

## BPA and PXR Activation

### Human Receptor Is Affected, Mouse Receptor Is Not

The high-production-volume chemical bisphenol A (BPA) is a key component in polycarbonate plastics and is used in a wide variety of consumer products. The U.S. general population is widely exposed to BPA, as demonstrated by the chemical's presence in more than 90% of biological samples tested. BPA has been associated with cardiovascular disease and diabetes in human population studies, but if causality were to be proven, it is doubtful it would arise from BPA's known weak interaction with estrogen receptors. Researchers previously determined that BPA targets another nuclear receptor, the pregnane X receptor (PXR), and have now determined that the chemical and several related compounds ("analogues") can induce metabolically important genes via PXR activation [*EHP* 120(3):399–405; Sui et al.].

PXR is activated by numerous endogenous and environmental chemicals. Earlier research established that PXR activation in mice and rats induces genes involved in lipid homeostasis, atherosclerosis, and carcinogenesis. Although PXR is not affected by BPA in rodents, the chemical activates the human receptor and induces target gene expression. This connection suggested a possible mechanism to explain BPA-related cardiovascular disease findings in human populations.

In the current study, transfection assays using mouse- and human-derived receptors showed that BPA induces strong, dose-dependent activation of human PXR but not mouse PXR. Computational docking

and modeling studies focusing on the structure of human PXR identified key amino acids within the ligand-binding domain that permit BPA to interact with the receptor. These studies also highlighted how species-related differences in this domain can affect how different species respond to specific chemicals.

The modeled predictions were confirmed *in vitro* using site-directed mutagenesis assays that focused on the amino acids critical for BPA docking within PXR. Additionally, several BPA structural analogues were found to activate the PXR. Experiments to determine interactions between BPA and specific analogues showed synergism when BPA was paired with 2-(4'-hydroxyphenyl)-2-phenylpropane (HPP); that is, the effect of the mixture exceeded the sum of the individual chemicals. In a final set of experiments, the ability of BPA and analogues HPP and bisphenol B to separately trigger expression of PXR target genes was tested in a human intestinal cell line. All 3 compounds were found to trigger expression of the metabolic genes *CYP3A4*, *UGT1A1*, and *MDR1*.

Although this study did not address questions of risk assessment, its findings suggest that BPA may adversely affect human health via PXR and thus provide a foundation for further exploration of the observed association between BPA and cardiovascular disease. Additionally, given the likelihood that real-life exposures involve chemical mixtures, the demonstrated synergism between BPA and HPP supports the need to include mixtures in *in vivo* experiments.

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## Air Pollution Intervention

### Study Links Use of Face Masks to Improved Cardiovascular Outcomes

Air pollution from traffic and industrial sources increases cardiovascular morbidity and mortality, especially in populations with underlying cardiovascular disease. Environmental interventions to reduce pollution would be ideal, but their implementation may be hampered in countries where emissions reductions are trumped by economic growth. A new study explores face masks as a simple and practical intervention for reducing individuals' exposure to particulate air pollution and finds their use improves several cardiovascular health measures in people with coronary heart disease [*EHP* 120(3):367–372; Langrish et al.].

Vehicle traffic and industry emit a variety of toxicants, including particulate matter, carbon monoxide, sulfur dioxide, and nitrogen dioxide. Previous studies have shown that inhaling combustion emissions may increase blood pressure and adversely affect vascular and cardiac function, plausibly explaining the detrimental cardiovascular effects associated with breathing heavily polluted urban air.

In the current study, nonsmoking patients with a history of coronary heart disease were recruited in March 2009 at 2 Beijing hospitals. After participants' health and physical condition were assessed, they completed 2-hour walks around Beijing's city center on

2 separate days. Participants were randomly assigned to wear a highly efficient air-filtering mask on 1 of the 2 walks. The mask was worn outdoors and during much of the time indoors for 24 hours before the study day as well as the entire study day itself. On study days,

participants also wore equipment to monitor their air pollutant exposure as well as blood pressure and heart function. They completed questionnaires on their physical symptoms, their perceptions of pollution levels and exertion, and the tolerability of the face mask.

The 98 participants that completed the study tolerated the face mask well and reported reductions in symptoms, perceived exertion, and perceived pollution levels. Use of a face mask was also significantly associated with beneficial cardiovascular characteristics, including reduced blood pressure and improved heart-rate variability.

The study was not double-blinded (in part because the researchers wanted to study the acceptability of wearing a face mask), and the findings may therefore be limited by subjective bias. The results suggest that face masks may effectively reduce individuals' air pollutant exposure and lower associated cardiovascular risks. However, it is unknown whether these effects would be sustained with face-mask use over a longer period and would ultimately result in clinically significant improvement in cardiovascular health.



During their walks through the city center, subjects wore backpacks equipped with air monitors.

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