccinic acid (DMSA).

A 22-month-old girl ingested 1 oz 2.27% sodium arsenate and developed immediate vomiting and diarrhea. The patient presented with a blood pressure of 96/72 mm Hg, pulse 160 beats/min, respirations 22 breaths/min. She was pale and lethargic.

Gastric lavage was performed, and abdominal X-ray was normal. She continued to have gastrointestinal symptoms and received 3 mg/kg BAL. She had sinus tachycardia up to 200 beats/min. In 12 hours, she was asymptomatic and was started on oral DP. On day one, 24-hour urine arsenic was 4,880 micrograms/L.

She remained asymptomatic and was discharged on day 6 on oral DP. She did well except for a rash that could have been a side effect of DP. DMSA was given for 4 days.

The excretion half-life was 2.5 days, faster than the spontaneous excretion half-life expected in adults.

Ref:
Acute arsenic toxicity is rare, with no pediatric cases of acute arsenic poisoning in the recent literature. We report a pediatric case of acute arsenic ingestion treated initially with dimercaprol (BAL) and D-penicillamine (DP), and later with dimercaptosuccinic acid (DMSA).

A 22-month-old girl ingested 1 oz 2.27% sodium arsenate and developed immediate vomiting and diarrhea. The patient presented with a blood pressure of 96/72 mm Hg, pulse 160 beats/min, respirations 22 breaths/min. She was pale and lethargic.

Gastric lavage was performed, abdominal X-ray was normal. Continued to have gastrointestinal symptoms and received 3 mg/kg dimercaprol (BAL).

Sinus tachycardia up to 200 beats/min. In 12 hours, asymptomatic and was started on oral D-penicillamine (DP). On day 1, 24-hour urine arsenic was 4,880 micrograms/L.

Remained asymptomatic and was discharged on day 6 on oral D-penicillamine (DP). She did well except for a rash that could have been a side effect of D-penicillamine (DP). Dimercaptosuccinic acid (DMSA) was given for 4 days.

The excretion half-life was 2.5 days, faster than the spontaneous excretion half-life expected in adults.

Ref:
An 18-year-old man deliberately ingested termiticide with a massive dose of arsenic trioxide. Arsenic concentration was 6.3 micromol/L in serum, and 253 micromol/L in the first 24-hour urine sample, with a urinary arsenic/creatinine ratio of 84 200 micromol/mol. He was treated with the chelating agent dimercaptosuccinic acid (DMSA), replaced by dimercaprol on days 2-5, and required intensive support for multisystem organ failure, but recovered slowly. Nine weeks after the ingestion the only ongoing clinical issue was persistent but slowly improving peripheral neuropathy.

Ref:
Arsenosis is the effect of arsenic poisoning, usually over a long period such as from 5 to 20 years. Drinking arsenic-rich water over a long period results in various health effects including skin problems (such as colour changes on the skin, and hard patches on the palms and soles of the feet), skin cancer, cancers of the bladder, kidney and lung, and diseases of the blood vessels of the legs and feet, and possibly also diabetes, high blood pressure and reproductive disorders.

Absorption of arsenic through the skin is minimal and thus hand-washing, bathing, laundry, etc. with water containing arsenic do not pose human health risks.

In China (Province of Taiwan) exposure to arsenic via drinking-water has been shown to cause a severe disease of the blood vessels, which leads to gangrene, known as ‘black foot disease’. This disease has not been observed in other parts of the world, and it is possible that malnutrition contributes to its development. However, studies in several countries have demonstrated that arsenic causes other, less severe forms of peripheral vascular disease.

Chronic arsenic toxicity occurred as a large epidemic in Bangladesh as shown in the next slides.

Refs:
Natural arsenic contamination is a cause for concern in many countries of the world including Argentina, Bangladesh, Chile, China, India, Mexico, United States, Vietnam, Thailand and Bangladesh. Case reports on the situation in various countries have been compiled and the arsenic problem in Bangladesh in particular has prompted more intensive monitoring in many other countries.

Note: The yellow and darker areas in the maps at the bottom of the slide mark the areas with higher arsenic concentrations in water.

Refs:

Millions of children are exposed to excessive amounts of fluoride through drinking water contaminated from natural geological sources. In China, the burning of fluoride-rich coal adds to the problem. Small amounts of fluoride are good for teeth; it is added to toothpaste and, in some countries, to drinking water. At higher doses, it destroys teeth and accumulates in bones, leading to crippling skeletal damage. With their bodies still growing, children are most at risk. Like fluoride, arsenic is widely distributed throughout the earth’s crust, and is present in almost all waters in very small amounts. In certain areas, however, there are dangerous levels of this toxin in children’s drinking water. The most tragic example is Bangladesh, where thousands of wells are causing a mass poisoning of the population. Unsafe wells are marked with red paint, warning people that this water is not for drinking. Image and notes from Gordon B et al. Inheriting the world, the Atlas on Children’s Health and the Environment. WHO, Myriad Editions Ltd, 2004.
**Children and heavy metals**

**US WATER ARSENIC MAP**

*Note:* The various colours indicate different concentrations of arsenic in water, with red being the highest.

**Ref:**
Children and heavy metals

BANGLADESH WATER ARSENIC MAP

Probability of Arsenic Exceeding 0.05 mg/l

- <5%
- 5 - 20%
- 20 - 45%
- 45 - 70%
- 70 - 100%
- No Data

Note: The various colours indicate different probabilities of high concentrations of arsenic in water, with violet being the highest.

The Bangladesh arsenic epidemic is considered one of the largest toxicological events in the modern era, affecting a huge proportion of the population, as described in this slide.

<<READ SLIDE>>

Ref:

The contamination of groundwater by arsenic in Bangladesh is the largest poisoning of a population in history, with millions of people exposed. This paper describes the history of the discovery of arsenic in drinking-water in Bangladesh and recommends intervention strategies. Tube-wells were installed to provide “pure water” to prevent morbidity and mortality from gastrointestinal disease. The water from the millions of tube-wells that were installed was not tested for arsenic contamination. Studies in other countries where the population has had long-term exposure to arsenic in groundwater indicate that 1 in 10 people who drink water containing 500 mg of arsenic per litre may ultimately die from cancers caused by arsenic, including lung, bladder and skin cancers. The rapid allocation of funding and prompt expansion of current interventions to address this contamination should be facilitated. The fundamental intervention is the identification and provision of arsenic-free drinking water. Arsenic is rapidly excreted in urine, and for early or mild cases, no specific treatment is required. Community education and participation are essential to ensure that interventions are successful; these should be coupled with follow-up monitoring to confirm that exposure has ended. Taken together with the discovery of arsenic in groundwater in other countries, the experience in Bangladesh shows that groundwater sources throughout the world that are used for drinking-water should be tested for arsenic.

Tube-wells have been used in Bangladesh since the 1940s. However, the problem of arsenic-contaminated water has only recently come to light due to the increasing number of tube-wells used over the past 20 years and the subsequent increase in the number of individuals drinking from them. Historically, surface water sources in Bangladesh have been contaminated with microorganisms, causing a significant burden of disease and mortality. Infants and children suffered from acute gastrointestinal disease resulting from bacterial contamination of stagnant pond water. Consequently, during the 1970s the United Nations Children’s Fund (UNICEF) worked with the Department of Public Health Engineering to install tube-wells to provide what was presumably a safe source of drinking-water for the population. These wells consist of tubes that are 5 cm in diameter that are inserted into the ground at depths of usually less than 200 m. The tubes are then capped with a cast iron or steel hand pump. At the time the wells were installed, arsenic was not recognized as a problem in water supplies, and therefore standard water testing procedures did not include tests for arsenic. During the 1980s, UNICEF’s support for installing tube-wells decreased because the private sector was able to supply and install millions more of them. By 1997, UNICEF indicated in its country report for Bangladesh that it had surpassed its goal of providing 80% of the population by 2000 with access to “safe” drinking-water in the form of
tube-wells, ring-wells and taps. Presently, three out of four tube-wells in Bangladesh are privately owned.
This slide includes the main manifestations of chronic arsenic toxicity.

<<READ SLIDE>>

Photographs by Nasrine Karim, NGO: Earth Identity Project, Bangladesh. Hands and feet "before" from an arsenicosis patient. Used with permission.
Children and heavy metals

ARSENIC - HEALTH RISKS

❖ Young children may develop arsenicosis
❖ Cancers appear after 20 years
❖ Huge epidemic expected in the near future

The Arsenic Mitigation - Water Supply Project for Bangladesh reduces mortality and morbidity in rural and urban populations caused by arsenic contamination of the country’s groundwater. The project aims to significantly reduce the quantity of arsenic ingested; increase access to a sustainable safe water supply; and increase the percentage of treated arsenicosis patients in the project areas. There are three components. The first, on-site mitigation, 1) provides technical assistance, training, and logistical support to build capacity and operate the project management unit (PMU); 2) implements community interventions by developing a community-based organization capable of supplying short-term, alternative water supply/sanitation infrastructure; 3) prepares and implements a technical and financial proposal; and 4) audits, evaluates, and monitors project impact and groundwater quality. The second component strengthens the PMU’s capacity to collect, manage, and evaluate data for water quality, arsenic contamination, and socioeconomic conditions; undertakes well screening and community education; and funds studies and research on participatory planning, implementing appropriate technology, cost recovery, appropriate technology for testing and treating arsenic in groundwater, and land use/arsenic interactions. The third component, institutional strengthening, builds capacity in arsenic mitigation and participatory water supply and sanitation.

The Arsenic Mitigation - Water Supply Project for Bangladesh World Bank Project.

The lessons learned included: A) Arsenic mitigation needs to be mainstreamed into the water supply sector in order to be sustainable, focusing on innovative ways to deliver safe water supply in both non-piped and piped water supply; B) Decentralized community-based planning and management of rural water supply and sanitation with a central role for local governments has been demonstrated as a model for future interventions by the Government of Bangladesh; C) Supply of bacteriologically safe water should be the priority, not just arsenic-safe water; and D) The rolling out of pilot village piped water supply with significant private financing and management through carefully controlled and guided assistance from both the PMU and the Bank is a good example of field-testing and development of large-scale investments.


Children and heavy metals

ARSENIC - REDUCING EXPOSURE

- Avoid (e.g. do not use treated lumber)
- Test drinking water
- Stop smoking
- Wash hands
- National monitoring arsenic in poultry

The Institute of Neurotoxicology and Neurological Disorders

Inorganic arsenic is a potent human carcinogen and general toxicant. More than one hundred million people are exposed to elevated concentrations, mainly via drinking water, but also via industrial emissions. Arsenic is metabolized via methylation and reduction reactions, methylarsonic acid and dimethylarsinic acid being the main metabolites excreted in urine. Both inorganic arsenic and its methylated metabolites easily pass the placenta and both experimental and human studies have shown increased risk of impaired foetal growth and increased foetal loss. Recent studies indicate that prenatal arsenic exposure also increases the risk of adverse effects during early childhood. There is a growing body of evidence that the intrauterine or early childhood exposure to arsenic also induces changes that will become apparent much later in life. One epidemiological study indicated that exposure to arsenic in drinking water during early childhood or in utero was associated with an increased mortality in young adults from both malignant and non-malignant lung disease. Furthermore, a series of experimental animal studies provide strong support for late effects of arsenic, including various forms of cancer, following intrauterine arsenic exposure. The involved modes of action include epigenetic effects, mainly via DNA hypomethylation, endocrine effects (most classes of steroid hormones), immune suppression, neurotoxicity, and interaction with enzymes critical for foetal development and programming.
Inorganic arsenic is a potent human carcinogen and general toxicant. More than one hundred million people are exposed to elevated concentrations, mainly via drinking water, but also via industrial emissions. Arsenic is metabolized via methylation and reduction reactions, methylarsonic acid and dimethylarsinic acid being the main metabolites excreted in urine. Both inorganic arsenic and its methylated metabolites easily pass the placenta and both experimental and human studies have shown increased risk of impaired foetal growth and increased foetal loss. Recent studies indicate that prenatal arsenic exposure also increases the risk of adverse effects during early childhood. There is a growing body of evidence that the intrauterine or early childhood exposure to arsenic also induces changes that will become apparent much later in life. One epidemiological study indicated that exposure to arsenic in drinking water during early childhood or in utero was associated with an increased mortality in young adults from both malignant and non-malignant lung disease. Furthermore, a series of experimental animal studies provide strong support for late effects of arsenic, including various forms of cancer, following intrauterine arsenic exposure. The involved modes of action include epigenetic effects, mainly via DNA hypomethylation, endocrine effects (most classes of steroid hormones), immune suppression, neurotoxicity, and interaction with enzymes critical for foetal development and programming.

Ref:

Inorganic arsenic is a potent human carcinogen and general toxicant. More than one hundred million people are exposed to elevated concentrations, mainly via drinking water, but also via industrial emissions. Arsenic is metabolized via methylation and reduction reactions, methylarsonic acid and dimethylarsinic acid being the main metabolites excreted in urine. Both inorganic arsenic and its methylated metabolites easily pass the placenta and both experimental and human studies have shown increased risk of impaired foetal growth and increased foetal loss. Recent studies indicate that prenatal arsenic exposure also increases the risk of adverse effects during early childhood. There is a growing body of evidence that the intrauterine or early childhood exposure to arsenic also induces changes that will become apparent much later in life. One epidemiological study indicated that exposure to arsenic in drinking water during early childhood or in utero was associated with an increased mortality in young adults from both malignant and non-malignant lung disease. Furthermore, a series of experimental animal studies provide strong support for late effects of arsenic, including various forms of cancer, following intrauterine arsenic exposure. The involved modes of action include epigenetic effects, mainly via DNA hypomethylation, endocrine effects (most classes of steroid hormones), immune suppression, neurotoxicity, and interaction with enzymes critical for foetal development and programming.
A dose-effect relationship was found between prenatal arsenic exposure and infant mortality rate in this cohort study in Bangladesh.

Ref:

Background: Millions of people worldwide are drinking water with elevated arsenic concentrations. Epidemiologic studies, mainly cross-sectional in design, have suggested that arsenic in drinking water may affect pregnancy outcome and infant health. We assessed the association of arsenic exposure with adverse pregnancy outcomes and infant mortality in a prospective cohort study of pregnant women.

Methods: A population-based, prospective cohort study of 2924 pregnant women was carried out during 2002–2004 in Matlab, Bangladesh. Spontaneous abortion was evaluated in relation to urinary arsenic concentrations at gestational week 8. Stillbirth and infant mortality were evaluated in relation to the average of urinary arsenic concentrations measured at gestational weeks 8 and 30.

Results: The odds ratio of spontaneous abortion was 1.4 (95% confidence interval [CI] = 0.96–2.2) among women with urine arsenic concentrations in the fifth quintile (249–1253 μg/L; median = 382 μg/L), compared with women in the first quintile (<33 μg/L). There was no clear evidence of increased rates of stillbirth. The rate of infant mortality increased with increasing arsenic exposure: the hazard ratio was 5.0 (95% CI = 1.4–18) in the fifth quintile of maternal urinary arsenic concentrations (268–2019 μg/L; median = 390 μg/L), compared with the first quintile (<38 μg/L).

Conclusions: We found evidence of increased risk of infant mortality with increasing arsenic exposure during pregnancy, with less evidence of associations with spontaneous abortion or stillbirth risk.
This study shows an association between arsenic exposure during pregnancy and increased morbidity in infectious diseases during infancy.

Ref:

Background: Previous studies have reported associations between prenatal arsenic exposure and increased risk of infant mortality. An increase in infectious diseases has been proposed as the underlying cause of these associations, but there is no epidemiologic research to support the hypothesis.

Objective: We evaluated the association between arsenic exposure in pregnancy and morbidity during infancy.

Methods: This prospective population-based cohort study included 1,552 live-born infants of women enrolled during 2002-4 in Bangladesh. Arsenic exposure was assessed by the concentrations of metabolites of inorganic arsenic in maternal urine samples at gestational weeks 8 and 30. Information on symptoms of lower respiratory tract infection (LRTI) and diarrhea in infants was collected by 7-day recalls at monthly home visits.

Results: In total, 115,850 person-days of observation were contributed by the infants during a 12-month follow-up period. The estimated risk of LRTI and severe LRTI increased by 69% [adjusted relative risk (RR) = 1.69; 95% confidence interval (CI), 1.36–2.09] and 54% (RR = 1.54; 95% CI, 1.21–1.97), respectively, for infants of mothers with urinary arsenic concentrations in the highest quintile (average of arsenic concentrations measured in early and late gestation, 262–977 µg/L) relative to those with exposure in the lowest quintile (< 39 µg/L). The corresponding figure for diarrhea was 20% (RR = 1.20; 95% CI, 1.01–1.43).

Conclusions: Arsenic exposure during pregnancy was associated with increased morbidity in infectious diseases during infancy. Taken together with the previous evidence of adverse effects on health, the findings strongly emphasize the need to reduce arsenic exposure via drinking water.
This study shows an association between arsenic exposure during pregnancy and increased morbidity in infectious diseases during infancy.

Ref:

**Background:** Previous studies have reported associations between prenatal arsenic exposure and increased risk of infant mortality. An increase in infectious diseases has been proposed as the underlying cause of these associations, but there is no epidemiologic research to support the hypothesis.

**Objective:** We evaluated the association between arsenic exposure in pregnancy and morbidity during infancy.

**Methods:** This prospective population-based cohort study included 1,552 live-born infants of women enrolled during 2002–2004 in Matlab, Bangladesh. Arsenic exposure was assessed by the concentrations of metabolites of inorganic arsenic in maternal urine samples collected at gestational weeks 8 and 30. Information on symptoms of lower respiratory tract infection (LRTI) and diarrhea in infants was collected by 7-day recalls at monthly home visits.

**Results:** In total, 115,850 person-days of observation were contributed by the infants during a 12-month follow-up period. The estimated risk of LRTI and severe LRTI increased by 69% (adjusted relative risk (RR) = 1.69; 95% confidence interval (CI), 1.36–2.09]) and 54% (RR = 1.54; 95% CI, 1.21–1.97), respectively, for infants of mothers with urinary arsenic in the highest quintile.

For diarrhea: corresponding figure of 20%.

**Conclusions:** Arsenic exposure during pregnancy was associated with increased morbidity in infectious diseases during infancy. Taken together with the previous evidence of adverse effects on health, the findings strongly emphasize the need to reduce arsenic exposure via drinking water.
This study in Chile shows how exposure to arsenic in drinking water during early childhood may result in an increase in childhood liver cancer mortality.

Ref:


Arsenic in drinking water is an established cause of lung, bladder, and skin cancers in adults and may also cause adult kidney and liver cancers. Some evidence for these effects originated from region II of Chile, which had a period of elevated arsenic levels in drinking water, in particular from 1958 to 1970. This unique exposure scenario provides a rare opportunity to investigate the effects of early-life arsenic exposure on childhood mortality; to our knowledge, this is the first study of childhood cancer mortality and high concentrations of arsenic in drinking water. In this article, we compare cancer mortality rates under the age of 20 in region II during 1950 to 2000 with those of unexposed region V, dividing subjects into those born before, during, or after the peak exposure period. Mortality from the most common childhood cancers, leukemia and brain cancer, was not increased in the exposed population. However, we found that childhood liver cancer mortality occurred at higher rates than expected. For those exposed as young children, liver cancer mortality between ages 0 and 19 was especially high: the relative risk (RR) for males born during this period was 8.9 (95% CI, 1.7-45.8; P = 0.009); for females, the corresponding RR was 14.1 (95% CI, 1.6-126; P = 0.018); and for males and females pooled, the RR was 10.6 (95% CI, 2.9-39.2; P < 0.001). These findings suggest that exposure to arsenic in drinking water during early childhood may result in an increase in childhood liver cancer mortality.

This study suggests that folic acid supplementation may reduce the risk of arsenic-related health outcomes.

Ref:

*Populations in South and East Asia and many other regions of the world are chronically exposed to arsenic-contaminated drinking water. To various degrees, ingested inorganic arsenic (InAs) is methylated to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) via folate-dependent one-carbon metabolism; impaired methylation is associated with adverse health outcomes. Consequently, folate nutritional status may influence arsenic methylation and toxicity.*

The objective of this study was to test the hypothesis that folic acid supplementation of arsenic-exposed adults would increase arsenic methylation.

**Design:** Two hundred adults in a rural region of Bangladesh, previously found to have low plasma concentrations of folate (≤9 nmol/L) were enrolled in a randomized, double-blind, placebo-controlled folic acid-supplementation trial. Plasma concentrations of folate and homocysteine and urinary concentrations of arsenic metabolites were analyzed at baseline and after 12 wk of supplementation with folic acid at a dose of 400 mcrog/d or placebo.

**Results:** The increase in the proportion of total urinary arsenic excreted as DMA in the folic acid group (72% before and 79% after supplementation) was significantly (P < 0.0001) greater than that in the placebo group, and reduction in the proportions of total urinary arsenic excreted as monomethylarsonic acid (MMA) (13% and 10%, respectively; P < 0.0001) and as inorganic arsenic (15% and 11%, respectively; P < 0.001).

**Conclusions:** These data indicate that folic acid supplementation to participants with low plasma folate enhances arsenic methylation. Because persons whose urine contains low proportions of DMA and high proportions of MMA and InAs have been reported to be at greater risk of skin and bladder cancers and peripheral vascular disease, these results suggest that folic acid supplementation may reduce the risk of arsenic-related health outcomes.
Nutritional factors are known to influence arsenic metabolism in adults, and poor nutritional status—as reflected in part by a lack of various B vitamins and antioxidants—is thought to confer greater susceptibility to arsenic toxicity.

Researchers in Bangladesh have reported that deficits in the B vitamin folate and the amino acid cysteine may adversely influence arsenic metabolism in children (Hall MN, 2009).

Compared with adults, children may metabolize arsenic more efficiently and excrete it more readily, regardless of folate status.

Study’s findings indicate that improved nutritional status could constitute a key strategy for reducing the risk of arsenic-related disease in Bangladeshi children (Freeman K, 2009).

Refs:
• Hall MN et al. Folate, Cobalamin, Cysteine, Homocysteine, and Arsenic Metabolism among Children in Bangladesh. Environmental Health Perspectives. 2009, 117:825-831.
General description of cadmium: A soft, bluish-white metallic element occurring primarily in Zinc, Copper and Lead ores, that is easily cut with a knife and is used in low-friction, fatigue-resistant alloys, solders, dental amalgams, Nickel-cadmium storage batteries, nuclear reactor shields, and in rustproof electroplating. Cadmium is soluble in acids but not in alkalis. It is similar in many respects to zinc. The Atomic number is 48.
Cadmium exerts toxic effects on the kidney, the skeletal and the respiratory systems, and is classified as a human carcinogen. It is generally present in the environment at low levels. However, human activity has greatly increased those levels. Cadmium can travel long distances from the source of emission by atmospheric transfer. It is readily accumulated in many organisms, notably molluscs and crustaceans. Lower concentrations are found in vegetables, cereals and starchy roots. Human exposure occurs mainly from consumption of contaminated food, active and passive inhalation of tobacco smoke, and inhalation by workers in the non-ferrous metal industry.

Ref:

Image in the middle from US Environmental Protection Agency (USEPA). Available at www.epa.gov/osw/conserve/materials/battery.html - accessed 22 September 2011
Holmes, WHO
Cadmium can be released to the environment in a number of ways, including:

- natural activities, such as volcanic activity (both on land and in the deep sea), weathering and erosion, and river transport;
- human activities, such as tobacco smoking, mining, smelting and refining of non-ferrous metals, fossil fuel combustion, incineration of municipal waste (especially cadmium-containing batteries and plastics), manufacture of phosphate fertilizers, and recycling of cadmium-plated steel scrap and electric and electronic waste;
- remobilization of historic sources, such as the contamination of watercourses by drainage water from metal mines.

Cadmium releases can be carried to and deposited on areas remote from the sources of emission by means of long-range atmospheric transport.

**Note:** Itai Itai disease is a form of renal osteodystrophy—osteomalacia with marked bone pain and painful fractures. It means "ouch ouch" in Japanese and was described in Japanese women due to cadmium accumulation in bone, caused by industrial pollutants.

**Refs:**

The tobacco plant naturally accumulates relatively high concentrations of cadmium in its leaves. Thus, smoking tobacco is an important source of exposure, and the daily intake may exceed that from food in the case of heavy smokers. Cigarette smoking can cause significant increases in the concentrations of cadmium in the kidney, the main target organ for cadmium toxicity.

<<READ SLIDE>>

Refs:


• The metal content in the tobacco comes from the soil, which is being concentrated by tobacco plants.

• Cadmium is used in cigarette paper to make the paper burn slower. These metals are either released into the air by tobacco smoke or are retained in the cigarette ash.

• A cigarette's tobacco contains about 0.5 - 2.0 μg of cadmium and about 10% of the cadmium content is inhaled when the cigarette is smoked (WHO 1992).

• The non-smoker may passively inhale significant amount of cadmium along with inhaled tobacco smoke.

Ref:
Children and heavy metals

CADMIUM - METABOLISM AND EXCRETION

❖ It has no known beneficial function in the human body
❖ It is transported in the blood bound to metallothionein
❖ Greatest concentrations in kidneys & liver
❖ Urinary excretion is slow
❖ Biologic half-life may last 25-30 years

Ref:
This slide presents the main mechanisms of cadmium toxicity. Specific acute and chronic toxicity are addressed in the upcoming slides.

Ref:

Note: Knowledge about acute toxicity comes mostly from the industrial exposures of adults.

Ref:
Note: Itai Itai disease is a form of renal osteodystrophy—osteomalacia with marked bone pain and painful fractures. It means "ouch ouch" in Japanese and was described in Japanese women due to cadmium accumulation in bone, caused by industrial pollutants.

Ref:
Ref:

The objective of the present study was to evaluate the potential effect of maternal cadmium exposure on pregnancy outcome and development in the offspring at age 4 ½ years. Between November 2002 and December 2003, 109 normal pregnant women were enrolled in Da-Ye Country, Hubei Province in Central China. The placental, whole blood, and cord blood levels of cadmium were determined by inductively coupled plasma mass spectrometer (ICP-MS). The 106 children at 4 ½ years of age were followed up and the following rate was 97.25%. Detailed questionnaire surveys, anthropometric measurements and IQ development was evaluated by Wechsler Preschool and Primary Scale of Intelligence Revised Edition (WPPSI-R). Multiple linear regression analysis indicated that cord blood cadmium level was significantly negatively correlated with fetus development. Low birth weight (less than 2,500 g) occurred significantly more frequently in infants with higher cord blood cadmium than in those exposed to lower levels of cord blood cadmium. Significantly negative correlation was found between cord blood cadmium exposure and WPPSI-R IQ full score after controlling for confounding variables. It was concluded that cord blood cadmium concentration was a factor that influenced fetus growth and later IQ development.
This study shows a link between cord blood cadmium concentration and fetal growth and later IQ development.

Ref:

The objective of the present study was to evaluate the potential effect of maternal cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. Between November 2002 and December 2003, 109 normal pregnant women were enrolled in our cohort from Da-Ye Country, Hubei Province in Central China. The placental, whole blood, and cord blood levels of cadmium were determined by inductively coupled plasma mass spectrometer (ICP-MS). The 106 children at 4.5 years of age given birth by the aforementioned women were followed up and the following rate was 97.25%. Detailed questionnaire surveys, anthropometric measurements were performed, and IQ development was evaluated by Wechsler Preschool and Primary Scale of Intelligence Revised Edition (WPPSI-R). Multiple linear regression analysis indicated that cord blood cadmium level was significantly negatively correlated with fetus development. Low birth weight (less than 2,500 g) occurred significantly more frequently in infants with higher cord blood cadmium than in those exposed to lower levels of cord blood cadmium. Significantly negative correlation was found between cord blood cadmium exposure and WPPSI-R IQ full score after controlling for confounding variables. It was concluded that cord blood cadmium concentration was a factor that influenced fetus growth and later IQ development.
This study shows a link between gestational environmental exposure to cadmium and significantly lower neonatal birth height.

Ref:

The objective of the present study was to evaluate the potential effect of environmental exposure to cadmium on pregnancy outcome and fetal growth. Normal pregnant women were selected from Da-ye city of Hubei province, a cadmium-polluted area, from November 2002 through January 2003. Whole blood of pregnant women, cord blood, and placenta were collected and cadmium levels were determined by inductively coupled plasma emission mass spectroscopy. Incidence rate of preterm labor (< or = 37 weeks) and neonatal asphyxia, neonatal birth height, and birth weight were compared between lower and higher cadmium exposure level groups. Whole blood cadmium of 44 mothers ranged from 0.80 to 25.20 microg/L. Cadmium in maternal blood was significantly higher than that in cord blood (t = 11.44, P < 0.01). Placenta cadmium ranged from 0.084 to 3.97 microg/g dry weight. After adjustment for maternal age, history of gestation, abortion and lactation, Logistic regression analysis showed that there was no significant association between cadmium exposure levels and pregnancy outcome (preterm labor or neonatal asphyxia). Multiple linear regression analysis showed that, cord blood cadmium level, but not maternal blood cadmium and placenta cadmium, was significantly negatively associated with neonatal birth height (t = -2.33, P < 0.05). Compared with lower cord blood cadmium level (< or = 0.40 microg/L), higher level of cord blood cadmium (>0.40 microg/L) was associated with 2.24cm decrease in neonatal birth height. There was no significant association between cadmium exposure and birth weight. It was concluded that environmental exposure to cadmium significantly lower neonatal birth height.
This study shows a link between environmental exposure to cadmium and significantly lower neonatal birth height.

Ref:

The objective of the present study was to evaluate the potential effect of environmental exposure to cadmium on pregnancy outcome and fetal growth. Normal pregnant women were selected from Da-ye city of Hubei province, a cadmium-polluted area, from November 2002 through January 2003. Whole blood of pregnant women, cord blood, and placenta were collected and cadmium levels were determined by inductively coupled plasma emission mass spectroscopy. Incidence rate of preterm labor (gestational age < or = 37 weeks) and neonatal asphyxia, neonatal birth height, and birth weight were compared between lower and higher cadmium exposure level groups. Whole blood cadmium of 44 mothers ranged from 0.80 to 25.20 microg/L. Cadmium concentration in maternal blood was significantly higher than that in cord blood (t = 11.44, P < 0.01). Placenta cadmium ranged from 0.084 to 3.97 microg/g dry weight. After adjustment for maternal age, history of gestation, abortion and lactation, Logistic regression analysis showed that there was no significant association between cadmium exposure levels and pregnancy outcome (premature labor or neonatal asphyxia). Multiple linear regression analysis showed that, cord blood cadmium level, but not maternal blood cadmium and placenta cadmium, was significantly negatively associated with neonatal birth height (t = -2.33, P < 0.05). Compared with lower cord blood cadmium level (< or = 0.40 microg/L), higher level of cord blood cadmium (>0.40 microg/L) was associated with 2.24 cm decrease in neonatal birth height.

There was no significant association between cadmium exposure and birth weight. It was concluded that environmental exposure to cadmium significantly lower neonatal birth height.

Children and heavy metals

EFFECT OF ENVIRONMENTAL EXPOSURE TO CADMIUM ON PREGNANCY OUTCOME AND FETAL GROWTH: A STUDY ON HEALTHY PREGNANT WOMEN IN CHINA

Results:
- No significant association between cadmium exposure levels and pregnancy outcome (premature labor or neonatal asphyxia)
- Cord blood cadmium, but not maternal blood cadmium and placenta cadmium, was significantly negatively associated with neonatal birth height (t=-2.33, P < 0.05)
- Compared with lower cord blood cadmium (< or = 0.40 ug/L), higher level of cord blood cadmium (>0.40 ug/L) was associated with 2.24 cm decrease in neonatal birth height.
- No significant association between cadmium exposure and birth weight.

Conclusion:
Environmental exposure to cadmium significantly lower neonatal birth height.

Zhang YL et al, 2004
This slide presents treatment and management options for dealing with acute and chronic exposure to cadmium. For chronic exposures, the best strategy is to prevent further exposure.

**Refs:**

Copper – general description: Copper is a reddish-brown, ductile and malleable metal. It belongs to group IB of the Periodic Table. In compounds found in the environment it usually has a valence of 2 but can exist in the metallic, +1 and +3 valence states. Copper is found naturally in a wide variety of mineral salts and organic compounds, and in the metallic form. The metal is sparingly soluble in water, salt or mildly acidic solutions, but can be dissolved in nitric and sulfuric acids as well as basic solutions of ammonium hydroxide or carbonate. Copper possesses high electrical and thermal conductivity and resists corrosion.

Ref:
Children and heavy metals

COPPER – PROPERTIES, ROLES AND TOXICITY

❖ Metallic copper – resistant to corrosion
❖ Copper compounds (oxide, sulfates, and others) may be toxic

PHYSIOLOGY:
- Normal copper homeostasis is essential for human growth and development, a cofactor in enzymes

DEFICIENCY:
- cardiac hypertrophy
- poor neuronal myelination
- blood vessel abnormalities
- impaired immune response.

TOXICITY: (copper sulfate was a popular murder weapon and abortifacient)
- Gastrointestinal, respiratory, renal, hematological symptoms

Refs:
Natural sources of copper exposure include windblown dust, volcanoes, decaying vegetation, forest fires and sea spray. Anthropogenic emissions include smelters, iron foundries, power stations and combustion sources such as municipal incinerators. The major release of copper to land is from tailings and overburdens from copper mines and sewage sludge. Agricultural use of copper products accounts for 2% of copper released to soil. Copper ores are mined, smelted and refined to produce many industrial and commercial products. Copper is widely used in cooking utensils and water distribution systems, as well as fertilizers, bactericides, fungicides, algicides and antifouling paints. It is also used in animal feed additives and growth promoters, as well as for disease control in livestock and poultry. Copper is used in industry as an activator in froth flotation of sulfide ores, production of wood preservatives, electroplating, azo-dye manufacture, as a mordant for textile dyes, in petroleum refining and the manufacture of copper compounds.

Ref:
Children and heavy metals

COPPER – MOSTLY ACUTE TOXICITY

❖ Usually mild overdose, due to its emetic effect
❖ Intentional - suicidal setting, may be severe and fatal

Symptoms:
- Gastrointestinal: metallic taste, nausea, vomiting, gastrointestinal bleeding
- Renal: hematuria, oliguria, elevated urea and creatinine, acute tubular necrosis
- Hematological: hemolytic anemia
- Respiratory: metal fume fever – industrial setting
  – nasal congestion, fever, chills, malaise, shortness of breath, resolve over weekends and recur
❖ Chronic – rare (except Wilson’s disease, genetic-metabolic)

Ref:
Children and heavy metals

SELECTED HEAVY METALS
THALLIUM
### THALLIUM – PROPERTIES and SOURCES

- Soft, white blue
- Colorless, tasteless, odorless
- When exposed to air, oxidizes and forms thallium oxide
- Sources: small quantities, industrial sources:
  - electronics
  - optical glasses
  - semiconductors
  - scintillation counters
  - mercury lamps
  - medical device – scintigraphy for the heart, liver and other tissues
  - jewelry
  - pigments
  - rodenticide

---

**Ref:**

<table>
<thead>
<tr>
<th>Children and heavy metals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>THALLIUM - ABSORPTION, DISTRIBUTION AND EXCRETION</strong></td>
</tr>
<tr>
<td>✓ Bioavailability, almost 100% by: ingestion, inhalation and dermal exposure</td>
</tr>
<tr>
<td>✓ Distribution: intracellular, mainly renal, also heart and liver</td>
</tr>
<tr>
<td>✓ Excretion: weeks (elimination $t_{1/2}$ - 10-30 days)</td>
</tr>
</tbody>
</table>

**Ref:**
Thallium poisoning can be mistaken for botulism.

Please note the information on this slide comes mostly from adult exposure data.

Ref:
Since there is no specific treatment of thallium toxicity, the mainstay treatment is:
* reducing absorption
* increasing its elimination
* and supportive treatment.
The question of the possible association of heavy metals and child health has frequently arisen during the last 50 years due to an increased incidence of autism, the presence of heavy metals as vaccine preservatives and other concerns. The following slides address some of these questions based on evidence and existing data.
The link between heavy metals and autism is presently an area of research. Final conclusions on this are premature at this moment.
Mercuric compounds are neurotoxic at high doses.

Thimerosal (thimerosal), a preservative used in vaccines, contains ethylmercury.

Studies of childhood vaccination with thimerosal-containing vaccine do not support link to autism.

information on use of all vaccines and vaccine-specific amounts of Thimerosal).

RESULTS: in all three countries, the incidence and prevalence of autism-like disorders began to rise in the 1985-1989 period, and the rate of increase accelerated in the early 1990s. However, in contrast to the situation in the United States, where the average Thimerosal dose from vaccines increased throughout the 1990s, Thimerosal exposures from vaccines in both Sweden and Denmark-already low throughout the 1970s and 1980s-began to decrease in the late 1980s and were eliminated in the early 1990s.

CONCLUSIONS: The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.
Children and heavy metals

NO CAUSAL RELATIONSHIP BETWEEN CHILDHOOD VACCINATION WITH THIOMERSAL-CONTAINING VACCINES AND DEVELOPMENT OF AUTISM-SPECTRUM DISORDERS

- Risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with thimerosal-containing vaccine and children vaccinated with thimerosal-free vaccine (relative risk 0.85 for autism; relative risk 1.12 for other autism-spectrum disorders).
- Ecological studies of the prevalence/incidence of autism in California, Sweden yielded similar results.
- Studies do not show a causal relationship between childhood vaccination with thimerosal-containing vaccines and autism-spectrum disorders.

Refs:
- Mercuric compounds are nephrotoxic and neurotoxic at high doses. Thimerosal, a preservative used widely in vaccine formulations, contains ethylmercury. Thus it has been suggested that childhood vaccination with thimerosal-containing vaccine could be causally related to neurodevelopmental disorders such as autism.
- OBJECTIVE: To determine whether vaccination with a thimerosal-containing vaccine is associated with development of autism.
- MAIN OUTCOME MEASURES: Rate ratio (RR) for autism and other autistic-spectrum disorders, including trend with dose of ethylmercury.
- RESULTS: During 2,986,654 person-years, we identified 440 autism cases and 787 cases of other autistic-spectrum disorders. The risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with thimerosal-containing vaccine and children vaccinated with thimerosal-free vaccine (RR, 0.85 [95% confidence interval [CI], 0.60-1.20] for autism; RR, 1.12 [95% CI, 0.88-1.43] for other autistic-spectrum disorders). Furthermore, we found no evidence of a dose-response association (increase in RR per 25 microg of ethylmercury, 0.98 [95% CI, 0.90-1.06] for autism and 1.03 [95% CI, 0.98-1.09] for other autistic-spectrum disorders).
- CONCLUSION: The results do not support a causal relationship between childhood vaccination with thimerosal-containing vaccines and development of autistic-spectrum disorders.
- It has been suggested that thimerosal, a mercury-containing preservative in vaccines, is a risk factor for the development of autism. We examined whether discontinuing the use of thimerosal-containing vaccines in Denmark led to a decrease in the incidence of autism.
- DESIGN: Analysis of data from the Danish Psychiatric Central Research Register recording all psychiatric admissions since 1971, and all outpatient contacts in psychiatric departments in Denmark since 1995.
- RESULTS: A total of 956 children with a male-to-female ratio of 3.5:1 had been diagnosed with autism during the period from 1971-2000. There was no trend toward an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990. From 1991 until 2000 the incidence increased and continued to rise after the removal of thimerosal from vaccines, including increases among children born after the discontinuation of thimerosal.
- CONCLUSIONS: The discontinuation of thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism. Our ecological data do not support a correlation between thimerosal-containing vaccines and the incidence of autism.
- In 1999, concerns were raised that vaccines containing the preservative Thimerosal might increase the risk of autism and/or other neurodevelopmental disorders.
- METHODS: Between the mid-1980s through the late-1990s, we compared the prevalence/incidence of autism in California, Sweden, and Denmark with average exposures to Thimerosal-containing vaccines. Graphic ecologic analyses were used to examine population-based data from the United States (national immunization coverage surveys and counts of children diagnosed with autism-like disorders seeking special education services in California); Sweden (national inpatient data on autism cases, national vaccination coverage levels, and information on use of all vaccines and vaccine-specific amounts of Thimerosal); and Denmark (national registry of inpatient/outpatient-diagnosed autism cases, national vaccination coverage levels, and
information on use of all vaccines and vaccine-specific amounts of Thimerosal).

RESULTS: In all three countries, the incidence and prevalence of autism-like disorders began to rise in the 1985-1989 period, and the rate of increase accelerated in the early 1990s. However, in contrast to the situation in the United States, where the average Thimerosal dose from vaccines increased throughout the 1990s, Thimerosal exposures from vaccines in both Sweden and Denmark—already low throughout the 1970s and 1980s—began to decrease in the late 1980s and were eliminated in the early 1990s.

CONCLUSIONS: The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.

The Global Advisory Committee on Vaccine Safety considered the presentation of a recently published pharmacokinetic study of mercury in premature and low-birth-weight infants who received a birth dose of hepatitis B vaccine containing thiomersal. The results suggest that exposure to thiomersal-containing vaccines does not result in accumulation of mercury in blood and that the blood half-life (2.9–4.1 days) of intramuscular ethyl mercury from thiomersal in vaccines in infants is substantially shorter than that of oral methyl mercury in adults. The study concluded that exposure guidelines based on oral methyl mercury may not be appropriate for use in assessing the risk of thiomersal in vaccines at dosages consistent with standard vaccination regimens.

The Global Advisory Committee on Vaccine Safety also considered the results of a study conducted in Italy that examined the neuropsychological performance 10 years after immunization in infancy with thiomersal-containing vaccines (Tozzi A., unpublished data, 2008). According to the results, higher thiomersal exposure through vaccines administered in the first year of life was significantly associated with lower scores on 2 neuropsychological outcomes (motor function, measured using the finger-tapping test, and language, measured using the Boston naming test). The differences in mean scores were very small, detected only in girls, of doubtful clinical relevance, and not consistent with results from other studies of ethyl mercury. The observed associations may reflect the effect of chance.

On the basis of the presented data, Global Advisory Committee on Vaccine Safety remains of the view that there is no evidence supporting any change in WHO’s recommendations for thiomersal-containing vaccines and the vaccination of low-birth-weight infants where indicated.
Some authors have reported higher blood mercury (Hg) levels in persons with autism, relative to unaffected controls. OBJECTIVES: We compared blood total mercury concentrations in children with autism or autism spectrum disorder (AU/ASD) and typically developing (TD) controls in population-based samples, and determined the role of fish consumption in differences observed. METHODS: The Childhood Autism Risk from Genetics and the Environment (CHARGE) Study enrolled children 2-5 years of age. After diagnostic evaluation, we analyzed three groups: autism spectrum disorder (AU/ASD), non-autism spectrum disorder (non-AU/ASD) with developmental delay (DD), and population-based typically developing (TD) controls. Mothers were interviewed about household, medical, and dietary exposures. Blood Hg was measured by inductively coupled plasma mass spectrometry. Multiple linear regression analysis was conducted (n = 452) to predict blood Hg from diagnostic status controlling for Hg sources. RESULTS: Fish consumption strongly predicted total mercury (Hg) concentration. Autism spectrum disorder (AU/ASD) children ate less fish. After adjustment for fish and other Hg sources, blood Hg levels in autism spectrum disorder (AU/ASD) children were similar to those of typically developing children (p = 0.75); this was also true among non-fish eaters (p = 0.73). The direct effect of autism spectrum disorder (AU/ASD) diagnosis on blood mercury not through the indirect pathway of altered fish consumption was a 12% reduction. Developmental Delay (DD) children had lower blood Hg concentrations in all analyses. Dental amalgams in children with gum-chewing or teeth-grinding habits predicted higher levels. CONCLUSIONS: After accounting for dietary and other differences in Hg exposures, total Hg in blood was neither elevated nor reduced in CHARGE Study preschoolers with autism spectrum disorder (AU/ASD) compared with unaffected controls, and resembled those of nationally representative samples.
Some authors have reported higher blood mercury (Hg) levels in persons with autism, relative to unaffected controls.

OBJECTIVES: We compared blood total mercury concentrations in children with autism or autism spectrum disorder (AU/ASD) and typically developing (TD) controls in population-based samples, and determined the role of fish consumption in differences observed.

METHODS: The Childhood Autism Risk from Genetics and the Environment (CHARGE) Study enrolled children 2-5 years of age. After diagnostic evaluation, we analyzed three groups: autism spectrum disorder (AU/ASD), non-autism spectrum disorder (non-AU/ASD) with developmental delay (DD), and population-based typically developing (TD) controls. Mothers were interviewed about household, medical, and dietary exposures. Blood Hg was measured by inductively coupled plasma mass spectrometry. Multiple linear regression analysis was conducted (n = 452) to predict blood Hg from diagnostic status controlling for Hg sources.

RESULTS: Fish consumption strongly predicted total Hg concentration. Autism spectrum disorder (AU/ASD) children ate less fish. After adjustment for fish and other mercury sources, blood Hg levels in autism spectrum disorder children were similar to those of typically developing controls children (p = 0.75). Developmental delay children had lower blood mercury in all analyses. Dental amalgams in children with gum-chewing or teeth-grinding habits predicted higher levels.

CONCLUSIONS: After accounting for dietary and other differences in mercury exposures, total mercury in blood was similar in the study preschoolers with autism spectrum disorder compared with unaffected controls, and resembled those of nationally representative samples. Hertz-Picciotto I et al, 2010

**Results**

Fish consumption strongly predicted total Hg concentration.

- After adjustment for fish and other mercury sources, blood Hg levels in autism spectrum disorder children were similar to those of typically developing controls children (p = 0.75). Developmental delay children had lower blood mercury in all analyses.
- Dental amalgams in children with gum-chewing or teeth-grinding habits predicted higher levels.

**Conclusions**

After accounting for dietary and other differences in mercury exposures, total mercury in blood was similar in the study preschoolers with autism spectrum disorder compared with unaffected controls, and resembled those of nationally representative samples. Hertz-Picciotto I et al, 2010
(AU/ASD) compared with unaffected controls, and resembled those of nationally representative samples.
We end with this beautiful reminder to us from a child in India, We must recognize the risks to our children and assume our responsibilities of preventing them, because we hold our future in our hands—and it is our children.

Thank you.
ACKNOWLEDGEMENTS

WHO is grateful to the US EPA Office of Children’s Health Protection for financial support that made this project possible and for some of the data, graphics and text used in preparing these materials for a broad audience. Further support was kindly provided by the UK Department of Health.

First draft prepared by Yona Amitai, MD, MPH (Israel)

With the advice of the Working Group Members on the Training Package for the Health Sector: Cristina Alonzo MD (Uruguay); Yona Amitai MD MPH (Israel); Stephan Boese-O’s Reilly MD MPH (Germany); Stefania Borgo MD (ISDE, Italy); Irena Buka MD (Canada); Ernesto Burgio (ISDE, Italy); Lilian Corra MD (Argentina); Liggia Fruchtengarten MD (Brazil); Amalia Laborde MD (Uruguay); Jenny Pronczuk MD (WHO) Christian Schweizer TO (WHO/EURO); Kathy Shea MD (USA).

Reviewers: Dr Huw Brunt (UK), Prof Gary Coleman (UK), Dr Raquel Duarte-Davidson (UK), Dr Elaine Lynch Farmery (UK), Alison M Good BSc Dip Med Tox MSc (UK), Dr Mark Griffiths (UK), Dr John Thompson (UK), Dr Laura Yates (UK)

WHO Project coordination: Ruth A. Etzel, MD PhD
Marie-Noëll Bruné, MSc

Latest update: October 2011
Children and heavy metals

Disclaimer

WHO/HSE/PH/EPE/11.01.07 © World Health Organization 2011. All rights reserved.

This e-learning training was developed by the World Health Organization (WHO). It is intended to be used as a self-learning course on Children's Health and the Environment.

All reasonable precautions have been taken by WHO to verify the information contained in this e-learning training. However, the e-learning training is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the e-learning training lies with the reader. In no event shall WHO be liable for damages arising from its use.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.