Research Brief 170: Biomarkers to Investigate the Toxicity and Carcinogenicity of PHAHs

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Background

Polyhalogenated aromatic hydrocarbons (PHAH) – polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) – are among the most prevalent pollutants found in the environment. Humans and wildlife are exposed daily to complex mixtures of these chemicals, primarily via trace amounts in food. While the actual exposure is unknown and difficult to estimate, these repeated, lifetime exposures may have potential for causing toxicity and carcinogenicity.

Understanding the mode of action of a toxicant provides the knowledge required to more accurately define dose-response characteristics and informs the risk assessment process. Dr. James Swenberg, Program Director of the SBRP at the University of North Carolina, Chapel Hill, leads a research effort to determine the molecular pathways involved in carcinogenesis from PHAH exposure. Many researchers believe that oxidative DNA damage is one of the key events involved in mutation and cancer. To study the role of oxidative DNA damage in the toxicity and carcinogenicity of PHAH, Dr. Swenberg's team investigated the correlation between PHAH exposure and the numbers of oxidative DNA lesions.

Advances

To begin, the researchers identified a potential biomarker to monitor oxidative DNA damage from *in vitro* and *in vivo* samples. The most common biomarker used in oxidative stress studies is 8-OH deoxyguanosine (8OHdG) but it is subject to artifactual formation during DNA isolation and analysis. The Swenberg group demonstrated that a DNA adduct formed from hydroxyl radical attack of the DNA backbone (3-(2´-deoxy-β-D-erythro-pentofuranosyl)-pyrimido[1,2-a]-purin-10(3H)-one, or M_1dG) is much less prone to artifactual formation than 8OHdG. Thus, M_1dG may be a more reliable biomarker for oxidative stress. Recently, they developed ultrasensitive and highly specific mass spectrometric methods for the quantitation of M_1dG adducts.

The researchers then examined the numbers of M_1dG adducts in tissues of rats or mice after single dose or repeated exposures to PHAHs. They exposed female mice to a single dose of either 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) or a PHAH mixture and found that the single exposure to PHAH had no significant effect on the number of M_1dG adducts compared to the control group.

PCB 126 is a "dioxin-like" contaminant. That is, like TCDD, its biochemical and toxic effects are the result of oxidative stress initiated by its binding to the aryl hydrocarbon receptor (AhR).

PCB 153 does not have dioxin-like activity.

To examine the effects of chronic exposure, the researchers analyzed samples from one of the largest and best characterized carcinogenicity bioassays: the NTP Toxic Equivalency Factor studies on PCBs/Dioxin in rats. In this study, rats were exposed for a year to PCB 153, PCB 126, or a mixture of the two.

Measurement of M_1dG adducts in the NTP study samples revealed that:

- At doses up to 3000 μg/kg/day, PCB 153 alone had no significant effect on the number of M_1dG adducts in liver and brain tissues from the exposed rats compared to controls.
- At 1000 μg/kg/day, PCB 126 alone resulted in M_1dG adduct accumulation in the liver.
- Co-administration of equal proportions of PCB 153 and PCB 126 (300 to 1000 ng/kg/day) resulted in dose-dependent increases in M_1dG adduct accumulation in the liver.
- Co-administration of different amounts of PCB 153 with fixed amounts of PCB 126 demonstrated more M_1dG adduct accumulation with higher doses of PCB 153.

The research group then compared the adduct accumulation findings to the findings of the NTP cancer assays and found consistent results. The patterns of liver tumor development observed after exposure to PCB 126 alone or PCB 153 alone were very similar to the dose responses for M_1dG adduct accumulation. The synergistic effect between PCB 126 and PCB 153 seen in the M_1dG adduct study was also observed in patterns of liver toxicity and tumor development. Subsequent research has shown similar increases in 8OHdG and 1,N^6-ethenodeoxyadenosine in the same tissue samples.

The change in the number of hepatic M_1dG adducts was detected after 1-year of exposure to PCBs – the increase in cancer incidence was not observed until after 2-years of exposure to PCBs.

Significance:

This demonstration of the correlations between PCB exposures, numbers of hepatic M_1dG adducts, and incidence of liver toxicity/tumor development is significant on two levels. First, the findings support the hypothesis that oxidative DNA damage plays an important role in cancer development associated with chronic exposure to PHAHs. This information will improve the scientific basis of risk assessments which depend on an in-depth understanding of how these chemicals cause toxicity and under what conditions they elicit responses.

Second, this work provides environmental health researchers and risk assessors with a new, sensitive biomarker of exposure to dioxin-like compounds.

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To learn more about this research, please refer to the following sources:

Jeong, Yo-Chan, N.J. Walker, D.E. Burgin, G. Kissling, M. Gupta, Lawrence L. Kupper, Linda S. Birnbaum, and James A. Swenberg. 2008. Accumulation of M1G DNA adducts after chronic exposure to PCBs, but not from acute exposure to polychlorinated aromatic hydrocarbons. Free Radical Biology and Medicine 45(5):585-591.
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