

Forensic labs warn of deuterated drug threat

Recent interest in making drugs in which some of the hydrogen atoms are replaced with deuterium has caused alarm in a key medical speciality that already uses such compounds: forensic toxicology.

Some pharmaceutical companies hope that deuterated drugs will survive for longer in the body, have fewer side effects and combine better with other drugs (see *Nature* 458, 269; 2009). But for the researchers who look for pharmaceuticals in post-mortem examinations or accident investigations the idea is “horri-fying”, says Sarah Kerrigan, director of the forensic science programme at Sam Houston State University in Huntsville, Texas.

The problem is that toxicologists already use deuterated versions of pharmaceuticals as reference standards when using gas chromatography mass spectrometry. The reference for a drug of interest usually has three (or more) hydrogen atoms replaced by deuterium, providing a precise signal in the resulting spectrum close to that of the drug being looked for. If the drug of interest were itself also deuterated both compounds would be in the same place. “The bottom line is that we will miss them,” says Kerrigan.

Concert Pharmaceuticals, based in Lexington, Massachusetts, is developing deuterated versions of an HIV protease inhibitor and of the antidepressant paroxetine. “In principle I don’t see that this should cause any problems,” says Roger Tung, chief executive of Concert. He points out that the drugs that Concert hopes to market will have a known number of deuterium atoms, making them easily distinguished from a reference standard with a different number. But Aldo Poletti, from the legal and occupational medicine department at the University of Verona in Italy, says that this overstates the sensitivity of the systems in use.

A reference standard with three deuteriums would in practice be impossible to distinguish from compounds with two to four deuteriums swapped, he says.

Another suggestion of Tung’s — that the unaltered drug could be used as a reference against a deuterated version — also fails to allay the toxicologists’ worries. “If all of a sudden deuterated paroxetine came onto the market and every vestige of the original went off the market and out of everyone’s medicine cabinet, [Tung would be] right,” says Graham Jones, chief toxicologist for the Office of the Chief Medical Examiner in Edmonton, Canada, who maintains a widely used mass-spectrometry database for forensic toxicologists. But with deuterated and undeuterated versions of the drug on the market, there would be plenty of scope for error. “Using the drug as the internal standard would be complete forensic suicide,” says Kerrigan.

“It’s not as simple as using a different drug, we’d have to develop specific methodology,” says Bruce Goldberger, director of toxicology at the University of Florida College of Medicine in Gainesville and editor of the *Journal of Analytical Toxicology*. This is a costly and lengthy process, he says. His lab spends up to \$10,000 for each new methodology validation, which toxicologists must perform every time an aspect of their testing is changed.

Reference standards are bought from specialist companies, such as Cerilliant, in Round Rock, Texas, that provide certified materials. Cerilliant has a number of standards on its books and also synthesizes deuterated versions of known drugs to order. This, though, could lead to new problems if deuterated drugs are patented, and thus need to be made under licence. “We are concerned that the granting of these patents could severely restrict the production of reference materials,” says Mitzi Rettinger, Cerilliant’s vice-president of sales and marketing.

Kerrigan hopes to alert the US Food and Drug Administration to her concerns, and let her colleagues internationally know of the situation through a letter in the *Journal of Analytical Toxicology*. She thinks it will be possible to cope with small numbers of such drugs. “If it is forced on us, we’ll adapt,” says Goldberger. “I’m all for forward-looking medicine,” Kerrigan says, “but the benefits have to outweigh this huge disadvantage.”

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It’s that damn deuterium again, Horatio.