

## AL09 **Advanced Study for Toxicity Induced by Hazards in the Aquatic Environment via Signaling Pathways of Nuclear Receptors**

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Currently, the water pollution problem is spreading on a global scale centering on emerging countries. Moreover, there is a possibility that a new environmental pollution occurs in the advanced country, and the problem is diversified. Chemical contaminants in the water environment are possibly exposed to human by drinking tap water from contaminated raw water or by ingesting the seafood from the polluted aqueous environment. Therefore, the risk assessment of such environmental chemicals is one of important research topics in the field of pharmaceutical health sciences and environmental toxicology. We have been focusing on nuclear receptors as a target molecules of environmental chemicals (hazards) that potentially harm human health and conducting systematic research on (1) Oceans, (2) Sewage treatment water and (3) Drinking water. Here are the details.

### (1) Hazards that exist in the oceans

Organotin compounds such as tributyltin which are one of typical marine pollutants (TBT) occur a sex differentiation abnormality that develops male sex organs in female in some species of gastropods at nanomolar level, but the toxic effect on human and their critical target molecules remained unclear. We examined the effect of organotin compounds on the placental endocrine function which plays an important role in the generation process. As a result TBT at nanomolar level, that is detectable level in human blood, stimulated estrogen production by increasing the mRNA transcription of the estrogen synthase such as aromatase. Apparently, these phenomena caused by organotins seem contradictory, but we identified that TBT cause both phenomenon by acting as nanomolar agonists for retinoid X receptor (RXR) and/or peroxisome proliferator-activated receptor (PPAR)  $\gamma$ . Our findings suggest that organotin compounds potentially have some impact on living organisms that have ligand-responsive RXR and PPAR $\gamma$ .

### (2) Hazards that exist in sewage treatment water

In the treatment water of sewage treatment plants in Beijing, we found potential hazards that had teratogenic effect to fish. The hazards also had agonist activity for retinoic acid receptor (RAR) that are speculated to be one of critical target molecule for malformation. We then tried to identify the hazard substances, two types of 4-oxo retinoic acid metabolites (4-oxo RAs) were identified. Our results suggest that the normal sewage treatment method can not sufficiently remove 4-oxo RAs derived from human waste and they remained in the sewage treatment water as a hazard.

### (3) Hazards that exist in drinking water

Currently, bisphenol A (BPA) substitutes are used to the plastic bottles for drinking water instead of bisphenol A (BPA) that is concerned about disrupting estrogen receptor (ER) action. However, we show that a BPA substitute, fluorene-9-bisphenol (BHPF), is released from commercial 'BPA-free' plastic bottles into drinking water and has strong antagonistic activity for ER. We also demonstrate that BHPF has anti-oestrogenic activity in vivo and induces low uterine weight, atrophic endometria and causes adverse pregnancy outcomes. In addition, we detect BHPF in the plasma of 7/100 individuals, who regularly drink water from plastic bottles. Our data suggest that BPA substitutes should be tested for anti-oestrogenic activity and call for further study of the toxicological effects of BHPF on human health.