Folate supplements needed but allergenic

To ensure that women of childbearing age receive enough folate—a B vitamin required to head off potentially debilitating fetal defects—the Food and Drug Administration has announced that it will require U.S. food manufacturers to fortify most grain-based products with a synthetic form of the vitamin. That decision preceded by 1 week publication of a British study that concludes such dietary supplementation may be the only way to guarantee that women receive enough folate.

However, the synthetic folate, or folic acid, used to fortify foods and vitamin supplements can provoke an allergic response, notes Mark S. Dykewicz of the St. Louis (Mo.) University School of Medicine. He reported the new finding last week in New Orleans at an American Academy of Allergy, Asthma, and Immunology meeting. Although FDA's new rule "has been made for excellent reasons," he says, the change will make more people likely to develop a life-threatening allergic reaction.

A host of studies has shown that babies born to women who don't consume enough folate early in pregnancy face an increased risk of neural tube defects (SN: 1/28/95, p. 53). Each year in the United States alone, some 2,500 babies are born with these defects.

Because more than half of all pregnancies are unplanned, and because neural tube defects occur before most women realize they have become pregnant, FDA decided to require manufacturers to add folic acid to enriched breads, flour, corn meal, pasta, rice, and other grain-based foods in quantities sufficient to provide most women with the necessary 0.4 milligram of the vitamin daily. That's more than twice the current recommended daily allowance, which most U.S. residents consume.

Until the rule takes effect—slated for Jan. 1, 1998—the Public Health Service recommends that women obtain the vitamin through dietary supplements or foods naturally rich in folate, especially dark green, leafy vegetables, citrus fruits and juices, and lentils.

Women, however, may find it all but impossible to derive what they need from such natural sources, according to a recent, 3-month-long study. Geraldine J. Cuskelly at the University of Ulster in Northern Ireland and her coworkers randomly assigned women to take daily supplements containing 0.4 mg of folic acid, to eat foods fortified with the same amount of the synthetic vitamin, or to eat foods naturally containing 0.4 mg more folate than the average diet.

Among the 41 women who completed the trial, concentrations of the vitamin in the blood rose only in those who consumed the folic acid, Cuskelly's team reports in the March 9 LANCET. The most likely explanation, these researchers say, "lies in the known increased bioavailability of folic acid over [natural] food folates."

The subtle chemical differences between food-derived folate and synthetic folic acid may also explain why a woman who could eat folate-rich foods without problems nearly died from an injection of folic acid, says Dykewicz. Though anecdotal reports of such allergies had surfaced now and again, many people discounted them, he says, in part because the vitamin molecule was smaller than those that the immune system typically recognizes.

Dykewicz figured that to trigger an allergic reaction, this chemical must first pump up its size by binding to proteins in the body. As a test, he linked folic acid to a protein in blood and then confirmed that this pairing was recognized by antibodies from the allergic woman.

This finding represents the first proof of antibodies to a vitamin, he says.

While calling the St. Louis study excellent proof of an allergy to folic acid, Timothy J. Sullivan of the Emory University School of Medicine in Atlanta questions the findings' relevance to food fortification. He notes that the allergic woman Dykewicz studied received an "astronomical" dose of folic acid as part of cancer therapy and thus may represent an anomaly unsuited for gauging the risks of vitamin quantities in fortified foods.

—J. Raloff

How the queen bee makes her pheromone

Much of a queen honeybee's power over other hive members comes from a mix of chemicals called a primer pheromone. Scientists have identified the compounds in the pheromone, and beekeepers use a synthetic version in their hives.

Now, researchers have figured out how the queen manufactures this potent scent, report Erika Plettner of Simon Fraser University in Burnaby, British Columbia, and her colleagues in the March 29 SCIENCE.

Primer pheromone in the air prevents workers from rearing a new sovereign and encourages them to care for the queen's brood. This perfume has more complex and longer lasting effects than other pheromones, such as compounds that simply attract potential mates (SN: 3/9/96, p. 159). Primer pheromones have been found in only one other animal, a goldfish.

Describing the natural synthesis of the bee's pheromone is "a significant development because of the pivotal role this substance plays in the regulation of social life," observes Gene E. Robinson of the Hebrew University in Jerusalem in a comment accompanying the report.

The three steps involved in making the royal pheromone resemble closely the processes by which workers produce a substance they feed to larvae, reports Plettner's group.

Both processes begin with the stearic acid that worker and queen honeybees (*Apis mellifera*) produce in their mandibular glands. Enzymes cause the acid to add a hydroxyl group—an oxygen atom and a hydrogen atom—to its chain of 18 carbon atoms. This hydroxyl group attaches at or near the end of the carbon chain.

Other enzymes then clip most hydroxylated chains down to 10 carbon atoms. In queens, enzymes cut some chains to only eight carbon atoms.

In worker bees, the enzymes target carbon chains that have a hydroxyl group at the end. In the queen, enzymes clip those with the hydroxyl near the end.

Both groups then add an oxygen to their shortened hydroxylated chains. The workers end up with a compound to feed to the larvae, and the queen has her pheromone.

The team tracked the conversion of the acids by adding heavier than normal hydrogen atoms to stearic acid and putting this labeled substance into the bees' mandibular glands. Plettner and her colleagues then used a mass spectrometer to map the activities of the molecules.

"This is the first time that anyone has worked out the biosynthesis of a primer pheromone," Plettner asserts. The difference between the queen's pheromone and the product of the workers' mandibular acids is remarkably subtle, she says. The systems overlap in intriguing ways, agrees Robinson. *—T. Adler*

Kenneth Lorenzen

Attracted by the pheromone the queen releases, worker honeybees touch and lick her.