Multi-omic approach to inform quantitative adverse outcome pathway development for acute organophosphorus poisoning

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Organophosphorus (OP) compounds constitute a class of acetylcholinesterase (AChE) inhibitors used as not only pesticides but also chemical warfare nerve agents. Acute OP poisoning (OPP) can result from occupational (agriculture, industry, research), accidental, suicidal or homicidal causes and can be graded by severity as mild, moderate and severe. Epidemiological studies regarding OP pesticides estimate approximately 3 million cases of severe OPP and 300.000 deaths annually, most of them in developing countries of the Asia-Pacific region. Recently, we generated zebrafish models for mild, moderate, and severe OPP by exposing zebrafish larvae to different concentrations of chlorpyrifos-oxon (CPO), the active metabolite of the pesticide chlorpyrifos and a prototypic OP compound. Whereas the molecular phenotype of these three OPP models has already been partially characterized by performing large-scale transcriptomic and metabolomic analyses, the integration of these two dataset have never been done. In this study, we performed a multi-omic analysis (transcriptomics, metabolomics, and proteomics) of these three zebrafish models for human OPP. Transcriptomic, proteomic and metabolomic data were integrated in order to identify new molecular key events in the pathophysiological pathways involved in the development of OPP. The multi-omics data are now being used to develop a quantitative Adverse Outcome Pathway (qAOP) for AChE inhibition leading to mortality. Bayesian network and physiological modeling approaches are being used to develop the qAOP that will be presented.