Editorial

Recent Advances in Understanding of Cigarette Smoke Free Radicals and Their Relationship to Smoking Related Diseases

The links between cigarette smoking and diseases such as lung cancer, chronic obstructive pulmonary disease and cardiovascular disease are now well established. Significant efforts have been made over the last 50 years to establish links between specific smoke constituents and the onset of these smoking related diseases. In recent years risk assessment approaches have also been developed to prioritise key toxicants amongst the thousands of identified species in cigarette smoke. The main focus of these models has been on stable, easily measured smoke constituents which have documented toxicity data. However, on a quantitative population basis, these models fail to predict the observed incidence of disease.

A number of researchers have suggested alternative aspects of smoke which may also contribute to the risk of cigarette smoking. Amongst these, cigarette smoke free radicals have a long history of research findings which point to their potential to induce oxidative stress in smokers. However, due to the analytical challenges in identifying and quantifying these species, and the lack of quantitative risk data, they are not amenable to analysis using current risk assessment models. This special issue therefore reviews recent advances in our understanding of cigarette smoke free radicals with an emphasis on examining evidence for their involvement in smoking related diseases.

Investigation of cigarette smoke chemistry is a specialised field, and this issue begins with an overview of recent advances in understanding of cigarette combustion and smoke formation, with focus on the sensitivity of smoke composition and chemistry to the methods used for smoke generation, trapping and analysis. Regulatory interest in smoke composition and the current generation of cigarette smoke risk assessment models are also discussed (Liu *et al*.).

Interest in the chemistry of cigarette smoke free radicals is driven primarily by evidence for the participation of *in vivo* free radical species in disease processes, particularly oxidative stress. Current understanding of the contribution of oxidative stress to smoking related diseases is summarised by Fearon *et al*., together with evidence for the involvement of reactive oxygen species, reactive nitrogen species and biological free radicals. A review of the role of these reactive species *in vivo* leads to the conclusion that reactive oxygen species are major species involved in damage at molecular, cell and organism levels. An important biological mechanism for the generation of oxygen free radicals is decomposition of hydrogen peroxide to hydroxyl radicals via the Fenton reaction (Sharan *et al*.). Biomarkers of oxidative stress have been used as a surrogate measure of radical damage in smokers; these biomarkers are critically reviewed in light of the consistency of their relationship with smoking status (Lowe and Cemeli).

Despite the consensus which has emerged over the role of biological free radicals in oxidative stress the specific involvement of cigarette smoke free radicals in these disease mechanisms has not been unambiguously established. A major uncertainty in establishing any link between cigarette smoke free radicals and smoking related diseases is the question of whether smoke free radicals act directly to cause biological damage, or *in-vivo* radical species are generated by the action of other smoke constituents. A review of the cytotoxic effects of some gas phase cigarette smoke constituents shows that a number of these species undergo metabolic activation in mammalian tissues via oxidation to radical species and thereby exert their toxic or carcinogenic effects. Other smoke constituents can also disturb the anti-oxidant/pro-oxidant status within the body (Starvidis and Baltalzis). Given the importance of hydrogen peroxide to oxygen metabolism within the body, and oxidative stress in particular, assessment of the contribution of cigarette smoke sourced hydrogen peroxide in comparison to other exogenous sources, as well as the endogenous levels *in-vivo* helps to cast light on the relevance of cigarette smoking to oxidative stress. Review of published hydrogen peroxide yields and estimates of exposure from cigarettes and of the body's defences against exogenous hydrogen peroxide throws doubt on cigarette smoke as a significant source of hydrogen peroxide within the body. However, these calculations do not discount the contribution of other smoke species, such as sources of the semi-quinone radical, to the body's overall hydrogen peroxide burden (Menshov and Trofimov).

An essential contribution to understanding of the potential toxicity of cigarette smoke free radicals lies with accurate identification and quantification of the species in smoke. Experimental approaches to free radical measurement are discussed by Robinson and Johnson, and the limitations of electron paramagnetic resonance spectroscopy are highlighted. In contrast, the use of this technique in tandem with spin-trapping and mass spectrometry techniques is proving to be a powerful diagnostic tool for structural characterisation.

Understanding the formation mechanisms of gas phase and particulate phase cigarette smoke radicals has seen some further developments. A major paradox in this area is the apparent inconsistency between the extreme reactivity of smoke radicals and their unexpectedly long lifetimes, ranging from tens of seconds in the gas phase to hours or even days in the particulate phase. It is the unexpected longevity of these species which means that they have the potential to enter smokers bodies and contribute to oxidative stress and other acute disease processes. Explaining this paradox is consequently an important contribution to understanding their potential toxicity. The steady-state mechanism for gas phase radicals was proposed nearly 30 years ago based on the pioneering work of Pryor and his colleagues, yet the latest evidence suggests that this mechanism requires further investigation. Wooten reviewed the implications of recent identification of a new class of organic gas phase radicals, and recent measurements of NO_2 production from cigarettes in which the use of a Cambridge filter pad to separate gas and particulate phases of smoke appears to modify NO/ NO_2 smoke chemistries. These observations do not conform to the established steady-state mechanism used to explain the observed lifetimes of gas phase radicals (Wooton). Recent progress in understanding radical production from the decomposition of tobacco constituents such as biopolymers and phenolic precursors, the effect of smoke ageing on radical generation, the stabilisation of radicals by condensed smoke particulates, the impact of metal redox reactions (Dellinger *et al*.) and a novel metal-independent route to hydroxide radical formation via halogenated quinines and hydrogen peroxide are also discussed and continue to highlight the complex nature of the smoke matrix (Zhu *et al*.). Free radicals play a role in the formation, oxidation and gasification of tobacco and biomass chars. Their thermal degradation and the influence of inorganic ions and water in these chemical reactions are also essential parts of the complex picture and these are discussed in the context of tobacco combustion and the formation of tobacco smoke constituents by Gao and Feng.

These articles brought together in this special series highlight recent progress in cigarette smoke free radical science, but also identify some of the remaining areas of uncertainty in this field. Resolution of these uncertainties represents valuable but challenging research opportunities across a wide range of scientific disciplines.

We are grateful to the authors for taking the time out of their busy schedules to write these review articles, and to the editors of Mini-Reviews in Organic Chemistry for the opportunity to organize this special issue.

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