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

Leo Mace, Sébastien Thome, Celine Gloaguen, Florence Bachelot, Chloe Brizais, Annabelle Manoury, Amandine Sache, Frederic Voyer, Dmitry Klokov, Francois Gensdarmes, et al.

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**Results:** Captan and Folpet presented a dose dependent cytotoxicity greater than Chlorpyrifos. However, the most important result was the depletion of total RNA and the increase of ARNr18S after cells were treated with Captan or Folpet only suggesting an inhibition of the RNA polymerase for no more than 24h causing an immunotoxic effect. Concerning the assessment of potential biomarkers of effect, IL-8 appears to be the most sensitive and early inflammatory biomarker of effect.

#### P20-38

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

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Being the main cause of contamination in nuclear facilities, 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 airborne 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, and to characterize its size distribution.

Adults rats were exposed to optimized and controlled W aerosols via inhalation at two different concentrations (5 and 80 mg.m<sup>-3</sup>) in a single acute or fractionated mode (4X daily exposures). Various assays were used to examine biological processes involved in brain toxicity, such as neuroinflammation, oxidative stress, cell death and neurogenesis.

Results obtained 24 hours after exposure suggest site-specific and concentration-dependent modifications of the transcripts of genes involved in these target processes. The impact of oxidative stress is currently being further evaluated using the Dihydroethidium probe sensitive to reactive oxygen species, complemented by immunohistochemistry and protein expression of 4HNE and Nrf2, which respectively reflect lipid peroxidation and antioxidant signalling. Immunohistochemistry experiments suggest a potential effect on the density and morphology of microglial cells involved in neuroinflammation, as well as an abnormal phenotype of the nuclei of some mature neurons indicating neuronal damage. At the cellular level, the effects were also site-specific, dependent on the mode of exposure and the concentration and could involve several signalling pathways, recently investigated by transcriptomics. ICP-MS assays show an increase in the concentration of W in brain structures in groups exposed to high concentrations, which could contribute to site-specificity of observed effects. Current work aims to investigate whether these effects are related to adaptive mechanisms or are neurotoxic and can ultimately alter neuronal integrity depending on exposure patterns. Co-exposure to W aerosols and ionizing radiation is another focus for our future research.

These results can help close knowledge gaps in understanding neurological health effects due to aerosols exposure, especially metallic ones, and thus help improve the system of human (radio)protection.

#### P20-39

##### **An insight into the toxic effects of imidacloprid through measurements of cholinesterase activities and markers of oxidative stress in the blood and brain of male Wistar rats**

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Imidacloprid is the first neonicotinoid insecticide that acts as a selective toxicant on nicotinic acetylcholine receptors in insects<sup>[1,2]</sup>. It is used for crop protection worldwide, as well as for non-agricultural uses<sup>[1]</sup>. Food is one of the main routes of human imidacloprid exposure<sup>[3]</sup>. Due to the ever-growing evidence for toxic effects of imidacloprid in animals and humans<sup>[4,5,6]</sup> and need to investigate them in more detail, we evaluated the effects of subchronic oral exposure to environmentally relevant doses of imidacloprid on relevant biochemical markers of toxicity in the blood and brain of adult male Wistar rats. Following a 28-day oral treatment with imidacloprid at 0.06 mg/kg b. w./day, 0.8 mg/kg b. w./day and 2.25 mg/kg b. w./day we measured total cholinesterase, acetylcholinesterase and butyrylcholinesterase activities as markers of cholinergic toxicity, and levels of lipid peroxidation, glutathione and reactive oxygen species as well as activities of glutathione peroxidase, superoxide dismutase and catalase as markers of oxidative stress. Exposure to low doses of imidacloprid did not cause significant changes in total cholinesterase, acetylcholinesterase and butyrylcholinesterase activity in rat blood and brain tissue. Concerning the influence on biomarkers of oxidative stress, treatment with the lowest dose of imidacloprid (which corresponds to the acceptable daily intake for imidacloprid) resulted with increased levels of lipid peroxidation and reactive oxygen species and decreased activities of antioxidant enzymes superoxide dismutase and catalase. The most pronounced effect was noticed in plasma. The highest levels of lipid peroxidation were detected in both plasma and brain tissue after treatment with the lowest dose of imidacloprid, being significantly elevated in plasma. Reactive oxygen species levels were also highest and significantly increased at the lowest dose in plasma. Superoxide dismutase activity in erythrocytes increased depending on the dose, being statistically significant at the highest dose. Treatment with the highest applied dose of imidacloprid also caused significantly increased activities of glutathione peroxidase in both plasma and brain tissue. Decreased superoxide dismutase and catalase activities were found in the plasma of rats treated with the lowest dose of imidacloprid. No changes in glutathione levels were found in the treated rats. Taken together, our findings suggest that oral 28-day exposure to low doses of imidacloprid caused a disturbance of redox homeostasis, i.e. the regulation of formation and removal of reactive oxygen species from the body system. These results call for further studies at molecular level to explain the toxicity of neonicotinoids after long-term exposure to environmentally relevant doses.

#### References

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