Internist and amateur detective Pieter Cohen is outraged that some of the supplements on the market are unsafe.

THE SUPPLEMENT SLEUTH

Some dietary supplements are spiked with drugs. Pieter Cohen is out to expose the hazards

By **Jennifer Couzin-Frankel**

Pieter Cohen's brush with death came at a most inconvenient time: just as he was about to nail another menacing ingredient in a dietary supplement.

Hiking last August in New Hampshire with his wife and three children, Cohen, an internist at Cambridge Health Alliance in Massachusetts, stumbled and fell. A rock punctured his left calf. "It was a little cut, but deep," recalls his wife, Lauren Budding. By the next day, bacteria were coursing through Cohen's bloodstream. The leg turned red and swelled. His blood pressure dropped precipitously. Cohen was rushed to a community hospital and soon after by ambulance to a trauma unit in Boston.

Doctors worked feverishly to stabilize him and stop the spread of infection. Over the next few days, the threat of death ebbed, though the risk that he would never walk normally remained. Cohen, meanwhile, fretted about the same matters he usually did: consumers, including his patients, who might be swallowing dietary supplements spiked with drugs. Bedbound and in searing pain, he asked for his computer. His wife refused.

"I'm like, 'I'm sorry, this person needs to sleep,'" she told the hospital staff. So Cohen had his mother smuggle in the laptop, along with data sets concealed inside *The Boston Globe*. "I could work on the manuscript when Lauren wasn't looking," he reasoned.

Eleven days after the accident, and after the fourth of what would be five surgeries, Cohen and two collaborators submitted their paper to *Drug Testing and Analysis*. The report was unnerving: At least a dozen supplements sold in the United States for weight loss, enhanced brain function, and improved athletic performance contained a synthetic stimulant. The compound, which Cohen and his co-authors named DMBA, resembled methamphetamine in its chemical structure. It had never been tested in people, only in two animal studies from the 1940s. "Its efficacy and safety are entirely unknown," they wrote.

By now ensconced in a hospital bed in his living room and waiting for skin grafts to heal, Cohen appealed to the journal: "I can't walk, I'm totally available. Can you guys crank this review?" The paper was published online a month later, last October. In April of this year, the U.S. Food and Drug Administration (FDA) issued warning letters to 14 companies selling products containing DMBA. "The FDA considers these dietary supplements to be adulterated," it wrote. And boom, Cohen was on to his next project.

Since 2005, when he found his patients were being sickened by a Brazilian weight loss supplement containing antidepressants and thyroid hormones, Cohen has become something of a mix of Indiana Jones and Sherlock Holmes in the supplement world. With chemist colleagues in the United States, Brazil, and Europe, he hunts for drugs illegally buried in supplements. Then he goes public. His unorthodox public relations strategy is to publish research fast in low-profile, specialty journals, reach out to a network of hand-picked journalists, and, he hopes, ultimately inspire new regulations. He has virtually no funding, nor does he aspire to secure any. "I have total freedom," he says. So far, he and his collaborators have identified three hidden stimulant drugs in supplements.

Cohen's discoveries highlight a broader problem, he and others contend: a dysfunctional system for policing dietary supplements. "It comes to this," says Paul Offit, director of the Vaccine Education Center at the Children's Hospital of Philadelphia, who published a book called *Do You Believe in Magic?* about alternative medicine. "Essentially a private citizen [is] doing the testing to make sure what's on the label is in the bottle. … It's absurd."

But that private citizen is having an impact. FDA actions have cited Cohen's work or followed his publications, as the DMBA warnings did. He has also caught the attention of supplement companies, including in a lawsuit filed against him in April seeking $200 million in damages. "Everything I write gets such scrutiny" that it creates tremendous pressure, he says. "I want our science to be bulletproof."

Tainted supplements

Prescription and illegal drugs are routinely found in supplements. Here's a sampling of more than 50 culprits from 2015.

PRODUCT NAME	CATEGORY	HIDDEN INGREDIENT
Smart Lipo	Weight loss	Sibutramine (a withdrawn weight loss drug); phenolphthalein (unapproved laxative ingredient)
Xcel	Weight loss	Fluoxetine (brand name Prozac)
Extreme Diamond 3000	Sexual enhancement	Desmethyl carbodenafil (unapproved, structurally similar to Viagra's active ingredient)
King of Romance	Sexual enhancement	Sildenafil (brand name Viagra)
Asihuri Plus Forte	Joint and nerve pain	Dexamethasone a (corticosteroid); phenylbutazone (discontinued NSAID)

THE MODERN SUPPLEMENT ERA began in 1994, when Congress passed the Dietary Supplement and Health Education Act, or DSHEA (pronounced duh-shay-uh). In the decades before, the supplements industry was overwhelmingly focused on vitamins and minerals. Much of the regulation centered on recommended daily allowances of products like vitamin C, iron, or calcium.

DSHEA established the first broad framework for regulating supplements. It also gave supplements a legal definition: as substances intended to "supplement the diet," containing "dietary ingredients" such as herbs, botanicals, or vitamins.

At the same time, the law sharply curtailed FDA's power. Companies were not required to notify FDA provided the dietary ingredi-

CREDITS: (PHOTO) DOMINICK REUTER; (DATA SOURCE) FDA

ent had a history of use before the law was passed. For the first time, DSHEA allowed them to make claims on the label suggesting supplements affected the structure or function of the body—for example, by boosting the immune system or protecting prostate health. And DSHEA codified a loose arrangement: Under the law, as FDA notes on its website, "unlike drug products that must be proven safe and effective for their intended use before marketing, there are no provisions in the law for FDA to 'approve' dietary supplements … before they reach the consumer." The agency can act only after a supplement is on the market and evidence shows it's unsafe.

Whereas the industry and many consumers celebrated DSHEA for expanding access to supplements, the act was skewered by physicians, journalists, and consumer protection groups. In an editorial shortly before DSHEA passed, *The New York Times* called it the "snake oil protection act," suggesting that it was "about the right of unscrupulous companies and individuals to maximize profits by making fraudulent claims." Meanwhile, the industry grew exponentially: Since 1994, the number of dietary supplements marketed in the United States has swelled from about 4000 to more than 75,000. About $36 billion worth were sold last year.

The ink had barely dried on DSHEA when trouble began. Within 2 years, a Chinese herb called ma huang or ephedra, which companies promoted as a legal alternative to ecstasy, was under scrutiny. Although a natural product, the herb contains the chemical ephedrine, which stimulates the nervous system and constricts blood vessels. By early 1996, it had been linked to at least 15 deaths. Meanwhile, FDA was regularly issuing warnings about liver, kidney, and other health risks tied to supplements.

"There are authentic dietary supplements—multivitamins, calcium, iron—which do supplement the diet" and can help many people, says rheumatologist and immunologist Donald Marcus of Baylor College of Medicine in Houston, Texas, an early critic of the supplement industry. But other supplements, like "St. John's wort, echinacea … are used as medicine," he points out. In part because "botanicals are complex mixtures of chemicals," supplements in this category present "a serious and growing public health problem," Marcus and a colleague, pharmacologist Arthur Grollman of the State University of New York at Stony Brook, wrote in *The New England Journal of Medicine* in 2002. Just how big a problem was unclear, however, because FDA hears about only a tiny fraction of adverse events from the companies, they noted.

Meanwhile, concerns about ephedra continued to mount. Army commissaries stopped selling it after it was implicated in the deaths of soldiers; after a 16-year-old taking the supplement died in Illinois, that state halted ephedra sales, too. FDA banned ephedra in 2004, after a 23-year-old Major League Baseball pitcher collapsed and died during practice and was found to be taking the herb.

53%
of U.S. adults report taking at least one dietary supplement.

34%
of U.S. adults report taking both a dietary supplement and a prescription medication.

18%
of U.S. adults report taking at least one natural product (not including vitamins and minerals).

$36 billion
The amount that Americans spend a year on dietary supplements

Cohen's initiation into supplements came on the job. After finishing at the Yale School of Medicine, he began his residency and then went to work at Cambridge Health Alliance, a network of neighborhood clinics and community hospitals. Many of Cohen's patients were Brazilian immigrants who had settled nearby.

Before long, the clinic's patients developed mysterious symptoms. One woman came in "with palpitations, sweating, anxiety, but also feeling very tired," remembers Daniel McCormick, a primary care internist in the same practice, who mentored Cohen in residency and shares a small office with him. Another wound up in the emergency room with kidney failure. One man lost his job after his urine tested positive for amphetamines.

Cohen made the connection: The patients were all taking weight loss pills known as rainbow diet pills, imported in bulk from Brazil. He sent the capsules off to a private lab for testing. The results shocked the doctors. The tests revealed amphetamines, thyroid hormones, diuretics, benzodiazepines, and antidepressants such as fluoxetine. "It was a pharmacopeia in one pill," McCormick says. "It became clear to a lot of us that you could explain the symptoms from the diet pills."

McCormick, Cohen, and three other colleagues conducted a survey of 307 Brazilian patients in their clinic and two nearby churches. They found that 18% in the clinic and 9% in the churches reported taking the pills, and two-thirds reported side effects. The paper was published online in 2007 in the obscure *Journal of Immigrant and Minority Health*.

"Less than 10 people are going to read that," Cohen admitted to himself, because the journal is so specialized. "I knew that if I wanted more … I needed to do some outreach." He contacted a local NPR reporter who had recently run a story on Latino bodegas selling antibiotics without a prescription, thinking he might be interested. The reporter invited him in for a studio interview. *Folha de S.Paulo*, a major Brazilian newspaper, contacted Cohen and ran a front-page story. Several years later, rainbow diet pills were banned in Brazil, though Cohen doesn't know whether his work had anything to do with that.

Cohen thought the spiked supplements were an anomaly confined to the Brazilian neighborhoods. But then he got a call from an official in the drug division at FDA. "What you found in those diet pills shipped up from Brazil," the official told him, "actually are found in weight loss supplements in the United States, and it's a major problem."

"WE HAVE BEEN WORRIED about contaminated dietary supplements for ages," says Amy Eichner of the U.S. Anti-Doping Agency in Colorado Springs, Colorado. In 2003 and 2008, two elite swimmers lost the chance to compete in the Olympics after testing positive for performance-enhancing drugs they said they didn't know were in their supplements. A similar fate befell two top cyclists. "That's our nightmare scenario," Eichner says.

Another with longstanding concerns is Patricia Deuster at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, who estimates that between 15% and 20% of military members are swallowing the supplements she and others fret about most: products marketed for bodybuilding, weight loss, and athletic performance. Another worrying category includes sexual enhancement products.

So in 2013, she and Eichner began systematically parsing supplement ingredients. Preliminary results, still unpublished, show that of the 169 high-risk products tested so far, 107 "contained at least one substance prohibited in sports," Eichner says, and often that substance wasn't listed clearly on the label. In many cases, she says, the ingredients are "either Schedule III substances on the Controlled Substances Act—that's pretty major—or they have been specifically declared illegal by the FDA."

DATA SOURCES: (TOP TO BOTTOM) CDC; *JOURNAL OF THE ACADEMY OF NUTRITION AND DIETETICS*; CDC; NIH

At around that time, Cohen had an electrifying phone conversation. A lab scientist who tests supplements for companies confided in Cohen that he was deeply disturbed by the prevalence of an ephedra substitute, a stimulant called dimethylamylamine or DMAA, which kept appearing in products despite mounting concerns about its safety. That conversation was "the catalyst that opened this whole new world to me," Cohen says.

With rainbow diet pills, he'd been focused on prescription drugs. Although DMAA had appeared in nasal sprays many decades ago before being removed from the market, it was now more like a "research chemical," Cohen says, which some companies argued came from plants but which Cohen and many others disputed. He began searching for dangerous additives in supplements. FDA declared supplements containing DMAA illegal soon after, in 2013, but as Cohen quickly learned, there was no shortage of other targets.

"It's a Sherlock Holmes situation," he says with relish. "There's a crime scene, there's hints of struggle, people are dying after taking supplements. … What is actually going on?"

He found a perfect partner more than 5000 kilometers away near Utrecht, the Netherlands: Bastiaan Venhuis, a medicinal chemist who was also analyzing supplement ingredients. One of their first joint publications, in collaboration with NSF International, which tests food, supplements, and other consumer products, appeared online in the fall of 2013 in *Drug Testing and Analysis*. It examined a popular workout supplement called Craze. When Venhuis diluted the powder and ran it through his analyzer, telltale peaks indicated DEPEA, a methamphetamine analog.

To garner publicity, Cohen expanded the strategy he had followed with the Brazilian supplements. He sought a final manuscript from the journal about a week in advance and sent personal emails to upward of three dozen journalists, carefully selected for their prior coverage or relationships he had nurtured with them.

Cohen's office buddy McCormick acknowledges that such media outreach, which he's done himself, can feel awkward. It's often regarded "as self-promotional," McCormick says. "In the beginning I felt that way intensely and it was very uncomfortable. But … the vast number of hours that go into thinking about a research project, writing it, is just wasted" if it stops there, especially when it might have an impact on health policy.

Cohen has caught the attention not only of myriad journalists but of the supplement industry, too. In late April, a company called Hi-Tech Pharmaceuticals filed a $200 million claim for damages against Cohen and two colleagues, after the researchers published a paper suggesting Hi-Tech and other companies were marketing supplements that contained an amphetaminelike stimulant, BMPEA, which they mislabeled as *Acacia rigidula*, a shrub that grows in Texas and south into Mexico.

The company vigorously disputes that BMPEA is not part of the plant. "A real scientist concerned with objectivity would have taken steps to ensure that they weren't disparaging products before they did this to the public," says Edmund Novotny, an attorney in Atlanta who represents Hi-Tech.

Cohen wasn't alone in singling out BMPEA: His study came about 18 months after FDA scientists reported detecting BMPEA in supplements, too, noting that nowhere could they find evidence that BMPEA was a natural component of plants. Soon after Cohen's publication, FDA sent warning letters to five companies selling BMPEA-laced supplements, including Hi-Tech.

Like others, Cohen agrees that FDA's supplement policing powers are too limited. But that doesn't mean the agency has no muscle. "There's so many things FDA could be doing that they're not doing," he says—for example, removing supplements from store shelves when companies don't fully pass FDA inspections. The agency, Cohen believes, is overwhelmed by the sheer volume of supplements and discouraged by political forces from acting aggressively. When it comes to pulling a supplement ingredient, FDA's attitude is "show us the dead bodies," he says.

FDA officials wouldn't put it that way, but they don't entirely disagree. "Under current law, the FDA faces a high burden before it can take enforcement action on a dietary supplement," wrote spokeswoman Lyndsay Meyer in an email message. The agency has its own frustrations. "The supply chain … is extremely fragmented," Meyer wrote. "The individuals and businesses selling these products may operate out of residential homes, and distribute via internet, small stores, and mail … We recognize that more can and should be done."

Nearly a year after his harrowing ordeal while hiking, Cohen has regained full function of his leg, though he still wears a black compression stocking. Sitting in his office in June, surrounded by photos of his three children and a jumble of supplement bottles patients have handed over to him for testing, Cohen shows little of the fatalism of others who have battled supplements for years. The reform movement "definitely has momentum," he says. "I think we're going to look back 50 years from now, and say 'How could supplements have been regulated like this?'"

In anticipation of that day, Cohen is working now to nail two more drugs that show up in supplements. He's also been studying yohimbine, a prescription drug that can be extracted from the bark of a species of West African evergreen tree and sometimes appears in bodybuilding capsules. Like ephedrine, yohimbine "comes from a plant but is pharmaceutically active," he says, blurring the line between drug and supplement.

His dream is an informed populace, with companies required to fork over the recipes and the risks of their products. "Whenever possible, we should have the freedom of being able to purchase whatever we want to put in our body," Cohen says. "People should be able to purchase echinacea. It's just, when they purchase echinacea, they should know what they're getting." ■

Top swimmer Jessica Hardy tested positive for a banned substance she said she didn't know was in a supplement she was taking. "That's our nightmare scenario," says a U.S. antidoping official.

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