Effects of Short- and Long-Term Exposure to E-Cigarette Vapour

DZL – Deutsches Zentrum für Lungenforschung
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The winners of the Balzan Prize 2019 – Erika von Mutius, Klaus Rabe, Werner Seeger and Tobias Welte – proposed to dedicate the Balzan Prize money to the cross-disciplinary project *Effects of Short and Long Term Exposure to E-Cigarette Vapour*. Given the importance of the subject, the prize winners decided to equip the scientific project with further funding from the German Centre for Lung Research (DZL). A group of DZL early career scientists started three subprojects relating to potential side effects of vaping during adolescence for the next generation, namely for their own children; the potential damage to the airways conferred by vaping; and the health effects of vaping in a large German general population (the National Cohort)

The development of the lung takes place during intrauterine life; pregnancy therefore represents a unique life stage in which harmful exposures can affect the respiratory health of the offspring for many decades to come. This has been firmly documented for maternal smoking in pregnancy which increases the offspring risk for asthma and chronic obstructive pulmonary disease (COPD). Moreover, there is increasing evidence that even exposures in the preconception period may influence the respiratory health of offspring born many years later. In addition to flavours and base liquid, nicotine is a regular ingredient in ECs, in similar or even higher amounts than in combustion cigarettes, whose nicotine content is limited to 1mg per manufactured cigarette by law (in the EU). Because nicotine readily crosses the placenta and accumulates in the foetal lung, it can adversely affect lung development. In the present subproject, in a simple model organism, namely the fruit fly *drosophila,* how preconception exposure to vaporized nicotine affects the respiratory health of offspring was investigated. The airways from male and female offspring of young virgin female flies exposed to vaporized nicotine (e-nicotine) were isolated. The airway development of the offspring was significantly disturbed upon maternal e-nicotine exposure exclusively during her own unfertilized life period. The shorter and locally constricted airways of the offspring are likely to lead to perturbations of gas flow and lower tissue oxygenation. The father's contribution to the health of his offspring was also studied. During puberty, primordial germ cells develop into spermatogonia, which in turn develop into mature spermatozoa. Therefore, environmental insults during prepubertal development may have long-lasting effects on the epigenetic make-up of mature sperm. Other findings also show that paternal exposure to e-nicotine had an impact on the airway

structure and a reduced capacity for airway development and repair in the offspring. Thus, data from the project suggest that teenage vaping can have long-term consequences for future generations and therefore an enormous socio-economic impact for decades to come.

The second project investigated potential harmful effects in a mouse model. It was found that in isolated ventilated and perfused mouse lungs, inhalation of e-cigarette vapour with nicotine or cherry, but not without any additive, induced endothelial dysfunction and oedema development. Similar to the experiments on isolated lungs, presence of nicotine in e-cigarette vapour promoted pulmonary inflammation and structural alterations after 8 months of *in vivo* exposure of mice. E-cigarette vapour without nicotine also caused slight alterations albeit to a lesser degree. The data on e-cigarette vapour with and without nicotine were published in the *European Respiratory Journal* (Roxlau *et al.*, 2023).

The third project turned towards effects on the general population. Information on e-cigarette use was obtained in the German National Cohort for more than 64,000 adult participants aged 20 to 75 years who either currently smoked conventional cigarettes or had never smoked these at the time of the survey. Of these participants, around 10% reported that they had ever used e-cigarettes or were currently using them, and the vast majority of these were dual users, i.e., using e-cigarettes and conventional cigarettes in parallel. Furthermore, the percentage of e-cigarette users was higher in men than in women, and the use of e-cigarettes decreased with increasing age from around 18% in the youngest age group to less than 5% in participants over 65 years of age. Consequently, possible health effects of e-cigarette use may particularly affect young adults. Dual users more often used nicotine-containing e-cigarette liquids than nicotine-free liquids. These findings suggest that e-cigarettes may primarily be used as an alternative way to consume nicotine alongside conventional smoking.

Across all participants with e-cigarette use, an increase in respiratory symptoms such as coughing and wheezing was observed as compared to participants without e-cigarette use, even when conventional cigarette smoking was taken into account, and this was especially observed in subjects without diagnosed respiratory disease. A higher proportion of patients tended to be treated for chronic bronchitis or chronic obstructive pulmonary disease (COPD) among e-cigarette users than among non-users. With respect to lung function adverse effects on pulmonary mechanical indices beyond the impact of conventional smoking were found, which can most probably be interpreted as mild alterations of peripheral, i.e., small airways. Taken together these data suggest that e-cigarette use may exert additional adverse effects on respiratory health beyond the well-established effects of conventional smoking, even in the absence of pre-existing respiratory disease.

The members and leaders of the German Centre for Lung Research are convinced from their own and other data that e-cigarette smoking is of major public health concern. While tobacco producers try to sell e-cigarettes as healthy substitutes of tobacco smoking, DZL's results show that ingredients of e-cigarette vapour have profound physiological effects, and they therefore envisage to pursue their research on e-cigarettes beyond the scope of the Balzan Prize project.

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