

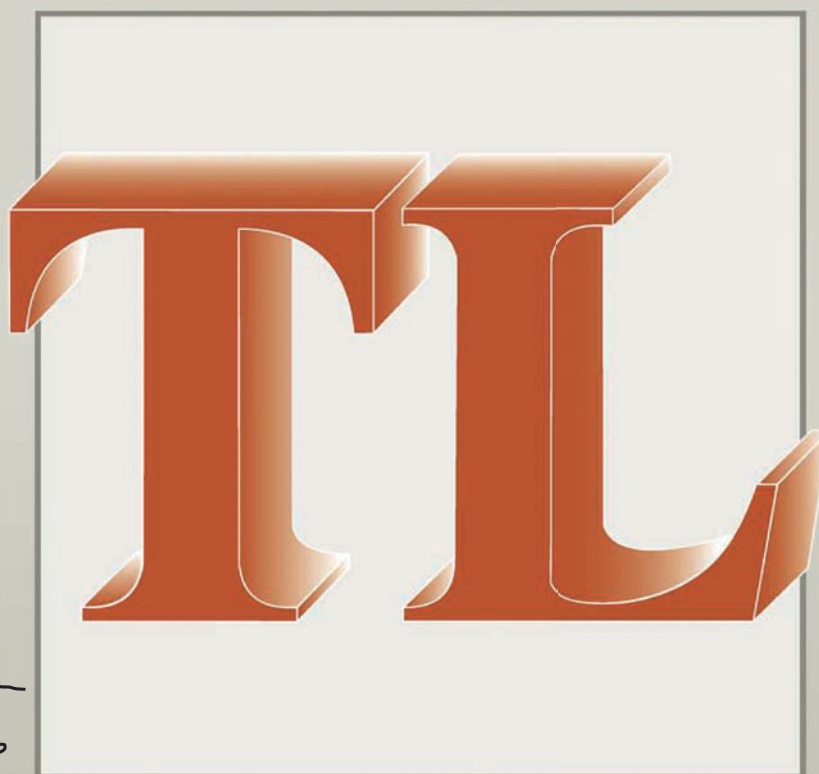
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TOXICOLOGY – SCIENCE PROVIDING SOLUTIONS
Helsinki, Finland, 8th–11th of September, 2019

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P24-015

AOP-based experimental models to evaluate effects of azole mixtures

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The effects of binary mixture of cyproconazole (CYPRO) and triadimefon (FON) sharing the same adverse outcome pathway (AOP) for craniofacial malformation were studied using different experimental models. The proposed AOP is based on the inhibition of CYP26, the retinoic acid (RA) local increase and key events leading to branchial defects in embryos and cranio-facial malformations at term of gestation. The activity of the two molecules on CYP26 enzymes was evaluated by an *in silico* method (docking), while teratogenic effects were evaluated both *in vitro* (postimplantation rat whole embryo culture at E9.5, WEC) and after *in utero* exposure. WECs were exposed for 48 hours to CYPRO (7.8–250 µM), FON 6.25–125 µM or mixtures. CD1 mouse females were treated at E8 (comparable to rat E9.5) by gavage with CYPRO (25–100 mg/kg), FON (37.5–500) or mixtures. Maternal and foetal outcomes were evaluated at term of gestation (E18). Some dams were sacrificed at E9 (midgestation, comparable to the rat stage at term of WEC) to evaluate embryonic morphology and compare with WEC results. Malformation data were modelled by PROAST 65.2 software. Docking results show a CYP26 inhibitory potential for both molecules. Both *in vitro* and *in vivo* results showed a clear dose–response for single fungicides, better defined by WEC, co-exposure resulted in an additive effect. Cranio-facial malformations recorded at E18 were related at midgestation to branchial defects similar to those observed in WEC experiments.

The obtained data support the hypothesized AOP and suggest that WEC results could be a simple but predictive alternative method applicable to the hazard evaluation of mixtures' exposure. On these bases, we suggest the use of WEC in order to test azole mixtures *in vitro* and their effects on cranio-facial morphogenesis.

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P24-016

Microbiome modification as possible way to reduce toxic load in agriculture (on the example of cereal spiked crops treatments)

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Receiving good yields of cereal spiked crops as major contributors of nutrients nowadays accompanies with sometimes enormous applications of pesticides (fungicides, herbicides etc.) and fertilizers (especially toxic in particular conditions nitrogen fertilizers). Farmers perform treatments of crops 3 to 5 times per vegetative periods and being exposed to various types of pesticides and fertilizers mixtures.

Purpose of our research: To evaluate efficiency of microbiome modification in relation to reduce toxic load in agriculture (on the ex-

ample of cereal spiked crops treatments).

Methods: Full-scale in-field hygienic experiment (2 series), microbiological and statistical (Mann–Whitney *U*-test) methods were used in our study. Cultures of *A.chroococcum* and representatives of *Pseudomonas*, *Rhizobium*, *Lactobacillus*, *Bacillus* genera and *T. aestivum*, *H. vulgare* were materials of research.

Results: Presowing prepared grains treated with microquantities of 2,4-D (as callus inductor), cytokinin (kinetin) and studied microbial cultures were planted and treated second time with microbial cultures after approx. 7 weeks in Ukrainian argoclimatic conditions. Amount of fungicides applied in this case was reduced twice, nitrogen fertilizers were totally excluded from the standard treatment procedure, and potassium-phosphorus fertilizers ($N_{16}P_{16}K_{16}$) reduced to $2/3$.

Biological parameters of plants' root system indicate its resistance to *X. Campestris* (common cereal crops pathogen).

Content of protein in grains was 16.08% in average samples and gluten content – 29.3%. Grains in harvest time did not contain the residue amounts of applied fungicides. Correspondent levels of them were below relevant LODs.

Fungicides level in the working zone air did not exceed 25% of AOEL.

Conclusion: Suggested approach helped to decrease toxic load on farmers during the treatment (absence of nitrogen fertilizers and decreased fungicides levels in working zone air), harvest did not contain fungicides and agriculture environment was protected. Microbiome modification in cereal spiked crops treatment reduces the amount of possible toxic substances applied and thus decreases toxic load on farmers, consumers and environment.

P24-017

Establishment of a multi-organ-chip based identification platform for endocrine disruptors

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The extrapolation of toxicities observed in rodent studies to human health still represents a major issue for toxicologists. Especially thyroid hormone disrupting compounds present a reoccurring problem for pharmaceutical and agrochemical industry. The levels of thyroid hormones are not only regulated via synthesis and secretion by the thyroid gland, but also by its metabolism and clearance via the liver. To this end, it is a pre-requisite to consider direct effects on the thyroid gland as well as indirect effects mediated by the liver when it comes to safety assessment of potential thyroid hormone disruptors. Furthermore, species differences between rodents and humans have to be taken into account and the extrapolation of data derived from rodent testings have to be critically evaluated.

Here, we describe the establishment of a human three-dimensional (3D) liver and thyroid co-culture model and its integration into a Multi-Organ-Chip (MOC) platform. Our organ chip model is composed of two culture compartments connected by microfluidic channels which allow an inter-organ specific cross-talk. On chip micro-pumps enable a near to physiological tissue-to-fluid ratio and enhance oxygen and nutrition supply of the integrated thyroid and liver organoids resulting in a long-term culture of at least 14 days. Our study presents first results of our MOC-based liver-thyroid assay including data which demonstrate the long-term viability of the co-culture model as well as required functionality of the assay. Thus, we