The diet is the main route of mercury (Hg) exposure for most of the population. The main Hg forms found in food are methylmercury (MeHg) and divalent inorganic Hg [Hg(II)]. Although the intestine is the main route of entry for Hg into the systemic circulation, studies on its toxicity at the intestinal level are scarce. The main objective of the present thesis has been the evaluation of the toxicity and the mechanisms of action of Hg(II) and MeHg at the intestinal level. Additionally, the efficacy of lactic acid bacteria (LAB) strains as strategies to reduce this toxicity has been tested.

A cell model for *in vitro* studies in which enterocytes, mucosecretory cells and macrophages have been combined in a bicameral system has been developed. Cells have been exposed to Hg(II) and MeHg (0.1-1 mg/L) for 10 days. The data have shown that both species induce an inflammatory response, with an increase in the release of the pro-inflammatory cytokines IL-8 and IL-1β, and a pro-oxidant response, an increase in reactive oxygen/nitrogen species (ROS/ RNS) and an overexpression of stress proteins (HSP70, HSP90 and MT2A). These effects have been more pronounced in macrophages, suggesting that the immune cells may govern the response to the metal. The situation of stress is accompanied by alterations in the expression of the tight junction protein ZO-1 and changes in the morphology of the intestinal monolayer. In addition, exposure, especially to MeHg, generates an increase in mucus secretion and an overexpression of its main mucin. The mechanisms of this hypersecretion could be related to the IL4/IL13/STAT6 pathway. All these effects on the epithelial monolayer lead to and increased permeability and a reduced regeneration capacity.

In vivo assays have been performed in BALB/c mice exposed to Hg(II) and MeHg (1-10 mg/L) for 4 months through drinking water. The data obtained have confirmed the previous results observed *in vitro*. Exposure to both species (especially at 5 and 10 mg/L) induces an inflammatory process in the colon, with an increase in TNF-α and IL1-β cytokines and the presence of neutrophil infiltrates. In parallel, exposure generates oxidative stress with an increase in ROS/RNS and lipid peroxides. The participation in this response of some signaling pathways targeted *in vitro*, specifically p38 MAPK and JNK, has been confirmed *in vivo*. In addition, alterations in the expression of tight junction proteins and the mucin MUC2 in the colon are also evidenced, accompanied by a hyperplasia of the mucosecretory cells, especially in MeHg treatments. In these animals, there is also an increase in the expression of IL-13 and IL-4 cytokines, which points to the participation of the IL4/IL13/STAT6 pathway, as indicated by the *in vitro* studies. In addition, these *in vivo* assays show an effect of both species on the metabolism of the intestinal microbiota, with a reduction in the luminal contents of short-chain fatty acids (SCFA), although changes in the intestinal microbiota composition are minimal. Finally, the treated animals showed an increase in permeability. All the data obtained *in vitro* and *in vivo* demonstrate that a continued exposure to Hg(II) and MeHg causes a disruption of the intestinal barrier.

The *in vitro* studies carried out to determine the efficacy of the BAL strains of murine origin LE1 and LE2 as a strategy of protection have been performed by co-exposing the combined cell model to

Hg(II) or MeHg (1 mg/L) together with the strains for 7 days. The data obtained have shown a protective effect of both strains, with a reduction in the inflammatory response, oxidative stress and the effects on tight junctions and mucus production. In the same way, the presence of both bacteria partially restores the permeability and the regenerative capacity of the monolayers. Bearing in mind that in this study the LABs are heat-inactivated, this protection is mainly associated with their ability to bind Hg, although it cannot be ruled out that some structural components of the bacterial wall may exert another type of beneficial effect.

In vivo assays carry out to confirm the protective effect of LAB have been performed in BALB/c mice exposed for 2 months to MeHg (5 mg/L) through drinking water. The strains of LAB, in this case viable, have been administered daily by gavage. The data obtained show that, although both strains equally reduce colonic MeHg contents, the reduction of the toxic effects is much more pronounced when LE1 strain is administrated. Reductions in the contents of inflammatory and stress mediators in the colon are observed, together with a recovery in the expression of proteins of the tight junctions and the mucus layer. The luminal levels of microbiota metabolites are restored, and intestinal permeability is partially reestablished. The results show that in addition to the chelation process, LE1 strain activates the Nrf2/Keap1/ARE signaling pathway and the production of the anti-inflammatory cytokine IL10. The data obtained *in vitro* and *in vivo* suggest that LE1 strain could be a good strategy to reduce Hg intestinal toxicity; reduction that can also have beneficial repercussions at a systemic level.