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"IN THIS ISSUE"

TOXICOLOGY TIDBITS

VETERINARY NOTES

ME and My Shadow
Everyone Is 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 the April issue of *Environmental Health Perspectives* by Dana Barr and colleagues of a study designed to measure ME in human blood serum. 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.

REF: *Environmental Health Perspectives*, 108(4), April 2000.

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 linear models--which link an increase in benzene exposure to a corresponding increase in disease--may overestimate the risk of leukemia.

In the April issue of *Environmental Health Perspectives*, 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. 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. Their new research shows that benzene in cigarettes is responsible for a significant proportion of deaths from leukemia and acute myeloid leukemia.

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.

REF: *Environmental Health Perspectives*, 108(4), April 2000.

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 the April issue of *Environmental Health Perspectives* give some suggestion of delayed neurological effects from exposure to chlorpyrifos, particularly among subjects with a history of poisoning.

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 termiticide 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 vibrotactile 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.

REF: *Environmental Health Perspectives*, 108(4), April 2000.

EPA, makers agrees on ban of chlorpyrifos pesticide

EPA and U.S. manufacturers of chlorpyrifos have reached an agreement that will stop manufacture of the organophosphate pesticide by Dec. 31, 2000, for nearly all residential uses.

The agreement was signed June 5 by all six manufacturers of the product, including the largest, Dow AgroSciences.

It will also phase out uses this year for places where children could be exposed, such as schools, day care centers and hospitals. By the end of 2001, termite control uses in buildings will be phased out as well. By the end of 2004, termiticide use on new construction is expected to be phased out, unless new information on the OP becomes available.

The agreement also calls for significant reductions in the allowable level of residues in several foods. These actions will be taken by the beginning of the next growing season.

The sale of chlorpyrifos products in the United States will be allowed until Dec. 31, 2001. Chlorpyrifos will remain

available for various U.S. nonresidential uses, such as golf courses and ornamental nurseries as well as for all U.S. crop uses. The agreement bans its use on tomatoes.

EPA said the restrictions are the first of "several steps we will probably take." The agency said it opted to reach an agreement with chlorpyrifos' manufacturers to get the fastest results possible.

"We were faced with the choice of moving this way or going through a protracted legal debate, and we felt the best thing to do was to move as quickly as possible to get the level of protection," EPA Administrator Carol Browner said. A complete legal process could have taken up to seven years, she said.

The review on chlorpyrifos began last October. Chlorpyrifos is one of the most widely used organophosphate pesticides in the United States, with more than 20 million pounds applied annually.

For more info see: http://www.epa.gov/oppsrrd1/op/chlorpyrifos/consumerqs.htm

REF: Food Chemical News Daily, 2(239), June 9, 2000.

A Contaminant in Mothers' Milk
The Persistent Threat of PBDEs

A class of compounds known as polybrominated diphenyl ethers (PBDEs)--flame-retardant additives used in high-impact plastics, foams, and textiles--has recently sparked concerns among environmental health scientists. PBDEs are part of a superfamily of related toxic compounds known as persistent organic pollutants (POPs). In the May issue of *Environmental Health Perspectives*, Kim Hooper, a research scientist with the Hazardous Materials Laboratory in the California Environmental Protection Agency, and Thomas McDonald, a staff toxicologist in the agency's Office of Environmental Health Hazard Assessment, discuss PBDEs and explore what prove to be many parallels between some PBDEs and other members of the POPs family. The POPs family also includes compounds such as dioxins, furans, and polychlorinated biphenyls (PCBs), which have been found in humans, animals, and environmental media all over the world.

According to Hooper and McDonald, the weak carbon-bromine bonds of PBDEs render them more susceptible to environmental degradation than the other POPs, most of which contain highly stable carbon-chlorine bonds. Nonetheless, PBDEs are persistent enough to bioaccumulate in fatty tissues as they make their way up the food chain to humans, where they can be passed directly to nursing infants via breast milk.

Of the three major commercial mixtures of PBDEs produced--deca-BDEs, octa-BDEs, and penta-BDEs--it is deca-BDEs (which have the least potential to bioaccumulate) that account for most commercial production. However, in sunlight, deca-BDEs degrade to penta- and tetra-brominated compounds, which bioaccumulate almost as well as PCBs. It is these lesser brominated compounds, particularly the tetra- to hexa-BDEs, that have been identified in Swedish breast milk.

Hooper and McDonald note that Swedish scientists report a doubling of concentrations of PBDEs in human breast milk samples from Sweden every 5 years since the first samples were taken 25 years ago. They warn that large gaps exist in what is known about PBDE toxicity, and suggest that the increasing presence of these compounds in biological tissues could pose a threat to human health. Based on the Swedish data set for PBDEs, Hooper and McDonald suggest that breast-milk monitoring programs are a valuable source of time-trend data that can be used to identify emerging pollutants (such as PBDEs), as well as track population-level changes in the tissue concentrations of known contaminants.

Hooper and McDonald suggest that such programs provide a convenient, noninvasive way to estimate body burdens of POPs in the mother, fetus, and breast-fed child. In addition, breast-milk monitoring programs can be used to identify geographical hot spots for POPs contamination and to identify groups of at-risk individuals that can be followed. Several European countries have operated breast-milk monitoring programs for as long as 30 years. These programs helped to identify PCBs and dioxins as important contaminants in humans. Currently, there are no systematic breast-milk monitoring programs in the United States, where little is known about PBDE concentrations in breast milk or PBDE body burdens.

REF: *Environmental Health Perspectives*, 108(5), May 2000.

Diabetes and Drinking Water
Exploring the Connection to Nitrate

Several recent studies have correlated nitrate in drinking water with the incidence of type 1 diabetes mellitus. Given a sharp increase in type 1 diabetes in the Netherlands, Jan M. S. van Maanen and colleagues attempted to clarify the possible nitrate-diabetes relationship. **Their results show no convincing evidence that nitrate in drinking water at concentrations of 25 milligrams per liter (mg/L) or less is a risk factor for the disease,** although a link at higher concentrations cannot be excluded.

The human body transforms nitrate to nitrite. Nitrite may also react with amines in the digestive juices to form N-nitroso compounds. N-nitroso compounds have been shown to attack pancreatic cells in animals, causing diabetes. Studies in the United Kingdom and United States have linked nitrate in water to type 1 diabetes, while studies in Sweden and Finland have shown a dose-response relationship between type 1 diabetes and foods rich in nitrate, nitrite, and nitrosamines.

In the Netherlands the incidence of type 1 diabetes among children 0-4 years old doubled between 1990 and 1995, and the overall incidence in children aged 0-14 years increased 32% between 1980 and 1995, from 11.1 to 14.6 cases per 100,000. Nitrate concentrations in drinking water are tracked in every postal code in the Netherlands. In their ecological and epidemiological study, the authors sorted by postal code the cases of 1,064 children aged 0-14 years who had been diagnosed with type 1 diabetes between 1993 and 1995. They then compared the incidence of diabetes to nitrate exposure as indicated by the water records.

The study found a correlation between increasing age and the incidence of type 1 diabetes, but no convincing evidence of a link between nitrate exposure and diabetes. Study results do indicate a possible correlation between diabetes risk and nitrate concentrations above 25 mg/L, but the number of children exposed to these concentrations was so small that the results are not statistically significant.

Only 1% of the children in the study were exposed to nitrate concentrations above 25 mg/L, and 18% to concentrations above 10 mg/L, in contrast to a U.K. study where 33% of children were exposed to concentrations above 15 mg/L. The U.K. study linked nitrate concentrations and diabetes at a threshold of 15 mg/L, while the Dutch study did not. The Dutch study was also unable to substantiate a U.S. study that indicated a risk threshold of 10 mg/L.

The authors conclude that more studies are needed to evaluate the possible role of environmental factors in the increase of type 1 diabetes in the Netherlands and to more accurately determine safe concentrations of nitrate in drinking water. According to the authors, the present World Health Organization maximum permissible level of 50 mg/L for nitrate in drinking water may not be adequate to prevent risk of diabetes.

REF: *Environmental Health Perspectives*, 108(5), May 2000.

California State Health Director Advises Consumers to Wash Cantaloupe Before Eating

Sacramento - State Health Director Diana M. Bontá, R.N., Dr. P.H., today reminded consumers to always thoroughly wash the outer skin of a cantaloupe before consuming the fruit, following a multistate outbreak of *Salmonella* poisoning that has sickened at least 39 individuals in California, Oregon, New Mexico, Nevada and Washington.

Consumption of tainted cantaloupe has been linked to at least 19 reported illnesses from an uncommon type of *Salmonella*, known as *Salmonella Poona*, in 13 California counties between April 14 and May 1. The illnesses include two cases each in Contra Costa, Los Angeles, San Diego, San Francisco, Santa Clara, and Solano counties and one each in Alameda, Amador, Butte, Fresno, Kern, San Luis Obispo and Santa Cruz counties. The usual number of cases of *Salmonella Poona* reported in California is fewer than four per month.

In California, all but five of the ill individuals were children 9 years old or under. At least six of the individuals were hospitalized; all have recovered. While most of the individuals ate melons that were purchased whole and cut at home, some ate pre-cut cantaloupes purchased from supermarkets or were served cantaloupes in restaurants. The location where the cantaloupes were grown, and the source of the contamination, are under investigation.

Cantaloupe has been implicated in previous *Salmonella* outbreaks, including a multistate outbreak of more than 400 cases due to *SalmonellaPoona* in 1991 and an outbreak in California of more than 20 cases due to *Salmonella Saphra* in 1997.

Because cantaloupes are grown on the ground, their outer skin can become contaminated in the field by human or animal waste, or during distribution prior to sale. "Cantaloupe meat can become contaminated when it is sliced through contaminated rind without prior scrubbing with soap and hot, running water," Bontá said. **"Consumers should handle cantaloupe as they would handle raw meat: they should wash their hands before and after handling the fruit and refrigerate unused cut portions immediately. In fact, all fruits and vegetables that are not peeled should be washed."**

Salmonella Poona causes the same kind of illnesses as other types of *Salmonella*. Symptoms, which include fever, abdominal cramps and diarrhea, generally occur one to three days after eating contaminated food and last two to five days. While most ill individuals recover without the need for medical attention, the infection can be life threatening to young children, the elderly and those with compromised immune systems.

REF: California Department of Health Services, Office of Public Affairs, Press Releases, #29-00, May 23, 2000.
http://www.dhs.ca.gov

State Offers Tips to Prevent Hantavirus Pulmonary Syndrome

SACRAMENTO - Four cases of hantavirus pulmonary syndrome (HPS) in California in the past three months have

prompted state health officials to remind individuals entering cabins, trailers and other buildings infested with rodents to take precautions to prevent exposure to the virus that causes HPS.

HPS, is a rare, but often fatal, respiratory disease caused by a virus transmitted to humans through the urine, feces and saliva of wild rodents, primarily deer mice. The illness starts with flulike symptoms, including fever, headache, muscle ache and vomiting or diarrhea. The illness may progress rapidly to respiratory failure and sometimes death.

Individuals become infected by breathing dust contaminated with mouse urine or droppings. Cleaning or occupying poorly ventilated spaces with heavy rodent infestations are considered particularly hazardous. Hiking and other outdoor recreational activities are not believed to pose significant risk for HPS infection.

The California cases include:

- A 27-year-old man from Ventura County who has been hospitalized since May 18. Where and how he was infected is under investigation.
- A 20-year-old Yolo County man who was hospitalized in May and has fully recovered. State health officials believe he likely was infected in the Four Corners area of New Mexico, where he cleaned storage facilities in late March. The case also is under investigation.
- A 41-year-old man from Yolo County who died in April. His death is under investigation.
- A 40-year-old woman from Mono County who died in March. State health officials have not determined where she was infected.

To reduce the risk of HPS, public health officials are recommending the following:

- Avoid settings, especially indoors, that are infested with wild rodents.
- Do not live-trap, touch or otherwise handle rodents.
- Do not allow rodents access to food and water in homes; wash dishes and store food in rodent-proof containers.
- Spray dead rodents or areas contaminated with droppings and urine with diluted bleach or other household disinfectant. Wear plastic gloves to place the waste in a plastic bag and discard it in the trash. Wash hands thoroughly after handling rodent waste.
- Prevent infestations by rodent-proofing buildings, removing debris, wood piles and other rodent habitats away from homes and by removing food sources.
- Contact local health officials for recommendations on reducing heavy rodent infestations of buildings.

HPS initially was identified in 1993 following an outbreak in the Four Corners region of the Southwestern United States. Since 1993, 252 HPS cases have been diagnosed in the United States. About 40 percent of the cases have been fatal. Fourteen of the 29 California residents diagnosed with HPS died.

REF: California Department of Health Services, Office of Public Affairs, Press Release #27-00, June 1, 2000.
http://www.dhs.ca.gov

State Health Director Offers Safeguards to Avoid Plague

SACRAMENTO - Visitors to rural picnic spots, campgrounds and wilderness areas should take precautions to protect themselves from plague, which can be carried by squirrels, chipmunks and other wild rodents, State Health Director Diana M. Bontá, R.N., Dr. P.H., advised.

Plague, a highly infectious bacterial disease that primarily affects rodents, is spread by fleas. When an infected

animal becomes sick and dies, the fleas look for a new host. Many warm-blooded animals, including humans, may unwittingly become host to infected fleas and subsequently acquire the disease. People also can be exposed through contact with infected cats, which are highly susceptible to the disease.

"Individuals can greatly reduce their risk of becoming infected with plague by taking simple precautions, including avoiding contact with wild rodents," Bontá said. **"Do not feed rodents in picnic or campground areas and never handle sick or dead rodents. Leave your pets at home when visiting rural areas."**

Other precautions against exposure to plague offered by Bontá:

- Avoid walking, hiking or camping near rodent burrows.
- Wear long pants tucked into boot tops to reduce exposure to fleas. Spray insect repellent on socks and trouser cuffs.
- Individuals living in areas where plague is known to occur should keep wild rodents out of homes, trailers and outbuildings and away from pets.

State and local health officials regularly monitor plague-prone areas. If sick and dying rodents or other evidence of plague are observed and a high risk of transmission to humans is determined, affected areas may be temporarily closed to protect the public and to implement control measures. In California, plague-infected animals are most likely to be found in the foothills, mountains and along the coast. Desert and Central Valley areas are considered low risk for plague.

Since 1970, 37 cases of plague have been confirmed in California. Although no human cases of plague have occurred in the state since 1998, the disease was identified last year in animals in 22 counties.

Early symptoms of plague in humans include high fever, chills, nausea, weakness and swollen glands in the neck, arm pit or groin. Individuals who develop these symptoms should seek immediate medical attention. With prompt diagnosis and proper treatment, the disease is curable in its early stages, but may be fatal if untreated.

REF: California Department of Health Services, Office of Public Affairs, Press Release #30-00, June 2, 2000.
http://www.dhs.ca.gov

As a reminder with Summer approaching.....

Heat-Related Illnesses, Deaths, and Risk Factors --- Cincinnati and Dayton, Ohio, 1999, and United States, 1979--1997

During the summer of 1999, a heat wave* occurred in the midwestern and eastern United States. This period of hot and humid weather persisted from July 12 through August 1, 1999, and caused or contributed to 22 deaths among persons residing in Cincinnati (18 deaths) and Dayton (four deaths). A CDC survey of 24 U.S. metropolitan areas indicated that Ohio recorded some of the highest rates for heat-related deaths during the 1999 heat wave, with Cincinnati reporting 21 per million and Dayton reporting seven per million.

United States

During 1979--1997, the most recent years for which data are available, an annual average of 371 deaths in the United States were attributable to "excessive heat exposure" (median: 249; range: 148 in 1979 to 1700 in 1980). This translates into a mean annual death rate of 1.5 per million and a median annual death rate of one per million. Because of a record heat wave, the heat-related death rate for 1980 was more than three times higher than that for any other year during the 19-year period. The median annual death rate for hyperthermia in persons aged >65 years was three per million. During

1979--1997, 7046 deaths were attributable to excessive heat exposure: 3010 (43%) were "due to weather conditions," 351 (5%) to heat "of manmade origin," and 3683 (52%) "of unspecified origin." Of the 2954 persons whose deaths were caused by weather conditions and for whom age data were available, persons aged >65 years accounted for 1783 (44%) deaths, and persons aged <14 years accounted for 127 (4%) deaths. Except children aged <14 years, the average annual rate of heat-related deaths increased with each age group, particularly for persons aged >65 years. During 1979--1997, among persons of all ages, the annual death rate "due to weather conditions" was two times higher for men (0.8 per million) than for women (0.4 per million), and more than three times higher for blacks (1.6 per million) than for whites (0.5 per million). Arizona and Missouri (four per million) and Arkansas and Kansas (three per million) had the highest annual age-adjusted rates for heat-related deaths "due to weather conditions."

Editorial Note:

Behavioral and environmental precautions are essential to preventing combined elements (e.g., heat and humidity) on the body. Illnesses associated with high environmental temperatures include heatstroke (hyperthermia), heat exhaustion, heat syncope, and heat cramps. Heatstroke is a medical emergency characterized by the rapid onset and increase (within minutes) of the core body temperature to >105 F (>40.6 C), lethargy, disorientation, delirium, and coma. Heatstroke is often fatal despite rapidly lowering the body temperature (e.g., ice baths), because frequently irreparable neurologic damage has occurred. Heat exhaustion is characterized by dizziness, weakness, or fatigue often following several days of sustained exposure to hot temperatures, and results from dehydration or electrolyte imbalance; treatment includes replacing fluids and electrolytes and may require hospitalization. Physical exertion during hot weather increases the likelihood of heat syncope and heat cramps caused by peripheral vasodilation. Persons who lose consciousness because of heat syncope should be placed in a recumbent position with feet elevated and given fluid and electrolyte replacement. For heat cramps, physical exertion should be discontinued and fluids and electrolytes replaced.

All persons are at risk for hyperthermia when exposed to a sustained period of excessive heat; however, factors that increase the risk for hyperthermia and heat-related death include age (e.g., the elderly), chronic health conditions (e.g., cardiovascular disease or respiratory diseases), mental illness (e.g., schizophrenia), social circumstances (e.g., living alone), and other conditions that might interfere with the ability to care for oneself. Other risk factors are alcohol consumption, which may cause dehydration, previous heatstroke, physical exertion in exceptionally hot environments, the use of medications that interfere with the body's heat regulatory system, such as neuroleptics (e.g., antipsychotics and major tranquilizers), and medications with anticholinergic effects (e.g., tricyclic antidepressants, antihistamines, some antiparkinsonian agents, and some over-the-counter sleep medication). Persons working in hot indoor or outdoor environments should take 10-14 days to acclimate to high temperatures. Although adequate salt intake is important, salt tablets are not recommended and can be hazardous to some persons. Although the use of fans may increase comfort at temperatures <90 F (<32.2 C), fans are not protective against heatstroke when temperatures reach >90 F (>32.2 C) and humidity exceeds 35%.

Measures for preventing heat-related illness and death during a heat wave include spending time in air conditioned environments, increasing nonalcoholic fluid intake, exercising only during cooler parts of the day, and taking cool baths. Elderly persons should be encouraged to take advantage of air conditioned environments (e.g., shopping malls, senior centers, and public libraries), even for part of the day. Public health information about exceptionally high temperatures should be directed toward persons aged >65 years and <5 years. Parents should be educated about the heat sensitivity of children aged <5 years, and should never leave them unattended, especially in motor vehicles. When a heat wave is predicted, friends, relatives, neighbors, and caretakers should check frequently on elderly, disabled, mentally ill, chronically ill, and home-bound persons, and during periods of high temperatures, prevention messages should be disseminated to the public as early and often as possible.

*Three or more consecutive days of air temperatures >90 F (>32.2 C).

REF: *Morbidity and Mortality Weekly Report*, 49(21), June 02, 2000.

Toxicology Tidbits

Homobatrachotoxin Poisoning from Pitohui

Pitohui kirhocephalus

The only recognized poisonous bird in the world is from the genus pitohui - pronounced "pit-oo-ey" - native to Papua, New Guinea. The pitohui's poison, similar to the toxin found in poison arrow frogs, is concentrated in its skin and feathers. Scientists think the poison is probably a defense against predators like hawks and snakes. The pitohuis are known as the "rubbish bird" to natives due to the taste of the birds skin. These birds were discovered by John P. Dumbacher and reported in the early 1990's. The pitohui are brightly colored birds (orange and black); both male and female share the showy plumage. The color scheme of the pitohui shares the same aposematic (warning) colors as the poison arrow frogs. The bright colors may also be for mating, but both male and female pitohui are colorful.

The toxin may be a chemical defense against predation. The toxin concentration varies depending on the species. Dumbacher noted numbness and burning in his mouth after he licked his hands following handling a pitohui. Aside from tasting bad, humans who have consumed small portions of the skin have not suffered severe effects.

The toxic principle of the pitohui is homobatrachotoxin, a steroidal alkaloid. Homobatrachotoxin is similar to batrachotoxin, the toxic principle of the Central American poison arrow frog, *Phyllobates aurotaenia*. Batrachotoxin and homobatrachotoxin act on the voltage-sensitive sodium channels of excitable tissues: nervous tissue, cardiac and skeletal muscle; and the neuromuscular junction. Voltage-sensitive sodium channel binding of batrachotoxin and homobatrachotoxin leads to depolarization of cell membranes due to increased sodium influx. These toxins bind to the sodium channel at a site different than tetradotoxin (puffer fish) and saxitoxin.

REF: *Veterinary and Human Toxicology*, 41(2), April 1999.

Methyl Bromide Field Fumigations

The California Department of Pesticide Regulation has posted proposed changes in the regulations pertaining to methyl bromide field fumigations on its Web site at http://www.cdpr.ca.gov/docs/legbills/rulepkgs.htm.

REF: California Department of Pesticide Regulation Advisory, June 5, 2000.

Two contributors challenge conclusion of NEJM study on antibiotic resistance

Two contributors to a study on antibiotic resistance are calling "unwarranted" and "without foundation" the study's conclusion that antibiotic-resistant strains of *Salmonella* evolve primarily in livestock. The study, "Ceftriaxone-Resistant *Salmonella* Infection Acquired by a Child from Cattle," was based on a Nebraska boy who contracted a *Salmonella* infection resistant to ceftriaxone. Its findings were reported in the April 27 issue of the *New England Journal of Medicine.*

"It is impossible from the data obtained and presented to determine the source of either the human or cattle infection," investigators Dale Grotelueschen and Jeffrey Gray of the University of Nebraska's Department of Veterinary and Biomedical Sciences said in a letter to the journal last week. "No investigation was performed on any potential source for either the child or the cattle. The statement indicating this is evidence that antibiotic resistant strains of *Salmonella* evolve primarily in livestock is without foundation and seems out of place. The manuscript presents no evidence of antimicrobial use in any of the cattle herds. ... More importantly, the case-study provided no data regarding where the antimicrobial resistance may have arisen."

Paul Fey of the University of Nebraska Medical School confirmed when the study was published that, as lead researcher, he was unable to determine whether antibiotics were used in the cattle studied. He also said that the evidence did not directly link the child's infection to cattle.

REF: *Food Chemical News Daily*, 2(235), June 5, 2000.

Scientific advances offer new findings for assessing birth defects caused by toxic chemicals, says report

The scientific analysis of chemicals for their potential to cause birth defects should rely on new findings in developmental biology and genetics, according to a report, "Scientific Frontiers in Developmental Toxicology and Risk Assessment" that will be made publicly available next month by the National Research Council of the National Academies.

The report notes that major developmental defects such as neural tube and heart deformities occur in approximately 120,000 of the four million infants born annually in the United States. Exposure to manufactured and natural toxic chemicals cause about three percent of all developmental defects, the report says, while at least 25% of them might be the result of a combination of genetic and environmental factors.

"Many manufactured chemicals, as well as chemicals that occur in nature, have not been adequately evaluated for developmental toxicity," said Elaine Faustman, chair of the committee that wrote the report. "Our report provides a blueprint for using new findings about the dynamic processes involved in normal development to further our understanding of how human development may be affected by potentially toxic chemicals."

REF: *Food Chemical News Daily*, 2(235), June 5, 2000.

Vitamins C, E do not prevent oxidation in smokers, study finds

A recent study on the effects of vitamin E and C supplementation on two biochemical measures of "oxidative stress" used as predictors of heart disease has shown mixed results. Using one measure (low density lipoprotein oxidizability) vitamin E supplementation alone, and the combination of vitamin E and C affected the oxidation kinetics, but vitamin C alone did not. Using another measure (neutrophil superoxide anion production) neither of the vitamins alone nor in combination had an effect. The authors state that the neutrophil measure is more physiologically relevant, and that their findings cast doubt on the ability of these antioxidants to reduce "oxidative stress" in young smokers.

"Therefore, smoking cessation remains the only means by which young smokers can prevent premature coronary heart disease."

Fuller said the study was particularly important because the newest Recommended Daily Allowance (RDA) for vitamin C is 90 mg/day for men and 70 mg/day for women, with an additional 35 mg daily for smokers. Her new research calls that recommendation of the National Academies into question.

REF: *Food Chemical News Daily*, 2(235), June 5, 2000.

FDA Concerned About Botanical Products, Including Dietary Supplements Containing Aristolochic Acid

The use of products containing aristolochic acid, including botanical products marketed as traditional medicines, has been associated with nephropathy. FDA is concerned about botanical-containing products known or suspected of containing aristolochic acid and will be pursuing appropriate regulatory actions regarding these products. Some of these botanicals include: *Aristolochia* spp., *Asarum* spp., *Bragantia* spp., *Stephania* spp., *Clematis* spp., *Akebia* spp.,

Cocculus spp., *Diploclisia* spp., *Menispernum* spp., *Sinomenium* spp., Mu tong, Fang ji, Guang fang ji, Fang chi, Kan-Mokutsu (Japanese), and Mokutsu (Japanese). For a more complete list of botanicals see: http://vm.cfsan.fda.gov/~dms/ds-bot2.html

The term *Aristolochia* species (spp.) refers to several botanical species most often found in traditional Chinese medicines. Cases of nephropathy and end-stage renal disease associated with their use have been reported in the medical literature; in some instances, dialysis or transplant was necessary. Moreover, because of the similarity of Chinese names for several herbs and because of the Chinese tradition of interchangeability of similarly named herbs, there is a great propensity for many innocuous herbs to be inadvertently substituted with *Aristolochia* spp. not only in traditional medicines but also in dietary supplements.

The FDA has not received any adverse event reports to date of a similar nature. However, with the increasing use of dietary supplements and traditional forms of botanical remedies, a thorough history of use of dietary supplements as well as traditional medicines, including Chinese and Ayurvedic (Indian), should be routinely sought as part of the medical history, particularly in cases of unexplained interstitial renal fibrosis.

Background: In July 1999, two new cases of nephropathy, associated with the use of Chinese botanical preparations, were reported from the United Kingdom. Both of these patients had ingested botanical preparations, for the treatment of "eczema." These botanical preparations were shown to contain aristolochic acid, a known nephrotoxin which can be found in *Aristolochia* spp., *Bragantia* spp. or *Asarum* spp. Biopsy samples from both patients showed extensive loss of cortical tubules with interstitial fibrosis, features typical of a nephrophathy sometimes referred to as “Chinese herbs nephropathy.” One patient has already undergone renal transplant and the other is on hemodialysis while awaiting transplant.

Previously, a series of end-stage renal disease cases had been reported from Belgium in which the affected patients had ingested a "slimming pill” containing botanical ingredients, that had been prescribed by the same clinic as part of a weight loss regimen. It was hypothesized that the botanical ingredient *Stephania tetrandra*, a botanical not known to contain aristolochic acid, had been inadvertently substituted with the botanical *Aristolochia fangchi*, which contains aristolochic acid as a normal constituent. This was thought to have occurred because of the similarity of the Chinese names for these 2 botanicals. Aristolochic acid, either solely or in conjunction with other medications/botanicals administered during the weight loss regimen, was suspected to have caused the nephropathy observed in these patients. To date, more than 100 patients in Belgium have been identified with this unusual type of nephropathy following the ingestion of this botanical preparation from the same clinic from 1990 to 1992. Of these, at least 70 patients have required renal transplant or dialysis.

Of further concern is the carcinogenic potential of aristolochic acid. Rodents administered aristolochic acid developed lymphoma, as well as cancers in the kidney, bladder, stomach, and lung. Moreover, urothelial carcinomas have been reported in some of the patients who had been diagnosed as having “Chinese herbs nephropathy.” Based on these studies, patients taking aristolochic acid may be at increased risk of developing malignancies.

REF: FDA Center for Food Safety and Applied Nutrition Press Release, May 31, 2000.

Chinese Herb Leads to Kidney Failure, Cancer Drugs With Similar Names Confused in Weight-Loss Formula

A mislabeled Chinese herb imported into Belgium has caused kidney failure and cancers in people who took a

prescription weight-loss mixture containing the herb, a new study reports.

All of the patients were treated at a single diet clinic, and all cases occurred after the clinic added Chinese herbs to its diet formula, according to the study published in The New England Journal of Medicine. The dangerous herb, *Aristolochia fangchi*, is available for purchase in the U.S., one expert writes in an editorial accompanying the study.

Study author Joelle L. Nortier, MD, PhD, states that the diet capsules were meant to include the herb Stephania tetrandra (called fangji in Chinese) but instead were made with *Aristolochia fangchi* (fangchi in Chinese). The mistake is thought to be due to the similarity of the two Chinese drug names.

"According to the Belgian Ministry of Health, about 10,000 subjects are thought to have ingested Chinese herbs in our country from 1990 to 1992. At least 70 individuals reached end-stage [kidney] failure requiring dialysis and/or transplantation," Nortier tells WebMD. Nortier studied tissue samples from 39 of these patients and found that 18 also had some form of kidney or bladder cancer. She is in the nephrology department at Erasmus Hospital in Brussels.

The mistake appears to have originated with a wholesaler who imported the so-called *Stephania tetrandra* (actually *Aristolochia fangchi*) from Hong Kong into Belgium. "The roots were reduced to powder before being sent to our country in packs. Belgian import agencies received these products vacuum-packed and processed them into small boxes of 6 to 12 grams for use by pharmacists," Nortier says.

Following medical prescriptions, the pharmacists combined the powdered herbs with three Western drugs into capsules for use by patients of the weight-loss clinic. The three Western drugs included two appetite suppressants and a diuretic.

When the cases of kidney failure began to appear, Belgian health authorities traced the capsules back to the pharmacies, analyzed the drugs and herbs the pharmacists had used, and identified the "substitute" herb. This was possible because in Belgium, unlike the U.S., herbal preparations are available only by prescription.

Kidney failure began anywhere from three months to seven years after the patients had stopped taking the weight-loss capsules. By the time of Nortier's report, 43 of the 105 patients studied had complete kidney failure, requiring transplant or dialysis.

In each of the 39 samples of kidney tissue she studied, Nortier found bits of DNA from the *Aristolochia fangchi* herb attached to the patients' chromosomes. Researchers think the DNA bits may turn on cancer genes or turn off genes that protect against cancer -- or both. The DNA bits were still in place over seven years after the patients stopped taking the weight-loss capsules.

Adriane Fugh-Berman, MD, an expert in herbal medicine, says attempts to include Chinese traditional remedies in diet drugs ignore the fact that there are no herbs traditionally used for weight loss in Chinese medicine. "Losing weight has not been a traditional goal in China," says Berman, a consultant with federal agencies on herbs and dietary supplements.

"The herb-drug combination used by these patients is clearly toxic, but this raises a larger issue," Fugh-Berman says. "There are no completely safe, painless weight-loss drugs or herbs. Any herb or drug that speeds up your metabolism can be dangerous. The only safe approach is diet and exercise."

REF: WebMD Medical News, June 7, 2000.

EPA Grants Two-Year Registration to New Biochemical Pesticide

A new biochemical pesticide which sets off natural defenses in plants has been given the green light by EPA as an alternative to conventional, synthetic pesticides such as methyl bromide. EPA, April 19, granted Eden Biosciences Corp. of Bothell, WA, a conditional, two-year registration for the Harpin protein (Messenger®), which may be used to control a wide variety of fungal, bacterial, and viral pathogens on field crops, trees, turf and ornamentals.

Harpin acts by eliciting a natural defense mechanism in the host plant, called systematic acquired resistance, which makes the plant resistant to pathogens. The new pesticide is applied at low rates and degrades rapidly in the field, which should result in residue-free produce. Since it does not act directly on pests, it is not expected to promote resistance in pest populations. The biopesticide showed "virtually no toxic effects" in tests for human and ecological effects prior to approval.

The conditional registration was due in part to significant public interest to get this product on the market. Information regarding the registration can be found on EPA's website at www.epa.gov/pesticides/news/news-harpin.htm.

REF: *Food Chemical News*, 42(15), May 29, 2000.

NIH Says Research Concludes All Consumers Should Reduce Their Sodium Intake

The National Institutes of Health (NIH) says a new study shows that all consumers -- not just those with high blood pressure -- should reduce their sodium intake.

NIH stated that by reducing dietary sodium intake to 1,500 milligrams a day, all Americans -- and especially those at high risk for hypertension -- can decrease their chance of developing high blood pressure as they age. The current guideline for daily salt intake is 2,400 mg/day.

However, The Salt Institute said it "would be a gross error to conclude on the basis of what has been reported that science supports a general intervention to reduce dietary sodium. It does not." The group also said it is unclear whether reducing blood pressure by restricting sodium intake improves health. The institute also stated that previous research on hypertension shows a short-term lowering of blood pressure from restricting salt intake, but that the reduction disappears over time. It said that the NIH study did not last long enough to take this into account.

For more information on this study: http://www.nih.gov/news/pr/may2000/nhlbi-17.htm.

REF: *Food Chemical News*, 42(15), May 29, 2000.

Consumer Confidence in Food Safety High, But Falling, FMI Survey Finds

Almost 75% of US consumers are confident that the food they buy at the supermarket is safe, but that number has been steadily declining over the last five years, according to a recent survey by the Food Marketing Institute (FMI). In January 1996 that number was up to 84%, the next year 83%, followed by 81% and last year 79%. The FMI report does not draw any conclusions about the possible cause for the decline. However, it does point out that in this year's survey, some shoppers in the East expressed less confidence, which could be related to a publicized *E. coli* outbreak in New York a few months before the survey.

This year's survey also showed that consumers are less concerned about the nutritional value of their food and care more about taste. This year, 46% of people say they are very concerned about nutrition, whereas in 1996 that number was 58% and has dropped slightly each year. However, in terms of nutritional content consumers do care about, the answers remain about the same as in recent years, with fat content at the top of the list, followed by cholesterol levels and salt content.

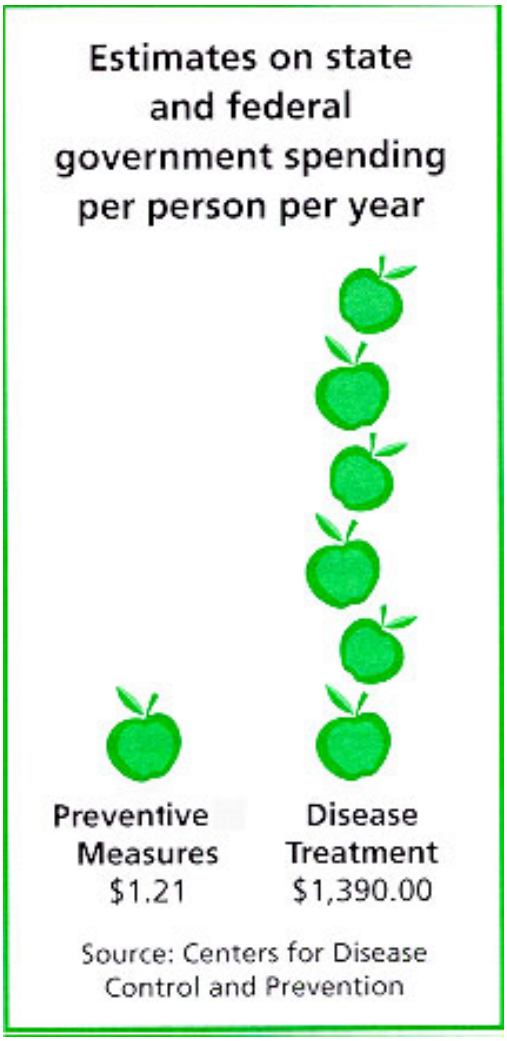
REF: *Food Chemical News*, 42(15), May 29, 2000.

Long-Term Effects of Dioxin

The long-term effects of dioxin may include a reduction in the number of male births, according to research published in a recent issue of *The Lancet.* The results are based on research done in Italy about 25 years after an industrial explosion in the northern part of that country. Earlier studies have shown that high serum concentrations of dioxin in parents are linked to a relative increase in the number of female births. Desio Hospital investigators continued to look at the gender ratio in offspring as well as considering whether the parents' age at exposure is a factor. After looking at samples from 239 men and 296 women, the investigators concluded that exposure of men to dioxin is linked to a lower number of male births and that this will continue for years after exposure. The concentration observed in the study subjects was about 20 times the estimated average concentration found in humans in industrialized countries.

REF: *Food Chemical News*, 42(15), May 29, 2000.

Spending differences between preventive measures and disease treatment



REF: *5A Day News*, 2(1), Spring 2000.

VETERINARY NOTES.....

Fumonisin Levels in Human Foods and Animal Feeds: Draft Guidance Draft released for comment on June 6, 2000

The purpose of this draft guidance is to identify recommended maximum fumonisin levels that FDA considers adequate to protect human and animal health and that are achievable in human foods and animal feeds with the use of good agricultural and good manufacturing practices. FDA considers this guidance to be a prudent public health measure during the development of a better understanding of the human health risk associated with fumonisins and the development of a long-term risk management policy and program by the agency for the control of fumonisins in human foods and animal feeds.

The recommended maximum levels for fumonisins in human foods and in animal feeds that FDA considers

achievable with the use of good agricultural and good manufacturing practices are presented below. FDA believes that controlling fumonisins to these recommended levels can reduce exposure to fumonisins that may be found in corn products intended for human and animal consumption.

HUMAN FOODS

Product	**Total Fumonisins (FB_1+FB_2+FB_3)**
Degermed dry milled corn products (e.g., flaking grits, corn grits, corn meal, corn flour with fat content of < 2.25 %, dry weight basis)	2 parts per million (ppm)
Whole or partially degermed dry milled corn products (e.g., flaking grits, corn grits, corn meal, corn flour with fat content of ≥ 2.25 %, dry weight basis)	4 ppm
Dry milled corn bran	4 ppm
Cleaned corn intended for masa production	4 ppm
Cleaned corn intended for popcorn	3 ppm

ANIMAL FEEDS

Corn and corn by-products intended for:	**Total Fumonisins (FB_1+FB_2+FB_3)**
Equids and rabbits	5 ppm (no more than 20% of diet)**
Swine and catfish	20 ppm (no more than 50% of diet)**
Breeding ruminants, breeding poultry and breeding mink*	30 ppm (no more than 50% of diet)**
Ruminants ≥3 months old raised for slaughter and mink being raised for pelt production	60 ppm (no more than 50% of diet)**
Poultry being raised for slaughter	100 ppm (no more than 50% of diet)**
All other species or classes of livestock and pet animals	10 ppm (no more than 50% of diet)**

*Includes lactating dairy cattle and hens laying eggs for human consumption

**Dry weight basis

For more info see: http://vm.cfsan.fda.gov/~dms/fumongui.html

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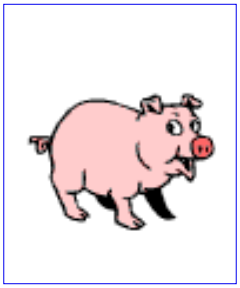

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