

Extramural papers of the month

By Nancy Lamontagne

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Superfund Research Program
Research Brief. New issues
are published on the first
Wednesday of each month.

Perinatal DDT exposure linked to later risk of metabolic syndrome

An NIEHS grantee and colleagues report that female offspring of pregnant mice exposed to the pesticide dichlorodiphenyltrichloroethane (DDT) have increased risk for obesity, diabetes, high cholesterol, and related conditions later in life. The study is one of the first to link DDT exposure with higher risk of developing metabolic syndrome as an adult.

Even though DDT was banned in the U.S. more than 40 years ago, it persists in the environment and is still used to control malaria in other parts of the world. People exposed to elevated levels of DDT and its metabolite dichlorodiphenyldichloroethylene (DDE) are more likely to have diabetes and insulin resistance. To find out if DDT impairs metabolism and energy expenditure, the researchers exposed mice from gestational day 11.5 to postnatal day 5 to doses of DDT comparable to exposures of people living in malaria-infested regions, and of pregnant mothers of U.S. adults who are now in their mid-50s.

The female offspring with DDT exposure showed reduced core body temperature, impaired cold tolerance, decreased energy expenditure, and a temporary early-life increase in body fat. In males, DDT exposure did not affect obesity or cholesterol levels and caused only a minor increase in glucose levels. The researchers gave the DDT-exposed offspring a high-fat diet for 12 weeks during adulthood. The female mice developed glucose intolerance; excess insulin levels and abnormal amounts of lipids circulating in the blood; and altered bile acid metabolism. The female mice fed the high-fat diet also showed further reductions in core temperature.

Based on their findings, the researchers say perinatal DDT exposure is likely a risk factor for reduced energy expenditure in people, even decades after DDT use has stopped.

Citation: La Merrill M, Karey E, Moshier E, Lindtner C, La Frano MR, Newman JW, Buettner C.
(<http://www.ncbi.nlm.nih.gov/pubmed/25076055>)

2014. Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring. *PLoS One* 9(7):e103337.

DDT alternative linked to transgenerational inheritance of disease

A study supported in part by NIEHS showed that ancestral exposure to the pesticide methoxychlor may lead to greater susceptibility of future generations to adult onset kidney disease, ovarian disease, and obesity. The research indicates that exposure to methoxychlor, which was widely used in the 1970s as a DDT replacement, can promote epigenetic transgenerational inheritance of disease, in both males and females. Epigenetic transgenerational inheritance is a nongenetic form of inheritance in which epigenetic changes are passed down to generations that had no direct environmental exposure.

Methoxychlor was banned in the U.S. in 2003 because of its toxicity and ability to disrupt the endocrine system, but it is still used in many countries. The scientists exposed pregnant rats to methoxychlor, at a range typical of high environmental exposures. Their offspring showed increases in the incidence of kidney disease, ovary disease, and obesity spanning three generations. Analysis of the third-generation sperm epigenome of the methoxychlor lineage males identified differentially DNA methylated regions, termed epimutations. Additional experiments showed that transgenerational disease transmission occurred primarily through the maternal germline.

These new findings add to the researchers' earlier studies showing a variety of epigenetic effects for contaminants including DDT, plastics, pesticides, fungicides, dioxins, hydrocarbons, and bisphenol A.

Citation: Manikkam M, Haque MM, Guerrero-Bosagna C, Nilsson EE, Skinner MK.
(<http://www.ncbi.nlm.nih.gov/pubmed/25057798>)

2014. Pesticide methoxychlor promotes the epigenetic transgenerational inheritance of adult-onset disease through the female germline. *PLoS One* 9(7):e102091.

Marine bacteria produce polybrominated diphenyl ethers

Researchers discovered a widely distributed group of marine bacteria that produce polybrominated diphenyl ethers (PBDEs) nearly identical to toxic man-made fire retardants. The study is the first to isolate and identify bacteria that produce these endocrine-disrupting compounds, and the findings may help explain the PBDEs observed to bioaccumulate in the marine food chain.

PBDEs were widely used as flame retardants in furniture and other consumer products, until most were removed voluntarily from the market a decade ago. For some time, scientists have observed bioaccumulation of PBDEs in the fatty tissues of marine animals but believed the compounds came from man-made sources. More recently, mounting evidence pointed to microbial sources of marine PBDEs, but scientists did not know which organisms were producing the compounds.

In this study, researchers identified and isolated bacteria that produce PBDEs and discovered 10 genes involved in the synthesis of more than 15 bromine-containing polyaromatic compounds, including some PBDEs. They have since conducted DNA sequencing analyses that will let them probe the ocean for other biological sources of these chemicals and begin to assemble a complete picture of their human health risk.

Citation: [Agarwal V, El Gamal AA, Yamanaka K, Poth D, Kersten RD, Schorn M, Allen EE, Moore BS.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/24974229>

2014. Biosynthesis of polybrominated aromatic organic compounds by marine bacteria. *Nat Chem Biol* 10(8):640-647.

Combined action of Srs2 and Exo1 enzymes helps maintain DNA

NIEHS grantees found that Srs2 and Exo1 enzymes act together to prevent and repair mistakes made during DNA replication in yeast cells. Many essential cellular functions are similar between yeast and people, so it is likely that similar DNA repair processes operate. These results have implications for understanding Aicardi-Goutieres syndrome, a rare disorder that affects the brain, immune system, and skin.

During DNA replication, ribonucleoside monophosphates, which are the building blocks of RNA, are inserted into DNA. During this process misinsertions can lead to lethal structural alterations. Among the study's key findings was that Srs2 helps open the DNA structure so that Exo1 can cleave out any misplaced ribonucleoside monophosphates. Both enzymes were previously known to play a role in DNA replication and repair, but the scientists say this is the first evidence of their role in preventing and correcting mutations derived from ribonucleoside monophosphates.

The research team also found that the Srs2-Exo1 cell repair mechanism prevents mutations from accelerating in yeast already deficient in the enzyme RNase H2. The enzyme serves as the primary removal mechanism for ribonucleoside monophosphate during cell growth. Yeast deficient in both RNase H2 and Srs2 had a tenfold increase in the number of mutations, chromosome losses, and chromosome breakages. These results may help scientists better understand Aicardi-Goutieres syndrome, which stems from inactivation of the human RNase H2 enzyme complex.

Citation: [Potenski CJ, Niu H, Sung P, Klein HL.](#)

<http://www.ncbi.nlm.nih.gov/pubmed/24896181>

2014. Avoidance of ribonucleotide-induced mutations by RNase H2 and Srs2-Exo1 mechanisms. *Nature* 511(7508):251-254.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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bruskec@niehs.nih.gov

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