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 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 synthetic 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 mussk 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 Trasololide 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 to 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.
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