

The New York Times

Cigarettes Are Enlisted to Test Ways of Quitting

October 28, 2011

By **DUFF WILSON**

When a truck recently delivered 45,000 cartons of cigarettes to a research company in North Carolina, it was a turning point in the government's war on smoking.

These were no ordinary cigarettes, but experimental ones, made of genetically altered tobacco to lower the nicotine content by 97 percent while preserving all the other tastes and smells and rituals for smokers of conventional cigarettes.

Researchers had been seeking a new and bigger supply because shortages had limited previous studies to just dozens of people. The experimental cigarettes are produced by a Massachusetts company, the 22nd Century Group, which holds 98 patents for genetic manipulation of tobacco plants to reduce or increase the amount of nicotine in cigarettes.

The National Institutes of Health bought nine million of these cigarettes, marked "for

research purposes only," from the 22nd Century Group as part of a broadening scientific effort to find ways to regulate cigarettes so that they are nonaddictive. The Spectrum brand test cigarettes have eight different levels of nicotine for research, from a nicotine content of 3 percent to 100 percent of the nicotine in the best-selling Marlboro Gold, though a 97 percent reduction is the most common level.

Dr. Nora D. Volkow, director of the National Institute on Drug Abuse of the N.I.H., which oversees the work, called the delivery crucial for the new federal research projects. These include last month's award of \$2.5 million for the first year of a planned five-year series of studies into threshold levels of nicotine addiction and the possible impact of a sharp reduction in nicotine on smoking and public health.

One study of the test cigarettes will follow about 500 smokers over six months to determine whether they are more likely to quit if they switch to those cigarettes quickly or gradually. The research, led by Dorothy K. Hatsukami, a professor of

psychiatry at the University of Minnesota, and Eric C. Donny, associate professor of psychology at the University of Pittsburgh, will use about 1.5 million of the recently acquired cigarettes.

For researchers, the availability of a new supply of test cigarettes is "a game changer," said Mitch Zeller, co-chairman of the Tobacco Harm Reduction Network at the National Cancer Institute and a consultant on nicotine replacement products. "It's still all about the nicotine. Only now we have the power to do something about it."

At the same time, officials in the \$80 billion tobacco industry have warned of unexpected side effects from addiction withdrawal and black market products, complex issues the Food and Drug Administration will have to study in considering regulation.

Under a 2009 law giving the F.D.A. authority over tobacco products, the agency cannot ban nicotine, but can require that it be reduced to extremely low levels if that is proved to benefit public health.



Dr. Michael Moynihan, above, of 22nd Century, examines genetically altered tobacco.

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“We really need to have good science to determine whether this might be a product standard, and to have good science, we need reduced-nicotine cigarettes,” said Dr. Hatsukami, who is also a member of the F.D.A. Tobacco Products Scientific Advisory Committee. Her work stalled when companies stopped making very-low-nicotine cigarettes. “In the middle of a study, we don’t have the cigarettes,” she said.

Dr. Neal L. Benowitz, another researcher and member of the

federal committee, had received specially manufactured low-nicotine cigarettes from Philip Morris, a division of the Altria Group, makers of Marlboro cigarettes. When he went back for more, Philip Morris had stopped making them. Dr. Benowitz is also relying on the new supply, which the government will give to researchers without charge.

The 22nd Century Group is also applying for F.D.A. approval of its own test cigarette, called “X-22,” as a prescription-only smoking cessation device.

“No one has ever sought F.D.A. approval of a cigarette as a medical device,” Joseph Pandolfino, the founder and chief executive of 22nd Century, said in an interview.

Preliminary studies show smokers can have an easier time quitting if they taper off the nicotine while still being able to do all the other things they do with cigarettes, he said, but larger studies are needed.



Joseph Pandolfino is chief of 22nd Century, which alters the tobacco plants.

Another cigarette in testing, called “Brand B,” has tobacco that was genetically modified to have high levels of nicotine. The company hopes it will be approved by the F.D.A. as a “modified risk” tobacco product — a safer cigarette because users would take fewer puffs to get the same amount of nicotine.

The growing industry of quit-smoking products — patches, gum, lozenges and pills — has not further dented the rather steady rate of smoking recently in the United States, which has stayed at about 20 percent since 2004 after years of notable decline. A new crop of [electronic cigarettes](#) and smokeless tobacco products seem aimed more at getting smokers through smoke-free times rather than quitting.

Earlier this month, the F.D.A. and N.I.H. also announced they were starting a [\\$118 million study to track about 44,000 people](#) over five years to assess usage trends, risk perception, quit-smoking attempts and the possible impact of new tobacco regulations. In 2006, a [federal judge found](#) that tobacco companies had designed cigarettes to precisely control the amount of nicotine and provide doses sufficient for addiction, while concealing

much of their nicotine research. They marketed so-called light cigarettes, which delivered a lower dose to smoking machines because of holes in the filter, but the same dose or worse to smokers who compensated by covering the holes with their lips and drawing harder.

In two small studies by Dr. Hatsukami and Dr. Benowitz, the genetically altered cigarettes were found to defeat the phenomenon of smoker “compensation.” But researchers said they needed much more evidence.

Tests so far on the experimental cigarettes are encouraging enough that Dr. Hatsukami is going into a Phase 3 clinical trial. That means Phase 2 trials have proven effectiveness on humans. Phase 3 measures both effectiveness and safety. 22nd Century is also planning to start Phase 3 trials next year.

The studies are examining gradual or rapid reductions of nicotine. In a regulated marketplace, the government could set limits on nicotine and ratchet down. And teenagers could still experiment with cigarettes, as they are wont to do, without getting addicted.

“It’s a hot topic,” said Clifford E. Douglas, director of the University of Michigan Tobacco Research Network. “But as difficult as [menthol](#) has been, nicotine will be more difficult, because it’s not 15 million smokers, it’s every smoker in the United States.” The F.D.A., under its new authority, has focused on Congressional [mandates over menthol](#), dissolvable products and [graphic warning labels](#) on cigarette packages, each a contentious issue of its own with tobacco companies challenging science and policy.

The F.D.A.’s advisory panel has not put nicotine on its agenda yet, which is why Dr. Gregory N. Connolly, a Harvard professor of public health and antismoking advocate, said he [resigned from the F.D.A. panel](#) in December.

“After 50 years of knowing cigarettes cause [cancer](#), it’s nice to know we have a supply we can investigate,” Dr. Connolly said. “But the real issue is the F.D.A. should have begun a process two years ago to see if we can eliminate nicotine in cigarettes, at least for children. If we can put a man on the moon, we can get rid of nicotine.”

Link:

www.nytimes.com/2011/10/29/health/research/cigarettes-are-being-used-in-studies-to-help-smokers-quit.html