



## Legal highs: the dark side of medicinal chemistry

Synthetic chemist David Nichols describes how his research on psychedelic compounds has been abused – with fatal consequences.

This is the start of the international year of chemistry, intended to celebrate the contribution of my field to mankind's well-being. Yet, during the previous year it has become disturbingly clear to me that some of my scientific contributions may not be aiding people's well-being at all. In fact, they could be causing real harm.

A few weeks ago, a colleague sent me a link to an article in the *Wall Street Journal*. It described a "laboratory-adept European entrepreneur" and his chief chemist, who were mining the scientific literature to find ideas for new designer drugs — dubbed legal highs. I was particularly disturbed to see my name in the article, and that I had "been especially valuable" to their cause. I subsequently received e-mails saying I should stop my research, and that I was an embarrassment to my university.

I have never considered my research to be dangerous, and in fact hoped one day to develop medicines to help people. I have worked for nearly four decades synthesizing and studying drugs that might improve the human condition. One type is designed to alleviate the symptoms of Parkinson's disease, and it works superbly in monkey models of the disease. That same research seeks drugs to improve memory and cognition in patients who have schizophrenia, one of the most devastating human conditions. The other substances I work on are psychedelic agents such as LSD and mescaline. It's in that latter area of research that I have published papers about numerous molecules that probably have psychoactive properties in humans. It seems that many of these are now being manufactured and sold as 'legal highs'.

I first became aware that unknown amateur chemists were watching my papers more than a decade ago. My laboratory was doing research on 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), a project we had started in 1982, before most people had even heard of the drug. We wanted to discover how MDMA worked in the brain because we thought drugs like it might help in psychotherapy. In the process, we studied many molecules that had structures similar to MDMA. One was 4-methylthioamphetamine, or MTA, which could inhibit the enzyme that breaks down serotonin in the body. Between 1992 and 1997, we published three papers on the effects of MTA in rats, including a study showing that MTA might have potential in the treatment of depression, and could possibly be superior to currently marketed drugs.

Without my knowledge, MTA was synthesized by others and made into tablets called, appropriately enough, 'flatliners'. Some people who took them died. Now, any knowledgeable person who had carefully read our papers might have realized the danger of ingesting MTA. It not only caused the release of serotonin from neurons, but also prevented the breakdown of this

neurotransmitter, potentially leading to a dangerous serotonin syndrome that can sometimes prove fatal. My laboratory had shown that rats perceived the effects of MTA as being like those of ecstasy. It seemed that that was the sole motivation for its illicit production and distribution to humans. I was stunned by this revelation, and it left me with a hollow and depressed feeling for some time. By 2002, six deaths had been associated with the use of MTA. It did not help that I knew some of these fatalities were associated with the use of multiple drugs, or had involved very large doses of MTA. I had published information that ultimately led to human death.

There really is no way to change the way we publish things, although in one case we did decide not to study or publish on a molecule we knew to be very toxic. I guess you could call that self-censure. Although some of my results have been, shall we say, abused, one cannot know where research ultimately will lead. I strive to find positive things, and when my research is used for negative ends it upsets me.

Over the past year or so, I have begun to get more e-mails asking questions about the human effects of other materials that my laboratory had studied. Forensic laboratories began to send me requests for samples of drugs that they suspected were appearing on the black market, but which were so new that there are no analytical standards. Thankfully, most of the other molecules we have published on could not kill, at least not at reasonable dosages. But at very high doses, or mixed with other substances, they could become part of a lethal mix.

We never test the safety of the molecules we study, because that is not a concern for us. So it really disturbs me that 'laboratory-adept European entrepreneurs' and their ilk appear to have so little regard for human safety and human life that the scant information we publish is used by them to push ahead and market a product designed for human consumption. Although the testing procedure for 'safety' that these people use apparently determines only whether the substance will immediately kill them, there are many different types of toxicity, not all of which are readily detectable. For example, what if a substance that seems innocuous is marketed and becomes wildly popular on the dance scene, but then millions of users develop an unusual type of kidney damage that proves irreversible and difficult to treat, or even life-threatening or fatal? That would be a disaster of immense proportions. This question, which was never part of my research focus, now haunts me. ■

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