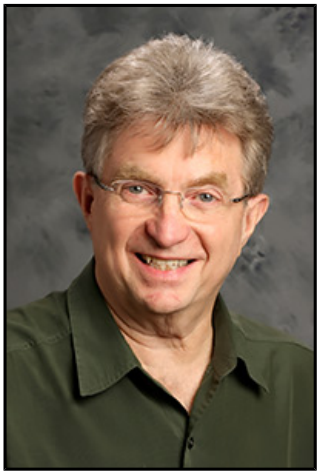
Diversity Outbred mice better predict potential human responses to chemical exposures

By Robin Mackar

In a new study, NIEHS researchers report that Diversity Outbred mice can accurately predict the range of response to chemical exposures that might be observed in human populations. The findings *(http://www.ncbi.nlm.nih.gov/pubmed/25376053)* were published online Nov. 6 in the journal Environmental Health Perspectives.

Researchers from the National Toxicology Program *(http://ntp.niehs.nih.gov/nnl/urinary/kidney/index.htm)* (NTP), an interagency program headquartered at NIEHS, were able to identify specific genes or chromosomal regions that make some of the Diversity Outbred mice more susceptible, and others more resistant, to the toxic effects of benzene. Benzene is a common air pollutant and human carcinogen found in crude oil, gasoline, and cigarette smoke, and naturally produced by wildfires and volcanoes.

The scientists found that, like humans, each Diversity Outbred mouse developed at The Jackson Laboratory *(http://www.jax.org/)* in Bar Harbor, Maine, responded to the effects of the chemical exposure differently.



French, who is now retired, devoted several years to studying in vivo animal models to explore individual variability in toxicity response. (Photo courtesy of Steve McCaw)

Witt manages the NTP genetic toxicology testing contract, and she provides genetic toxicology test data review and evaluation for inclusion in the NTP Technical Reports. (Photo courtesy of Steve McCaw)

Measuring micronucleated red blood cells

Exposure responses were assessed by measuring the frequency of micronucleated red blood cells, a biological marker of chromosomal damage, which is a hallmark of benzene exposure. The researchers measured the levels of this biomarker in each mouse before and after exposure.

Some mice demonstrated extraordinary sensitivity to the exposure, while others showed no response. The range of response from lowest to highest was approximately 5-fold. Since the researchers knew the genetic makeup of each mouse, they could pinpoint the regions involved in susceptibility or resistance to the chemical exposure, and then look for related genetic regions in human chromosomes.

“This paper points out the significant genetic differences that are found throughout every population that must to be taken into account when extrapolating data from animals to humans,” said Linda Birnbaum, Ph.D., director of NTP and NIEHS. “The Diversity Outbred mouse is a useful model for predicting the range of response that might be observed in humans following exposure to a chemical.”

Benzene as a case study

Benzene was selected by NTP as a case study for testing the mouse model, because there is an abundance of animal and human toxicity data for comparison. Benzene can affect people differently, depending on the level and duration of exposure, making it important to accurately estimate the levels at which it may cause harm to the most susceptible individuals.

“These genetically diverse mice provided a reproducible response to benzene exposure across two independently exposed groups, suggesting that each group of genetically unique mice demonstrated the same range of differential susceptibility, much like what you would find in human epidemiology studies,” said Jef French, Ph.D., lead author on the paper.

Kristine Witt, a co-author on the paper, and group leader for the NTP Genetic Toxicology Branch added that the model can provide valuable data for use by regulators and manufacturers conducting chemical risk assessments.

The full text of the paper is available online *(http://ehp.niehs.nih.gov/1408202/)* in the journal Environmental Health Perspectives.

Citation: French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA.
(http://www.ncbi.nlm.nih.gov/pubmed/25376053)
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