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**NIEHS**

 National Institute of  
Environmental Health Sciences

**Environmental Factor, November 2012**

## Dioxin exposure causes transgenerational health effects

By Brant Hamel

A new study, funded in part by NIEHS, found that dioxin affects not only the health of an exposed rat, but also unexposed descendants through a mechanism of epigenetic transgenerational inheritance.

The study (<http://www.ncbi.nlm.nih.gov/pubmed/23049995>) was conducted in the laboratory of Michael Skinner, Ph.D., (<http://skinner.wsu.edu/piskinner.html>) a professor in the Center for Reproductive Biology in the Department of Biological Sciences at Washington State University (WSU) who designed the study. (<http://www.ncbi.nlm.nih.gov/pubmed/23049995>) Co-authors included assistant research professor Mohan Manikkam, Ph.D., research technician Rebecca Tracey, and postdoctoral researcher Carlos Guerrero-Bosagna, Ph.D.

“Although not designed for risk assessment, these results have implications for the human populations that are exposed to dioxin and are experiencing declines in fertility and increases in adult onset disease, with a potential to transmit them to later generations,” the authors concluded.



In a WSU press release, (<http://news.wsu.edu/pages/publications.asp?Action=Detail&PublicationID=33053&TypeID=1>) Skinner said of his latest findings, “It is not just the individuals exposed, but potentially the great-grandchildren that may experience increased adult-onset disease susceptibility.” (Photo courtesy of Steve McCaw)

### Dangers of dioxin last for decades after initial exposure

Dioxin, 2,3,7,8-tetrachlorodibenzo[p]dioxin (TCDD), is a chemical compound that constitutes part of the Agent Orange herbicide used as a defoliant in the Vietnam War. According to research cited in the study, exposure is estimated to have caused 400,000 deaths and 500,000 birth defects. Dioxin has also been released from industrial accidents, leading to human exposures. Due to its extremely long half-life of up to 10 years in humans, dioxin may still affect pregnancies occurring even 20 years after exposure.

In the Skinner group’s experiments, exposure to dioxin caused changes in the DNA methylation patterns of sperm that were transmitted across generations, in an imprinted-like manner, to affect the health of multiple generations of descendants. The grandchildren of exposed rats showed dioxin-induced effects ranging from polycystic ovarian disease to kidney disease. The work raises the serious concern that even if toxic chemicals, such as dioxin, were completely removed from the environment, they could continue to cause disease for multiple generations.

### Health effects of dioxin include early onset of puberty in females

Skinner's group used low *in vivo* doses of dioxin, so that toxic effects were not expected. Female rats were exposed while pregnant, and both their direct progeny and descendants two generations removed were examined.

Although the most prominent phenotypes were kidney disease in males and polycystic ovarian disease in females, a number of other effects including abscesses, colon impaction, lung abnormalities, and missing testes were also observed in animals from the dioxin-treated lineage. Additionally, females from the dioxin-exposed lineage experienced the early onset of puberty. Conversely, males showed delayed puberty, suggesting sex-specific effects of exposure. Early puberty in humans has increased over recent decades and is believed to have an environmental link.

### **Dioxin alters methylation patterns in germ line DNA across generations**

The researchers were able to identify 50 specific regions of DNA that were differentially methylated in the dioxin-treated animals. These regions were permanently reprogrammed and protected from DNA methylation, in a manner that allowed them to be passed down across generations. In the future, these regions may serve as biomarkers that would allow early detection of exposure and risk for disease.

Other chemical compounds, including bisphenol A, phthalates, the insecticide DEET, and the jet fuel JP8 have all been shown to promote disease across generations, through a similar mechanism of epigenetic transgenerational inheritance (see story). This pathway of disease propagation exists not only in rats, but also in humans, mice, worms, flies, and even plants. Thus, future research will be needed to see if other environmental compounds may also lead to health effects across generations.

In addition to NIEHS, NIH and the U.S. Department of Defense provided support for the study.

*Citation:* Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. (<http://www.ncbi.nlm.nih.gov/pubmed/23049995>) 2012. Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. PLoS One 7(9):e46249.

(Brant Hamel, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Laboratory of Signal Transduction.)

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