

## Toxicological effects of plastic additives on cetaceans: an “ex-vivo” approach to assess the marine debris impact

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Currently, one of the main toxicological issues, in the management and conservation of marine environment, is the study of the impact of compounds released from marine plastic litter. On this regard, the assessment of toxicological risk in marine mammals requires the development of sensitive biomarkers to evaluate the exposure to plastic additives, such as bisphenol A (BPA) and phthalates. BPA and phthalates are widely distributed in marine environment, acting as agonist or antagonist for endocrine receptors. To propose new gene expression biomarkers in cetaceans we developed an “ex vivo” approach (organotypic cultures), exposing cetacean skin biopsies to increasing doses of mixture of contaminants. Fin whale, killer whale, sperm whale and bottlenose dolphin organotypic cultures were exposed to increasing concentration of BPA and phthalates. We selected two potential biomarker genes such as the peroxisome proliferator-activated receptors  $\alpha$  and  $\gamma$  (PPAR  $\alpha$  and  $\gamma$ ), which belong to a superfamily of ligand-dependent nuclear receptors and regulates physiological processes of lipids homeostasis, inflammation, adipogenesis, reproduction, etc. The mRNA levels of the two PPARs were quantified in response to the two different treatments in the four species. The results revealed that the BPA and phthalates treatments induce the expression of the genes PPAR $\alpha$  and PPAR $\gamma$  showing a dose-response trend. Based in this results, the gene expression biomarker were also measured in skin biopsies from free-ranging fin whales and bottlenose dolphins from Mediterranean Sea and Sea of Cortez in order to validate the “ex-vivo” approach and to assess the potential exposure of the two species to plastic additives. These data represent the first evidence of emerging contaminants effect both on an *ex vivo* experiment and in free-ranging organisms, suggesting the potential use of this diagnostic markers as early warning signal of exposure to plastic released compounds in marine mammals monitoring.