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Response to Letter to the Editor

Response to letter regarding article, "Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers"

We thank Drs. Farsalinos and Voudris for their careful reading of our study (Schober et al., 2013) on the effects of e-cigarette consumption. In this study, we performed a comprehensive inner und outer exposure assessment by analyzing the indoor air concentration of e-cigarette emissions and by monitoring acute effects on FeNO release and urinary metabolite profile of e-cigarette users. We showed, that vaping can increase FeNO levels of consumers and impairs indoor air quality by the release of high amounts of potentially harmful substances including volatile organic compounds, particles and polycyclic aromatic hydrocarbons (PAH). In response to the comments we would like to point out the following.

It is stated that control and vaping sessions were performed on different days, and, therefore, differences in PAH levels may be caused by day-to-day changes in environmental levels. Motor vehicle emissions represent a major source of ambient PAH and, thus, in urban areas time-dependent variations in PAH levels are primarily traffic-related (Lintelmann et al., 2005; Schauer et al., 2003). Aerosol samples collected over 3 years for 24 h at busy roads in Munich (Germany) showed PAH contents between 1.67 ng/m^3 and 15.13 ng/m^3 (Schnelle-Kreis et al., 2001). Such background PAH levels would contribute <5% to the overall PAH burden observed during the vaping sessions (276.5 ng/m^3 to 663.0 ng/m^3) and would not be of relevance. Furthermore, we do not consider the mere presence of subjects without any vaping activity as a serious indoor source for PAH or other pollutants. Thus, control measurements were taken without room occupancy.

As shown in Figure 2D of our article, vaping e-cigarettes, either with or without nicotine, resulted in a distinct increase of urinary levels of the acrolein metabolite 3-hydroxypropylmercapturic acid (3-HPMA). In pre-post comparison, this increase was statistically significant for nicotinic vaping ($p = 0.007$), but only slightly significant for nicotine-free vaping ($p = 0.06$) due to higher standard deviations. Nevertheless, after e-cigarette use urinary 3-HPMA levels were substantially elevated in all subjects irrespective of the nicotine content of the aerosolized liquid.

Regarding FeNO, an increase is commonly considered as adverse in the field of eosinophil-related respiratory diseases. However, as indicated by experimental and observational data, e.g. (Schneider et al., 2013, 2014), neutrophilic inflammation can lower FeNO. Thus, the interpretation of FeNO needs some caution, even more in non-specific interventions. E-cigarette vapor could cause neutrophil and/or eosinophil activation, as well as changes in enzyme activity; all of these effects have some a priori plausibility. Based on this, it is not odd to consider both a reduction and an increase of FeNO as signs of inflammatory activation, depending on the circumstances. We tried to understand the opposite changes in the two studies via a time-dependent action of nicotine and consider this a sensible hypothesis. We also used FeNO only as an indicator of physiological changes in the lung and never expected changes leading from the normal range (which is fairly broad, see Dressel et al., 2008), into the asthma range. If e-cigarettes would have such tremendous effects, clinical alterations would have been observed long before. The subjects' low FeNO reflected the absence of respiratory allergies and respiratory tract infections. FeNO is known to be fairly stable in repeated measurements and we implemented pre-post comparisons within a short period of time. There were also no measurement procedures that are known to bias FeNO. Thus, we do not recognize the need for a placebo control. Whether the observed change of FeNO indicates a long-term risk, cannot be answered by a study designed to detect short-term effects. We did not pretend such an extrapolation and this question is open at present. We observed a non-trivial physiological response to nicotine-containing e-cigarette vapor, which in common parlance is called "inflammatory", as we did in the abstract; a more detailed discussion, which included a mechanism not directly involving eosinophilic inflammation can be found in the discussion.

In contrast to conventional smoking, particles related to vaping activity are not generated from a combustion process, but by direct evaporation. Due to this different operation principle, e-cigarette particles differ of course in chemical composition and size distribution from that of tobacco cigarettes. However, it cannot be deduced from this, that long-term inhalation of 1,2-propanediol nano-droplets must be completely safe. Because of the high vapor pressure of 1,2-propanediol, the dynamics of the aerosol is fast (Verevkin, 2004). In our study, particle number concentrations reached high median values (up to 88,386 particles/cm^3), with peaks at diameters 24–36 nm. Such particles are assumed to be deposited in the deeper parts of the lung. Moreover, it has been shown, that the size distribution of e-cigarette particles may change within the lung and lead to the exhalation of even smaller particles (Schripp et al., 2013). Since 1,2-propanediol has the potential to cause upper airway irritations (Wieslander et al., 2001), further research is needed to address long-term effects of exposure to e-cigarette aerosols.

Our judgment on the toxicity of nicotine was based on the available data which are internationally accepted (IPCS, 1991). Thank you for pointing to the analysis given by Mayer (2014) which became available after publication of our paper and which questions the common view on lethal doses of nicotine. On the other hand, we primarily referred to the hazards for children, and children might be more vulnerable than adults. In fact, there are data for children, e.g. regarding transdermal nicotine patches or gums or other forms of exposure (Davies et al., 2001; Smolinske et al., 1988; Wain and Martin, 2004; Woolf et al., 1997), which suggest that only

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<0.1 mg/kg are safe and 0.2 mg/kg may be sufficient to cause at least clinical symptoms. Significant physiological responses were seen after ingestion of 0.5–4 nicotine resin gums; such gums commonly contain about 2 mg nicotine each. We would therefore not be too much confident on the doses hazardous for children, in particular, if a small child consumes 1–3 ml of the nicotine liquids used in our study (equivalent to 22–66 mg nicotine), and we insist that this is an issue that has to be taken into account in considering the distribution of e-cigarettes.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

Davies, P., Levy, S., Pahari, A., Martinez, D., 2001. Acute nicotine poisoning associated with a traditional remedy for eczema. Arch. Dis. Child. 85, 500–502.

Dressel, H., de la Motte, D., Reichert, J., Ochmann, U., Petru, R., Angerer, P., Holz, O., Nowak, D., Jörres, R.A., 2008. Exhaled nitric oxide: independent effects of atopy, smoking, respiratory tract infection, gender and height. Respir. Med. 102, 962–969.

IPCS, 1991. International Programme on Chemical Safety. INCHEM, Nicotine. http://www.inchem.org/documents/pims/chemical/nicotine. htm#SubSectionTitle: 7.2.1Human data

Lintelmann, J., Fischer, K., Karg, E., Schröppel, A., 2005. Determination of selected polycyclic aromatic hydrocarbons and oxygenated polycyclic aromatic hydrocarbons in aerosol samples by high-performance liquid chromatography and liquid chromatography-tandem mass spectrometry. Anal. Bioanal. Chem. 381, 508–519.

Mayer, B., 2014. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch. Toxicol. 88, 5–7.

Schauer, C., Niessner, R., Pöschl, U., 2003. Polycyclic aromatic hydrocarbons in urban air particulate matter: decadal and seasonal trends, chemical degradation, and sampling artifacts. Environ. Sci. Technol. 37, 2861–2868.

Schneider, A., Faderl, B., Schwarzbach, J., Welker, L., Karsch-Völk, M., Jörres, R.A., 2014. Prognostic value of bronchial provocation and FENO measurement for asthma diagnosis – results of a delayed type of diagnostic study. Respir. Med. 108, 34–40.

Schneider, A., Schwarzbach, J., Faderl, B., Welker, L., Karsch-Völk, M., Jörres, R.A., 2013. FENO measurement and sputum analysis for diagnosing asthma in clinical practice. Respir. Med. 107, 209–216.

Schnelle-Kreis, J., Gebefügi, I., Welzl, G., Jaensch, T., Kettrup, A., 2001. Occurrence of particle-associated polycyclic aromatic compounds in ambient air of the city of Munich. Atmos. Environ. 35, 71–81.

Schober, W., Szendrei, K., Matzen, W., Osiander-Fuchs, H., Heitmann, D., Schettgen, T., Jörres, R.A., Fromme, H., 2013. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. Int. J. Hyg. Environ. Health, http://dx.doi.org/10.1016/j.ijheh.2013.11.003, pii: S1438-4639(13)00153-3 (Epub ahead of print).

Schripp, T., Markewitz, D., Uhde, E., Salthammer, T., 2013. Does e-cigarette consumption cause passive vaping? Indoor Air 23, 25–31.

Smolinske, S.C., Spoerke, D.G., Spiller, S.K., Wruk, K.M., Kulig, K., Rumack, B.H., 1988. Cigarette and nicotine chewing gum toxicity in children. Human Toxicol. 7, 27–31.

Verevkin, S.P., 2004. Determination of vapor pressures and enthalpies of vaporization of 1,2-alkanediols. Fluid Phase Equilib. 224, 23–29.

Wain, A.A., Martin, J., 2004. Can transdermal nicotine patch cause acute intoxication in a child? A case report and review of literature. Ulster Med. J. 73, 65–66.

Wieslander, G., Norbäck, D., Lindgren, T., 2001. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. Occup. Environ. Med. 58, 649–655.

Woolf, A., Burkhart, K., Caraccio, T., Litovitz, T., 1997. Childhood poisoning involving transdermal nicotine patches. Pediatrics 99, E4.

Wolfgang Schober*
Bavarian Health and Food Safety Authority, Department of Chemical Safety and Toxicology, Pfarrstrasse 3, 80538 Munich, Germany

Rudolf A. Jörres
Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Inner City Clinic, University Hospital of Munich, Ziemssenstrasse 1, 80336 Munich, Germany

Hermann Fromme
Bavarian Health and Food Safety Authority, Department of Chemical Safety and Toxicology, Pfarrstrasse 3, 80538 Munich, Germany

* Corresponding author. Tel.: +49 09131 6808 4242; fax: +49 09131 6808 4297.
E-mail address: wolfgang.schober@lgl.bayern.de (W. Schober)

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