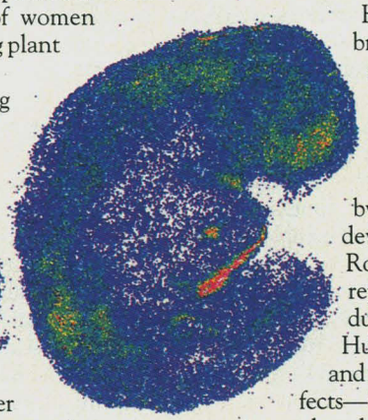
Trail of Toxins Leads Through Conference Rooms in Dallas

More than 4000 toxicologists met in Dallas last month for the annual meeting of the Society of Toxicology. While there was no lone star attraction, the gathering featured presentations on everything from the effects of environmental arsenic on pregnant women in Bulgaria to current approaches to regulating fat substitutes, as well as a study linking environmental tobacco smoke and arteriosclerosis in chickens (*Science*, 1 April, p. 30).

Arsenic and the Unborn

Assassins have long sworn by arsenic-laced red wine, a potable poison that some historians say may have felled Pope Alexander VI during the Middle Ages. Arsenic's latest victims, however, didn't get the poison in wine: They're unborn children of women living near a copper-smelting plant in Bulgaria.

Toxicologists are paying increasing attention to women's exposure to metals—particularly arsenic, lead, and mercury, all of which have been shown to interfere with fetal development in animals. That's why a Bulgarian team led by developmental toxicologist Sonia Tabacova of the National Center of Hygiene, Ecology, and Nutrition in Sofia studied some 15,000 women living near a copper-smelting plant in the Srednogorie region of central Bulgaria. The Bulgarian study is "groundbreaking" because of the large size of the study population and the women's high levels of arsenic exposure, says reproductive toxicologist Judy Zelikoff of New York University, who organized the symposium at which the results were presented. "They build a strong case for a link between arsenic and certain birth defects."



Poisoned fetus. Colored regions show arsenic deposition in a mouse embryo.

SID HUNTER

It didn't take long for Tabacova's team to ascertain that something was wrong with the pregnancies near Srednogorie: Fatal defects occurred at a rate of 3.6 per 1,000 births, almost three times the national rate. After concluding there was an environmental hazard, Tabacova began collecting placentas from Srednogorie and from a control area; arsenic levels were three times higher in Srednogorie placentas. "That gave us a hunch that the congenital malformation rate was due to arsenic," Tabacova says.

That was a good lead, but Tabacova wanted animal data to support her theory that it was arsenic, rather than cadmium or other metal contaminants in the copper ore, that was responsible for the birth defects. She enlisted the aid of Sid Hunter, a developmental biologist at the Environmental Protection Agency, with whom she had worked at the National Institute of Environmental Health Sciences when she was a visiting scientist.

Hunter exposed mouse embryos to arsenic in vitro and found that the mouse fetuses developed malformations. This result was expected, because other groups—including one led by University of Alabama developmental toxicologist Ronald Hood—had already reported on arsenic's reproductive effects in mice. But Hunter also found some new and startling results: Specific defects—including small forebrains and underdeveloped ear pits—were strikingly similar to those prevalent among the Srednogorie fetuses.

Just implicating arsenic wasn't enough, however. Hunter and Tabacova wanted to know the mechanisms that allow the chemical to do its dirty work. Tabacova found high levels of lipid peroxides and low levels of reduced glutathione in the placentas, which suggested that arsenic was acting as an oxidant. To test this possibility, Hunter treated mouse embryos with arsenic and with antioxidants such as vitamin E and superoxide dismutase. He found that the two species of arsenic appear to act on mouse embryos by different mechanisms. (Arsenic reacts with other elements in two valence states, arsenic III and arsenic V.) In the presence of arsenic III, the antioxidants greatly reduced birth defects; in the presence of arsenic V, they had little effect. Tabacova plans to follow up by looking at the species of arsenic deposited in Bulgarian placentas.

Substitute Fat, Not Safety

If you're one of those people who, like the Duchess of Windsor, can never be too rich or too thin, food scientists may be able to help you—at least on the second count. Substances are now being developed to replace fat in processed foods so that people can eat heartily while ingesting fewer calories. But as luscious as they sound, the fat substitutes, known as macronutrient additives (MAs), haven't gone down easily at the Food and Drug Administration (FDA). Indeed, they're causing heartburn: The campaign to approve MAs is forcing the agency to develop a new standard to certify the safety of fat substitutes.

Some 100 fat substitutes are now in development, ranging from proteins modified to taste like fat to sugar polymers that pass through the body undigested. However, "given FDA's current approaches, it's unlikely that any but the safest MA will be approved without great controversy," says Walter Glinsmann of Georgetown's Center for Food and Nutrition Policy.

The problem is that current rules on food additives are not practical for MAs, which could comprise up to 20% of the calories in a person's diet. To gain FDA approval under current standards, additives must be shown to cause no harmful effects in animals at 100 times the anticipated dose in people. The massive dose of MAs required to prove them safe would therefore affect animals no matter how benign they are, says George Pauli, director of FDA's division of product policy in the Center for Food Safety and Applied Nutrition (CFSAN).

As a result, FDA has hurried to find new approaches to measuring safety. As they search, they are taking into account two concerns that were discussed at a symposium here. The first is that undigested MAs could rob the body of the fat-soluble vitamins A, D, E, and K. Hence companies that sell MAs may have to add those vitamins to their products, according to David Hattan, FDA's acting director of health effects evaluation at CFSAN. The second concern is that more information is needed on the effect of undigestible MAs on the absorption of other foods.

CFSAN is considering fat substitutes as part of a broader review of a 35-year-old toxicology guidance document on food additives, commonly known as the Redbook. While criteria for approval of MAs are still being worked out, Pauli says, "at this stage we're going to evaluate compounds on a case-by-case basis." Some researchers think the extra hassle of evaluating these products will be effort well spent—since Americans currently eat too much fat and don't show any signs of stopping. "It's important to consider the risk of not substituting for fat," says Sanford Miller, dean of the graduate school of biomedical sciences at the University of Texas Health Science Center. "We don't want to lose an opportunity to improve health in this country," he says.

–Richard Stone