requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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References

Courtney Heideloff Courtney Heideloff
Jessica Gabler Jessica Gabler
Chao Yuan Chao Yuan
Lin Zhang Lin Zhang
Sihe Wang Sihe Wang

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Fig. 1. Formation of 6AM from morphine and M3G after 12 and 18 h of incubation in 1.0 mol/L acetate buffer. 6AM concentrations below 5 µg/L (15 nmol/L) are considered undetectable.

Issues Related to the Study of Cannabinoids in Exhaled Breath

To the Editor:

In the December 2013 issue of Clinical Chemistry, Huestis and colleagues published an article on cannabinoids in exhaled breath following smoked cannabis (1). This intriguing study prompted a valuable conversation regarding current legislation and future possibilities for detecting cannabis-induced impairment. We therefore commend the authors for their initial efforts to assess a breath test for cannabinoid detection. There are, however, several aspects of this study that deserve further discussion.

First, the possibility of laboratory interference must be considered. Although all study participants tested negative 1 h before smoking, there were positive tests that were not well explained. Two participants (I and K) had a detectable 9-tetrahydrocannabinol concentration on admission. In this scenario, the positivity of THC can be explained by 2 possibilities: those participants smoked marijuana after admission, which is unlikely, or the assay also detected 11-nor-9-carboxy-THC (THCCOOH), which is often increased in chronic users. Subsequently, by the 1-h assessment, the THCCOOH concentration may...
have fallen below the detection limit of 50 pg/pad, which could possibly be translated to a moderately high concentration in serum. This also may explain why the chronic smokers showed higher concentrations of THC in the breath compared to occasional smokers despite a fixed dose. However, this needs further validation, since the authors state that the samples were negative for THCCOOH. A control group made up of nonsmokers or recently abstinent smokers would have helped to elucidate the positive predictive value of this test.

Second, although we recognize that this test is in its infancy, collection of additional data may have improved the applicability of the test results to the assessment of functional impairment as underscored by the authors: at the workplace and behind the wheel. A protocol for testing functional impairment (reaction time, coordination) may have been beneficial to delineate how breath concentrations relate to actual changes in participant impairment. Most importantly, this would help to determine the degree to which impairment persists even after the participant is out of the detection window. Functional testing may also have illuminated variations in the degree of impairment between chronic and occasional smokers and how this correlated with the statistical differences in median breath THC concentration reported.

These issues will be essential as we legally and chemically define functional impairment for marijuana use. As real-time testing for alcohol intoxication took time to mature, so too will the development of tools to assess cannabinoid intoxication.

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Reference


Eileen P. Mercurio2
Daniel Taupin2
Mai Takematsu3,4*
Robert S. Hoffman3
Lewis S. Nelson3,4

2 Medical student
New York University School of Medicine
New York, NY

3 Division of Medical Toxicology
Department of Emergency Medicine
New York University School of Medicine
New York, NY

4 New York City Poison Control Center
New York, NY

* Address correspondence to this author at:
The University Hospital for Albert
Einstein College of Medicine
111 East 210th St.
Bronx, NY 10467
E-mail: mtakemat@montefiore.org

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In Reply

We appreciate the constructive feedback and opportunity to respond to the comments and suggestions (1) on our recent breath cannabinoid publication (2).

In response to the question about positive admission breath specimens, Δ⁹-tetrahydrocannabinol (THC)-positive⁴ breath from frequent smoking participants I and K at admission was likely the result of cannabis smoking just before arrival on our closed research unit. Our study design involved admission of participants to a secure research unit the night before smoking (16–20 h before smoking), to ensure lack of intoxication at the time of controlled dosing. Participants I and K were daily smokers who reported smoking 2.4 and 1.2 h before admission, respectively (3). These were among the shortest times reported between last smoke and admission (3). These participants also were the only 2 with blood THC concentrations at baseline and after 30 h postdose of >5 µg/L, the current per se limit in Washington state for driving under the influence of cannabis. These data were reported in a more recent paper regarding these same participants’ blood and plasma cannabinoid concentrations (3).

As noted, all participants provided breath that was cannabinoid-negative 1 h before smoking. The reason that these 2 participants’ breath samples were THC-positive was that they smoked just before and not after admission.

We wish to stress that breath THC, 11-nor-9-carboxy-THC (THCCOOH), and cannabinol were identified and quantified with a highly specific LC-MS/MS assay. Therefore, we respectfully disagree with the comment that our results are due to possible laboratory interferences. It is true that THCCOOH is present at higher concentrations and for longer durations in frequent smokers’ blood (3), plasma (3), urine (4), and oral fluid (5) compared with occasional smokers. We have presented these

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1 Nonstandard abbreviations: THC, Δ⁹-tetrahydrocannabinol; THCCOOH, 11-nor-9-carboxy-THC.