

# Biological effects of a mixture of environmental contaminants on mouse. Modulation by selenium and the gut microbiota.

P.V. Huertas-Abril, N. Abril, J. Jurado Carpio and M.J. Prieto Álamo

*Department of Biochemistry and Molecular Biology, Edificio Severo Ochoa, 2ª planta, Campus Universitario de Rabanales (Universidad de Córdoba). Autovía Madrid-Cádiz, Km 396ª. 14071-Córdoba. SPAIN*  
E-mail: [b52huabp@uco.es](mailto:b52huabp@uco.es)

Environmental contaminants often occur in mixtures where they can interact and suffer changes in their properties. The individual concentrations in the environment of metals and pharmaceuticals, that usually contaminate water and food, are normally harmless, but their joint action must be analyzed and considered when establishing exposure risk factors for the population. This study focusses on a mixture of contaminants formed by three metals/metalloids (As, Cd and Hg), which are widely spread in the environment due to their importance in industry; and two pharmacologically active compounds (diclofenac and flumequine), which are broadly used and highly resistant to degradation in wastewater plants. The aim of this study is to analyze the biological response against this contaminant mixture (CM) using *Mus musculus* as model organism. To this end, we have investigated the effect of the CM on survival, gut bacterial composition and liver metabolism, trying to determine the role that the gut microbiota (GM) or the intake of a selenium (Se) nutritional supplement could play in the toxicity of CM.

The CM significantly decreased the survival of mice, especially of those with an altered microbiota suggesting that the GM is required to metabolize and detoxify this mixture. The results show that the CM caused oxidative stress and metabolic dysfunction in the liver, corroborated by increased levels of bile acids and impaired carbohydrate metabolism. Additionally, the CM provoked a profound alteration in the composition of the GM, which was enriched in acetate- and butyrate-producing bacteria, affecting host metabolism and gene expression. In this line, some transcripts implied in the antioxidant response under the control of NRF2, such as *MT1* and *Hmox1* increased, but key enzymes such as glutathione peroxidase, superoxide dismutase or catalase decreased. This indicates that, pollutants not only generate an oxidative stress situation, but also compromise the defense against this stress. A selenium supplement in the diet during exposure partially prevented the toxic effect of the CM.

In short, the exposure to environmentally relevant concentrations of mixed metals (As, Cd and Hg) and drugs (diclofenac and flumequine) present in water and food constitute a health risk. Thus, it is necessary to minimize their incorporation to ecosystems and to improve water purification procedures to reduce their presence in the environment.

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