ME and My Shadow
Everyone Exposed to Methyleugenol

Whether you intend to or not, chances are you will consume approximately 6 micrograms of methyleugenol (ME) today, according to a report in this month's issue by Dana B. Barr and colleagues of a study designed to measure ME in human blood serum [EHP 108:323–328]. ME is a compound that occurs naturally in a variety of spices and herbs, including clove oil, nutmeg, allspice, and walnuts. In both its natural and synthetic forms, it is an FDA-approved additive, and it is widely used as a flavoring agent in desserts, condiments, and cigarettes, as an attractant in insecticides, and as a fragrance in perfumes and soaps.

Because of its structural similarity to other flavorants that are known to be carcinogenic such as safrole and estragole, ME has come under suspicion of carcinogenicity. Recent research, some of which was conducted by the National Toxicology Program at the NIEHS, has shown clearly that ME causes cancer in laboratory rodents and suggests that it may be a human carcinogen as well. To accurately evaluate the level of risk associated with a compound, both toxicologic and human exposure data are required.

The investigators—collaborating teams from the National Center for Environmental Health at the Centers for Disease Control and Prevention and from the NIEHS—used extremely sophisticated tools and carefully planned methodologies to arrive at the conclusion that low-level exposure to ME is virtually ubiquitous in the U.S. adult population. They analyzed serum samples from 206 adults who had participated in the Third National Health and Nutrition Examination Survey (NHANES III), conducted between 1988 and 1994. With the sensitivity and accuracy afforded by isotope dilution gas chromatography–high resolution mass spectrometry, they detected ME in 98% of the samples. They then used pertinent questionnaire data from NHANES III to analyze the laboratory results for statistical significance among a wide variety of variables. Unfortunately, none of those demographic and lifestyle variables were statistically significant markers of ME exposure. The fact that there were no clear "smoking guns" correlating to ME exposure led the authors to conclude that it comes from a variety of sources, including air, water, and foods containing naturally occurring ME. They also believe these findings are a good indicator of the prevalence and expected serum concentrations that are likely to be encountered in the U.S. population.

So, like it or not, most adults in America are probably exposed to this suspected carcinogen every day and probably have no way of avoiding the compound altogether. Barr and colleagues also point out that children are likely to have higher concentrations of ME, given their smaller size and the nature of some of the identified commercial sources of ME, such as candy, ice cream, chewing gum, and other sweets. Therefore, they say, ME exposure and risk assessment in children is a crucial area in which to focus future studies.

The authors are cautious to draw no further conclusions beyond what their data warrant—that the appropriate information is now in place to allow more comprehensive assessment of the risk associated with human exposure to ME. However, it seems clear that the end result of that assessment could be the eventual elimination of ME from the commercial marketplace. That would at least remove the possibility of ME exposure from avoidable sources, substantially reducing the overall prevalence of the compound in the population and the level of risk it poses to human health.

Smoking-Induced Leukemia
How Much Is Benzene to Blame?

Benzene, known to cause leukemia, is present in cigarette smoke. However, although smokers are one-and-a-half to two times more likely to develop leukemia than nonsmokers, the degree to which the risk of leukemia can be attributed to the low doses of benzene in cigarette smoke is uncertain. Also uncertain is the validity of linear models of dose–response with respect to benzene and leukemia, particularly at doses lower than those encountered in the workplace (and studied) in the past. Some scientists have been concerned that the linear models—which link an increase in benzene exposure to a corresponding increase in disease—may overestimate the risk of leukemia.

In this month's issue, Jeffrey E. Korte and colleagues from the University of North Carolina at Chapel Hill compared published epidemiological data to their own risk assessment predictions to determine the proportion of all types of leukemia and acute myeloid leukemia (AML) attributable to benzene in cigarette smoke [EHP 108:333–339]. They used linear models and one quadratic model to formulate their predictions, which allowed them to test linear models' ability to accurately predict occupational and nonoccupational risk from benzene exposure. This may be important to the future of setting exposure limits in facilities where benzene is used.

The researchers determined the proportion of smoking-induced leukemia deaths caused by benzene by following a five-step process in which they calculated the lifetime leukemia risk from smoking, determined the potency of benzene in causing leukemia, estimated the benzene dose from smoking, characterized the low-dose risk of leukemia from benzene, and compared the predicted lifetime risk of leukemia from benzene in cigarettes with the observed risk due to smoking. They applied their calculations to light (20 cigarettes daily) and heavy (40 or more cigarettes daily) smokers, with comparisons to those who never smoked.
When applying linear models to these steps, the researchers calculated that benzene is responsible for 8–48% of all smoking-induced leukemia deaths and 12–58% of smoking-induced AML deaths. These results, the researchers say, are reasonable, compared to published data on the numbers of such deaths. The quadratic model yielded far less plausible results, suggesting that less than 1% of smoking-induced leukemia deaths are benzene related. Some studies have found benzene to be most strongly associated with AML, but the chemical's link to other forms of the disease has not been ruled out.

The study not only provides information on the quantitative contribution of benzene to cancer deaths from cigarette smoking, it also helps demonstrate the validity of linear models in extrapolating to low doses of benzene. Benzene is an important industrial chemical used in making nylon, film developer, and solvents. Industrial workers are exposed to benzene concentrations that are 10–100 times greater than those encountered by smokers. For the past decade, the Occupational Safety and Health Administration and the U.S. Environmental Protection Agency have used linear models to set workplace benzene standards and evaluate environmental risks, respectively; both are reviewing that approach. The researchers point out that their results, being plausible predictions, contradict the theoretical argument that linear models may overestimate the low-dose risk from benzene. The results also show that if there is a threshold dose below which benzene does not cause leukemia, it is considerably lower than that received by smokers.

The researchers caution, however, that benzene is not the only leukemia-causing chemical in cigarette smoke. They note that 1,3-butadiene, styrene, N-nitrosodi-n-butylamine, urethane, and radioactive elements are also suspected of being leukemogenic. Benzene, however, appears to cause a substantial proportion of the leukemia deaths induced by smoking. -Harvey Black

**Getting On Our Nerves**

The Long-Term Effects of Chlorpyrifos

In the United States, termite treatments with chlorpyrifos, a widely used organophosphate pesticide, are currently applied about 20 million times per year to houses and lawns, and 82% of U.S. adults have detectable levels of the chlorpyrifos metabolite known as TCP in their urine. Like other organophosphates, chlorpyrifos exhibits moderate acute toxicity, with symptoms that include diarrhea and increased urination, perspiration, tearing of the eyes, and salivation. In addition, it readily inhibits the enzyme plasma cholinesterase at low doses and red-blood-cell cholinesterase at high doses. Results of a study by Kyle Steenland of the National Institute for Occupational Safety and Health and colleagues in this month's issue give some suggestion of delayed neurological effects from exposure to chlorpyrifos, particularly among subjects with a history of poisoning [EHP 108:293–300].

First marketed in 1965, chlorpyrifos came into rapidly increasing use after chlordane was banned for termite applications in 1988. Summarizing reports from poison control centers, the U.S. Environmental Protection Agency has concluded that chlorpyrifos is one of the leading causes of insecticide poisoning in the United States: 4,000–5,000 cases of accidental chlorpyrifos exposure were reported in 1993–1994. However, few epidemiological studies on chlorpyrifos neurotoxicity have been conducted.

Accordingly, the authors conducted a study of 191 termiteicide applicators who had used chlorpyrifos for at least one year between 1987 and 1997 in a 12-county area of North Carolina. The applicators had worked with chlorpyrifos for an average of 2.4 years, with an average of 2.5 years spent working with other pesticides. Steenland and colleagues note that before 1988 some of these applicators had used chlordane, so that compound was included in their analysis.

The test protocol included conducting interviews and taking work histories, as well as administering neurological tests. Among the latter were a vibratortactile sensitivity test and an evaluation of arm/hand tremor, manual dexterity, vision, smell identification, and nerve conduction velocity. The scientists also performed clinical examinations, which involved urine samples and buccal (inner cheek) swabs, as well as a questionnaire to be completed with listings of any neurological symptoms. These included trouble remembering during the previous month, loss of muscle strength, numbness or tingling in toes, and lack of coordination or loss of balance.

The average urinary TCP level for 65 recently exposed applicators was 629.5 micrograms per liter, as compared with 4.5 micrograms per liter for the general U.S. population. Few significant differences between applicators and controls were found in arm/hand tremor, vision, smell, nerve conduction velocity, or visuomotor or neurobehavioral skills. On the other hand, the exposed group did not perform as well as controls in the pegboard test (which involves putting as many pegs into slots in a board as possible within a fixed time period) and some postural sway tests. Exposed subjects also reported significantly more memory and emotional problems, fatigue, and loss of muscle strength. Although the authors did not find evidence of these symptoms during their evaluation, they note that their quantitative tests may not have been adequate to detect them.

In general, Steenland and colleagues found few exposure-related effects for most tests, including the clinical examination. However, the exposed subjects consistently reported more current psychological and physical symptoms than the nonexposed subjects. The differences in symptoms were more marked for former rather than current applicators, suggesting a long-term effect. However, these differences were generally not more apparent for those with longer exposure to chlorpyrifos. Future studies should consider the temporal sequence of exposure and any self-reported symptoms. Although the North Carolina study involved a large, well-defined target population, the authors suggest that it may not be representative of all exposed workers and that caution should be exercised in generalizing its results.

-Julian Josephson

The cancer culprit. New research shows that benzene in cigarettes is responsible for a significant proportion of deaths from leukemia and acute myeloid leukemia.