UCLouvain

LTAP

# Toxicologie, impact sociétal et transdisciplinarité

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Louvain centre for Toxicology and Applied Pharmacology

SFT, Lille, 27 octobre 2018

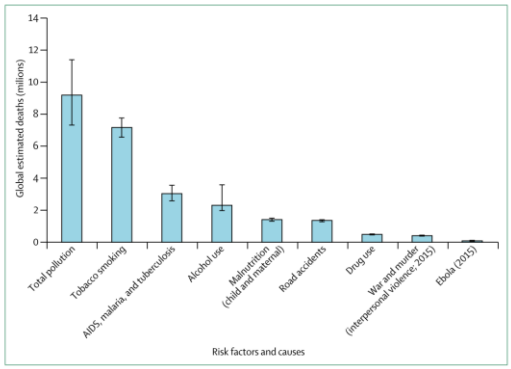



*Figure 5:* **Global estimated deaths by major risk factor and cause, 2015**
Using data from the GBD Study, 2016.[41]

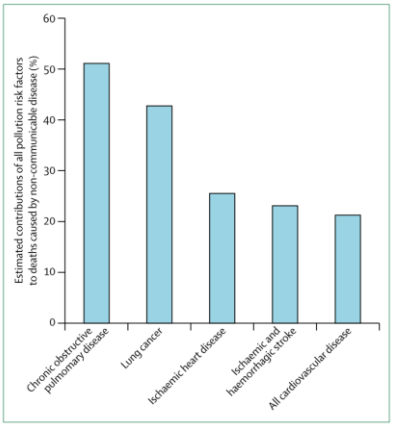
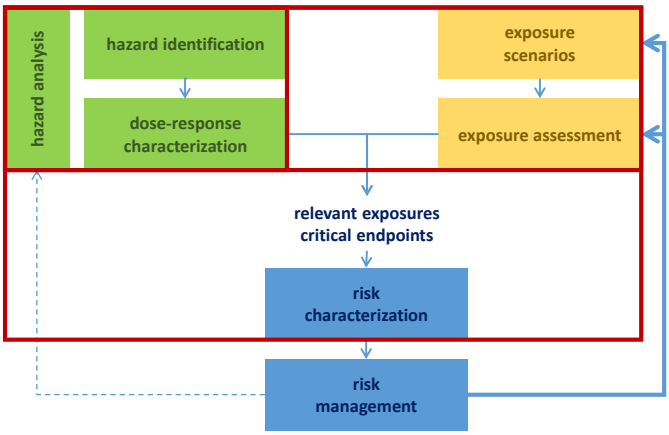


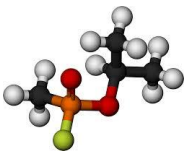

*Figure 6:* **Estimated contributions of all pollution risk factors to deaths caused by non-communicable diseases, 2015**
GBD Study, 2016.[42]

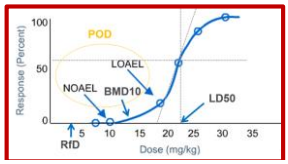
*Landrigan et al, 2017*

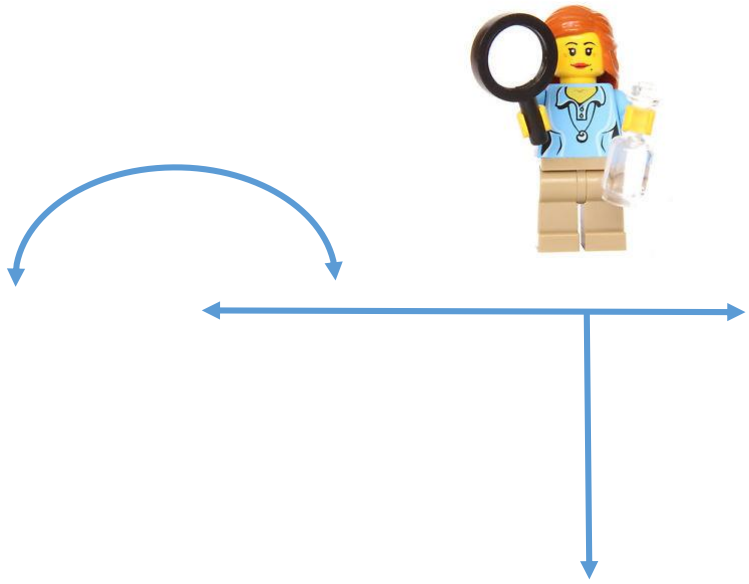
# hazard, risk, safe use of chemicals











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# Le toxicologue, Mendeleev et le téléphone

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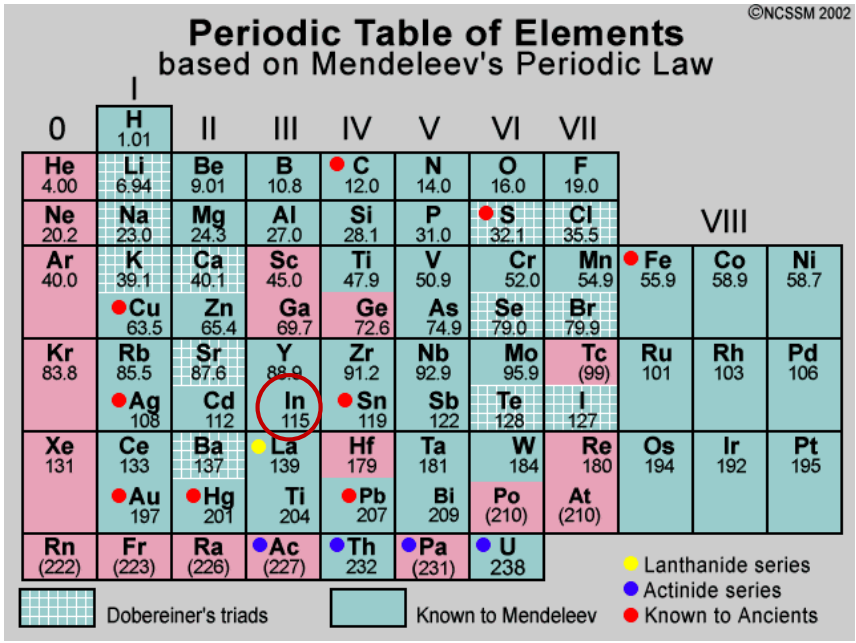



## ITO a new pneumotoxic entity

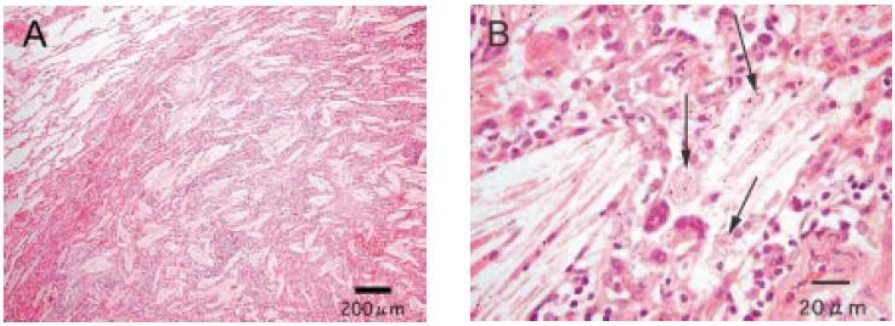



**Fig.3.** Histopathological sections of lung biopsy, showing interstitial pneumonia. Alveolar spaces are filled with red blood cells, fibrin, cholesterol clefts and alveolar macrophages, but few neutrophils. In the interstitial spaces, perivascular lymphocyte and plasma cell infiltration was seen. (A). Numerous fine particles were observed within the alveolar macrophages and the alveolar spaces (B). Stained with hematoxylin-eosin.

*T. Homma et al., 2003*

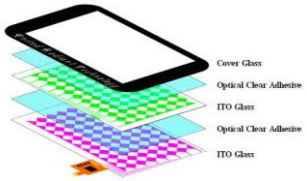
$In_2O_3$ $SnO$

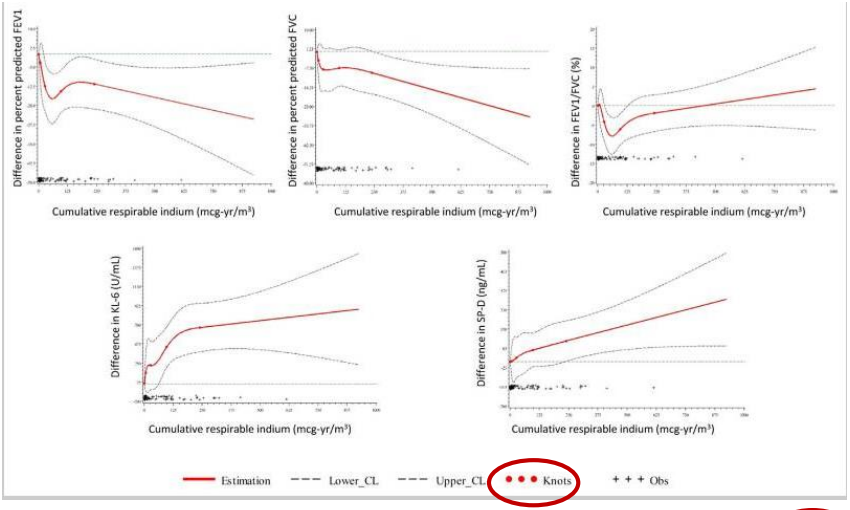
**90%** **10%**

**sintering**

**sputtering**

**ITO**




*Cummings et al., 2016*

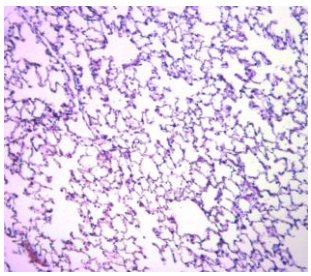
Difference From Reference Values for Pulmonary Function Parameters and Serum Biomarkers by Cumulative Indium Exposure for Workers at an Indium-Tin Oxide (ITO) Facility[a]

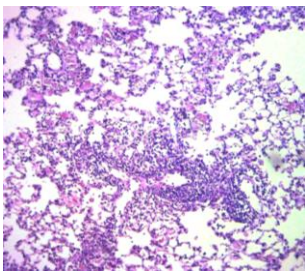
| | Difference (95%CI)[c] | | | | |
|---|---|---|---|---|---|
| Cumulative indium exposure (μg-yr/m$^3$)[b] | $FEV_1$% | FVC% | $FEV_1$/FVC (%) | KL-6 (U/ml) | SP-D (ng/ml) |
| 5.0 | −2.4 (−7.7; 2.9) | −3 (−8.3; 2.3) | 0.2 (−2.4; 2.8) | 98.8 (−61; 259) | 1.5 (−50; 53) |
| 12.0 | −5.9 (−15.8; 4.1) | −6.2 (−16.1; 3.7) | −0.4 (−5.3; 4.5) | 195 (−103.7; 493) | 5.3 (−91; 102) |
| 22.0 | **−10.4 (−20.7; −0.1)** | −8 (−18.3; 2.3) | −2.7 (−7.8; 2.3) | 222 (−81.8; 530) | 13.6 (−85.1; 11) |
| 27.5 | **−12.5 (−22.2; −2.8)** | −8.2 (−17.9; 1.5) | −4.2 (−9; 0.6) | 219 (−67.3; 505) | 18.5 (−73.7; 111) |
| 30.0 | **−13.3 (−22.9; −3.8)** | −8.3 (−17.8; 1.3) | **−4.8 (−9.5; −0.1)** | 217 (−64.4; 498) | 20.7 (−70; 111) |
| 63.0 | **−17.4 (−27; −7.7)** | −8.3 (−17.9; 1.4) | **−7.9 (−12.6; −3.1)** | **285 (2.1; 567)** | 41.2 (−49.9; 132) |
| 232.0 | **−11.6 (−21.4; −1.8)** | −9.5 (−19.3; 0.3) | −2 (−6.8; 2.8) | **662 (376; 948)** | **92.3 (0.02; 185)** |
| 240.0 | **−11.7 (−21.5; −2)** | **−9.8 (−19.5; −0.02)** | −2 (−6.7; 2.8) | **665 (380; 950)** | **94.6 (2.7; 187)** |
| 300.0 | **−12.9 (−22.5; −3.4)** | **−11.5 (−21.1; −2)** | −1.4 (−6.1; 3.3) | **684 (407; 965)** | **111 (20.5; 202)** |

*Cummings et al., 2016*

## Histopathology (day 60) : alveolar level

NaCl 0.9%
10x

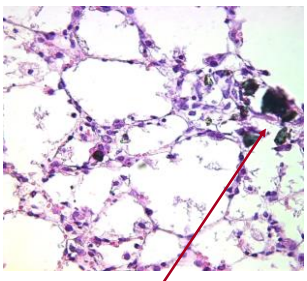




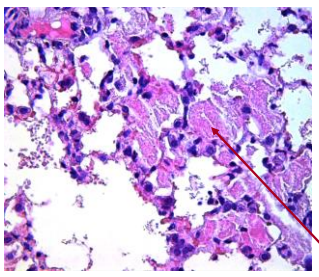
ITO – 2 mg
10x

Alveolitis

ITO – 20 mg
40x



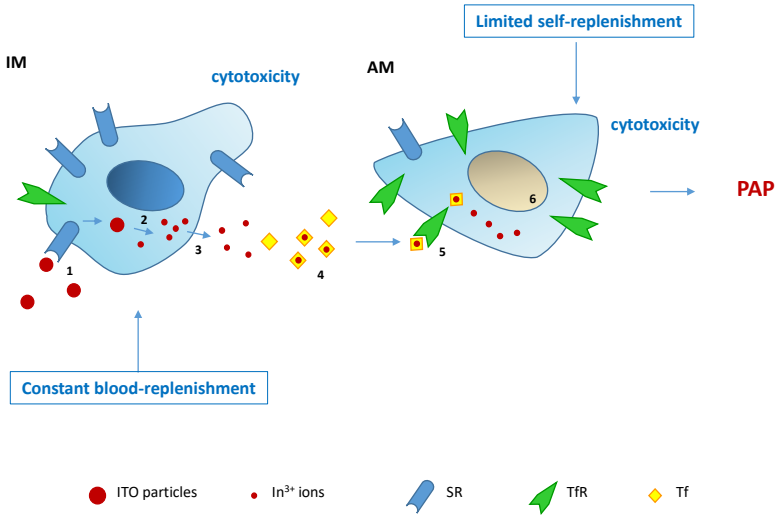
particles



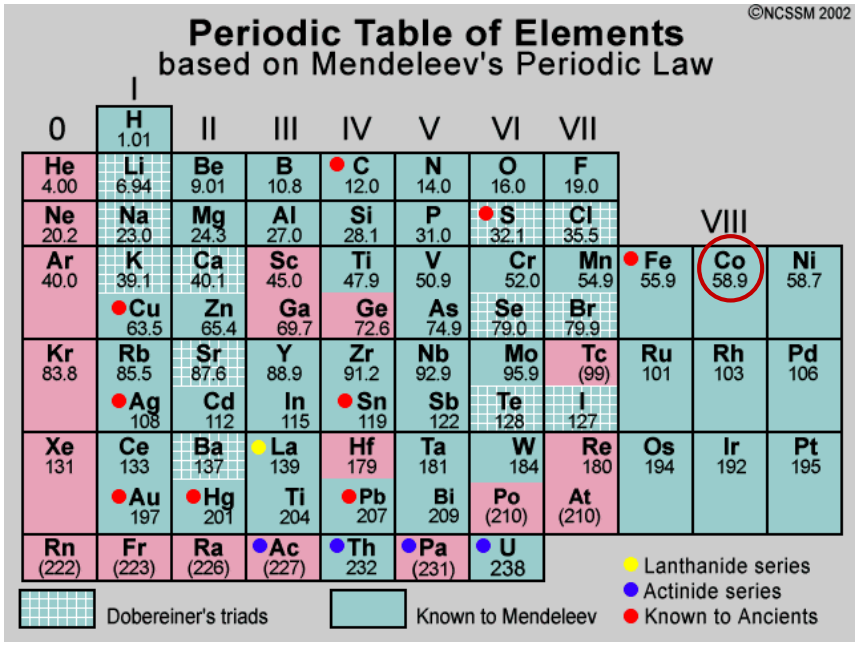
ITO – 2 mg
40x

**PAP**

*Lison et al., 2013*




*Huaux et al., 2018*

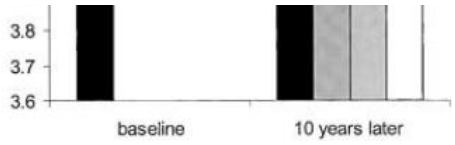


**Lung Function Changes in Workers Exposed to Cobalt Compounds**

A 13-Year Follow-up

TABLE 2. RANDOM COEFFICIENTS MODEL FOR $FEV_1$* AND FVC†

| | $FEV_1$ | | | FVC | | |
|---|---|---|---|---|---|---|
| Effect | Estimate | SE | p Value | Estimate | SE | p Value |
| Smoking | | | | | | |
| Intercept | 0.1887 | 0.0083 | < 0.001 | 0.2086 | 0.0106 | < 0.001 |
| Age at baseline | −0.0017 | 0.0003 | < 0.001 | −0.0015 | 0.0003 | < 0.001 |
| Log Co-U | −0.0024 | 0.0011 | 0.026 | −0.0024 | 0.0014 | NS |
| Time | −0.0016 | 0.0002 | < 0.001 | −0.0019 | 0.0004 | < 0.001 |
| Nonsmoking | | | | | | |
| Intercept | 0.1688 | 0.0091 | < 0.001 | 0.1921 | 0.0092 | < 0.001 |
| Age at baseline | −0.0010 | 0.0003 | < 0.001 | −0.0010 | 0.0003 | < 0.001 |
| Log Co-U | −0.0013 | 0.0011 | NS | −0.0003 | 0.0014 | NS |
| Time | −0.0017 | 0.0002 | < 0.001 | −0.0017 | 0.0002 | < 0.001 |

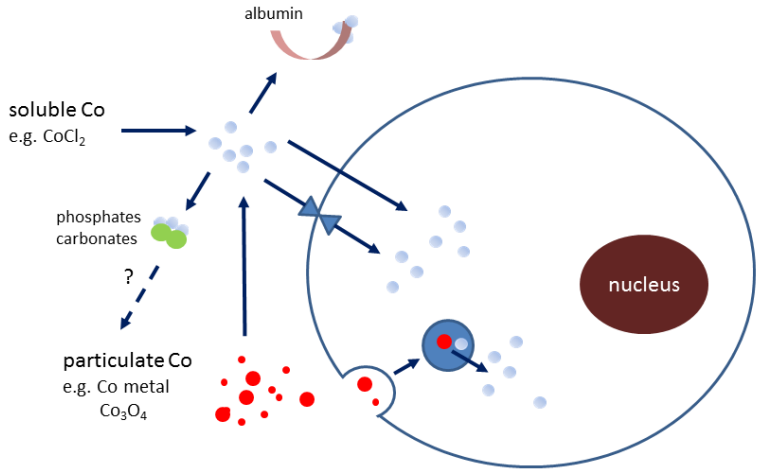



*Verougstraete et al., 2004*

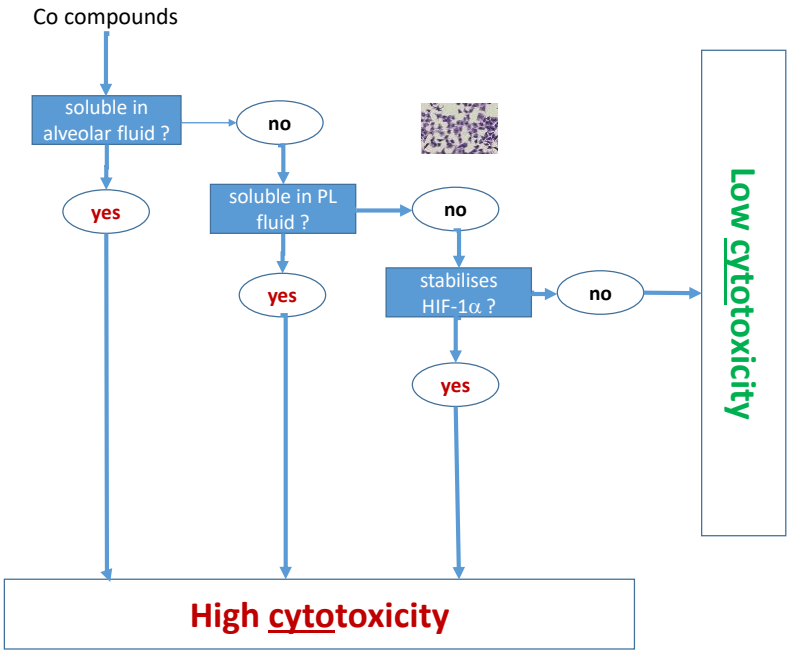
# Cobalt compounds

- Cobalt metal
- Cobalt chloride
- Cobalt sulfate
- Cobalt (II) oxide
- Cobalt (II,III) oxide
- Cobalt hydroxide
- Cobalt sulfide
- Cobalt octoate
- Cobalt naphtenate
- …

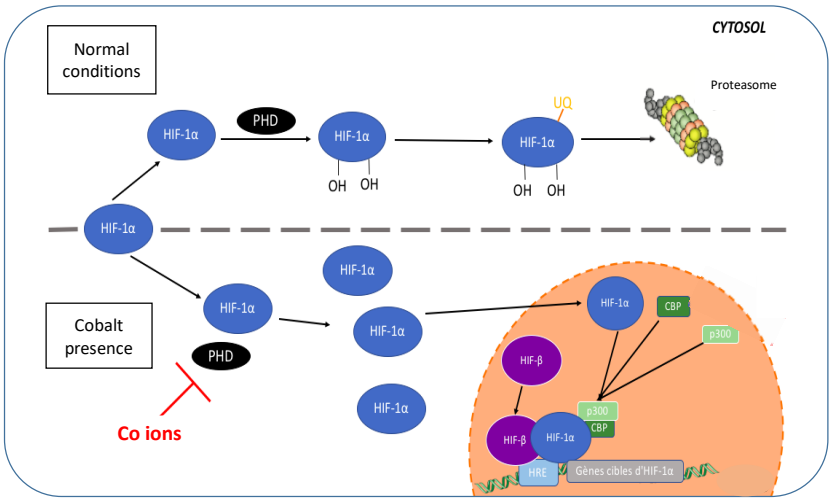
*Grouping ?*
*Read across ?*




*Lison et al., 2018*



## HIF-1α

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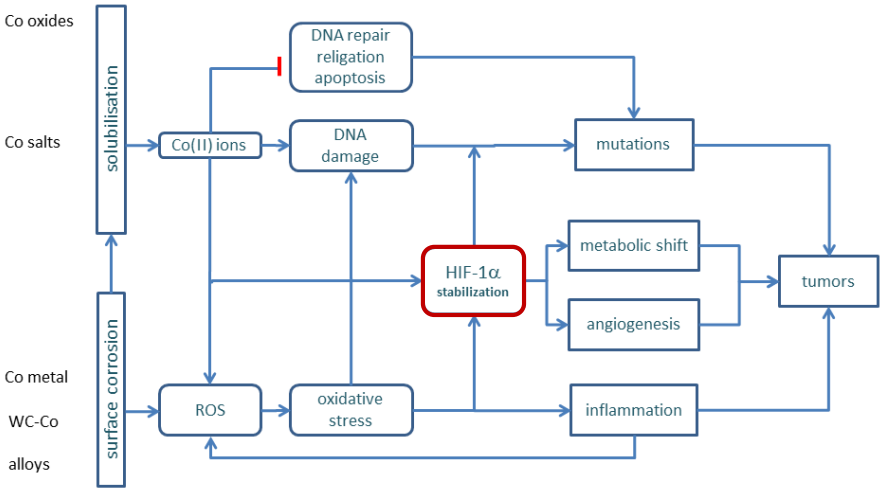
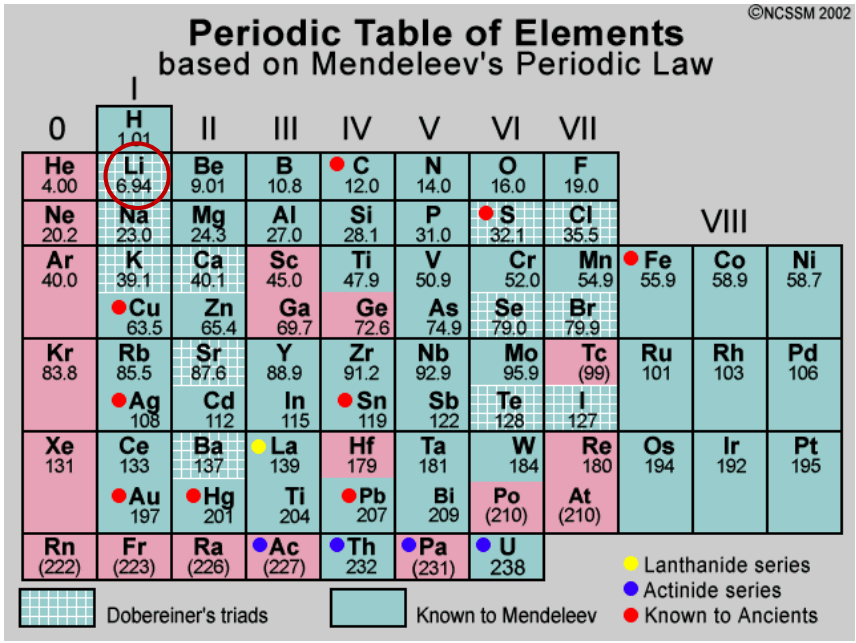
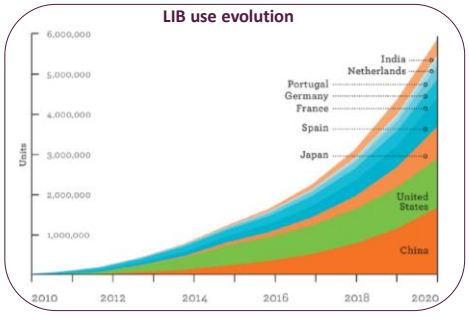
| chemicals | MIE | macromolecular | cellular | outcome |
|---|---|---|---|---|




*Lison et al., 2018*




## Li-ion battery (LIB)




**LIB particles**

$LiFePO_4$ (**LFP**), $LiCoO_2$ (**LCO**), $LiMn_2O_4$ or $Li_2MnO_3$ (**LMO**),

$Li_4Ti_5O_{12}$ (**LTO**), $LiNiMnCoO_2$ (**NMC**), $LiNiCoAlO_2$ (**NCA**)

## Is lung toxicity due to Co?
### Comparison of the lung toxicity of a large range of LIB particles

$Co_3O_4$
**73 % Co**

$LiCoO_2$ (**LCO**)
**60 % Co**

$LiNiCoAlO_2$ (**NCA**)
**27 % Co**

$CoLiNiMnCoO_2$ (**NMC**)
1:1:1 **20 % Co**
6:2:2 **12 % Co**
8:1:1 **6 % Co**

$LiFePO_4$ (**LFP**)

$Li_4Ti_5O_{12}$ (**LTO**)

$LiMn_2O_4$ or $Li_2MnO_3$ (**LMO**)

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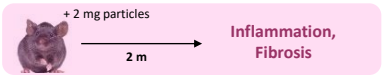
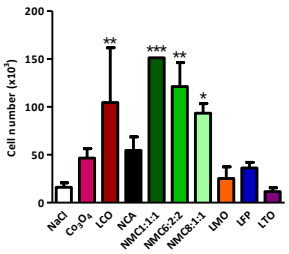
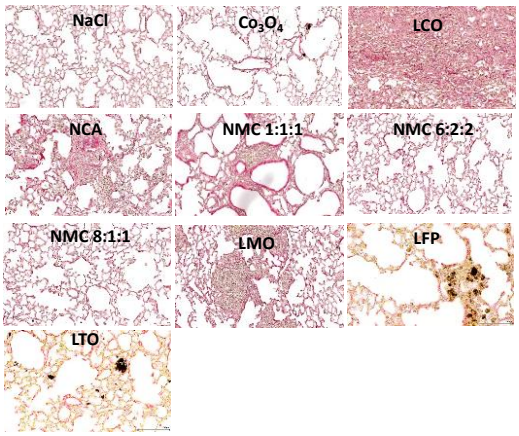
## Is lung toxicity due to Co?
### Comparison of the lung toxicity of a large range of LIB particles




Inflammatory cell infiltration




Fibrosis: Sirius red staining

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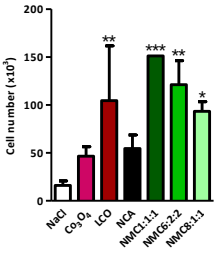
→ No association with Co content

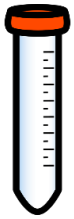
# Is lung toxicity due to Co?

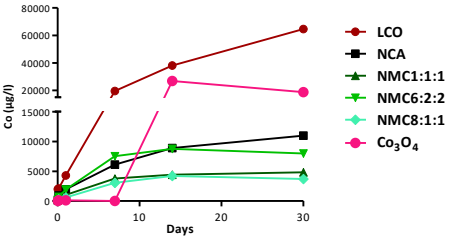
## Comparison of the lung toxicity of a large range of LIB particles


Inflammatory cell infiltration




% released Co



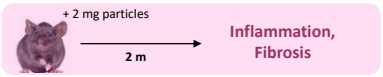



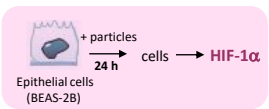

→ No association between Co %, Co bioaccessibility and LIB lung toxicity



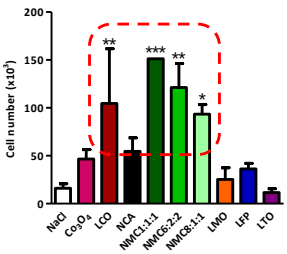
# Is lung toxicity due to Co?

## Comparison of the lung toxicity of a large range of LIB particles

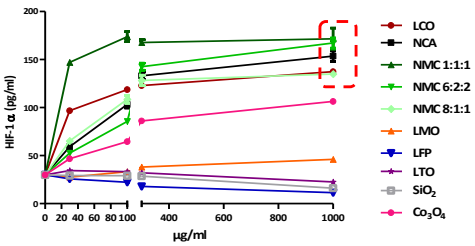



Inflammatory cell infiltration

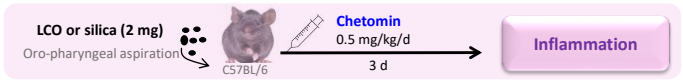



HIF-1α

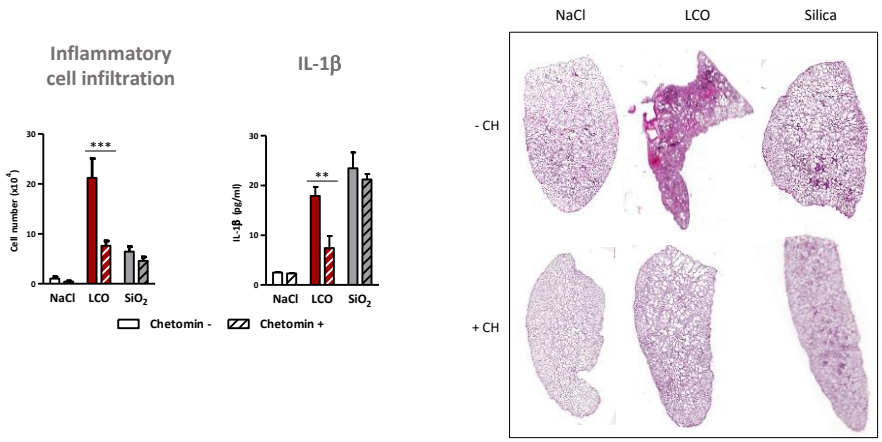



→ Association with biologically active Co (and other transition metals)

## Implication of HIF-1α in LCO toxicity:



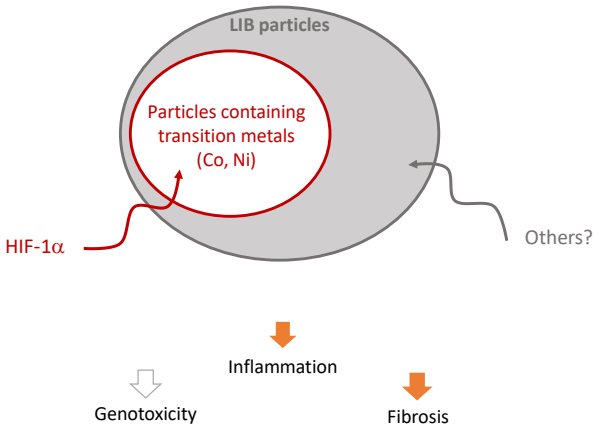

Inflammation: HE staining

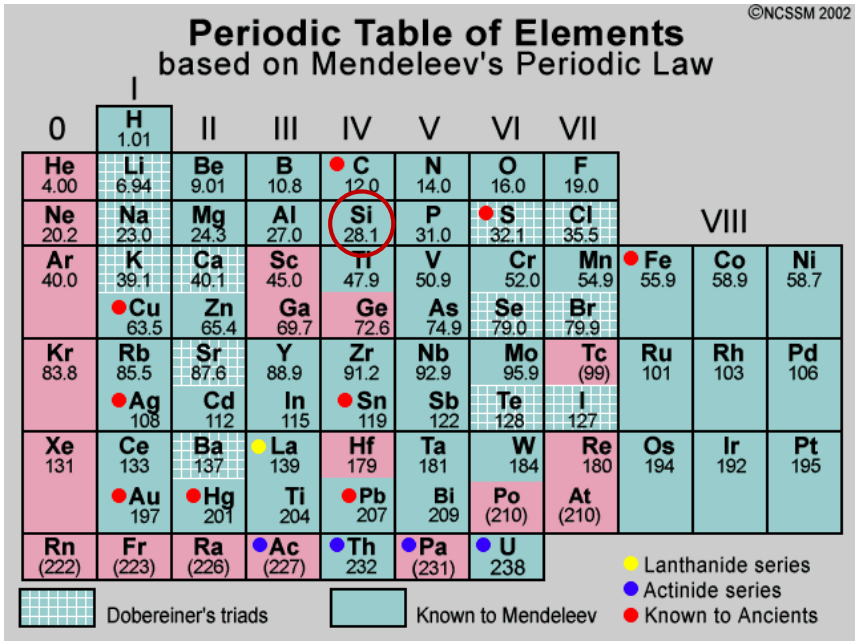



→ HIF-1α is implicated in LCO lung toxicity

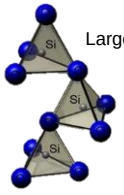
→ HIF-1α could represent a key event of LIB particle containing Co and/or transition metals

## Societal usefulness

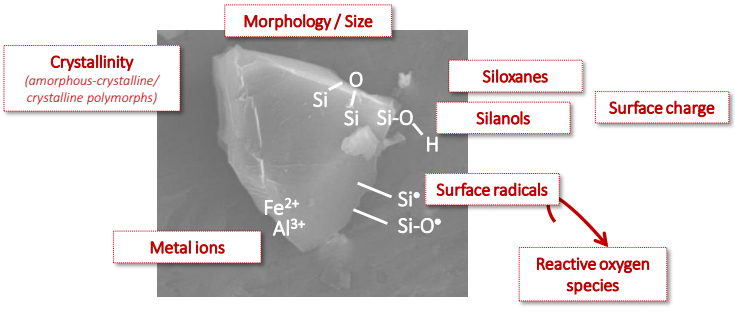





## Many physico-chemical properties of silica may impart toxicity




Large variety of physico-chemical features mostly in evolution with fast or slow kinetics




***Variety of particles*** with different surface properties → reactivity → pathogenicity

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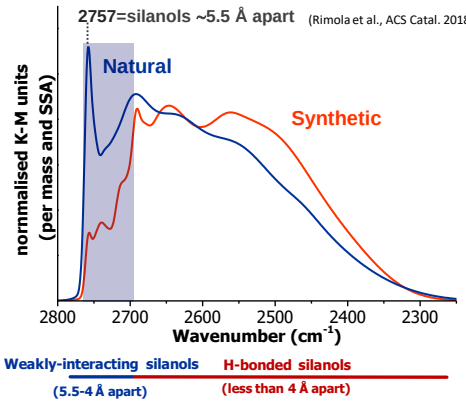
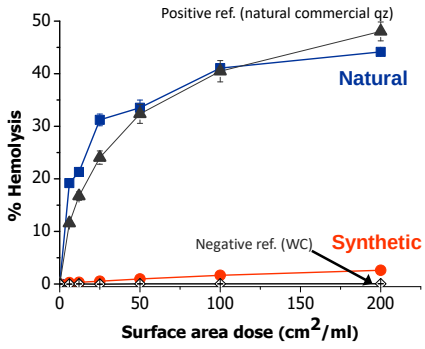
## **Synthetic** vs **natural** quartz: silanol arrangements & membranolysis

*Analysis of silanol profile via Diffuse Reflectance IR spectroscopy*




*Membranolytic activity (RBC lysis)*




Weakly-interacting silanols appear related to the membranolytic activity of natural quartz

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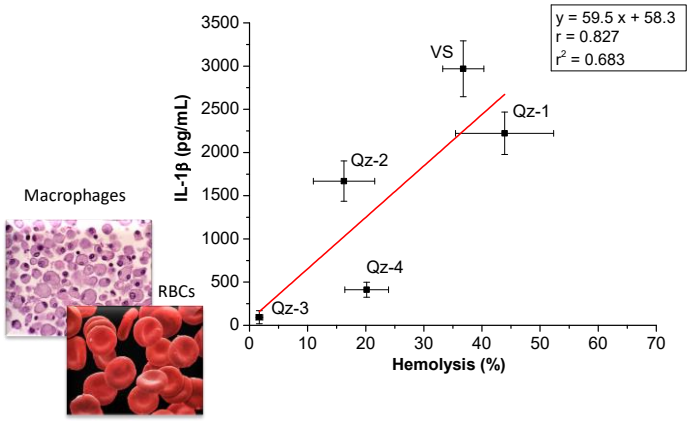
## IL-1β release correlates with silica hemolytic activity




*Pavan et al., Part & Fibre Tox, 2014*

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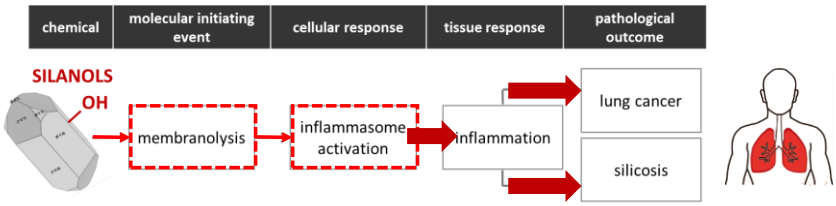
Proposed adverse outcome pathway (AOP) for silicosis and lung cancer




*Pavan & Fubini, Chem. Res. Toxicol. 2017*

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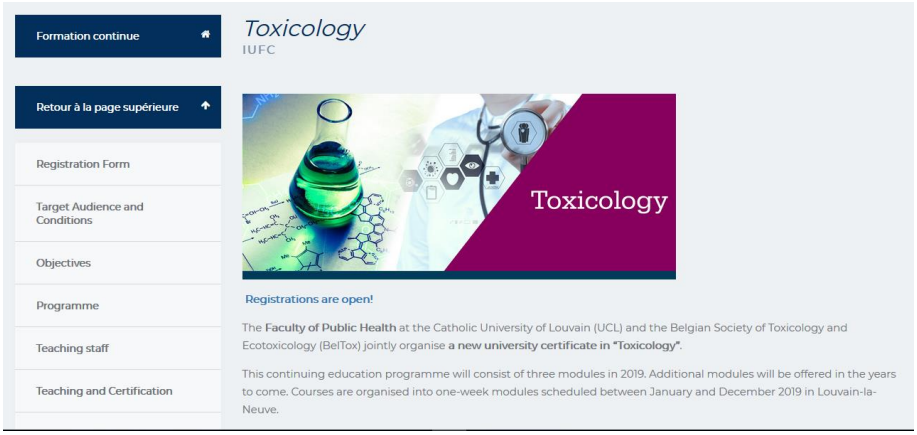
# Messages

- →Impact sociétal
  - descriptive
  - dose-réponse
  - mécanisme … KE … PoD … acceptable exposure
- Trans-disciplinarité
  - in vitro alone ?
  - Tox et Ecotox (microbiote)
  - Hors toxicologie
- Un rôle pour
  - académiques
  - sociétés scientifiques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Registrations are open!
The Faculty of Public Health at the Catholic University of Louvain (UCL) and the Belgian Society of Toxicology and Ecotoxicology (BelTox) jointly organise a new university certificate in "Toxicology".
This continuing education programme will consist of three modules in 2019. Additional modules will be offered in the years to come. Courses are organised into one-week modules scheduled between January and December 2019 in Louvain-la-Neuve.