



Effects of PCB congeners on the immune function of *Mytilus* hemocytes: alterations of tyrosine kinase-mediated cell signaling.

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Polychlorinated biphenyls (PCBs) are industrial chemicals which have been released into the environment resulting in widespread and persistent contamination. PCBs exist as 209 different congeners depending on the chlorine substitution on the biphenyl rings; the physical properties and the toxic effects of a PCB congener are structure-dependent. In this work, individual ortho-substituted non coplanar PCB congeners were tested for their effects on the function of mussel (*Mytilus galloprovincialis* Lam.) hemocytes. Moreover, the possibility that in mussel hemocytes different PCBs may affect the signal transduction pathways involved in the immune response was investigated, with particular regards to relevant components of tyrosine-kinase mediated cell signaling. The results were compared with those obtained with a model of non-ortho-substituted coplanar congener. The results demonstrate that the di-ortho-substituted, non coplanar PCB congeners P47 (2,2',4,4'-tetrachlorobiphenyl) and P153 (2,2',4,4',5,5'-hexachlorobiphenyl) can alter immune parameters of mussel hemocytes, such as microbicidal activity and lysosomal enzyme release, respectively. Both congeners, as well as the non-ortho, coplanar congener P77 (3,3',4,4'-tetrachlorobiphenyl) significantly reduced hemocyte lysosomal membrane stability; however, P77 had no effect on either bacterial killing or lysozyme release. P47, P153 and P77 affected different components of tyrosine kinase-mediated cell signalling; in particular, they lead to a time-dependent increase in the phosphorylation level of the stress activated p38 and JNK Mitogen Activated Protein Kinases (MAPKs), as evaluated by Western blotting of hemocyte protein extracts with specific anti-phospho-MAPK antibodies. P153 also increased the level of phosphorylated ERK (extracellularly regulated) MAPKs. Moreover, non coplanar P47 and P153 caused increased tyrosine phosphorylation of the transcription factor STAT5, thus possibly affecting gene expression, whereas coplanar P77 was ineffective. The results demonstrate that MAPKs, and in particular the stress-activated p38 and JNK MAPKs, that represents a key step in the response of mussel hemocytes to bacterial infection, are a target for different non coplanar and coplanar PCB congeners. The results also show functional differences between different PCB congeners with respect to the hemocyte functions. However, chlorine substitution at the ortho positions is not necessarily related to immunotoxicity: the hexachlorinated P128 (2,2',3,3',4,4'-hexachlorobiphenyl) had no significant effect on mussel hemocytes, whereas its isomer P153, that represents a major component of environmental PCBs, and that is accumulated in mussel

tissues, significantly affected both aspects of the immune response and relevant signal transduction pathways. These are the first data on the effects and possible mechanisms of immunotoxicity of non coplanar PCBs in mussel hemocytes. The results support the hypothesis that the innate immune system is a sensitive target for these contaminants in both vertebrates and invertebrates. Moreover, when considering that non coplanar congeners are present both in commercial mixtures and, in higher proportions, in environmental samples, the results suggest that bivalve hemocytes represent a useful model for evaluating the potential immunotoxicity of PCB contamination.

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