Extramural papers of the month

By Nancy Lamontagne

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

Preterm birth may increase risk for type 2 diabetes

Researchers, supported in part by NIEHS, found that premature infants are more likely to have elevated insulin levels at birth and into early childhood than are infants born at term. Since elevated insulin levels can be an indication of insulin resistance, the findings suggest that preterm birth could be a risk factor for future development of insulin resistance and type 2 diabetes.

The researchers measured plasma insulin levels of 1,358 children at birth and in early childhood. They found that plasma insulin levels were higher in children born before full term. Average insulin levels at birth were 9.2 micro international units per milliliter for full term (39 weeks or later) and 18.9 micro international units per milliliter for early preterm (less than 34 weeks) births. In early childhoos, plasma insulin levels were higher for children born early term (37-38 weeks), late preterm (34-36 weeks), and early preterm than for those born at full term.

The fact that the higher levels of plasma insulin at birth could be tracked into early childhood strengthens the argument for a trajectory of diabetes risk that begins very early in life, according to an accompanying editorial. It also points to the need for rigorous studies of early life interventions, to better understand how to reduce risk for noncommunicable diseases, such as diabetes.

Citation: Wang G, Divall S, Radovick S, Paige D, Ning Y, Chen Z, Ji Y, Hong X, Walker SO, Caruso D, Pearson C, Wang MC, Zuckerman B, Cheng TL, Wang X.
(http://www.ncbi.nlm.nih.gov/pubmed/24519298)
2014. Preterm birth and random plasma insulin levels at birth and in early childhood. JAMA 311(6):587-596. (Editorial)
(http://www.ncbi.nlm.nih.gov/pubmed/24519295)

DDT metabolite linked to higher Alzheimer's risk

In one of the first studies to identify a strong environmental risk factor for Alzheimer's disease, NIEHS grantees report that patients with Alzheimer's have significantly higher levels of a dichlorodiphenyltrichloroethane (DDT) metabolite than people without the disease. Researchers also found evidence of a gene-environment interaction, as well as a possible mechanism for the pesticide's effects.

In the United States, DDT was used extensively as an insecticide from the 1940s through 1972, and it persists in the environment today. DDT continues to be used in other countries to control malaria. DDE, a DDT metabolite, accumulates in the body as people grow older.

The study compared 86 Alzheimer's patients from Georgia and Texas with 79 healthy elderly people, and found that DDE levels were 3.8-fold higher in the blood serum of the patients with Alzheimer's. DDE levels in the highest range were associated with an odds ratio of 4.18 for increased risk of Alzheimer's, as well as lower scores for the Mini-Mental State Examination (MMSE), a test used to screen for cognitive impairment.

The researchers also looked at the role of the apolipoprotein E (APOE) genotype. They found that among those with the highest DDE levels, participants who carried the APOE4 allele, or form of the APOE gene, had MMSE scores 1.753 points lower than those who carried the APOE3 allele, indicating that carriers of an APOE4 allele may be more susceptible to the effects of DDE.

The researchers also exposed cultured neuronal cells to DDT and DDE, at levels observed in highly exposed people in the United States, and observed an increase in amyloid precursor protein, which is linked with Alzheimer's, indicating a possible mechanism for the association between DDT exposure and Alzheimer's.

Citation: Richardson JR, Roy A, Shalat SL, von Stein RT, Hossain MM, Buckley B, Gearing M, Levey AI, German DC.
(http://www.ncbi.nlm.nih.gov/pubmed/24473795)
2014. Elevated serum pesticide levels and risk for Alzheimer disease. 2014. JAMA Neurol 71(3):284-290. Story

Phthalate exposure trends from 2001 to 2010

An NIEHS grantee and colleagues report that Americans are being exposed to significantly lower levels of some phthalates and higher levels of others. Phthalates, used to make plastic more flexible, are found in hundreds of consumer products. A federal law that took effect in 2009 permanently banned some phthalates, banned others from use in children's articles such as toys, and set an interim ban, pending further study, on three phthalates, barring their use in toys that can be placed in a child's mouth.

To examine how phthalate exposure is changing over time, the researchers combined data on 11 phthalate metabolites from 11,071 participants in five cycles of the Center for Disease Control National Health and Nutrition Examination Survey. From 2001 to 2010, the researchers found decreases in exposures to permanently banned phthalates - butylbenzyl phthalate, di-n-butyl phthalate, and di(2-ethylhexyl) phthalate (DEHP). Children showed consistently higher DEHP exposures than adults, but the difference between the age groups lessened over time.

Exposures increased for the phthalates under the interim ban - di-n-octyl phthalate by 15 percent, diisodecyl phthalate by 25 percent, and diisononyl phthalate (DiNP) by nearly 150 percent. The increase in DiNP is likely because industry is using it to replace banned phthalates. Exposure tripled for diisobutyl phthalate (DiBP), which hasn't been subject to federal restrictions. DiBP may be replacing diethyl phthalate (DEP), which was a focus of early activism regarding chemicals in cosmetics. Exposure to DEP decreased 42 percent.

The researchers say that the trends they observed are difficult to explain, but may reflect the effects of legislative activity, as well as advocacy efforts of nongovernmental organizations on consumer behavior and the use of phthalates in consumer products.

Citation: Zota AR, Calafat AM, Woodruff TJ.
(http://www.ncbi.nlm.nih.gov/pubmed/24425099)
2014. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001-2010. Environ Health Perspect 122(3):235-241. Story

Grasp protein aids protective function of p53 in skin

Research, funded in part by NIEHS, revealed that the Grp1-associated scaffold protein, or Grasp, helps the P53 tumor suppressor gene to function correctly in skin. Finding ways to maintain or increase the effectiveness of Grasp could offer an important new avenue for human cancer therapies.

The researchers created mice that lacked the Grasp gene and compared how these mice and normal mice reacted to the mild environmental stress of ultraviolet light, similar to moderate sun exposure. The mice lacking Grasp began to develop cellular abnormalities much more rapidly than ordinary mice. Significantly, mutated skin cells did not die as they should have. In normal mice, the same moderate light exposure caused a rapid increase in expression of the Grasp gene, allowing the p53 protein to stay in the nucleus, and normal protective mechanisms to do their work. Overall, these results suggest that a physiological role of Grasp may be to regulate skin homeostasis after UVB exposure, potentially by influencing p53-mediated apoptotic responses in skin.

Citation: Venkataraman A, Coleman DJ, Nevrivy DJ, Long T, Kioussi C, Indra AK, Leid M.
(http://www.ncbi.nlm.nih.gov/pubmed/24407555)
2014. Grp1-associated scaffold protein regulates skin homeostasis after ultraviolet irradiation. Photochem Photobiol Sci 13(3):531-540.

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