Use of modelisation tools to assess risks related to cadmium exposure for workers and consumers

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EFSA Conference, 2018 September 18-21, Parma.
Problem Formulation

Hazard

• Highly persistent environmental toxicant Bioaccumulable -> elimination half-life: 10 to 30 years
• Accumulation in liver and kidneys
• Acute Toxicity («itaï-itaï» disease)
• Chronic Toxicity: repeated exposure → kidney diseases, bone disease, reprotoxicity....
• Carcinogenic group 1 (IARC) and 1B (EU)

Cd

Exposure

• Food as the most important source of exposure (excluding tobacco)
• Anses opinion from 2011 and 2016 following TDS2 and TDSi showing increased exposure to Cd and part of the population above the reference values: children (15%) and adults (0.6%)
• Recommendation to reduce exposure by limiting cadmium in the fertilizing materials

SCOPE

→ Update of the reference values (oral and internal values)
→ Market studies on fertilizing materials
→ Proposals for limits values of cadmium in fertilizing materials to reduce soil contamination and exposure
Conceptual Scheme

**Fertilizing materials SECTOR**

- Rock phosphate deposit (varying concentrations)
- Mineral fertilizers
  - Phosphate fertilizers
- Organic amendments
- Livestock effluents
- Compost
- Sludge
  - Wastewater treatment

**SOIL**

- Atmospheric deposits
- Fertilizers and agricultural spreading
- Irrigation water
- Geochemical background
- Leaching
  - Phosphorus solubility

**PLANT**

- Process
  - Food of animal origin

**CONSUMERS**

**TOXICOLOGY**

- Cadmium transfer
- Cadmium exposure
- Contamination cycle of cadmium linked to fertilizers
Hazard Characterization
Cadmium Toxicity

Target organs following repeated oral exposure: kidneys and bone tissues

**JECFA, EFSA, ATSDR, ANSES**

**Kidney:**

Accumulation of Cd in renal tissue (proximal tubes, renal cortex)

- Degenerescence and tubular atrophy

- Release of low molecular weight proteins (β-2-microglobulin, retinol-binding protein (RBP), α-1-microglobulin, ...)

**Bone effects:**

- Decrease in bone density
- Osteomalacia, Osteoporosis
- Fractures
- In women and men
Hazard Characterization
« Swedish Mammography Cohort » (sub cohort included)

2003-2009 ♀ living in Uppsala

Engström 2011
2688 ♀ (56-69 ans)
Relation between long-term exposure to Cd and bone effects
(osteoporosis + fractures)

Engström 2012
2676 ♀ (49-62 ans)
Association between $\text{Cd}_{\text{food}}$ and bone density
Food questionnaire (1997) + $[\text{CdU}]$
(2004-2008)
Osteoporosis and 1st fracture

Reference Population: $< 0.5 \, \mu g / g \, \text{creat.}$

$J \text{ Bone Miner Res. 2011, 26, 3, 486-495}$

Reference Population: $\text{CdU}<0.5 \, \mu g / g \, \text{creatinine} + \text{Cd al}<13 \, \mu g/d$

$Bone 2012, 50, 1372-1378$
Increased risk of osteoporosis and fractures after long term exposure to CdU > 0.5 µg / g créat.

<table>
<thead>
<tr>
<th></th>
<th>ORs (95% IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Σ Women</td>
</tr>
<tr>
<td>Neck of femur</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 µg / g creat</td>
<td>1.00 (réf)</td>
</tr>
<tr>
<td>0.5-0.75 µg / g creat</td>
<td>2.17 (1.51-3.11)</td>
</tr>
<tr>
<td>&gt;0.75 µg / g creat</td>
<td>2.45 (1.51-3.97)</td>
</tr>
<tr>
<td>Rachis</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 µg / g creat</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>0.5-0.75 µg / g creat</td>
<td>1.30 (0.91-1.86)</td>
</tr>
<tr>
<td>&gt;0.75 µg / g creat</td>
<td>1.97 (1.24-3.14)</td>
</tr>
</tbody>
</table>
Urinary Cd µg/g creat

Reference value

0.5 µg/g creat

Internal TRV for 50 years to take into account accumulation over life
Urinary Cd µg/g creat

Reference value

Internal TRV for 50 years to take into account accumulation over life

0.5 µg/g creat

50 years

?? µg/g creat
Inhalation 

Gaz exchange 

Lungs 

Not well-perfused tissues 

Well perfused tissues 

Adipose Tissue 

Kidney 

Liver 

Stomach 

Intestin 

Feces 

urinary excretion 

PBPK Model

not to be above 0.5 µg/g creat at 50 years old
models of Kjellström and Nordberg (1978)

Schematic representation of Cd mass flow in the KN/OB model

\[ A = \text{AIR} \]

Nasopharyngeal
Tracheobronchial

\[ C_2 \times \text{AIR} \]

\[ C_3 \times \text{E1} \]

\[ E_1 = \text{Lung} \]

\[ C_1 \times \text{AIR} \]

\[ C_4 \times \text{E1} \]

Gastrointestinal tract

\[ C_5 (G + C_1 \times \text{AIR} + C_4 \times \text{E1}) \]

\[ E_2 = \text{Intestine} \]

\[ C_6 \times \text{E2} \]

\[ I_2 = C_7I \ [\leq C_8] \]

\[ I = \text{Daily uptake} \]

\[ B_1 = \text{Blood 1} \]

\[ C_{18} \times \text{K} \]

\[ C_{10} \times \text{T} \]

\[ C_{13} \times \text{L} \]

\[ T = \text{Other tissues} \]

\[ C_{12} \times \text{B1} \]

\[ C_{11} \times \text{B1} \]

\[ C_{15} \times \text{L} \]

\[ F = \text{Feces} \]

\[ C_{14} \times \text{L} \]

\[ C_{19} \times \text{K} \]

\[ K = \text{Kidney} \]

\[ C_{17} \times \text{B3} \]

\[ 1.5 \times \text{K/K}_w \]

\[ \text{CKBW = Cortex conc.} \]
- Berkeley Madona tool

- PBPK model from Kjellström and Nordberg (1978)
  Codes sent to Anses by ATSDR

- Specific Algorithm to take into account increased body weight depending on age: French data

  Gault et Cockroft equation (not for children):
  \[
  \text{Cr 24h/day} = (28 - 0.2 \times \text{age}) \times \text{weight}
  \]
Specific Algorithme to take into account increased body weight depending on ages:

French data

Polynomiale regression based on TDS2 and TDSi population 3 months to 79 years, n = 4781

Weight = 3.68 + 4.47 \times age - 0.093 \times age^2 + 0.00061 \times age^3
Algorithm for urinary excretion of creatinine: French data depending on body weight and ages
## Urinary excretion of creatinine: depending on body weight and ages

<table>
<thead>
<tr>
<th>age (year)</th>
<th>Urinary creatinine excretion in g per day</th>
<th>Body weight in Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimated</td>
<td>measured</td>
</tr>
<tr>
<td>3</td>
<td>0.17</td>
<td>0.23</td>
</tr>
<tr>
<td>4 to 5</td>
<td>0.27</td>
<td>0.32</td>
</tr>
<tr>
<td>6 to 8</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>9 to 13</td>
<td>0.86</td>
<td>0.75</td>
</tr>
<tr>
<td>14 to 18</td>
<td>1.28</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Based on Remer et al. 2002

### Usual Values

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>1.2-2</td>
</tr>
<tr>
<td>Woman</td>
<td>0.9-1.8</td>
</tr>
</tbody>
</table>
Urinary Cd evolution

Threshold value
## Urinary Cd evolution

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Urinary Cd in µg/g creatinine</th>
<th>Estimated body weight</th>
<th>Creatinine Excretion in 24 hours in g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.02</td>
<td>8</td>
<td>0.06</td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td>16</td>
<td>0.17</td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
<td>20</td>
<td>0.23</td>
</tr>
<tr>
<td>....</td>
<td>......</td>
<td>......</td>
<td>......</td>
</tr>
<tr>
<td>10</td>
<td>0.06</td>
<td>40</td>
<td>0.77</td>
</tr>
<tr>
<td>15</td>
<td>0.08</td>
<td>52</td>
<td>1.21</td>
</tr>
<tr>
<td>20</td>
<td>0.10</td>
<td>61</td>
<td>1.53</td>
</tr>
<tr>
<td>....</td>
<td>......</td>
<td>....</td>
<td>....</td>
</tr>
<tr>
<td>30</td>
<td>0.16</td>
<td>71</td>
<td>1.68</td>
</tr>
<tr>
<td>40</td>
<td>0.29</td>
<td>73</td>
<td>1.38</td>
</tr>
<tr>
<td>50</td>
<td>0.44</td>
<td>71</td>
<td>1.10</td>
</tr>
<tr>
<td>65</td>
<td>0.51</td>
<td>69</td>
<td>1.07</td>
</tr>
</tbody>
</table>
Cadmium-reverse dosimetry

External Dose → Internal Dose → Dose at the target organ → Toxicity

PB-PK modeling
PBPK Model

All life exposure
0.35 µg Cd /kg bw/day

not to be above 0.5 µg/g creat at 50 years old
Risk assessment and limits values in fertilizers
Cadmium inflow due to fertilizer materials

Various scenarios of soils fertilization
- fertilizer materials:
  1) 100% mineral -> Phosphate fertilizers (major source)
  2) Organic origin or combination of mineral and organic
- Cultures: selection of cultures that are representatives of the French exposure
- French situations - parameters influencing Cd transfer: Geochemical background, pH, organic material, clay, carbone
- Annual precipitations, yields

Determination of Cd contamination in agricultural soils

\[ [Cd]_{sol,i} = [Cd]_{sol,i-1} + \frac{(Cd \text{ flux soil input} - Cd \text{ flux soil output})}{\text{soil density}} \]

Determination of Cd contamination in cultures

- Soil to Plant transfer Modélization
- French specificities
- updated ANSES model: Cd concentration variations in the wheat grain and potatoes

Determination of Cd leaching

- Soil-leaching transfer Modélization

Monte-Carlo Simulations (10 000 parcelles) → R-shiny

99 years projection time

Conceptual Scheme

Modelisation

Contamantes: \( M_{\text{contamoles}} \times \% \) → \( M_{\text{CATS}}\times\% \)

Consumer exposure

\[ E_i = \sum_{k=2}^{n} \frac{C_{i,k} \times L_k}{PC_i} \]

Risk Assessment

Toxicological Reference value

Risk

21
Geochemical background

Agricultural practices

[Cd] field soils

[Cd] atmospheric deposits

[Cd] irrigation water

[Cd] lixiviation

[Cd] cultures

[Cd] lixiviation

[Cd] fertilizers

Food consumption

[Cd] food

Cd exposure via food
Selection of Cd inflow via fertilizing materials

### Phosphate fertilizers

<table>
<thead>
<tr>
<th>Culture</th>
<th>annual Inflow (kg P₂O₅·ha⁻¹)</th>
<th>Inflow every 3 years (kg P₂O₅·ha⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat monoculture</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Rotation potatoes/wheat/wheat</td>
<td>100</td>
<td>180</td>
</tr>
</tbody>
</table>

**Concentration of Cd in phosphate fertilizers**

<table>
<thead>
<tr>
<th>Limits (mg. kg P₂O₅⁻¹)</th>
<th>99 years projection time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Progressive reduction</td>
<td>years 1 to 3</td>
</tr>
<tr>
<td>(mg. kg P₂O₅⁻¹)</td>
<td>60</td>
</tr>
</tbody>
</table>

**On-going discussions at EU level on the limits**

**20 scenarios with or without culture rotation**

**Inflow from organic fertilizers**: Livestock effluents, Sludge, Compost
Tools output and hypothesis
The output data of the model allow derivation of the adult and child consumer’s average chronic exposure and 95th percentile, as a function of the projection time of the modelisation (10, 20, 60, 99 years), in correlation with the study of the evolution of the Cd contamination in crops (wheat grain and potato) linked to fertilization scenarios. These data have then to be compared with measured data to check if the model provides a predictive support to estimate Cd levels in the plants and in the final related food products.

### Tools output: some illustrations

#### Example: based on previous hypothesis

<table>
<thead>
<tr>
<th>Soil</th>
<th>Culture (wheat seed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated (2018)</td>
<td>RMQS-GIS SOL</td>
</tr>
<tr>
<td></td>
<td>Estimated (2018)</td>
</tr>
<tr>
<td>P50</td>
<td>P50</td>
</tr>
<tr>
<td>0.2 mg/kg</td>
<td>0.19 mg/kg</td>
</tr>
<tr>
<td></td>
<td>P50</td>
</tr>
<tr>
<td></td>
<td>0.07 mg/kg</td>
</tr>
<tr>
<td></td>
<td>P50</td>
</tr>
<tr>
<td></td>
<td>0.02 mg/kg</td>
</tr>
</tbody>
</table>
Preliminary Results

Figure 9. % of exceedance of the TRV of 0.35 µg Cd.kg b.w⁻¹.d⁻¹ (IC₉₅%) based on the various scenarios, in adults (on the left panel) and children (in the right panel), in LB.

S.initiale: initial situation : current exposure as the one published in EAT2 study (Anses, 2011a), with the TRV of 0.35 µg Cd.kg b.w⁻¹.d⁻¹

Sc1-Sc20: various scenarios
Conclusions & Perspectives

These mathematical models (from field to fork) are useful tools to support the risk assessment and decision-making processes. Based on such simulations, acceptable levels of cadmium pollution in fertilizers, soils, and at the end food items may be determined.

These tools may also be used to identify data gaps and the more sensitive parameters which need to be better documented to have more robust estimations.
Thank you for your attention!

And Special Thanks to:

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* Les co-auteurs classés par ordre alphabétique ont participé à parts égales aux travaux d’expertise scientifique.