1-22-2015

Hidden Formaldehyde in E-Cigarette Aerosols

R. Paul Jensen
Portland State University

Wentai Luo
Portland State University

James F. Pankow
Portland State University, pankowj@pdx.edu

Robert M. Strongin
Portland State University, strongin@pdx.edu

David H. Peyton
Portland State University, peytond@pdx.edu

Citation Details

Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. N Engl J Med 2015;372:392-4.
DOI: 10.1056/NEJMc1413069

interpretation by Boron and Vaughan-Jones that "changes in the strong ion difference are a consequence of adding acid and base as strong-ion salts; they do not cause pH to change." The debate about cause and effect and fact and opinion is really a debate about interpretation, given that causation is notoriously difficult to prove.[4]

Julian L. Seifter, M.D.
Brigham and Women's Hospital
Boston, MA

Since publication of his article, the author reports no further potential conflict of interest.

1. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 2000;162:2246-51.
2. Adrogué HJ, Gennari FJ, Galla JH, Madias NE. Assessing acid-base disorders. Kidney Int 2009;76:1239-47.
3. Boron WF. Regulation of intracellular pH. Adv Physiol Educ 2004;28:160-79.
4. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.

DOI: 10.1056/NEJMc1414731

Hidden Formaldehyde in E-Cigarette Aerosols

TO THE EDITOR: E-cigarette liquids are typically solutions of propylene glycol, glycerol, or both, plus nicotine and flavorant chemicals. We have observed that formaldehyde-containing hemiacetals, shown by others to be entities that are detectable by means of nuclear magnetic resonance (NMR) spectroscopy,[1] can be formed during the e-cigarette "vaping" process. Formaldehyde is a known degradation product of propylene glycol that reacts with propylene glycol and glycerol during vaporization to produce hemiacetals (Fig. 1). These molecules are known formaldehyde-releasing agents that are used as industrial biocides.[5] In many samples of the particulate matter (i.e., the aerosol) in "vaped" e-cigarettes, more than 2% of the total solvent molecules have converted to formaldehyde-releasing agents, reaching concentrations higher than concentrations of nicotine. This happens when propylene glycol and glycerol are heated in the presence of oxygen to temperatures reached by commercially available e-cigarettes operating at high voltage. How formaldehyde-releasing agents behave in the respiratory tract is unknown, but formaldehyde is an International Agency for Research on Cancer group 1 carcinogen.[4]

Here we present results of an analysis of commercial e-liquid vaporized with the use of a "tank system" e-cigarette featuring a variable-voltage battery. The aerosolized liquid was collected in an NMR spectroscopy tube (10 50-ml puffs over 5 minutes; 3 to 4 seconds per puff). With each puff, 5 to 11 mg of e-liquid was consumed, and 2 to 6 mg of liquid was collected. At low voltage (3.3 V), we did not detect the formation of any formaldehyde-releasing agents (estimated limit of detection, approximately 0.1 μg per 10 puffs). At high voltage (5.0 V), a mean (±SE) of 380±90 μg per sample (10 puffs) of formaldehyde was detected as formaldehyde-releasing agents. Extrapolating from the results at high voltage, an e-cigarette user vaping at a rate of 3 ml per day would inhale 14.4±3.3 mg of formaldehyde per day in formaldehyde-releasing agents. This estimate is conservative because we did not collect all of the aerosolized liquid, nor did we collect any gas-phase formaldehyde. One estimate of the average delivery of formaldehyde from conventional cigarettes is approximately 150 μg per cigarette,[3] or 3 mg per pack of 20 cigarettes. Daily exposures of formaldehyde associated with cigarettes, e-cigarettes from the formaldehyde gas phase, and e-cigarettes from aerosol particles containing formaldehyde-releasing agents are shown in Figure 1.

Inhaled formaldehyde has a reported slope factor of 0.021 kg of body weight per milligram of formaldehyde per day for cancer (http://oehha.ca.gov/risk/pdf/TCDBcas061809.pdf). Among persons with a body weight of 70 kg, the incremental lifetime cancer risk associated with long-term cigarette smoking at 1 pack per day may then be estimated at 9×10^{-4}. If we assume that inhaling formaldehyde-releasing agents carries the same risk per unit of formaldehyde as the risk associated with inhaling gaseous formaldehyde, then long-term vaping is associated with an incremental lifetime cancer risk of 4.2×10^{-3}. This risk is 5 times as high (as compared with the risk based on the calculation of Miyake and Shibamoto shown in Fig. 1), or even 15 times as high (as compared with the risk based on the calculation of Counts et al. shown in Fig. 1) as the risk associated with long-term smoking. In addition, formaldehyde-releasing agents may deposit more efficiently in the respiratory tract than gaseous formaldehyde,

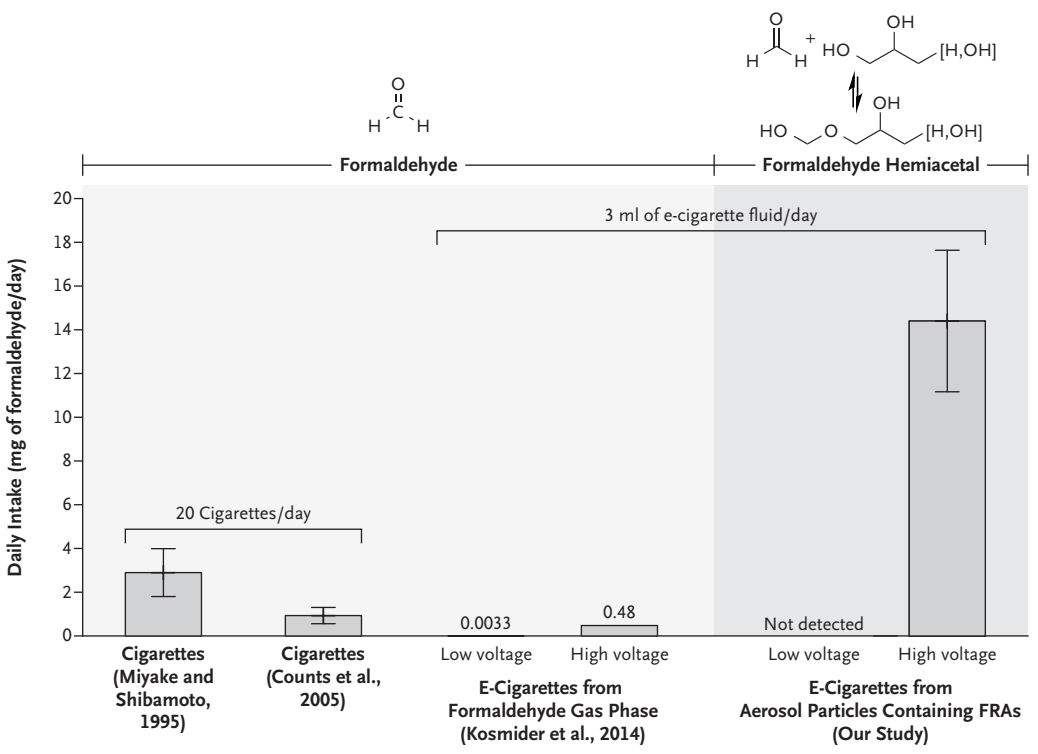

Figure 1. Daily Exposures to Formaldehyde Associated with Cigarettes and E-Cigarettes.

Data on the daily exposure from cigarettes (the average [±SD] of all values [milligrams of formaldehyde per cigarette]) were derived from Miyake and Shibamoto[2] and Counts et al.[3] These values were multiplied by 20 cigarettes per pack. Thus, they are an average of the values used in the protocols from the International Organization for Standardization, the Massachusetts Department of Public Health, and Health Canada. Data on the daily exposure from e-cigarettes from the formaldehyde gas phase were calculated from the data in Kosmider et al.[4] We estimated daily exposure by applying our measured e-liquid consumption rates of 0.13 mg per milliliter (at 3.3 V) and 0.18 mg per milliliter (at 5 V) of vapor produced to the measured gas-phase formaldehyde values described by Kosmider et al.[4]: 0.13 μg per 1050 ml of vapor (at 3.2 V) and 27 μg per 1050 ml vapor at (4.8 V) for mixed glycerol and propylene glycol samples. Data on the daily exposure from liquid-phase aerosol particulate matter in e-cigarettes were calculated as the value of formaldehyde (as a formaldehyde-releasing agent [FRA]) exposure per day for commercial e-liquid (Halo "café mocha" flavor, 6 mg per milliliter of nicotine), measured from 10 successive aerosolized samples analyzed at 3 concentrations each. FRAs were identified by means of nuclear magnetic resonance spectroscopy (see the Supplementary Appendix, available with the full text of this letter at NEJM.org) and quantified by relative integration against an internal standard. The two I bars on the left indicate standard deviations, and the I bar on the right indicates the standard error.

and so they could carry a higher slope factor for cancer.

R. Paul Jensen, B.S.
Wentai Luo, Ph.D.
James F. Pankow, Ph.D.
Robert M. Strongin, Ph.D.
David H. Peyton, Ph.D.

Portland State University
Portland, OR
peytond@pdx.edu

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was updated on January 22, 2015, at NEJM.org.

1. Balashov AL, Danov SM, Krasnov VL, Chernov AY, Ryabova TA. Association of formaldehyde in aqueous-alcoholic systems. Russ J Gen Chem 2002;72:744-7.
2. Miyake T, Shibamoto T. Quantitative analysis by gas chromatography of volatile carbonyl compounds in cigarette smoke. J Chromatogr A 1995;693:376-81.
3. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul Toxicol Pharmacol 2005;41:185-227.
4. Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. Nicotine Tob Res 2014;16:1319-26.
5. de Groot A, Geier J, Flyvholm M-A, Lensen G, Coenraads P-J.

Formaldehyde-releasers: relationship to formaldehyde contact allergy — part 2: metalworking fluids and remainder. Contact Dermatitis 2010;63:129-39.

DOI: 10.1056/NEJMc1413069

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

- Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.
- Letters not related to a *Journal* article must not exceed 400 words.
- A letter can have no more than five references and one figure or table.
- A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. Disclosures will be published with the letters. (For authors of *Journal* articles who are responding to letters, we will only publish new relevant relationships that have developed since publication of the article.)
- Include your full mailing address, telephone number, fax number, and e-mail address with your letter.
- All letters must be submitted at authors.NEJM.org.

Letters that do not adhere to these instructions will not be considered. We will notify you when we have made a decision about possible publication. Letters regarding a recent *Journal* article may be shared with the authors of that article. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal*'s various print and electronic publications and in collections, revisions, and any other form or medium.

CORRECTION

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke (January 1, 2015;372:11-20). In the stub column of Table 1 (page 15), under "Prestroke modified Rankin scale score," the final subcategory should have been >2, rather than <2. The article is correct at NEJM.org.

NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal's *website (NEJM.org/medical-conference). The listings can be viewed in their entirety or filtered by specialty, location, or month.*

MAYO CLINIC SCOTTSDALE

The following courses will be offered in Scottsdale, AZ: "Mayo Clinic 3rd Annual Collaborative Symposium: Update in Minimally Invasive Gynecologic Surgery" (Feb. 5–7); "11th Annual Mayo Clinic Women's Health Update" (March 5–7); and "Clinical Reviews 2015: 26th Annual Family Medicine and Internal Medicine Update" (March 26–29).

Contact Mayo School of Continuous Professional Development, Mayo Clinic, 13400 E. Shea Blvd., Scottsdale, AZ 85259; or call (480) 301-4580; or fax (480) 301-8323; or e-mail mca.cme@mayo.edu; or see http://www.mayo.edu/cme.

8TH INTERNATIONAL DIP SYMPOSIUM ON DIABETES, HYPERTENSION, METABOLIC SYNDROME & PREGNANCY

The symposium will be held in Berlin, April 15–18.

Contact Comtec Med, 53 Rothschild Blvd., P.O. Box 68, Tel Aviv, 6100001, Israel; or call (972) 3-5666166; or fax (972) 3-5666177; or e-mail dip@comtecmed.com; or see http://www.comtecmed.com/dip/2015.

EUROPEAN MOLECULAR BIOLOGY LABORATORY

The following meetings will be held in Heidelberg, Germany: "Mechanisms of Neurodegeneration" (June 14–17) and "Cancer Genomics" (Nov. 1–4).

Contact European Molecular Biology Laboratory, Course and Conference Office, Meyerhofstr. 1, D-69117 Heidelberg, Germany; or call (49) 6221 387 8359; or fax (49) 6221 387 8158; or see http://www.embl.de/training/events or http://www.embo-embl-symposia.org/symposia.

MINDFUL PRACTICE ADVANCED WORKSHOP

The workshop, entitled "Enhancing Quality of Care, Quality of Caring, and Resilience," will be held in Batavia, NY, April 27–May 1.

Contact Diane Frank, Center for Experiential Learning, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Box 709, Rochester, NY 14642; or call (585) 275-7666; or fax (585) 256-2682; or see http://www.cvent.com/d/64qrfs.

10TH ANNUAL PERIOPERATIVE MEDICINE SUMMIT

The summit will be held in Scottsdale, AZ, Feb. 26–28. It is presented by Rush University and cosponsored by the Cleveland Clinic in collaboration with the Society for Perioperative Assessment and Quality Improvement (SPAQI).

Contact Elizabeth Wilkerson, Horizon CME, 9123 SE St. Helens St., Suite 280, Clackamas, OR 97015; or call (503) 659-5558; or e-mail elizabeth.wilkerson@horizoncme.com; or see http://www.periopmedicine.org.

ADVANCED EUROPEAN BIOETHICS COURSE

The course, entitled "Suffering, Death, and Palliative Care," will be offered in Nijmegen, the Netherlands, Feb. 10–13. It is organized by the section of Medical Ethics, IQ healthcare, Radboud University Nijmegen Medical Centre.

Contact Simone Naber, Medical Ethics, P.O. Box 9101, 114 IQ health care, 6500 HB Nijmegen, the Netherlands; or e-mail simone.naber@radboudumc.nl; or see http://www.masterbioethics.org.

THE *JOURNAL*'S WEB AND E-MAIL ADDRESSES

To submit a letter to the Editor: authors.NEJM.org

For information about the status of a submitted manuscript: authors.NEJM.org

To submit a meeting notice: meetingnotices@NEJM.org

The *Journal*'s web pages: NEJM.org