Development of an adverse outcome pathway for kidney tubular necrosis

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explore the mutagenicity and genotoxicity of reduced graphene oxide (rGO) using the mouse lymphoma assay (MLA) and the standard and enzyme- modified comet assays in the Caco-2 cell line. Materials and Methods L5178Y Tk+/- cells were used for MLA. Cells were exposed to 0-250 µg/mL rGO for 4 and 24 h. RPMI medium was used as a negative control, and methylmethanesulfonate (MMS 10 µg/mL) as positive control. For the comet assay, Caco-2 cells were incubated with rGO for 24 h (176.3, 88.2, and 44.1 µg/mL) and 48 h (166.5, 83.3, and 41.6 µg/mL), equivalent to mean effective concentration (EC50), EC50/2 and EC50/4. Medium was used as negative control and H2O2 as positive control. The Endonuclease III (Endo III) and formamidopyrimidine-DNA glycosylase (Fpg) enzymes were selected for the enzyme-modified comet assay. Results For MLA, rGO increased the frequency of mutation at 125 and 250 µg/mL after 4 h of exposure. No mutagenic effects were observed at any concentration tested after 24 h of exposure. In the standard comet assay, Caco-2 cells did not undergo DNA breaks after 24 h and 48 h of exposure at any concentration assayed. rGO did not induce oxidative DNA damage. Discussion and Conclusion Our results evidence that rGO has a good toxicity profile for its potential applications in the food packaging industry, but further toxicological tests are required. Acknowledgement: Fondo Europeo de Desarrollo Regional (FEDER) and Consejería de Economía, Conocimiento, Empresas y Universidad de la Junta de Andalucía, within the Programa Operativo FEDER 2014–2020 for the project US-1259106. And project P18-RT1993 (PAIDI-2020/FEDER, Consejería de Transformacion Economica, Industria, Conocimiento y Universidades, Junta de Andalucía).

P-MODELS-9

Development of an adverse outcome pathway for kidney tubular necrosis ABSTRACT #359

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Background and Objectives Adverse outcome pathway (AOP) networks combine AOPs that share one or more key events (KEs). Our aim is to develop an AOP network determining KEs and the relationships that drive chemical-induced kidney tubular necrosis (TN). To weigh the evidence between KEs, the network will be assessed in accordance with guidelines from the Organization for Economic Co-operation and Development (OECD) (1). The objective is to develop an ontological knowledge framework that integrates biological, toxicological, and chemical data toward predicting systemic repeated dose toxicity effects of nephrotoxic chemicals associated with kidney TN (2). Materials and Methods Embase was used to search for literature on chemical-induced kidney TN using key search terms relevant to clinical presentations, biochemistry, histology, and chemically applicable, data-rich nephrotoxic compounds. Initial title/abstract screening of papers employed SysRev, a computational tool for systematic reviewing and data extraction, using labeling strategies for inclusion/exclusion criteria. Tailored Bradford-Hill criteria described in OECD guidelines will assess confidence levels and weight of evidence for KEs within the AOP network. Kidney physiological maps were designed to establish mechanisms contributing to TN, with systemic mapping of currently reported AOPs involving nephrotoxicity identifying relevant MIEs and KEs. Results The Embase search retrieved 2735 papers to upload to SysRev. The title/abstract screening would further identify papers eligible for data extraction in the full-text screening process. A total of 19 existing AOPs related to kidney dysfunction were identified and analyzed to support the implementation of additional in vitro endpoints for TN. Discussion and Conclusion Data extracted will assess confidence levels in previously described KEs and KERs and identify potential new KEs. The AOP network will form the conceptual basis for establishing a test battery of in vitro assays to characterize nephrotoxic

chemicals by measuring individual KEs for the generation and evaluation of AOPs of TN-related kidney failure.

References
1. OECD. Revised Guidance Document on Developing and Assessing Adverse Outcome Pathways, (2017). 2. Vinken M., et al. (2021) 'Safer chemicals using less animals: kick-off of the European ONTOX project', Toxicology 458, 152846.

P-MODELS-10

Neurotoxic effect of potential countermeasures in case of nerve agent poisoning
ABSTRACT #249

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Nerve agents (NAs), the deadliest organophosphates, act as inhibitors of cholinesterase enzymes that are vital in the cholinergic system. Phosphylation of acetylcholinesterase (AChE), a pivotal enzyme in hydrolysis of the neurotransmitter acetylcholine, and its related enzyme butyrylcholinesterase (BChE) leads to a cholinergic crisis that could ultimately result in death. Medical countermeasures include compounds, containing oxime group with the ability for nucleophilic reactivation of phosphylated cholinesterase, which until now have shown limited potency in reactivation of inhibited AChE in the central nervous system (CNS). With that purpose, in previous studies, we have designed and defined several pyridinium oximes with high potency in reactivation of inhibited BChE that can act as a protector of AChE in CNS. Now through a combination of in silico, in vitro, ex vivo results we want to demonstrate a feasible approach to develop a safe oxime-assisted bioscavenger of NAs based on the efficient reactivation of BChE. Selected oximes have shown to be the most prominent reactivators of BChE inhibited with nerve agent cyclosarin through their overall kinetic reactivation rate. Tested oximes also showed no effect on the viability of neuroblastoma cells upon 4-hours treatment, contrary to cyclosarin exposure. Furthermore, the cytotoxicity profiles on neural cells were determent for oxime-assisted catalytic BChE degradation of cyclosarin, wherein case of post-treatment approach 50 % of neural cells had preserved, while in pre-treatment almost all of the cells have been protected. The most promising bioscavenger combination was then evaluated in ex vivo conditions of human blood resulting in up to 80% of restored phosphylated cholinesterase activity within a short time. Taken all together our findings offer a platform for further safe and promising antidote development in case of NAs exposure. Acknowledgments: The Croatian Science Foundation (IP-2018-01-7683) supported this work.

P-MODELS-11

New Salmonella strains resistant to sulfonylurea and triazole-pyrimidine herbicides and their use in the Ames test
ABSTRACT #201

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Cytotoxicity of some pesticide technical grade active ingredients (TGAIs) is a drawback of Sallmonella/microsome assay with regard to objective assessment of their equivalence to the original products. The impossibility of testing for genotoxicity of some TGAIs, e.g. sulfonylureas and triazole-pyrimidines, at high concentration due to their cytotoxicity makes difficult to detect low-level mutagenic impurities. Selection based on the cultivation of S.typhimurium TA100 with thifensulfuronmethyl was applied to obtain a mutant insusceptible to sulfonylurea toxic effect. We obtained the strains resistant not only to sulfonylureas but also triazole-pyrimidines that may be mediated the same mechanism of action of the pesticides from these classes – inhibition of acetohydroxyacid synthase. The first mutant