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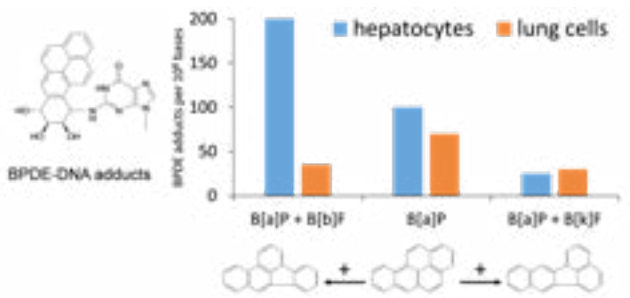
Non-additive genotoxic effects of polycyclic aromatic hydrocarbons in mixtures in human *in vitro* models

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous pollutants found in food and urban atmospheres and associated with numerous professional occupations. One major health effect of PAH is their carcinogenic properties which result mostly from their ability to damage the genome. While parent PAH are not reactive, their metabolites damage biomolecules and in particular DNA through the formation of covalent adducts. These processes are well described for individual PAH, in particular benzo[a]pyrene (B[a]P). The genotoxic effects of mixtures of PAH have been less studied. In the recent years, we investigated the effects of synthetic mixtures and environmental extracts on hepatocytes, lung cells and skin explants. Emphasis was placed on the induction of phase I CYP450 mono-oxygenase genes and the formation of B[a]P-diol-epoxide (BPDE) adducts to DNA. In most cases, we observed lack of additivity, either synergy or inhibition, even in simple binary mixtures. In addition, a same mixture did behave the same way in different models, with synergy being frequent in hepatocytes and inhibition in lung cells and skin. Surprisingly, no correlation could be found between the induction of *CYP* genes, which is always larger with mixtures than with pure B[a]P and the extent of DNA damage. The bulk of these observations are in agreement with other data of the literature and show that the toxicity equivalency factor approach currently used for the prediction of risk is not optimal. New tools based on more sophisticated modelization are necessary.



Addition of B[b]F to B[a]P leads to an increase of BPDE-DNA adducts while an opposite trend is observed with B[k]F. Both PAH inhibit the formation of BPDE-DNA adducts in lung cells.

Recent Publications

1. Von Koschembahr, Youssef, Béal, Calissi, Bourgart, Marques, Leccia, Giot, Maitre and Douki. (2018) Solar simulated light exposure alters metabolization and genotoxicity induced by benzo[a]pyrene in human skin. Scientific Reports 8:14692.
2. Genies, Jullien, Lefebvre, Revol, Maitre and Douki (2016) Inhibition of the formation of benzo[a]pyrene adducts to DNA in A549 lung cells exposed to mixtures of polycyclic aromatic hydrocarbons. Toxicol *In Vitro*. 35:1-10.
3. Genies, Maitre, Lefebvre, Jullien, Chopard-Lallier and Douki. (2013) The extreme variety of genotoxic response to benzo[a]pyrene in three different human cell lines from three different organs. PLoS One 8:11.
4. Tarantini, Maitre, Lefebvre, Marques, Rajhi and Douki (2011) Polycyclic aromatic hydrocarbons in binary mixtures modulate the efficiency of benzo a pyrene to form DNA adducts in human cells. Toxicology 279:36-44.
5. Tarantini, Douki, Personnaz, Besombes, Jafrezzo and Maitre (2011) Effect of the chemical composition of organic extracts from environmental and industrial atmospheric samples on the genotoxicity of polycyclic aromatic hydrocarbons mixtures. Toxicol Environ. Chem. 93:941-954.

Biography

Thierry Douki is a Senior Scientist interested in the genotoxic properties of several physical (UV radiation) and chemical agents (pollutants, warfare agents). Chemist by training, he is expert in the reactivity of DNA and uses HPLC-tandem mass spectrometry assays to quantify DNA damage in relevant cellular models. He is co-author of more than 250 articles and book chapters and is expert for the French Agency for Food, Environmental and Occupational Health & Safety (ANSES).

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