

Exposure to metals and decreased renal function?

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Present knowledge

- Very high exposure to Pb, Cd, and inorganic Hg and As can cause acute kidney injury
- High occupational exposure to lead, cadmium and mercury is associated with increased risk for endstage renal disease
- Occupational exposure to lead, cadmium and mercury is associated with markers of adverse renal function
- General population studies and endstage renal disease
 - Lead: inconclusive
 - Cadmium: possibly
 - Mercury: no data
 - Arsenic: no data
- General population studies and markers of adverse renal function:
 - Lead: eGFR
 - Cadmium: tubular proteins
 - Mercury: proteinuria (?)
 - Arsenic: proteinuria (?)

Methods for risk assessment

- Assessment of contaminants in environmental media (air, soil, water) and food
 - Simple comparison with guidelines/permissible levels (includes safety margin to *a specific effect*)
 - More complex modelling of intake, and comparison with known dose-response/dose-effect relationships *for renal function*
- Biomarkers of exposure (parent compound or metabolite; various matrices) integrates all routes of exposure
 - Comparison with reference values in the general population
 - Comparison with permissible levels (includes margin to *a specific effect*) in occupational settings
 - Comparison with known dose-response/dose-effect relationships *for renal function*

Methods for assessment of association between exposure and effect (decreased glomerular filtration, proteins in urine, diagnosis of disease)

TIMING IS CRUCIAL! Assessment of exposure before effect.

Acute effect? Chronic/cumulated effect?

- Longitudinal cohorts observed over several years
 - occupational cohorts (many existing for Pb and Cd, also for U, Ni....)
 - exposure before outcome
 - population-based cohorts
 - exposure before outcome
- Cross-sectional study (prevalence of outcome in defined study groups)
 - exposure before outcome (self-report, modelled)
 - exposure assessed at the same time as outcome (biomarkers)
- Case-control studies
 - exposure before outcome (self-report, modelled)
 - exposure assessed at the same time as outcome (biomarkers)

Design issues

- Biomarker kinetics (compartments, half-lives)?

Timing of exposure in relation to initiation of disease

- Preanalytical and analytical issues (contamination, analytical quality)

- Is reverse causation possible ?

example: U-Cd and tubular dysfunction

Caveat in cross-sectional studies, and in case-control studies

Biomarkers of metal exposure

Sri Lanka

Summary of biomarker results from 8 published studies

(Jakobsson, Brooks, personal communication)

Urine levels of Pb, Cd in controls from endemic areas were not higher than in controls from non-endemic areas.

No consistent finding of higher metal levels in cases compared to controls

Abstracts submitted to this workshop

- Kambham et al. No metal deposits in CKDu patient biopsies
- Lebov et al. Regional survey and case-control study

Central America

Very little data on metal levels in the general population

Data in active sugarcane workers:

No increased levels of metals in urine (Nicaragua, Brooks et al)

No increased levels of metals in blood (El Salvador, Jakobsson et al)

Abstracts submitted to this workshop

- Fischer et al (sugar cane, Nicaragua). Ni in AKI?
- Jaramillo et al (sugar cane, Guatemala). Small proportion of workers had higher levels of metals in urine, compared to NHANES observations
- Keogh et al (El Salvador). Longitudinal cohort, multiple occupations

Metals in environmental media (air, soil, water) and food

Sri Lanka

International Expert Consultation on CKDu, April 2016

- Snapshot data
- Little /no evidence of elevated levels

Abstracts submitted to this workshop:

- Vlahos et al. Within permissible levels in drinking water
- Lebov et al: Regional survey and case-control study

Central America

Limited data, no review

Abstracts submitted to this workshop:

- Villegas et al (Costa Rica). As in water
- Jaramillo et al (Guatemala). Within permissible levels in drinking water

Present knowledge

Metal	Arsenic	Cadmium	Lead	Lithium	Mercury
Evidence of nephrotoxicity in humans	+	+++	++	+++	+++
Specific clinical and morphological findings in human nephrotoxicity	-	+++	+	++	++
Specific biochemical and/or morphological findings in animal nephrotoxicity	-	+++	++	++	++
Established dose-effect and dose response relations between exposure and renal effects in humans	-	+++	-	+	++
The possibility to use measurements in blood and or urine (biological monitoring) to assess exposure	+	+++	+++	+++	+++
The existence of established dose-effect and dose response relations between results from biological monitoring and renal effects in humans.	-	+++	-	++	++

From Elinder CG. Does exposure to toxic metals have a role in the development of MeN?
 In: Report from 2nd International workshop on MeN (2015)