Electronic cigarette aerosols induce DNA damage and reduce DNA repair: Consistency across species

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We read with great interest the work of Lee et al. (1), in which the authors report that mice exposed to electronic cigarette aerosol have increased levels of DNA lesions and decreased DNA repair activity. This work sparked important discussion both in PNAS (2, 3) and science media (4). We do share some concerns previously raised, including the very high dose of electronic cigarette aerosol exposure and the lack of plasma nicotine measurements. Additionally, while we agree with the authors that the exposure to electronic cigarette aerosol led to an increase in O^6-methyl-deoxuguanosine and γ-hydroxy-1,N^2-propano-deoxyguanosines adducts, we do not share their conclusion that these adducts are necessarily induced by nicotine. The extremely high dose of nicotine (100 μM) required in vitro to induce adduct formation in lung cells suggests that other electronic cigarette genotoxics, rather than nicotine, were the main cause of adduct formation. Alternatively, since exposure to electronic cigarette aerosol significantly decreased tissue DNA repair activity and these types of adducts were also observed in unexposed mice (1), it is possible that the high level of adducts measured reflects an accumulation of unrepaired adducts, rather than an increase in adduct formation. If this were to be the case, these data have significant implications for the large population of dual combustible tobacco and electronic cigarette users.

Despite the concerns raised, the work of Lee et al. (1) is highly relevant from a public health perspective. First of all, it is the second independent study documenting that exposure to electronic cigarette aerosol not only increases DNA damage but also reduces DNA repair capacity. Ganapathy et al. (5) exposed human cells to electronic cigarette aerosol extract yielding nicotine levels (0–39 ng/mL) similar to those present in the plasma of vapers. Remarkably, despite using completely different experimental settings, both groups observed precisely the same phenotype: a significant increase in DNA damage and decrease in the expression of proteins essential for nucleotide [ERCC1 (5) and XPC (1)] and base [OGG1 (1, 5)] excision repair. This consistency suggests that these are key mechanisms that will have significant health consequences for electronic cigarette users.

Finally, given the current debate over tobacco harm reduction, the focus on the detrimental effects of electronic cigarettes in the absence of direct comparison with tobacco smoke has raised major concerns (3, 4). Shedding some light on this matter, side-by-side experiments have shown that oral and lung cells exposed to electronic cigarette aerosol have significantly lower levels of DNA damage than those exposed to tobacco smoke (5). Nonetheless, perhaps due to decreased oxidative damage repair, the levels of 8-oxodG, a highly mutagenic lesion, were slightly higher in cells exposed to electronic cigarette than in those exposed to tobacco smoke (5).

Altogether, these data support the notion that electronic cigarette use increases cancer risk but is still safer than combustible tobacco. Importantly, given the observed decrease in DNA repair activity, the cancer risk associated with electronic cigarette use might be amplified in individuals exposed to other carcinogens, such as tobacco smoke.

1 Lee H-W, et al. (2018) E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci USA* 115:E1560–E1569.

2 Tang MS (2018) Reply to Li Volti et al.: E-cigarette smoke exposure and effect in mice and human cells. *Proc Natl Acad Sci USA* 115:E3075–E3076.

3 Li Volti G, Polosa R, Caruso M (2018) Assessment of E-cigarette impact on smokers: The importance of experimental conditions relevant to human consumption. *Proc Natl Acad Sci USA* 115:E3073–E3074.

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4 Science Media Centre (January 29, 2018) Expert reaction to E-cigarettes and DNA damage. Available at www.sciencemediacentre.org/expert-reaction-to-e-cigarettes-and-dna-damage/. Accessed April 28, 2018.
5 Ganapathy V, et al. (2017) Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage. *PLoS One* 12:e0177780.

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