A Whiff of Danger

Synthetic Musks May Encourage Toxic Bioaccumulation

A class of widely used fragrances that are considered nontoxic may pose a hidden threat to human health by enhancing the effects of compounds that *are* toxic—a paradox discovered by Stanford University researchers Till Luckenbach and David Epel in a recent study of synthetic musk compounds [***EHP* 113:17–24**]. The duo, based at Stanford's Hopkins Marine Station, found that musks inhibited natural defenses against toxicants in California mussels, and that the effect remained long after exposure. Their findings raise a red flag for human health because musk compounds concentrate in fats (including breast milk) and endure in human tissue long after exposure.

People typically are exposed to musks transdermally, through soap, cosmetics, and clothes washed with scented detergents. Musks also are inhaled, through cologne sprays. Every year, some 8,000 metric tons of the inexpensive synthetic fragrances are produced worldwide.

The science of scents. New data on musks show the compounds may inhibit cellular defenses against chemicals and bioaccumulate, with potentially hazardous results.

The discovery of musk compounds in human fat a decade ago prompted Japan and Germany to ban some musk compounds. German researchers who measured human body burdens found musks in the fat of all their subjects and concluded that humans are constantly exposed to these highly stable compounds. The United States and other countries, though, allowed continued use of the fragrances because they were considered safe; a battery of routine toxicology screens have shown musk compounds to be nontoxic.

Epel and Luckenbach speculated that musks enhance the effects of toxicants by confounding cellular defense systems. Cells naturally resist toxicants through multidrug/multixenobiotic resistance (MDR/MXR) efflux transporters, proteins that keep foreign chemicals from entering cells. Epel and Luckenbach built on earlier findings reported in the September 1997 issue of *EHP Supplements* that man-made fat-soluble chemicals could inhibit MDR/MXR efflux transporters. Because musks are fat-soluble, they suspected synthethic musk compounds of having this effect.

The researchers chose mussel gill tissue for their study because its efflux transporters are particularly active. They incubated the tissue for 90 minutes in a solution containing musk compounds and the fluorescent dye rhodamine B. The dye reflects efflux transporter activity; finding rhodamine B in the tissue would indicate the transporters were failing.

Immediately after incubation, Epel and Luckenbach found rhodamine B uptake to be 38–84% higher in tissue treated with musk compounds than in controls. They were surprised to find, 24 hours later, that rhodamine uptake was still 30–74% higher in tissue exposed to musks. Efflux transport remained compromised 48 hours after exposure in tissue treated with certain commonly used compounds: musk xylene, musk ketone, Galaxolide, and Celestolide. Only tissue exposed to the compounds Traseolide and Tonalide recovered before 48 hours postexposure.

Epel and Luckenbach believe their study is the first to demonstrate long-term inhibition of the MDR/MXR system by synthetic musks. They warn that musk compounds, and possibly other chemicals as well, might similarly compromise the MDR/MXR system in humans. Evidence for this theory comes from the effectiveness of chemosensitizing drugs, which inhibit efflux transporters much as musk compounds do. Chemosensitizers are now being tested in clinical trials to prevent tumor cells from resisting harsh chemotherapeutics.

Luckenbach and Epel conclude that it is important to determine whether musks and other chemicals cause similar effects in humans. If so, they write, the result could be unanticipated accumulation of toxicants that would confound safety predictions of seemingly harmless chemicals. –**Cynthia Washam**

ETS and Learning

Children's Exposure Linked to Cognitive Effects

Previous studies have linked exposure to environmental tobacco smoke (ETS) with lower performance on tests of intelligence, reasoning ability, and language development, as well as higher risk for grade retention, suggesting that such exposure may cause cognitive deficits. Other adverse effects linked with ETS exposure include middle ear infections, colic, sudden infant death syndrome, and exacerbation of asthma. New findings now show that even extremely low-level exposure to ETS may be neurotoxic, according to a team led by Kimberly Yolton of the University of Cincinnati College of Medicine and Cincinnati Children's Hospital Medical Center [***EHP* 113:98–103**]. In fact, although a dose–response relationship held for all exposures, the greatest deficits proportionally speaking occurred when overall exposure was low, a phenomenon also noted in lead exposure.

The current study is notable for being the largest of its type, including 4,399 children aged 6–16 years who participated in the Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994. It is also the first to rely solely on a biological marker of exposure—serum cotinine—rather than on data from interviews or questionnaires. "Reports of ETS exposure are complicated by poor recall, an inattention to crucial details such as adjustment for the amount of tobacco exposure, the child's proximity to the smoker, room ventilation, and other factors that may compromise the validity of exposure measures," the authors write.

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Furthermore, people tend to underreport smoking, which is increasingly being seen as a socially undesirable behavior.

While participating in NHANES III, children provided blood samples and took the reading and math subtests of the Wide Range Achievement Test–Revised and the block design and digit span subtests of the Wechsler Intelligence Scale for Children–III (the former Wechsler subtest measures visual construction abilities, and the latter, short-term and working memory). For the current analyses, children were excluded from the sample if they had reported using tobacco products within five days of cognitive testing and blood collection, or if their serum cotinine concentration indicated they probably were active smokers.

Yolton and colleagues measured serum cotinine concentrations in the samples and correlated the data with the children's test scores. The results showed that children exposed to ETS had mildly to moderately depressed scores on tests of math, reading, and visuospatial skills as compared to children who lacked such exposures, but no deficits in memory. "The range of decrement in scores is very roughly equivalent to the loss of two to five IQ points at varying levels of exposure," says Yolton. The authors estimate that more than 21.9 million U.S. children are at risk for ETS-related reading deficits.

The study is limited by NHANES III's lack of measures of parental cognitive abilities and quality of home environment. Also, it is unclear whether the serum cotinine levels, taken just once for each subject, represented chronic or acute levels. However, other studies have shown serum cotinine concentrations to be stable in both smokers and nonsmokers. And although more research is needed to confirm these findings, the authors say this analysis adds to the evidence supporting policy to further reduce childhood exposure to ETS. **–David C. Holzman**

Asbestos and Autoimmunity

More Bad News from Libby?

Autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus seem to be the product of a complex and poorly understood interaction between environmental exposures and genetic predisposition. Autoantibodies may be markers of subclinical disease, so epidemiological studies that look for autoantibodies in populations exposed to likely environmental triggers offer one possible way to better understand this gene–environment interaction. To study whether asbestos could be such an environmental trigger, Jean Pfau and colleagues at the University of Montana in Missoula went to the nearby town of Libby, where they found evidence that asbestos exposure may indeed induce autoimmunity [***EHP* 113:25–30**].

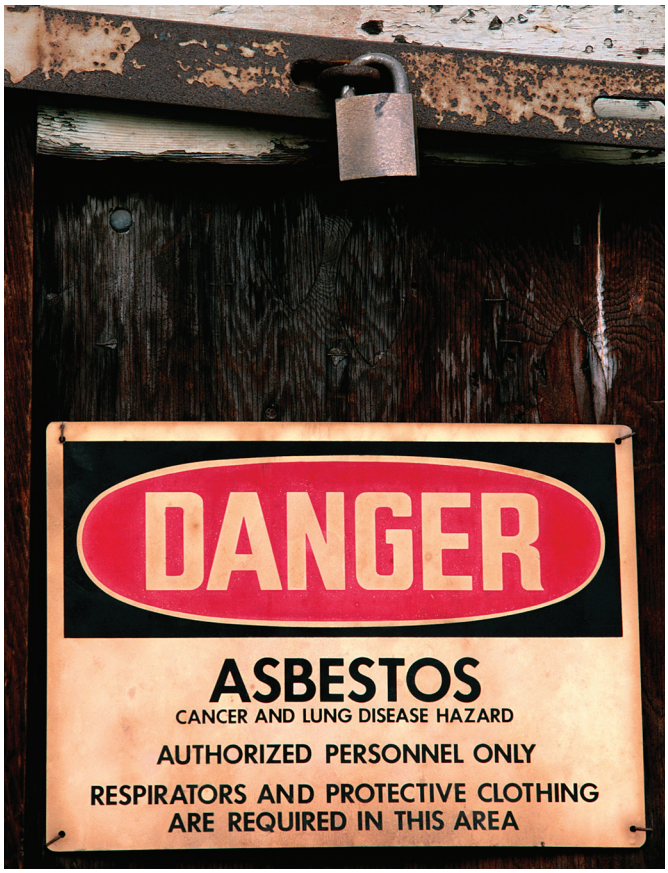
Asbestos exposure in Libby stems from the mining of vermiculite, which is used for insulation and fireproofing. The vermiculite, mined extensively from the 1920s to 1990, was laced with toxic amphibole asbestos, and the mining operations released asbestos into the air and contaminated the mine, processing sites, and many of the buildings and properties in town. Homes also became polluted through the use of vermiculite for insulation and garden fill, according to U.S. Environmental Protection Agency investigations. Virtually the entire town was designated a Superfund National Priorities List site in October 2002.

The decades of occupational and environmental exposure to amphibole asbestos in Libby have been linked to a high incidence of asbestos-related diseases including fibrosis, pleural plaques, and cancer. Anecdotal evidence suggests there may also be a link in Libby between asbestos exposure and autoimmunity. In a 2000–2001 screening of 7,307 Libby area residents by the Agency for Toxic Substances and Disease Registry, 6.7% reported having been diagnosed with an autoimmune disease. Pfau and colleagues note that figure typically should be less than 1%.

In the current study, the researchers sampled the blood of 50 middle-aged men and women from Libby and 50 matched controls from Missoula, where there is no known asbestos exposure. The samples were analyzed for antinuclear antibodies (ANAs) using a commercially available indirect immunofluorescence test. ANAs are a class of autoantibody often found in the blood of people whose immune systems may be predisposed to cause inflammation against their own body tissues. The researchers also looked for correlations between length of asbestos exposure, presence of asbestos-related disease, and ANA levels among the Libby subjects.

They found that ANAs occurred 28.6% more frequently in the Libby samples than in those from Missoula. This finding is consistent with the results of a limited number of other studies of populations exposed to asbestos. In addition, individuals who had been exposed to asbestos for more than five years tended to have higher concentrations of ANAs than those with less exposure. Of the people from Libby, 12 had no lung abnormalities, but the rest had asbestos-related lung problems; those with more severe lung problems also had higher concentrations of autoantibodies.

Based on the correlation between asbestos-related disease and ANA levels, the results suggest that asbestos is an agent of systemic autoimmunity and that autoimmune responses may play a role in the progression of asbestos-related diseases, according to the authors. Pfau and colleagues intend to continue their studies of actual autoimmune diseases among the Libby population. **–Rebecca Renner**



Libby, Libby, Libby. The saga continues for the residents of Libby, Montana, as new research suggests that amphibole asbestos exposure may induce autoimmunity.

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