From smoke to disease risk modelling. An integrated approach for risk assessment of potential reduced-risk tobacco products.

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Philip Morris International is committed to the development of Reduced-Risk Tobacco Products (RRTP). This requires a state-of-the-art scientific approach to product risk assessment, integrating toxicological and clinical assessment together with disease risk modelling. Tobacco products provide a unique opportunity for developing such an approach, because extensive epidemiological datasets are available to validate the models.

Analytical
Testing smoke chemistry and relative toxicity of smoke constituents from a potential RRTP is the first stage of this process.

Toxicological
Further investigations are then performed to evaluate the toxicological profile and to assess the potential for reduced disease risk.

Clinical
Short-term confinement studies to evaluate changes in biomarkers of exposure in subjects switching to potential RRTPs are performed. If clear reductions in exposure are demonstrated, longer-term clinical studies are performed to evaluate biomarkers of effect in real-life situations.

Epidemiology
Epidemiology is the classical tool to be used for risk assessment once the potential RRTP is launched.

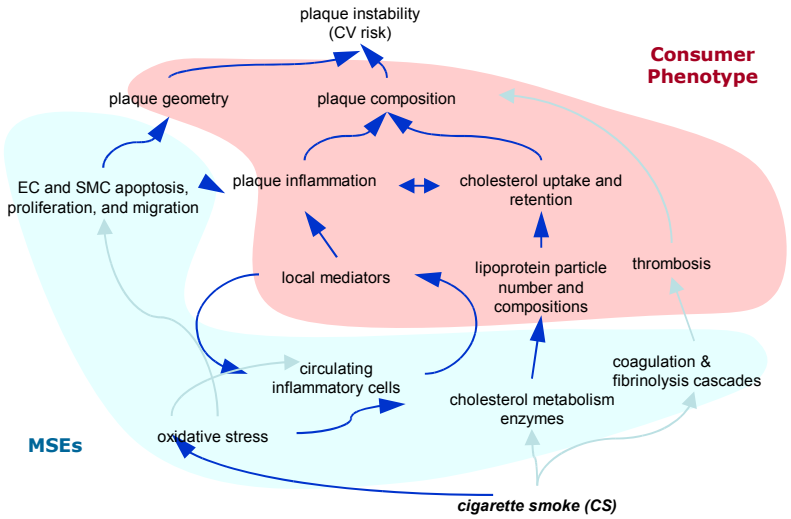
Increasing Measurement Certainty

Disease Risk Modeling
Effectively quantifying risk is a complex task. Predictive mathematical and computational models are being developed and refined for three major smoking-related diseases (cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer). This aims to apply knowledge of disease mechanisms to define the earlier studies (analytical, toxicological, and clinical) and to integrate data from well-designed combinations of studies which can lead to improved interpretation in terms of prediction of disease risk. Epidemiological data is used to validate the model.

The Atherosclerosis Model

The diagram on the right illustrates an example of a model of atherosclerosis which comprises various physiological modules (*i.e.* cholesterol metabolism, thrombosis, plaque rupture). This model is used to simulate the effect of smoking on key mechanistic pathways.

Using longitudinal data from clinical studies, changes in biomarkers of effect (mechanistic smoke effects – MSEs) are translated into an index of plaque instability, which can be used to predict overall cardiovascular risk associated with use of RRTPs.



Risk Prediction and Measurement Certainty

When extrapolated over time, early changes in biomarkers can be used to predict cardiovascular risk for both an individual and a consumer population using virtual consumer phenotypes.

The certainty of the risk is evaluated using a Measurement Certainty Index based on the validity and reliability of the integrated data.

This abstract describes an integrated risk assessment process which enables objective categorization of potential RRTPs according to their predicted risk.