Inhalation of tungsten particles: impact on the central nervous system, an unsuspected target organ

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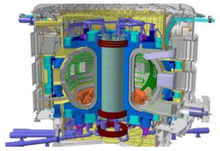
CONTEXT AND STUDY OBJECTIVES

- Being the main cause of contamination in nuclear facilities, particulate aerosols represent a health risk factor raising serious concerns. The brain represents a direct target for inhaled aerosols, in particular through the involvement of the olfactory nerve entry pathway. There is a lack of knowledge about the toxicity of tungsten (W) in the central nervous system, although it is considered as an emerging contaminant. To study the potential effects of exposure to W particles, preliminary metrological work was carried out to optimize and control the generation of the aerosol at concentrations in the order of the Occupational Exposure Limit Value.
- **Our objective is to study the biological impact of exposure to tungsten aerosol on the brain**
  - ➢ Expose animals to an aerosol of interest for specific nuclear activities
  - ➢ Use molecular biology and immunohistology to assess toxicological impact

Tungsten, an emergent contaminant…

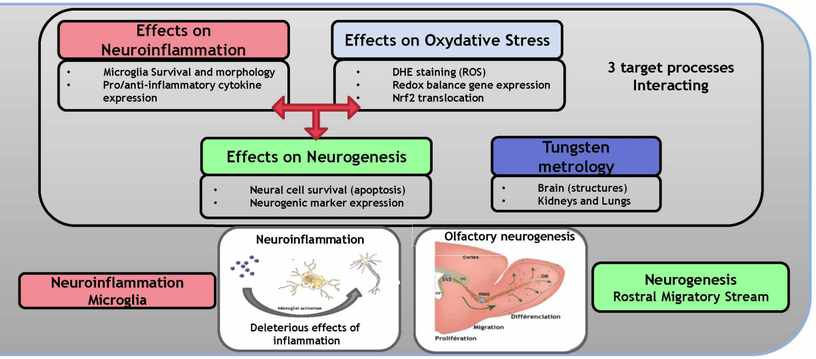
- **Nuclear fusion reactors:** Tungsten dusts are produced in Tokamaks (by erosion phenomena of the plasma facing components)
- Tungsten aerosols dispersion and exposure due to accidental situations or maintenance



- **Other sources:** Dismantling - Alloys for military use, Environment around mines - Hard metal industry

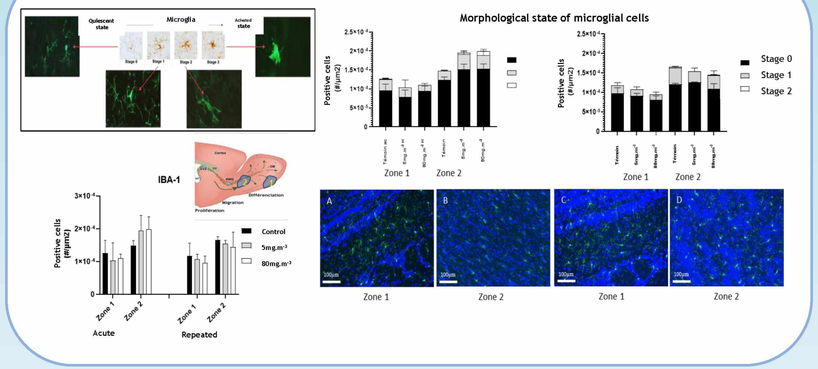
MATERIALS AND METHODS

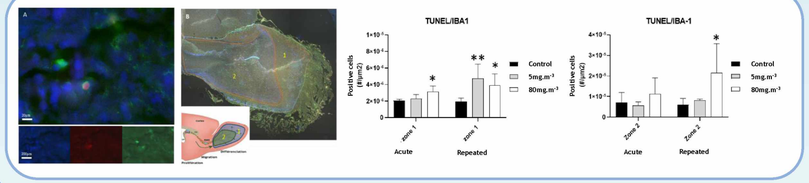
- Adult male rats
- « Nose only » Exposure to a W_0 polydispersed aerosol
  - Acute (30min) or repeated (30min/Day 4x)
- Two target concentrations (based on VLEP)
  - Low (5mg.m^{-3}) et High (80mg.m^{-3})
- Inhalation campaign and analyses at 4h et 24h post-exposure
  - Immunohistochemistry, molecular biology, biochemistry, metrology



MAIN RESULTS

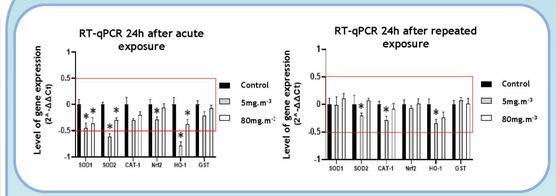
Effects in the Olfactory Bulb: Neuroinflammation as a target process

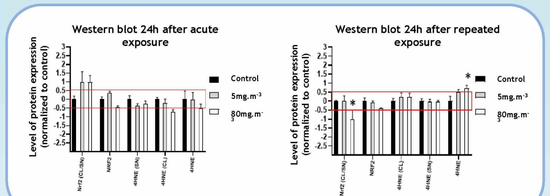


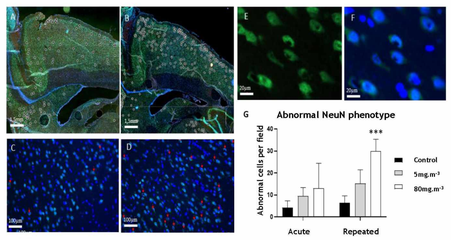


- Induction of morphological changes of microglial cells in the acutely exposed group
- Decrease in the number of microglial cells in the repeatedly exposed group
- In parallel, increase of tunel/Iba1 positive cells in the repeatedly exposed group suggesting a trigger of apoptosis phenomenon
- Anatomical regionalization of the effects

Effects in the Prefrontal Cortex: Oxidative stress as a target process

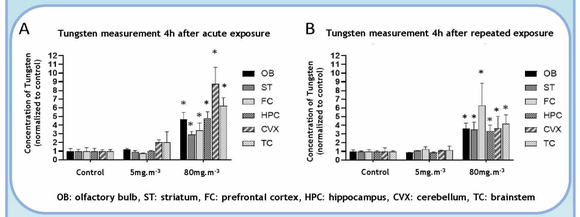






- Modifications of gene expression of redox balance enzyme mostly at low concentration
- Modification of protein expression of Nrf2 and 4HNE for the repeatedly high exposed group
- In parallel, the number of neurons showing an abnormal phenotype is increasing in the repeatedly exposed group suggesting a potential negative impact of tungsten

Tungsten concentration in brain structures



OB: olfactory bulb, ST: striatum, FC: prefrontal cortex, HPC: hippocampus, CVX: cerebellum, TC: brainstem

- Brain concentrations of tungsten are increased in the high acutely and repeatedly exposed animals

CONCLUSION

- Inhalation of tungsten particles produces biological responses as soon as 24hours post-exposure on neuroinflammation and oxidative stress. Effects appear to be site-specific, dependent on the mode and concentration of exposure. Signaling pathways will be investigated by transcriptomics.
- The increase in tungsten concentration in brain structures in high exposed groups could contribute to site-specificity of observed effects.
- Current work investigate whether these effects are related to adaptive mechanisms or are neurotoxic and can ultimately alter neuronal integrity.

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