

Pondering on Pesticides Long-Term Low Levels Impair Thinking

As Homer wrote, “Wine can of their wits the wise beguile,” but what of the grapes that make the wine—or rather, the pesticides with which they are treated? Isabelle Baldi of the Institut de Santé Publique d’Epidémiologie et de Développement in Bordeaux, France and colleagues went to their local vineyards to measure workers’ cognitive well-being and see how it related to the amount of pesticides they had encountered over the years [*EHP* 109:839–844]. Previous studies had shown that high-dose pesticide poisoning can cause acute human health effects such as motor skill damage, impaired intellectual functioning, and memory loss. In this study, the first to assess long-term neuropsychologic effects of chronic, low-level pesticide exposures in a large sample of workers, Baldi and colleagues found many examples of impaired cognitive functioning among exposed workers.

The team interviewed 917 men and women, aged 43–58, between February 1997 and August 1998. Of the study participants, 528 had been directly exposed to pesticides through mixing or spraying over a mean of 22 years, another 173 had been indirectly exposed by contact with treated plants, and 216 had never been exposed. The pesticides used were primarily fungicides.

The team administered nine neuropsychologic tests to the workers, including the Mini-Mental Status Examination (which measures different cognitive components), the Wechsler Paired Associates Test of memory, the Benton Visual Retention Test, the Isaacs Set Test (which measures the ability to quickly generate lists of words in different semantic categories), and the Finger Tapping Test (which assesses motor speed). The team controlled for factors that could alter test scores, including educational level, age, sex, alcohol consumption, smoking, environmental exposures, and depressive symptoms.



Lost in thought among the vines. A study conducted on vineyard workers showed for the first time that long-term low-level exposures to pesticides have measurable effects on cognition.

Workers who were either directly or indirectly exposed performed worse on tests of memory, selective attention, verbal fluency, and abstraction compared with nonexposed workers. On a test of both selective attention and working memory, directly exposed workers were 3.5 times more likely to score low compared with nonexposed subjects. On a similar test of selective attention and mental flexibility, the exposed individuals were 3.1 times more likely to score low. The exposed men and women processed information less quickly than nonexposed colleagues, although performances of exposed workers were similar to those of the nonexposed if the tasks were slowed.

The study participants’ symptoms were subclinical and didn’t appear to interfere with their work, the team writes, and the participants didn’t complain about their cognitive deficits. But they might run into cognitive problems as they age, Baldi notes. “This is why we planned a four-year follow-up of the population [starting in 2001] to assess evolution of performances,” she says.

One surprising finding: although large amounts of alcohol are neurotoxic, the workers who drank moderately had better test scores than nondrinkers. Other studies have shown a protective effect of moderate wine consumption on cognitive performance. Baldi can’t explain the finding, but notes that among these workers alcohol is considered “a noble product.” —Tina Adler

Lead in Your Body Genotype Determines What Stays, What Goes

The same lead exposure can cause widely varying symptoms of lead intoxication and levels of organ dysfunction in different people. According to Howard Hu of Harvard University and his colleagues, an underlying cause may be genetic polymorphism in the δ -aminolevulinic acid dehydratase (*ALAD*) gene [*EHP* 109:827–832].

The team studied *ALAD* polymorphism and its relation to altered concentrations of bone and blood lead among 726 middle-aged and elderly men who had been exposed to lead nonoccupationally. Given their ages, these men would have faced now-obsolete lead exposures such as inhaling combusted leaded gasoline and ingesting food from lead-soldered cans, as well as still-present exposures such as eating vegetables grown in lead-contaminated soil. The men were participants in the Normative Aging Study, a longitudinal study of aging begun in 1963. Middle-aged to elderly men are at the highest risk for the onset of certain chronic diseases such as hypertension, stroke, heart attack, and dementia, and Hu and colleagues believe that cumulative lead exposure may be a significant risk factor for these problems.

Bone lead measurements were taken at the thigh and the knee. These sites were chosen because they consist, respectively, of pure cortical and pure trabecular bone. Cortical bone has very slow turnover; lead that is deposited there persists for many decades and thus provides a good reflection of total lead exposure. Conversely, trabecular bone has a relatively rapid turnover and releases a good deal of lead into the blood. Trabecular bone is therefore a good reflection of bone lead stores that can be mobilized into circulation.

The results showed that patella lead was the major predictor of blood lead in this aging nonoccupationally exposed population and that *ALAD* polymorphism significantly affected this association. For example, when patella lead exceeded 60 $\mu\text{g/g}$, blood lead concentrations in carriers of the *ALAD 2* allele were higher than those in *ALAD 1-1* carriers. By contrast, when patella lead concentrations were lower than 40 $\mu\text{g/g}$, blood lead concentrations were higher in *ALAD 1-1* carriers than in *ALAD 2* carriers. On the basis of their results, Hu and his colleagues suggest that when blood lead concentrations are relatively low—less than about 8 $\mu\text{g/dL}$, for instance—*ALAD 1-1* carriers will have higher blood lead concentrations than *ALAD 2* carriers.

Some earlier studies on *ALAD* polymorphism and blood lead found that individuals with the *ALAD 2* allele had higher blood lead concentrations. Others did not find this relationship. The results of Hu's study suggest a possible reason for this discrepancy: the relationship between the *ALAD* polymorphism and blood lead may actually depend on how much lead is in bone, a parameter that had not been previously measured in most *ALAD* polymorphism studies. Hu and colleagues caution, however, that this finding is tentative and needs to be verified in other community-exposed population studies.

ALAD polymorphism, then, might modify the exchange of lead between blood and bone, which in turn could modify a person's risk for lead toxicity. Several previous studies have indeed found that *ALAD* polymorphism modifies certain symptoms of lead intoxication, such as impaired kidney, reproductive, and neuropsychological function. For instance, one study found the *ALAD 2* allele to correlate with impaired kidney function, yet other studies found this same allele to be protective of neuropsychological and male reproductive function. More research is needed for a precise definition of the mechanism of function and of the potential impact of *ALAD* polymorphism on lead kinetics and toxicity. —Julian Josephson

Mice Beat Rats

The Best Model for Testing Endocrine Disruptors

Endocrine disruptors, or chemicals that interfere with hormone activity, abound in our environment. They are found in such synthetics as pesticides, preservatives, paints, and plastics, as well as in natural sources such as soy products. To date, approximately 50 chemicals have been identified as endocrine disruptors. However, in the United States alone there are more than 80,000 chemicals now in commercial use that have not yet been tested for such effects. A 1998 U.S. Environmental Protection Agency report called for testing of all environmental chemicals for their estrogenic effects and recommended using an *in vivo* screen measuring uterine growth in rodents. In this issue, Elizabeth Padilla-Banks, Wendy N. Jefferson, and Retha R. Newbold, all of the NIEHS, compare the sensitivity of mice versus rats as a model for the testing of estrogenic effects of endocrine disruptors [*EHP* 109:821–826].

In humans, exposure to endocrine disruptors has been proposed to be linked to reproductive and developmental abnormalities, increases in hormone-related cancers, attention deficit/hyperactivity disorder, and behavioral problems. Animals are particularly sensitive to effects from exposure to endocrine disruptors, and as such make good models for testing.

Rats are most commonly used in toxicity testing, but they are more expensive to use than mice—nearly twice as expensive to purchase and three times as expensive to house. Rats can have other disadvantages as well; they are more variable in factors such as body size and uterine response, so more of them must be tested to pick up subtle differences.

In their study, the researchers compared the sensitivity of the immature CD-1 mouse to that

of the immature Sprague-Dawley rat. Each species was exposed to varying doses of the female sex hormone 17 β -estradiol and compared to an unexposed cohort. After three days of exposure, the animals were sacrificed and their uterine weight:body weight ratios determined. The researchers measured uterine epithelial cell height and number, as well as gland number, all of which increase with estrogenic activity and are therefore useful markers for testing chemicals with unknown estrogenicity. They also measured expression of the estrogen-inducible proteins lactoferrin and complement C3.

In general, the rats and mice proved to be equally well suited for uterotrophic bioassay. Both species showed a similar dose–response increase in uterine wet weight as a result of exposure to 17 β -estradiol, although mice were more sensitive than rats at all doses tested. (Uterine wet weight, which includes both the tissue and fluid content of the uterus, is a more meaningful measure than dry weight because estrogens increase water absorption and the amount of fluid in the uterine cavity.) Both species showed an increase in uterine epithelial cell height over their respective controls. With respect to epithelial cell number, mice showed a greater increase than rats at any given dose. Further, mice showed an increase in gland number, while rats did not. Both rats and mice showed strong expression of lactoferrin and complement C3 in the uterine epithelial cells following 17 β -estradiol treatment.

Over the course of testing, researchers found a significantly greater variation in body weight in the rats versus the mice. Such variability in an experiment can decrease the significance of the results, such that weak estrogens may not be detected. The lower the variability, the fewer animals need to be used for testing. Thus, the ability to use mice might potentially translate into lower animal husbandry costs. Further, the smaller size of the mouse would mean that lesser amounts of chemical compounds would be required for testing. “The bottom line is that we can test more chemicals more efficiently using the mouse model versus the rat model,” says Newbold. —John S. Manuel



Murine supermodel? A comparative analysis shows that mice should provide a more accurate and less expensive model for testing endocrine disruptors than the traditionally used rats.