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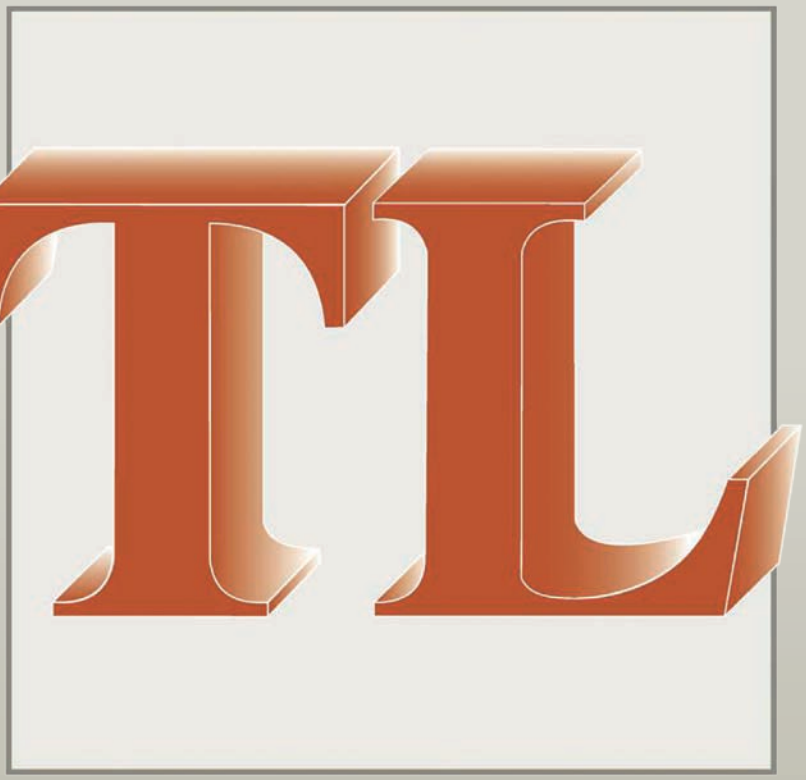

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ABSTRACTS of the 56th Congress of the European Societies of Toxicology (EUROTOX 2021)
TOXICOLOGY OF THE NEXT GENERATION
virtual congress, 27th of September – 1st of October 2021

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methods for preliminary studies without animal in order to reduce the number of animal studies and increase the quality of studies. In our project, we have developed an *in vitro* 3D model anatomical model of the macaque airway. We use a high precision CT-scans of Non-Human Primates and the 3D printing technique with stereolithography method.

We have developed a refined *in vitro* 3D Cast model, which accurately mimics the upper airway of 3 macaques and the lower airway down to the second bronchial division.

However, the 3D model needs to be validated. To validate this model, a comparative study between the aerosol deposition obtained with the 3D model and the deposition obtained with the three macaques was carried out by scintigraphy imaging. Aerosols will be generated using three nebulizers generating three different particle sizes in order to target and study three different deposition areas in the airways: the first nebulizer with a 10µm in terms of Volume Median Diameter (VMD) predicting a major deposition in the upper airways (90%), the second nebulizer with a 1, 35µm in terms of Mass Median Aerodynamic Diameter (MMAD) predicting a deposition in upper and lower airways (50%) and the third with a 0, 36µm of MMAD predicting a major deposition in lower airways (90%).

If the 3D model is validated by the comparison between in *vitro* and in *vivo* results in terms of scintigraphy deposition measurement, it will allow to reduce the number of experiments on macaques and will participate to the improvement of the quality of studies.

LP-06
Genotoxicity and inflammatory potential of stainless steel welding fume particles – an *in vitro* study on standard vs Cr(VI)-reduced flux-cored wires and the role of released metals

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Welders are a large occupational group exposed to metal-containing particles in the fumes generated during the welding process. Exposure to welding fumes has been linked to several respiratory health effects which serves as a driving force to develop new methods that generate less toxic fumes. The individual contribution of the various metals found in welding fumes is not fully understood, but the carcinogen hexavalent chromium (Cr(VI)) has been proposed to be largely involved in the toxicity of stainless steel welding fumes. To explore the role of released metals for welding particle-induced toxicity and test the hypothesis that a reduction of the Cr(VI) content in the fumes of FCWs results in welding fume particles less hazardous to welders, we compared the toxicity of stainless steel welding fume particles generated with standard flux cored-wire (FCWs) electrodes to those generated with Cr(VI)-reduced FCWs *in vitro*. The endpoints of cell viability, DNA damage and inflammation were examined using human bronchial epithelial cells (HBEC-3kt) and human monocyte derived macrophages (THP-1) as models. To elucidate the role of particles versus released metals, the cells were exposed to either the welding fume particles or solely its released metal fraction. The welding fume particles generated with Cr(VI)-reduced FCWs released small levels of Cr(VI), indicating a successful development and they were further found to be considerably less cyto- and genotoxic compared to the those of standard FCWs. The released fraction of the fumes generated with standard FCWs, being predominantly Cr(VI), was concluded to be toxic and may therefore explain a large part of the cytotoxicity and DNA damage observed in response to the particles. In contrast, an increase in the release of inflammatory cytokines was observed in response to all welding fumes, independent of Cr(VI)-reduction. The released metal fractions of the welding fumes did not induce similar inflammatory effects as the particles, indicating this endpoint not to be dependent on the release of Cr(VI). In conclusion, these results suggest the release of Cr(VI) to be at least partly responsible for the acute toxicity of standard FCW generated stainless steel welding fumes. This suggests a potential benefit of substituting standard FCWs with Cr(VI)-reduced wires to reduce the toxicity of the welding fumes and improve the occupational environment of welders.

LP-07
How maternal exposure to aflatoxin B1 impacts the development of progeny intestinal immune system

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Exposure to toxic contaminants during early-life is associated with the development of diseases. Individuals are exposed to mycotoxins since early stages of life[1]. However how maternal exposure to mycotoxins influences the development and function of the offspring's immune system remains largely unexplored. Recently, we showed that *in utero* maternal exposure to micronutrients is critical for the development of the immune system, which sets long term immunity if the progeny[2]. Here we show that presence of aflatoxin B1 in the diet of pregnant murine females affects the development and function of the intestinal immune system. Notably, maternal exposure to AFB1 promoted an increase of overall T cell population, while it also resulted in a selective reduction of cytokine-producing innate lymphoid cells group 2 (ILC2) population in intestine of the progeny. These alterations were associated with decreased expression of Reg3b, Reg3g and Fut2 by the intestinal mucosa of progeny. Thus, these results indicate that maternal exposure to mycotoxins impacts the development of offspring intestinal immune system. ILC2 are critical in intestinal epithelial repair, whether mice exposed to AFB1

display defective tissue damage response needs to be investigated. Also FUT2-dependent fucosylation is key in host–commensal symbiosis suggesting alterations in the intestinal microbiota. Our work reveals that maternal exposure to dietary contaminants such as mycotoxins alters the normal development of intestinal immune system framework of the progeny and may have impact in their immune function.

This work was funded by FCT/MCTES through national funds, to early-MYCO (PTDC/MED-TOX/28762/2017), and CESAM (UIDP/50017/2020+UIDB/50017/2020).

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LP-08
Test System of Gonadotoxic Activity Identification is more Sensitive and Informative than 3-generations Reproductive Toxicity Study in the Endocrine-Disruptor Mesotrione Research

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The mesotrione pesticide is one of the three main chemical classes of compounds - 4-hydroxyphenylpyruvate-dioxygenase inhibitors, namely the class of tricetones.

The mechanism of pesticide mesotrione action is determined by a violation of tyrosine metabolism, which during embryo- and fetogenesis periods can lead to eye and skin damage, mental retardation, and impaired motor coordination in children. This pesticide is an explicit endocrine-disruptor and is more dangerous for offsprings than for parental generation animals. Like most endocrine-disruptors that violate the endocrine activity of the thyroid gland, it can induce transgenerational epigenetic effects when exposed during gametogenesis.

In reproductive toxicity studies of mesotrione in three generations rats (1997), a lowest-observed-adverse-effect level (LOAEL) was established for reproductive toxicity at 2500 ppm (297.2 mg/kg body weight). No-observed-adverse-effect level (NOAEL) in this experiment was 100 ppm (11.7 mg/kg body weight). It should be emphasized that such important indicators as sperm parameters in males and the estrous cycle in females were not studied in this experiment.

We conducted studies of the mesotrione reproductive toxicity in the test-system of gonadotoxic activity identification. The test substance was administered to females (10 weeks) and males (11 weeks) before mating with intact animals (untreated). Based on the analysis of the results obtained, it was concluded that at a dose of 12.0 mg/kg body weight when exposed to males, the mesotrione has manifested antiandrogenic activity (a decrease in the total number of sperm, the number and percentage of motile sperm, an increase in the percentage of pathological forms of sperm, a decrease of conception and fertility indexes). When exposed to females, the estrous cycle disorder was observed (a decrease in the estrogen-dependent stage of proestrus).

NOAEL in this experiment is 0.3 mg/kg body weight.

Thus, in this test system, a greater sensitivity of males was found in comparison with females to the endocrine-disruptor effect of mesotrione when exposed during gametogenesis.

LP-09
Isoflucypram: A new fungicide with no thyroid related endocrine disrupting properties and an overall favorable mammalian safety profile

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Isoflucypram is a new cereal fungicide currently undergoing evaluation for European registration. Based on its extensive data package, isoflucypram is not genotoxic nor carcinogenic and has no developmental toxicity potential. Furthermore, although a delay in puberty was observed in the 2-generation study, isoflucypram has no overall impact on fertility or reproduction. As per EU Regulation 283/2013 the endocrine disrupting (ED) potential of isoflucypram was evaluated as part of the safety assessment package. As the liver (all species) and thyroid (rat only) are target organs of isoflucypram, the main focus of the ED evaluation was the mode of action (MoA) responsible for the minimal effects observed on the rat hypothalamus-pituitary-thyroid (HPT) axis and determining the human relevance of the perturbation of this axis.

A combination of standard repeat dose toxicity studies and short-term mechanistic investigations conducted in the rat demonstrated that isoflucypram is a marked hepatic enzyme inducer, most notably of the cytochrome P450s, Cyp3a and Cyp2b, and of UDP-glucuronosyltransferases (UDPGT; including T4-UDPGT).This increased enzyme activity was associated with increased liver weight and hepatocellular hypertrophy. In the same studies, minimal thyroid follicular cell hypertrophy was observed but only at doses where liver stimulation was already established. A slight, statistically significant, increase in thyroid stimulating hormone, with no concomitant decrease in T4, was recorded at the same dose level as that triggering follicular cell hypertrophy. Overall, the profile of observations was indicative of a liver mediated MoA giving rise to the minimal thyroid findings. The homeostasis of the HPT axis could, however, still be maintained as evidenced by the absence of clear effects on T4. Direct thyroid effects via thyroid peroxidase (TPO) and sodium iodide symporter (NIS) inhibition could be excluded providing further support for a liver mediated MoA. An *in vitro* comparison of hepatic enzyme induction conducted in rat and human hepatocytes confirmed the rat *in vivo* profile of increased Cyp3a, Cyp2b and T4-UDPGT activities. In contrast, marked quantitative differences were observed when comparing the rat and human responses, particularly for T4-UDPGT, where the basal and induced levels were 4-fold and up to 11-fold lower respectively in the human hepatocytes compared to those observed in the rat. The *in vivo* rat data demonstrate that the minimal perturbation of the HPT axis induced by isoflucypram was secondary to liver enzyme induction. Furthermore, the *in vitro* comparison of hepatic enzyme induction demonstrated marked species differences thus providing evidence that this MoA for isoflucypram is not relevant for humans. Overall, it can be concluded that this molecule is not an ED via the T-modality for mammals based on the weight of evidence derived from the *in vitro* and *in vivo* standard and mechanistic investigations.

LP-10
Development of a novel QSAR model for predicting the synergistic effect of binary mixtures of estrogen receptor agonists

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Worldwide, there are growing concerns about the potential health threat caused by endocrine-disrupting compounds (EDCs) manufactured in the chemical industry [1,2]. Estrogenic EDCs can interact with estrogen receptors (ERs) and induce ER-mediated responses. In hu-