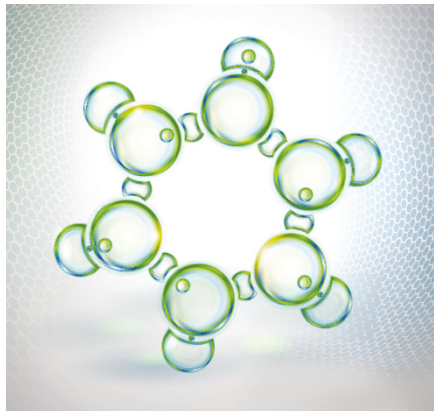
Outbred mice may better model benzene toxicity

Benzene is an airborne pollutant that is known to have carcinogenic effects: exposure to this compound alters gene expression in peripheral blood cells and induces chromosomal damage. Human exposure to benzene occurs mainly through inhalation in both environmental and occupational settings. The US Occupational Safety and Health Administration has set an 8-hour time-weighted-average exposure limit of 1 ppm, but workers exposed to air concentrations of benzene below this level have shown evidence of hematotoxicity. Occupational exposures as low as 0.3 ppm have been shown to increase the risk of leukemia and myelodysplastic syndrome. Current exposure limits therefore may be insufficient to protect against the damaging effects of benzene exposure.

Benzene metabolism and clearance varies in the human population, likely owing to the effect of genetic variation on toxicity responses. This effect remains poorly understood, however, because toxicity is typically evaluated using genetically identical animal models. For example, toxicology assessments at the National Toxicology Program are done in B6C3F1 mice, which are derived from crossing two inbred strains, C57BL/6J and C3H/HeJ.

Diversity outbred (DO) mice are a recently developed population derived from eight inbred founder strains and have a level of genetic diversity that is similar to that of humans. As such, they may more accurately reflect the range of toxicity responses observed in human populations. Furthermore, because of their genetic diversity, genetic associations can be localized in these mice with high precision. John French and other researchers used DO mice to study how genetic variability influences toxicity responses as well as to provide more insight into benzene-induced genotoxicity.

The researchers exposed male DO mice to various doses of benzene (75 mice per group) via inhalation for 28 days (6 hours per day for 5 days per week). The study was repeated using two independent cohorts of 300 animals each. Toxicity response to benzene exposure varied among individuals of the genetically diverse DO population (*Env. Health. Perspect.* doi:10.1289/ehp.1408202; published online 6 November 2014). A dose-dependent increase in benzene-induced chromosomal damage was observed, and a



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locus was identified that encoded a pair of over-expressed sulfotransferases that were inversely correlated with genotoxicity.

Using the results in the DO mice, the scientists estimated a benchmark exposure limit of 0.205 ppm benzene, an order of magnitude below the value estimated using B6C3F1 mice. The DO-based estimate is consistent with observed exposure toxicity in human subjects and may provide a more appropriate estimate of exposure thresholds that would protect the most sensitive human subpopulations.

Kara Rosania

FOR LACK OF GUT MICROBES, THE BLOOD–BRAIN BARRIER 'LEAKS'

The blood–brain barrier is a selectively permeable barrier between the brain extracellular fluid and the blood formed by capillary endothelial cells connected by tight junctions. The blood–brain barrier prevents potentially harmful molecules and cells from entering the brain and maintains microenvironmental conditions suitable for neuron growth. Its integrity is therefore crucial to proper brain function. A recently published article (*Sci. Transl. Med.* **6**, 263ra158; 2014) identifies a surprising regulator of the integrity of the blood–brain barrier: the microorganisms that colonize the gut.

The study involved two groups of mice: one that had never been exposed to live bacteria (bacteria-free) and one that was kept in an environment that excluded commonly monitored mouse pathogens but had normal gut microbial communities (pathogen-free). Permeability of the blood–brain barrier in mice of both groups was examined during embryonic development and into adulthood. In fetal mice from bacteria-free mothers, the blood–brain barrier was more permeable than in those from pathogen-free mothers at the same stage of development. Increased blood–brain barrier permeability persisted after birth and during adulthood in mice raised in the absence of bacteria and was associated with dysregulation of tight junctions. Exposure of adult bacteria-free mice to fecal microbiota from adult pathogen-free mice restored the integrity of the blood–brain barrier.

The results show that communication between the gut microbiota and the brain is established during embryonic development and continues throughout life. Sven Pettersson (Karolinska Institute, Stockholm, Sweden), one of the senior authors of the report, said in a press release, "These findings further underscore the importance of the maternal microbes during early life and that our bacteria are an integrated component of our body physiology."

The mechanisms that underlie gut–brain signaling and enable regulation of the blood–brain barrier by gut microbes are not yet known, nor are the consequences of increased permeability of the blood–brain barrier. The study's authors suggest that more physiological data are needed to confirm the findings and guide their interpretation. Regarding future applications of this work, Pettersson says, "This knowledge may be used to develop new ways for opening the blood–brain barrier to increase the efficacy of… drugs and for the design of treatment regimes that strengthen the integrity of the blood–brain barrier."

Monica Harrington