Systems toxicology analysis of cardiovascular and respiratory endpoints from ApoE<sup>-/-</sup> mice showed similar effects when switching to a candidate Reduced Risk Product, THS2.2, or ceasing smoking

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Cigarette smoking is a risk factor for chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). ApoE-deficient mice are prone to developing premature atherosclerosis and emphysema making it an ideal model in which both pathologies can be assessed simultaneously. We evaluated the effects of cigarette smoke (CS) and aerosol from Tobacco Heating System (THS) 2.2, a candidate Reduced Risk Product (RRP). ApoE<sup>-/-</sup> mice were exposed for up to 8 months to the test aerosol for 3 hours/day, 5 days/week to a target nicotine concentration of 30 μg/l. After 2 months of exposure to CS, cessation and switching groups were further exposed for up to 6 months to fresh air, or THS2.2, respectively. Multiple markers of disease progression were investigated including atherosclerotic plaque formation, pulmonary inflammation, pulmonary function and lung emphysema. Exposure to CS induced time-dependent molecular, physiological and inflammatory pulmonary responses consistent with emphysematous changes. The area and volume of atherosclerotic plaques measured in the aortic arches were higher in CS-exposed animals compared to both sham and THS2.2-exposed animals at all time-points. Significant changes in the lung transcriptome and proteome were observed in response to CS-exposure compared to sham-exposed mice. Smoking cessation and switching to THS2.2 resulted in lower activation levels compared to continuous exposure to CS and halted the rate of disease development as assessed by histopathological and molecular endpoints.

Reduced Risk Products ( "RRPs" ) is the term we use to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes.