

Bendectin linked to birth defects

Research linking Bendectin, the government-approved drug to combat nausea and vomiting in pregnant women, to birth defects has prompted U.S. Food and Drug Administration officials and a public health group to call for protective action.

The FDA met with the manufacturing firm Merrell Dow Pharmaceuticals last week to update Bendectin's label information. According to an FDA spokesman, the new label, expected this month, will warn physicians that preliminary studies connect Bendectin to a sometimes fatal birth defect called diaphragmatic hernia and to fetal heart defects.

Also last week, the Washington-based Public Citizen Health Research Group, which wants Bendectin banned, petitioned Health and Human Services Secretary Richard S. Schweiker to revoke the drug's marketing approval. HRG spokesman Cary Lasheen said, "We feel there is enough evidence for the drug to be taken off the market. Any increased risk of a birth defect is unacceptable."

Among the evidence implicating Bendectin is a 1981 study done for the West German Health Ministry by Reimar Roll in which pregnant rats were fed doxylamine succinate, the active chemical in Bendectin. Six of 100 offspring were born with a hole in the wall or diaphragm that separates the lungs from the intestines. Roll reports, "The occurrence of diaphragmatic hernia was striking because this malformation has never been seen in all our control groups checked so far. In the present case doxylamine succinate looks like a clearcut teratogen [an agent causing malformations] in Wistar rats from 100 mg/kg/day and higher."

William R. Donaldson, spokesman for Merrell, said rats in Roll's study were given 375 times the maximum human dose, which is equal to about 1,500 pills each day. Donaldson said preliminary animal studies don't necessarily prove the drug causes problems for humans.

But this isn't the first time Bendectin's safety has been questioned (SN: 12/27/80, p. 395; 6/13/81, p. 376). The drug's recent history is riddled with lawsuits claiming Bendectin caused birth defects, but until now studies could show no unequivocal connection between Bendectin and any specific problem (SN: 6/27/81, p. 406).

Past studies gave unclear results because they lumped diaphragmatic hernias together with other birth defects. Dr. Franz W. Rosa of the FDA recently looked at isolated diaphragmatic hernia rates in U.S. surveys and found that the rate was 7.8 times higher in infants whose mothers had taken Bendectin.

Barbara B. Manard, health policy consultant to the Surgeon General, reported that examination of one million hospital

birth records showed the rate of diaphragmatic hernia had risen by 64 percent from 1970 to 1980. Manard said Bendectin use nearly doubled during this time period and said, "The data from the increased pill usage is consistent with the increase in hernia incidence and death." She said this information alone doesn't prove anything but adds to the growing evidence that suggests a connection between the drug and diaphragmatic hernia.

There is also a suggestion that Bendectin causes a hole in the heart wall called ventricular-septal defect. Andrew G. Hendrickx of the University of California at

Davis reported to the FDA that studies with small numbers of animals showed that two out of three fetuses taken from monkeys fed 10 to 20 times the human dose of Bendectin developed this defect.

HRG's Lasheen said Bendectin, which is prescribed only for pregnant women with severe nausea and vomiting, has never been shown to work effectively. She said, "This is a drug used by a large proportion of the population and it isn't necessary." Lasheen suggests pregnant women with nausea and vomiting problems eat small frequent meals and soda crackers to alleviate symptoms. —K.A. Fackelmann

Sounding an internal reveille

Spontaneous awakening from sleep is controlled by an internal and quite rigorous waking mechanism linked to oscillations in deep body temperature, according to new data from a Harvard researcher. This natural alarm appears furthermore to be unrelated to prior wakefulness or sleep satiety, lending support to the complaints of shift workers that they wake up exhausted.

According to Charles A. Czeisler, several studies over the past few years have indicated that sleep duration is more closely linked to the time of day people go to bed than it is to how long they have been awake. What has remained unclear is why —whether the need for rest fluctuates during the day, perhaps, or whether sleep is more efficient if taken at certain hours. Czeisler's recent research — reported at the meeting of the Association for the Psychophysiological Study of Sleep in San Antonio — indicates that the explanation may instead involve the existence of an active waking system that is powerful enough to rouse sleepers before they are fully rested.

Czeisler has analyzed data from five subjects who were "free running" — going to sleep and waking without interference from the outside world — for over six months. What he found is that as subjects free run, certain components of the circadian system fall apart; specifically, the sleep-wake cycle advances from the habitual 24-hour cycle to a 30-, 40- or 50-hour cycle, while the core body temperature maintains a stable 24- to 25-hour cycle.

Core body temperature, Czeisler says, is a marker for the deep body oscillator that controls waking. Analyzing the subjects' sleep episodes for over six months, he found that sleep onset was distributed around the clock; the subjects, that is, fell asleep just as often when their body temperatures were rising as they did when temperatures were falling. In contrast, the preponderance of awakenings occurred as body temperature was rising, and further analysis revealed that, regardless of whether subjects had slept four, eight or 12 hours, they tended to wake spontaneously

as temperature began to rise.

For most people, Czeisler explains, the body temperature cycle is synchronized with the normal nocturnal sleep cycle, though there seem to be slight differences between "night people" and "morning people." These findings have important implications for occupational health policy, Czeisler says. When workers are forced to go to sleep at abnormal hours — early morning, for example, which normally comes well after the trough of the core temperature oscillation — they are apt to sleep poorly and wake poorly rested a few hours later. People who work rotating shifts — airline pilots, for example — are especially susceptible to disturbed sleep, because they are constantly moving in and out of phase with the commands of the internal alarm. —W. Herbert

Timely addition

A leap second was added simultaneously to timekeeping standards throughout the world on June 30, just prior to 8 p.m. Eastern Daylight Time. It's the eleventh full leap-second adjustment to be made since adoption of the practice in 1972 and it reset the international Coordinated Universal Time (UTC) in synchrony with solar time. According to the National Bureau of Standards, because atomic clocks used to keep international time standards "are much more precise than solar time, they run at a slightly different rate and thus need to be reset."

Ever wonder how that's done? Well, in the United States, at least, the atomic clock itself is not truly reset. Instead computers that monitor its oscillations to "count time" are programmed to add a second at the appropriate instant. For most of us, the only apparent change would have come in broadcasts of UTC by radio stations WWV and WWVB in Ft. Collins, Colo., and WWVH in Hawaii. All three literally read the time, second by second, 24 hours a day. On June 30, alert listeners would have heard those stations broadcast 61 seconds in the minute designated 2359 UTC. □