

BRITISH AMERICAN TOBACCO
Science & Technology

2015 report



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About this Report

This is a British American Tobacco p.l.c. report describing some of the activity of British American Tobacco Group Research & Development in the UK. References to 'British American Tobacco', 'we', 'us' and 'our' when denoting opinion or activity refer to British American Tobacco Group Research & Development.

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e have spoken for some years about the importance of tobacco harm reduction for British American Tobacco, for our consumers and for regulators. We believe that developing less risky tobacco and nicotine products is transformational in many dimensions, and know we must take a strong lead in doing this.

In 2013, we were the first international tobacco company to launch an e-cigarette, Vype, in the UK. Since then we have continued to innovate in the category, and have since launched three new products, Vype ePen, Vype eStick and Vype eTank and a wide range of liquids, and are expanding our geographic footprint. We are also the first tobacco company to receive, in 2014, a medicines licence for a nicotine inhalator called Voke, and in 2015 we launched a tobacco heating product. To develop less risky choices for smokers that give them a true alternative choice to cigarettes will require strong consumer insights, tremendous innovation, and comprehensive science to ensure these next generation products do offer reduced-risk potential. We think it is important to offer a range of products, including tobacco heating products, e-cigarettes and licenced nicotine products because consumer needs vary.

The next few years are incredibly important and will determine whether the opportunity of tobacco harm reduction becomes widely adopted. Just as we saw with snus, some regulators have prohibited e-cigarettes, and the World Health Organisation has not been very supportive. We are working hard to ensure that our products are fully characterised and

understood, and are as safe as possible.

New nicotine products should continue to increase in relevance, which is why we have expanded our research efforts to focus on these emerging product categories. The swift evolution of these categories and the diversity of available products means that we are constantly pushing the boundaries to develop more advanced mechanics and better performing products to give our consumers what they want. Our research efforts continue to focus on understanding how the different product categories perform under various conditions and how consumers use them; the constituents of the aerosol, as well as the possible creation of thermal breakdown products; and the effects on the body of inhaling the aerosol.

By working together with our consumers, we better understand their needs and can offer greater expertise and insight into areas such as materials science, formulation chemistry, and engineering. We must also play our part in the ongoing regulatory debate, providing the data to enable regulators around the world to make evidence-based decisions. We have embraced and will continue to embrace new scientific disciplines to create the knowledge needed to ensure the potential of this category is realised as well as our intention to be a leader in these new product categories.

Through this our second Science and Technology Report we continue to build on our heritage of scientific engagement and transparency, and maintain our desire to work with others to deliver the opportunities that tobacco harm reduction offer. □



DR DAVID O'REILLY
Group Scientific and R&D Director

David first joined us in 1991 with a PhD in molecular virology and he was appointed to the Management Board of BAT in 2012. He directs the company's scientific research, which seeks to develop innovative reduced-risk products along with the tools to test and substantiate their risk potential. He has also been the driving force behind the investment and growth of BAT's R&D into a forward-looking, consumer-led, multidisciplinary environment. Previously, he led our programmes in corporate social responsibility and public health policy and engagement.



Movie 1 of 8 > **Dr David O'Reilly** — R&D at BAT



Movie 3 of 8 > **Dr Kevin McAdam** — Evolution of e-cigarettes



Movie 2 of 8 > **Dr Christopher Proctor** – Stewardship and next generation products



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Movie 6 of 8 > **John McCaughey** – Aerosol science



Movie 8 of 8 > **Sarah Cooney** – Our open approach

STEWARDSHIP AND NEXT GENERATION PRODUCTS

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he risks of cigarette smoking to human health are very well understood. Given that we have had an R&D unit at BAT since 1956, we have decades of expertise, as well as published research, on tobacco and tobacco smoke toxicants. We have completed a multi-year research programme, aimed at trying to reduce the risks associated with conventional cigarettes by using a number of toxicant-reducing technologies. Although this research gave some encouraging results, we found few differences in clinical studies between biomarkers of biological effect in volunteers who were switched to reduced-toxicant prototype cigarettes and those who continued to smoke regular cigarettes. Through well-established principles of toxicology and safety risk assessments, our product stewardship approach, therefore, focuses on ensuring that any ingredient, material, or design feature used in our products do not add to the inherent risk of cigarette smoking.

The research taught us that if we hoped to find tobacco or nicotine alternatives for cigarette smokers that might be determined to be less risky than cigarettes, we probably had to substantially reduce the toxicant emissions over and above what is possible, even with multiple toxicant-reducing technologies, in cigarettes.

We began with Swedish snus, given the well-documented epidemiological data accumulated in Sweden showing sole use to be far less risky than cigarette smoking. Snus is not risk free, and, as we began developing our own products, even though they complied with industry standards for manufacturing and low levels of toxicants, such as nitrosamines, we needed to develop our own understanding of how the products worked and were used by consumers. We completed and published surveys of behavioural use, developed and used new toxicological tests, undertook a

pharmacokinetic study, and did extensive chemical characterisation in a manner consistent with consumer use. These data were all used to build our knowledge on how to apply our own stewardship standards to snus, ensuring that we minimised risks associated with our products to every extent possible. However, as a product with potential for reducing risk, snus received little regulatory support, being banned in the European Union outside Sweden, and little consumer interest in the markets where we tried to introduce it.

More recently, we have focused on two other potentially reduced-risk product categories, tobacco heating products (THPs) and electronic cigarettes (e-cigarettes). We also hope to add licensed medicinal nicotine products, but will not discuss this category further in this report as these types of products are subject to quite different regulatory oversight and procedures from the THP or e-cigarette categories.

We were the first international tobacco company to launch an e-cigarette when Vype was marketed in the UK in July, 2013. Just as with snus, entering into a new product category required an accelerated research programme to develop understanding of how the products work, what emissions they produce, and how consumers were likely to use them, so that our testing regimes could be set up to be relevant to consumer use.

To add to the complexity of testing, the e-cigarette category is much broader than that of, for example, snus. We began with disposable 'cig-a-like' devices with simple formulations, but rapidly developed a range of devices with a wider range of flavours and battery sizes, and are currently introducing new innovations at a rapid rate. Emissions from e-cigarettes are very different from those of cigarettes; they are much simpler and substantially

lower in certain toxicants that are associated with conventional cigarettes.

To investigate toxicants not seen in cigarettes, given possible interactions between formulations and device materials, and, therefore, we have had to take a fresh approach to e-cigarette stewardship, with a strong focus on materials and formulations use. We have taken the approach of non-targeted chemical characterisation of the aerosols to ensure we can develop a full understanding of what our e-cigarettes are emitting. In parallel, we have had to develop new techniques to measure the ways in which vapers use these products and to establish toxicological tests sensitive enough to deal with the significantly reduced levels of toxicants produced by them.

In stewarding these new product categories, it is critical for us to demonstrate that innovations don't give rise to unintended consequences, including increased exposure and risk. We readily share our approach to stewardship of next generation products with the regulatory and scientific community. We have already published several papers on this topic and expect to publish many more in the coming years.

In addition, we expect to undertake a broader set of research studies, including chemical toxicological, clinical, and population studies, to assess next generation products as potentially reduced-risk products. As strong supporters of the move to replace animal testing we will continue to invest in and collaborate on *in vitro* models, and are excited about the emergence of systems science.

We believe that it is essential to provide

regulators with confidence in the potential for next generation products, through robust science. A key challenge is agreeing methodologies and implementing standardisation across the various tests. As such, we are working with standards organisations, such as the British Standards Institute and the French organisation, AFNOR, to contribute to what may constitute sensible industry-wide standards.

It would be beneficial if a single scientific framework could be agreed upon by all stakeholders (ranging from regulators, to public health bodies, to industry). This should in turn allow an evidence-based regulatory approach for next generation tobacco and nicotine products that would include an agreed mechanism for substantiating exposure- or health-related claims. Transparency is critical and can be facilitated through the publication of data and working in an open and collaborative manner. The recent advent of workshops moderated by independent organisations, such as the Institute for In Vitro Sciences, is an example of where stakeholders can come together with a view to debating and then agreeing a science framework that could be used for evidence-based regulation of products across the risk spectrum.

Today we stand at a defining moment in the development and future regulation of tobacco and nicotine products. We believe it is critical for everyone with an interest in this emerging field to remain open to dialogue and collaborative working where possible, to ensure the advancement of an evidence-based approach to substantiating risk for next generation products. □



DR CHRISTOPHER PROCTOR
Chief Scientific Officer

Chris is our Chief Scientific Officer and also Group Head of Scientific Product Stewardship based at R&D Southampton. His teams look at product safety issues and are working on research methodologies to substantiate the reduced-risk potential of next generation products. Chris regularly engages on various topics related to tobacco regulatory science and has presented at multiple workshops of the US Food and Drug Administration in recent years.



TOXICANT REDUCTION – FROM SEED TO SMOKE



obacco (*Nicotiana tabacum*), a member of the nightshade family (*Solanaceae*), is an important plant biology model. It was the first plant adapted for tissue culture and to be genetically transformed, which were crucial advances in the early development of molecular plant biology.

Our tobacco biotechnology research programme focuses on basic research on the tobacco genome and practical plant modification research. R&D Cambridge seeks to develop biotechnology solutions that will help to push characteristics of tobacco leaf in ways that are consumer acceptable. Our research programme has several key areas: toxicant reduction strategies, sustainability of tobacco agriculture, and genomics and molecular breeding tools for faster delivery of solutions.

The levels of toxicants in tobacco aerosol come not only from the physical design parameters of cigarettes or tobacco-heating products (THPs), but also from the physical and chemical properties of the tobacco and other ingredients that are burned or heated. The diverse range of effects that can impact the levels of toxicants make modifying elements of tobacco leaf to reduce levels of harmful toxicants while preserving the integrity of the plant itself a major challenge. The properties can vary due to multiple factors, including the environment in which the tobacco is grown (climate, soil, etc.), position of the tobacco leaf on the plant, the genetic characteristics of the tobacco plant, and the way that the tobacco leaf has been harvested, cured, and processed.

A key part of our work lies in understanding the genetics of the tobacco plant and which metabolic or biochemical pathways and genes drive the characteristic traits of interest, so that we can apply

a suite of biotechnology tools (including molecular biology, genomics, biochemistry, and systems biology) to understand and modify these traits. The use of transgenic and marker-assisted breeding techniques means we use genetic modification (GM) and non-GM (molecular breeding) approaches in our research. We understand that the use of GM plants remains controversial in some countries, and it remains BAT's policy to not use GM tobacco in any of its commercial products worldwide. However, GM is an important technology within our research programme, as it provides opportunities for toxicant reduction to be explored and enables investigation into solutions to address challenges that other technologies may not be able to tackle so effectively. GM technologies allow the rapid investigation of target genes or pathways as a research tool to help narrow down the areas of interest, before they are translated into non-GM solutions that BAT can then look to apply commercially.

As well as changing the quality of tobacco leaf, BAT is developing solutions to help its farmers grow tobacco sustainably, by breeding plants that will give increased yields and reducing the required resources (chemicals, water etc) for growth.

Toxicant reduction strategies — tobacco-specific nitrosamines (TSNAs). Nitrogen is a nutrient essential for growth. Tobacco, like other plants, is very efficient at taking up and using nitrogen or related compounds. Excess nitrogen is stored in the leaves and what the plant does not use during its life cycle remains in the leaf through to harvest, largely as nitrate and nitrite oxides. The remaining nitrogen compounds contribute to the formation of TSNAs, which in turn contribute to



DR KIERON EDWARDS
Molecular Breeding Manager

Kieron's background includes biological sciences; ranging from genetics to bioinformatics and systems biology. After his PhD in plant genetics, Kieron's post-doctoral work focused on circadian plant biology. He joined us in 2008 and is now responsible for developing and implementing molecular breeding capabilities in tobacco. He also manages several critical projects, including identification of genetic markers and predictive biomarkers for complex traits.

the toxicity of tobacco smoke; exposure to these compounds has been linked to several cancers. TSNAs are formed when nicotine and related nitrogen-containing compounds undergo a chemical reaction during harvesting and curing of the leaves.

Using the genomics programme as well as available scientific literature, we identified sets of genes that influence the uptake, transportation, and metabolism of nitrogen in plants. We then identified a suitable target gene (for an enzyme in the nitrogen pathway) and devised a strategy for developing a new tobacco variety that would produce reduced levels of TSNAs through incorporation of the additional gene in the tobacco plant's DNA. Biochemical analysis of these new plants confirmed a decrease in the levels of some TSNAs (specifically, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or NNK, and N'-nitrosornicotine or NNN) in the cured tobacco when compared with control plants.

Toxicant reduction strategies – heavy metal reduction. Heavy metals are a major concern in tobacco smoke because they are linked to cancer and cardiovascular disease. Many plants absorb heavy metals (for example, cadmium, mercury, lead, arsenic, and chromium) through their roots. In most plant species, the heavy metals are stored within the roots, but tobacco is unusual because the heavy metals are translocated to and stored in the leaves. We have been working to identify the genes responsible for heavy metal translocation to identify whether tobacco could be modified so that the heavy metals remain in the root. Research has been on target genes linked to a promoter (gene switch) that is specific for the roots; engineering of this gene might ultimately result in any metals transported into the plant root remaining there.

Agricultural sustainability – reducing use of chemicals. Side shoots or 'suckers' have to be manually or chemically removed by the farmer, which is a significant outlay for them. If suckers are allowed to grow, however, yield, productivity, and quality of the leaf will decrease. Our aim is to prevent or decrease this growth, using a specific promoter that is active in the leaf axil (the point in the plant of side shoot growth), thereby reducing use of crop

protection chemicals (so-called sucker-cides) and improving the sustainability of tobacco agriculture. The promoter is linked to genes that either interrupt the cell cycle, which impairs growth, or produces termination signals that can lead to cell death and no sucker growth.

Recent successes

We have sequenced the large and complex tobacco genome (around 50% larger than the human genome), which has enabled the mapping of 69,500 genes and advanced our understanding of how the tobacco plant functions. Genome-scale sequencing, assembly, and characterisation of the tobacco genome is a major accomplishment that took nearly 3 years.

As well as providing insights into gene-directed growth, regulation, and biochemistry, the sequence can be used as a reference to identify genetic differences between different varieties of tobacco, providing the potential to breed new cultivars with improved characteristics for industrial applications. These could include cultivars that are less likely to produce harmful compounds upon burning or, through understanding the genetic regulation of metabolism, for example, with improved yields.

We aim to utilise the genome data in combination with other '-omics' data types, such as transcriptomics, which measures gene expression, to better understand the metabolic and biochemical pathways driving the qualities of tobacco leaf. Improving the quality of the genome sequence and extent of annotation and information related to the genome will aid this process greatly. Such improvement has many facets and will require a significant amount of work, so there is a great deal of potential for collaboration in this area; it is too big a task for any one party to carry out in isolation.

Aims for future

- » Develop greater understanding of the genetic drivers for toxicant precursors in tobacco, sustainability traits, and leaf quality
- » Improve the quality of the tobacco genome sequence to a gold standard level to support continued greater understanding of the tobacco plant
- » Grow our molecular breeding programme, developing genetic markers for key traits of interest



JOHN MCBREARTY
Quality Assurance Manager

Before joining us, John worked for 20 years in the pharmaceutical industry at global companies such as Cyanamid, Wyeth, and Pfizer, where he gained a wide range of qualifications, skills, and experience to ensure processes and systems adhere to regulatory standards within the R&D environment. As R&D Quality Manager, John is responsible for ensuring our systems and processes meet existing regulatory requirements, are well prepared for future requirements, and adhere to Good Research Practices.

GOOD RESEARCH PRACTICE — SECURING INNOVATION

Good Research Practice (GRP) describes the culture and processes that R&D have adopted to ensure that our scientific research is conducted in a manner that aligns with industry, business, consumer, and regulatory expectations.

Originally introduced by the Medical Research Council in the UK to establish common standards among its many research partners across the globe, GRP is now accepted in most well-known research institutes and is becoming a minimum standard benchmark for conducting any type of scientific research. Although not a regulatory requirement itself, GRP is a standard that enables R&D to be responsive in meeting current and future regulatory requirements, such as good laboratory, manufacturing, and clinical practices, and ISO standards.

We build the principles of GRP into our standard operating procedures and test methods. We have incorporated GRP into the R&D electronic quality management system that manages and governs our study plans, scientific reports, procedures and training records, and is integrated into our

data-capture technologies. In the ever-changing R&D environment, this software platform has been aligned to support product development design and control documentation needs. This allows our researchers across R&D to access the necessary procedures and information for conducting their work and publishing their results.

As well as building common understanding across R&D to improve the integrity of our data and results and how they are used, GRP also provides a common research platform already used in other organisations. Thus, GRP ensures transparency in the research standards applied in R&D.

Ensuring that GRP underpins all our scientific research not only provides confidence when publishing in peer-reviewed scientific journals, but also enables us to attain external licences or accreditation for performing our research work. Most recently our analytical laboratories achieved accreditation from United Kingdom Accreditation Service in maintaining a global standard for competence in testing and calibration laboratories



CHEMICAL CHARACTERISATION OF NEXT GENERATION PRODUCTS



In accordance with our commitment to the stewardship of new technologies and products, we have invested in leading-edge capabilities for the evaluation of product chemistries. Assessing the chemical and toxicological profiles of e-cigarettes and tobacco-heating products (THPs) presents technical challenges, especially when a comparison with tobacco cigarettes is required for context.

Historically, the chemical evaluation of cigarettes and cigarette smoke has focused on a relatively small number (44) of substances, the so called Hoffmann analytes. These substances largely comprise members of several chemical classes (including tobacco-specific nitrosamines or TSNAs, carbonyl compounds, aromatic compounds, and trace elements) that have been frequently identified by numerous researchers in tobacco smoke, are known human carcinogens or other human toxicants, and are present at abundances expected to cause adverse health effects in humans. In addition to the Hoffmann list, however, over 6,000 other chemicals have been identified in cigarette smoke.

In contrast, our knowledge of the trace chemistry of e-cigarettes and THPs is much less complete, largely because these products are based on relatively new technologies that are still undergoing significant evolution. For example, e-cigarettes are available in several formats, including disposable 'cig-a-like' products, replaceable cartomiser systems, and refillable designs, each with many variations in the materials used and power. We evaluate the chemistry of new products in order to ensure that any novel substances are identified and assessed, and to do this we have developed non-targeted analytical techniques. Although

established targeted methods are used to look for and measure very accurately a small number of substances, non-targeted methods are designed to detect the widest possible range of substances. For example, the aerosol emitted by a THP might yield over 700 chromatographic peaks. However, because no single non-targeted method can be compatible with the very wide range of substances that could potentially be present in e-cigarettes, we must develop additional methods to maximise this capability, including liquid chromatography-based methods.

Recent successes

An area in which we have made significant advances is the application of adsorption sampling of aerosols, gas chromatographic separation, and mass-selective detection. Briefly, our approach comprises drawing the aerosol through a small tube containing chemical adsorbents, which retain most of its constituents by a combination of impaction and chemisorption. When the tube is heated, the aerosol constituents are released, trapped, and passed into a gas chromatograph (GC). After separation into their individual components in the GC, the aerosol constituents are eluted and passed into a time-of-flight mass spectrometer (TOF-MS).

The information produced using this thermal desorption GC-TOF-MS method has enabled us to detect substances in aerosols from e-cigarettes and THPs at very low concentrations – a few nanograms per puff, or less. The sensitivity of the method allows structured evaluation of potential consumer exposure (for example, by applying thresholds of toxicological concern). Although not intended to be accurately quantitative, the method is internally



DR CHRISTOPHER WRIGHT
Head of Analytical Science

As the Head of Analytical Science, Chris is the chemistry lead for analytical strategy and scientific practice. He is an experienced analytical chemist with nearly 30 years of research experience in the areas of food, environment, consumer products, and tobacco. He joined us in 2008, with a focus on improving the robustness of toxicant analysis and the development of exploratory chemical screening programmes. Chris has worked on committees for the International Organization for Standardization, Royal Society of Chemistry, and Ministry of Agriculture, Fisheries and Food/Department of Health scientific committees.

standardised and gives us orders of magnitude of the concentrations of the aerosol constituents. Results to date are consistent with other published research demonstrating that e-cigarette aerosols contain much lower concentrations of certain toxic substances than cigarette smoke.

A major technical challenge has been the very wide range of amounts of aerosol constituents. For instance, glycerol can comprise more than 50% of the mass of an e-cigarette aerosol, whereas substances of potential concern may require monitoring at levels below 0.0000001%. Measurement at both ends of this range simultaneously is physically impossible. Therefore, we have developed and

optimised an approach that automatically diverts large chromatographic peaks away from the TOF-MS to a different (flame ionisation) detector. This approach, which is highly reproducible, avoids overloading the TOF analyser and provides data that can be processed further.

We have also collaborated with researchers at the University of Liège in Belgium to develop two-dimensional GC (GCxGC) methods with which to evaluate our technologies. The advantage of GCxGC is significantly increased chromatographic capacity to separate complex mixtures into their individual components, which in turn improves our confidence in the chemical identity of the detected substances. These techniques allow us to demonstrate bulk and specific chemical differences between our technologies, visually and statistically (Figure 1).

The processing and interpretation of such complex data sets also presents technical challenges, which we have addressed by developing, in conjunction with a commercial partner, Genedata, a suite of chemical informatics tools to visualise and statistically analyse our data. The Genedata Expressionist software platform allows us to take data from many replicate analyses of a sample, build composite data files that capture all the relevant features and sort, cluster, and compare the information with a wide range of peer-validated statistical algorithms. These analyses enable us to make incremental chemical profile comparisons between established or well-characterised products and novel products or new variants to observe key chemical differences or correlations between different suites of chemicals. This new knowledge supports product assessment, product development, and the extension of technical standards.

Aims for the future

- » Apply next generation multidimensional (GCxGC) chromatography and accurate mass technologies to increase the confidence of identification of substances in e-cigarette and THP aerosols to 90% or greater; this approach has already enabled us to identify substances in e-cigarette aerosols quickly that would otherwise be extremely difficult, and in some cases almost impossible, to identify
- » Develop high-mass-accuracy spectral libraries for high performance liquid chromatography/TOF mass spectrometry applications □

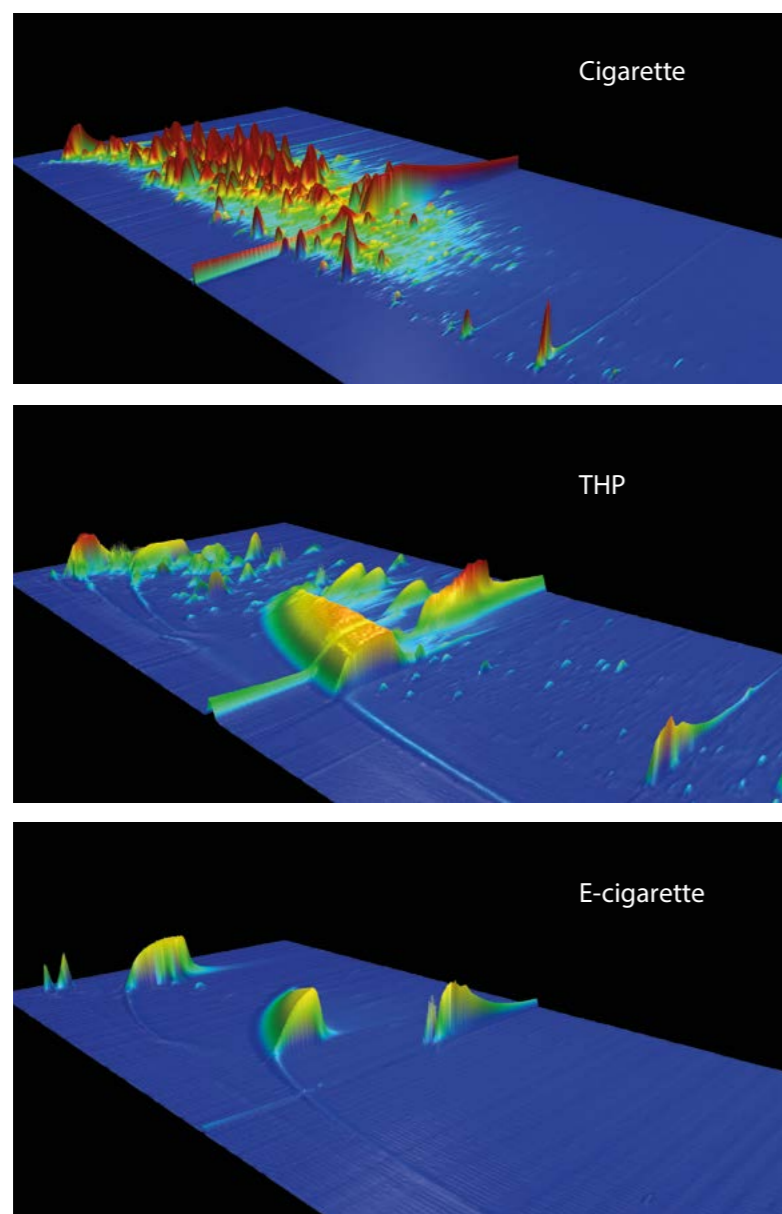
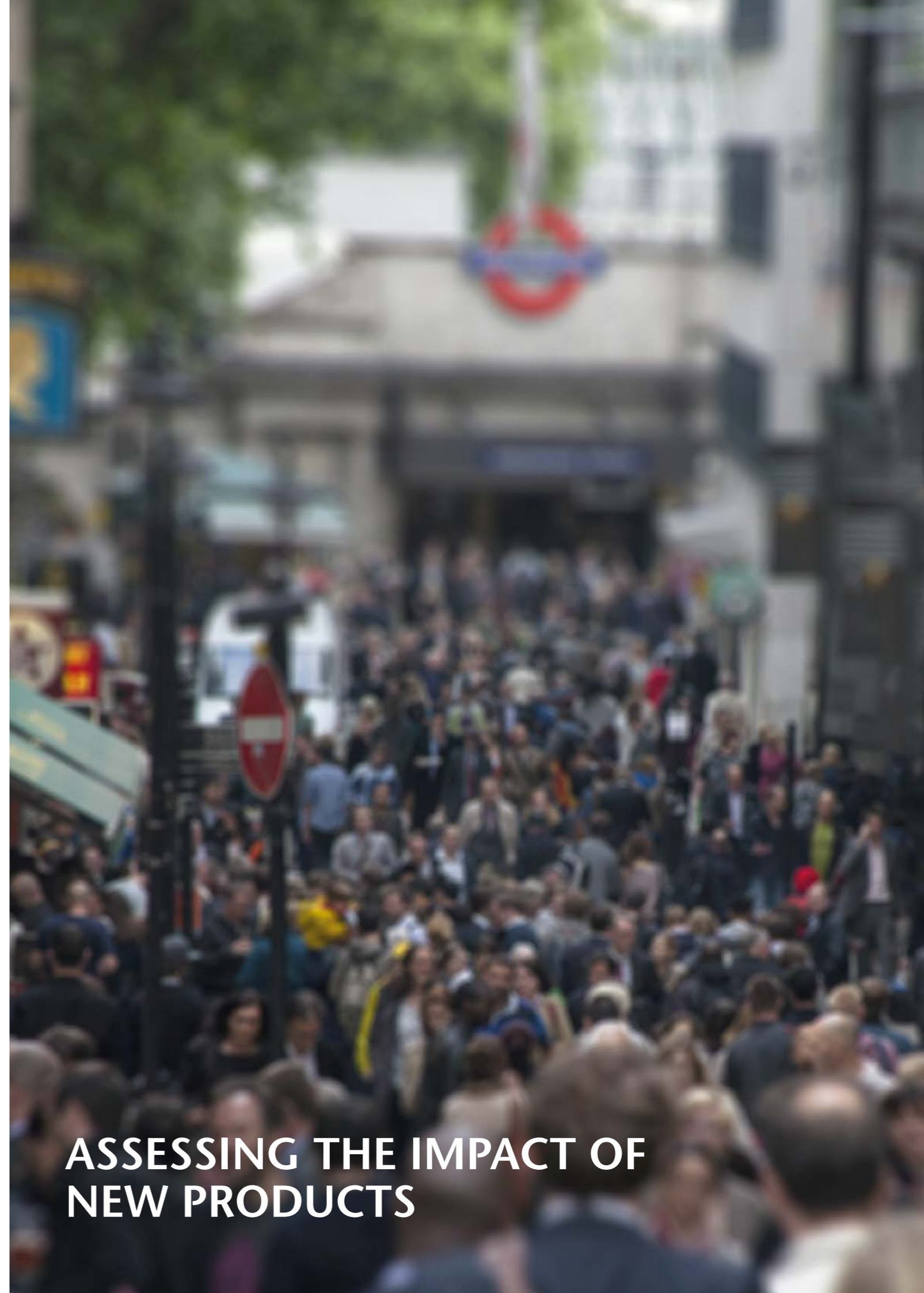


Figure 1: GCxGC-TOF-MS chromatograms of cigarette smoke (solid phase micro-extraction sampling) and aerosols from next generation products (thermal desorption sampling). The dynamic range of the e-cigarette chromatogram is compressed by the high levels of glycerol in the aerosol.



ASSESSING THE IMPACT OF NEW PRODUCTS

W

hen the Family Smoking Prevention and Tobacco Control Act was introduced in the United States in 2009, the US Food and Drug Administration (FDA) described it as a population approach to minimising the harm caused by tobacco use. The agency was explicit in its wish to ensure that any regulations introduced should have positive public health outcomes, not only for smokers but also for ex-smokers, non-smokers, adults, and vulnerable populations. The FDA's industry guidance for introducing new products – whether through substantial equivalents, pre-market tobacco applications, or modified-risk tobacco product (MRTP) applications – expects tobacco companies to provide data on the likely impact a new product will have on the population as a whole.

This guidance seems consistent with approaches taken by regulators outside the USA. It could be argued, for example, that the EU's ban on snus outside Sweden is unrelated to the product's effect on individual risk, but the fear that its introduction will increase initiation into tobacco, and eventually lead consumers to cigarette smoking. This fear has proven to be unfounded in the case of snus consumers in Sweden¹.

The potential impact of a new product is highly complex, as it is contingent on not only who consumes the product and in what amounts, but also how and why it is used (eg, in combination with other nicotine products or as an aid to quit smoking). Moreover, behaviours are dynamic and are likely to change over time, for instance as consumers switch products or quit. To assess fully the potential impact of a product on a population, a model must encompass many variables and be sensitive to changes. Our approach, which aligns with previous models recognised by regulators, is based

on a compartmental model using system dynamics. We think this is the best way of realistically representing complex behaviours in an intuitive and transparent way.

The model takes into account all types of smokers, including dual users of cigarettes and other tobacco products; factors such as age, gender, and consumption; and types of behaviour, including experimentation, initiation, regular use, and cessation (Figure 1). We try to reflect patterns of usage, utilising what's happened in the past to predict what might happen in the future. The model is updated every year with birth, death, and migration rates to provide long-term projections of the impact of a new product.

By using a *status quo* scenario (in which nothing changes) as a benchmark, such models can answer 'what if?' questions and predict how outcomes will change over time.

The uptake of a new product is likely to be influenced by a wide range of factors, including fundamental characteristics, actual performance, availability, price, smoking history of the consumer, and, potentially, for MRTPs, perception of its relative health risks. Thus, any studies performed before the product is launched can only broadly suggest what might happen after the product is introduced.

In the case of MRTPs, FDA guidance suggests post-market surveillance as a way of determining the actual population impact a product has after launch. As 'real' post-market data are acquired on usage patterns and fed into our model, we should be able to estimate the potential long-term morbidity and mortality effects on the population.

To enable information to be collected soon after a new product is introduced, an active sampling approach could be used to obtain information directly from

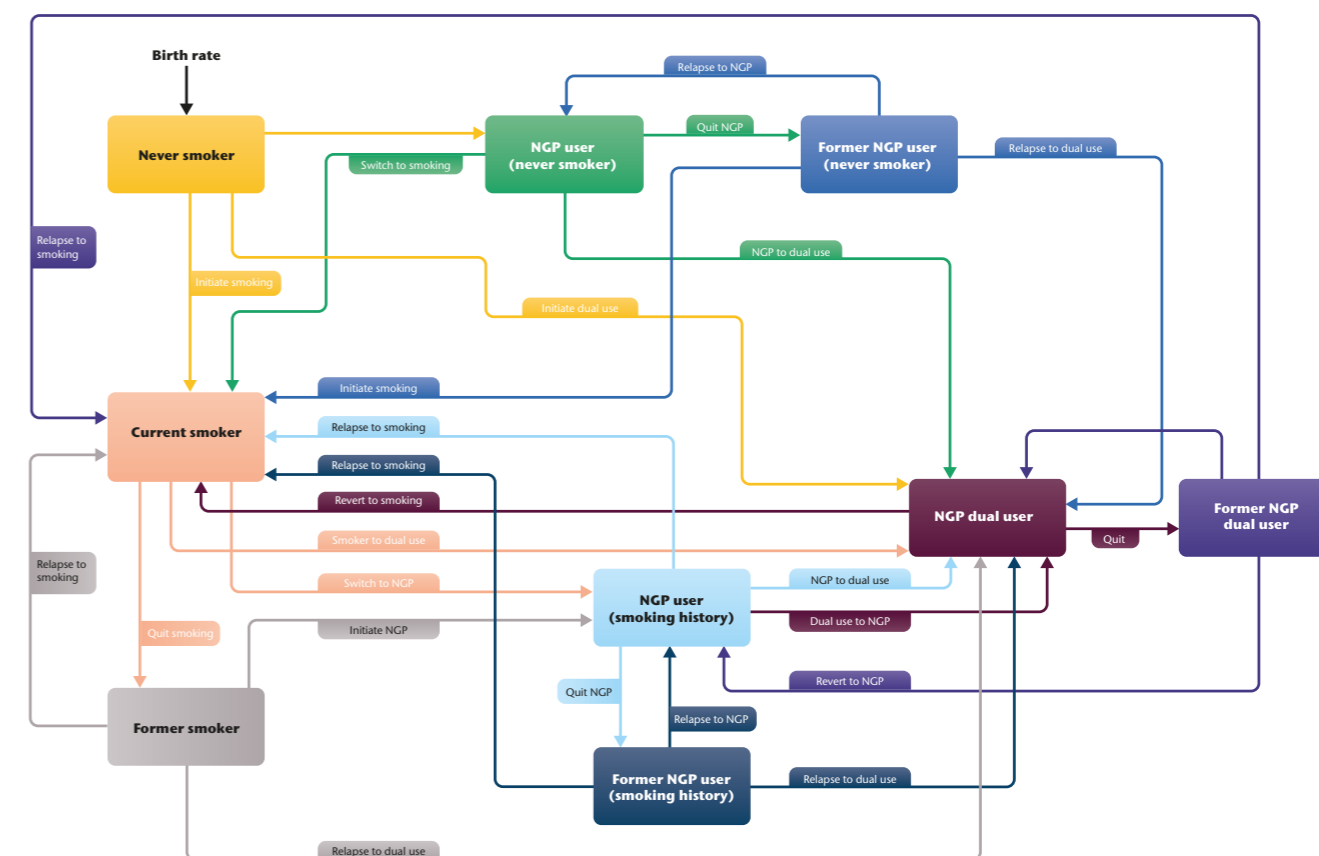


Figure 1. System dynamics model illustrating the introduction of a novel reduced-risk tobacco or nicotine product in a market.



OSCAR CAMACHO
Computational Tools and
Statistics Manager

Oscar holds a BSc in Mathematics with Statistics, as well as an MSc in Biometrics, and an MSc in Applied Bioinformatics, before joining us in 2010 as a technical specialist in statistics. He now leads a group of data scientists providing support in statistics, bioinformatics and mathematical modelling to R&D; guiding our scientists to ensure sound data analysis techniques, data dissemination and design of efficient experiments are applied throughout studies' life cycle.

consumers on current and historical use of tobacco and nicotine products. Parallel to this, the introduction of a system to gather consumer comments, including any adverse health events, could also provide valuable insights.

The ability to collect meaningful post-market information will depend on how popular a new product becomes. As popularity grows, cross-sectional studies could observe the use of the product in the context of other products. Prospective observational studies could also be used to look at different usage patterns, and if the numbers of study participants are sufficient, changes in health-related measures could be assessed.

The appropriateness of tobacco companies undertaking surveys with non-smokers, and particularly those who are underage, presents a challenge. Our marketing principles do not allow such research and, therefore, if necessary, we would need to develop, with regulators, third-party approaches to collecting such data.

Recent successes

We are working with external experts to develop and validate questionnaires and other research tools that can provide insights into the likely uptake of novel products before they are actually launched. These address factors such as intent to use, risk perception, and abuse potential. We have

made good progress in developing questionnaire-based tools to assess the impact of novel products on current smokers².

Additionally, we are analysing the integrated output from population studies and other data (eg, relative risk with respect to specific endpoints) to develop a dynamic population model for predicting the impact of novel products.

Our population model has been built and is currently undergoing validation testing with data sets on e-cigarette use in the UK and with historic data on snus use in Sweden.

Aims for the future

- » In collaboration with other external groups, develop suitable protocols for:
 - Abuse liability assessment
 - Consumer (smokers and non-smokers) risk perception and comprehension
- » Build a framework for potential product uptake by various groups
- » Develop a tiered approach for post-market surveillance
- » Publish the first analysis using the dynamic population model □

1. ESTOC. Factsheet on Gateway to Smoking. <http://estoc.org/library/fact-sheets> (accessed Nov 17, 2015).
2. Ashley, M *et al.*, Pilot study to evaluate selected questions of subjective measures of individuals' motivations for, and use of, tobacco and nicotine products. Presented at CORESTA SSPT 2015; Jeju, South Korea: 4–8 October 2015.

LEADING THE WAY IN PRODUCT RISK ASSESSMENT

R

&D's Product Stewardship function consists of scientists and regulatory professionals who have a global remit to ensure that our products are developed and manufactured to meet our duty-of-care standards, and are compliant with all relevant regulations in the country or jurisdiction of sale.

We aim to be a recognised leader in the responsible stewardship of all tobacco and nicotine products, including e-cigarettes, tobacco heating products and snus. We actively guide research and development activities enabling product risk to be characterised and minimised as much as possible.

Our approaches are based on well-established principles of toxicological and safety risk assessment. They enable us to define acceptability criteria for many aspects of product specification and performance, in the interests of consumer safety. These in turn form the basis of the company's stewardship guidelines and standards across our product portfolio.

Our stewardship remit incorporates the entire product lifecycle and, as such, we provide expert advice and support to the development, manufacture and distribution of products.

The product stewardship team oversees the compilation of key product data and scientific support packages required for regulatory reporting. We provide expert technical guidance to all our group companies, for example, on chemicals legislation, ingredients restrictions and bans, and legislated disclosure processes to enable regulatory engagement and compliance.

Recent successes

We have incorporated new methods into our risk assessment approach, including:

- » Advanced non-targeted analysis techniques to assess emissions from

next-generation products to identify and assess risks related to any compounds above thresholds of toxicological concern

- » A three-dimensional *in vitro* model of lung epithelium to assess the irritation potential of product ingredients

We presented our contact sensitisation risk assessment approaches for snus and e-liquid ingredients at the Congress of the European Societies of Toxicology in 2014. Additionally, we have developed and published our risk assessment approach to the screening of flavours for e-liquids. This information formed part of a presentation to the FDA in early 2015.

We have used self-reported vaping behaviour and consumption data from recent surveys of e-cigarettes users to increase the relevance of the evidence-based exposure paradigms that inform our quantitative toxicological risk assessments.

Product Stewardship partnered with Nicoventures to propose product standards for electronic cigarettes; these have been shared with some external scientific and regulatory parties, including the British Standards Institute (BSI). Following consultation with a number of interested parties, the BSI has now published a voluntary standard for the product category.

Challenges requiring collaboration

The field of toxicology is evolving rapidly as research into *in silico* and *in vitro* methods and systems biology, for example, reveal valuable approaches to risk assessment. We continue to keep abreast of the latest developments and apply new techniques when they add value to our current approaches. One particular challenge is translating *in vitro* data into

quantitative risk assessment to support specific ingredient levels in new products for all product categories. As this issue impacts the field of toxicology generally, we will engage in the development of new approaches through scientific forums and follow qualified recommendations and best practices as they emerge.

Consumer behaviour changes constantly in relation to many factors, including lifestyle choices, environmental and financial pressures, and becoming accustomed to new products. Exposure estimates are a key factor in our risk assessment paradigms, so we need to be mindful of trends and collect data that will enable us to review our guidelines

and standards on a regular basis. External experts in consumer research with a strong interest in tobacco and nicotine products provide valuable guidance on methodologies and approaches to gathering relevant data as well as alerting us to trends and behaviours in particular consumer groups.

Aims for the future

- » Continue to work in partnership with our Analytical Development Centre to develop and deliver new methodologies for the characterisation and quantification of emissions from next-generation products to address new challenges and knowledge gaps
- » Standardise our risk assessment processes

and supporting data sets for next-generation products as they become mainstream commercial products

- » Contribute to the development of global voluntary and regulatory product standards for e-cigarettes and other emerging product categories
- » Quantify the risks and potential toxicant reduction benefits of next-generation products with use of the latest scientific data, in the context of tobacco harm reduction
- » Continue to publish and communicate externally on our approaches to the risk assessment of next-generation products to enable dialogue and engagement with scientists and regulators



DR AUDREY RICHTER
Head of Product Stewardship

Audrey started her career in Medical Laboratory Sciences before moving to academia. She spent 15 years at the University of Southampton both in Medical Oncology, where she gained her PhD, and in Respiratory Cell and Molecular Biology. Audrey joined us in 2002 and set up an *in vitro* models work programme before taking on a series of leadership roles in Biosciences, Smokeless Tobacco Science and Clinical Studies. In her current role, as Head of Product Stewardship, she now ensures that we perform rigorous stewardship assessments on product innovations.

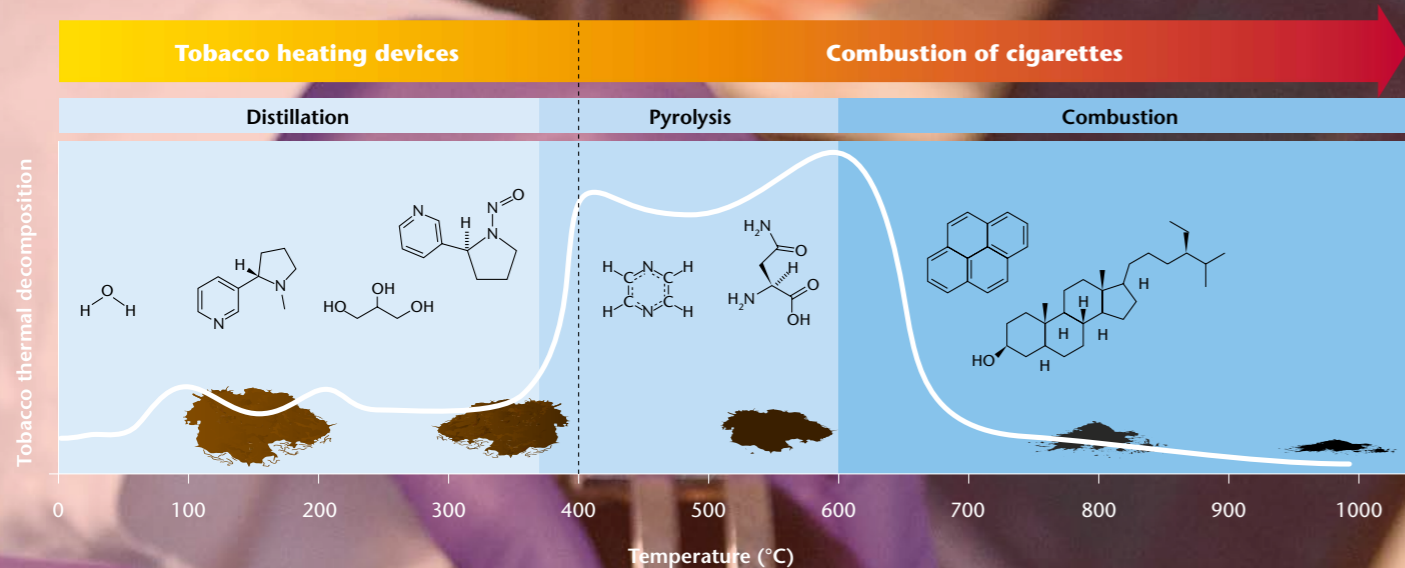


Figure 1: Generation of toxicants at different temperatures. Heating at lower temperatures rather than burning generates fewer and lower levels of toxicants.

ELIMINATING COMBUSTION TO POTENTIALLY REDUCE RISK



The scientific community widely agrees that the majority of smoking-related diseases are caused not by nicotine but by toxicants formed during the combustion and pyrolysis of tobacco. Research in tobacco thermochemistry has established that different classes of tobacco constituents decompose at different temperatures, releasing chemical compounds into the aerosol as they do so. Because the tip of a burning cigarette undergoes a very wide range of temperatures (from ambient to about 1000°C), the smoke it produces contains a vast array of chemicals (Figure 1).

Studies have shown, for example, that at lower temperatures (between 100°C and 200°C), water and volatile substances, including flavour molecules, loosely bound to the surface of the tobacco leaf are the first to be released through distillation and evaporation. Although the boiling point of nicotine is around 250°C, it starts to vaporise and enter the aerosol between 170°C and 200°C. At 300–400°C, some decomposition components start to form from the breakdown of cellulose and other structural components of the tobacco plant, but it is not until temperatures of more than 400°C are reached that the main pyrolysis occurs. Leaf components, such as amino acids and esters, decompose at 400–600°C, and carboxymethylcelluloses and carbonates at 600–900°C, producing the bulk of the carbon monoxide, polycyclic aromatic hydrocarbons, and other combustion products that form the tar in cigarette smoke.

Recent successes

Attempts to selectively modify the complex combustion process in conventional cigarettes have not been successful. Although a reduction in toxicant exposure was achieved, the biological impact of these

reductions was unclear. To reduce toxicant formation but retain a taste resembling cigarette smoke, therefore, we have been developing tobacco heating products (THPs) that heat tobacco to between 200°C and 300°C, a temperature range sufficient to vaporise the nicotine (and some other volatile compounds) into an inhalable aerosol stream, but not enough to burn the tobacco and cause pyrolysis or combustion. As a result, the aerosol produced by these products contains nicotine and compounds that provide the consumer with taste and flavour but with far fewer or lower levels of toxicants than are present in cigarette smoke.

There are two main types of THPs. The first is based on a battery-powered heating source and often resembles an e-cigarette (Figure 3). A user inserts the tobacco rod into the heating chamber, which contains the control circuitry necessary for regulating temperature and is turned on by pressing a button. The second, a carbon-tip-fuelled product, normally looks like a conventional cigarette and is lit in the conventional manner.

During use, air is heated as it is drawn through the lit carbon source. The hot air passes through the tobacco, extracting flavour and releasing nicotine (and other aerosol constituents) to form a vapour. This vapour passes through a filter or mouthpiece and is delivered as an aerosol stream. These products do not burn down or emit a strong smell like conventional cigarettes, and the tobacco within, which may also be blended and treated to ensure nicotine release, maintains its shape after use.

Although THPs generate aerosols containing significantly fewer toxicants than cigarette smoke, the exact fractions depend on many variables, including



DR CHUAN LIU
Head of Tobacco Heating
Product Science

Chuan holds a PhD in materials science from Cambridge University, and since joining us in 2000, has become one of our key experts on pyrolysis, smoke formation, and toxicant-reduction technologies for cigarettes. Since 2014, Chuan has been the lead scientist for our tobacco-heating products, ensuring high-quality standards of research for this emerging product category.

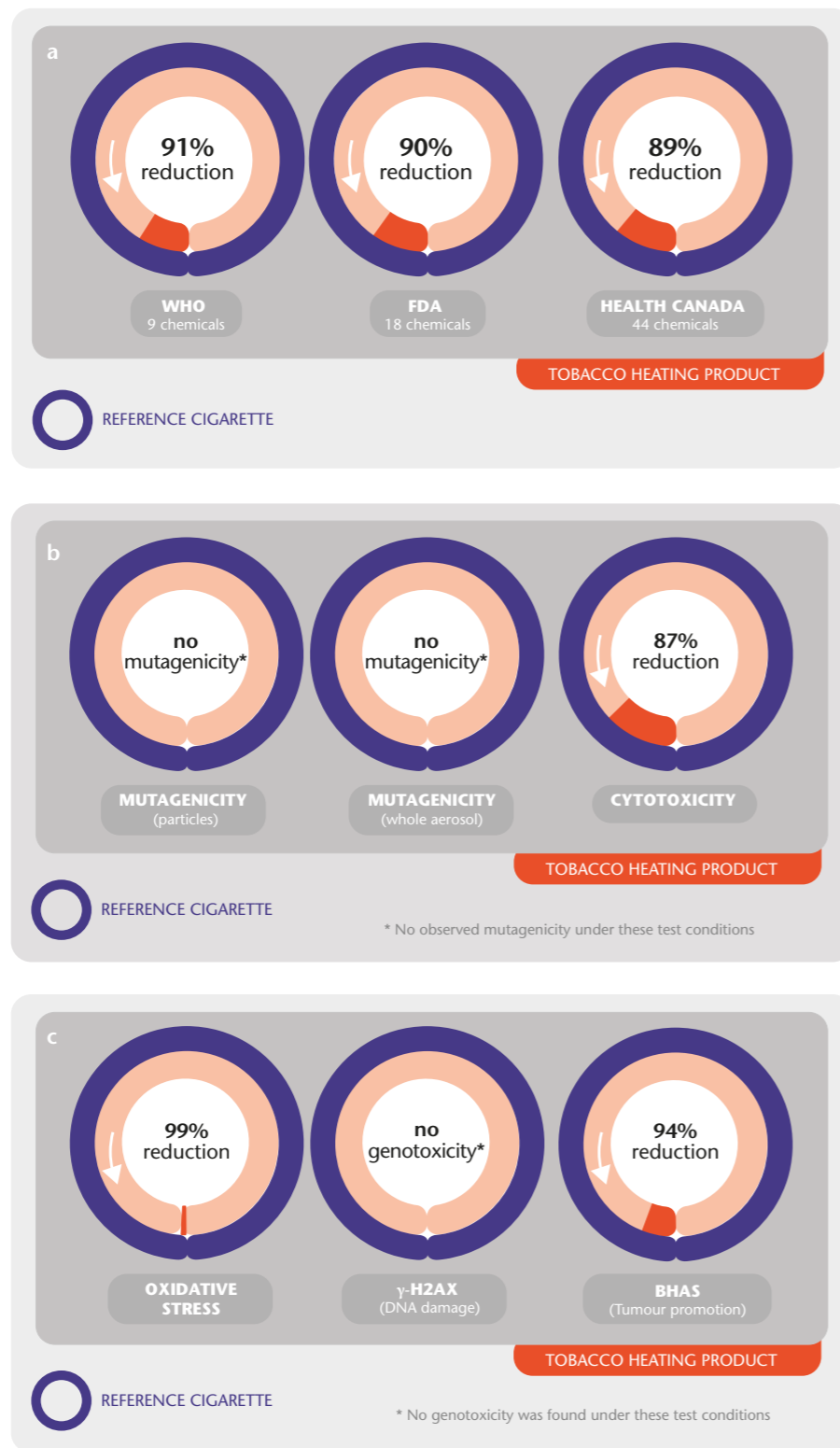


Figure 2. Testing of aerosols from prototype THPs shows fewer toxicant emissions and substantially reduced mutagenicity, genotoxicity and oxidative stress compared with smoke from conventional cigarettes.

operating temperature and the tobacco blend used. To guide the responsible development and appropriate oversight of these next-generation products, we need to develop a full understanding of how THPs operate, how consumers use them, and a suitable approach to stewardship.

It must be remembered that the stewardship of cigarettes is not suitable for THPs. The lower temperatures involved means that some of the processes seen in cigarettes do not occur in heated tobacco and *vice versa*. Testing regimes might need to be adapted and standardised for

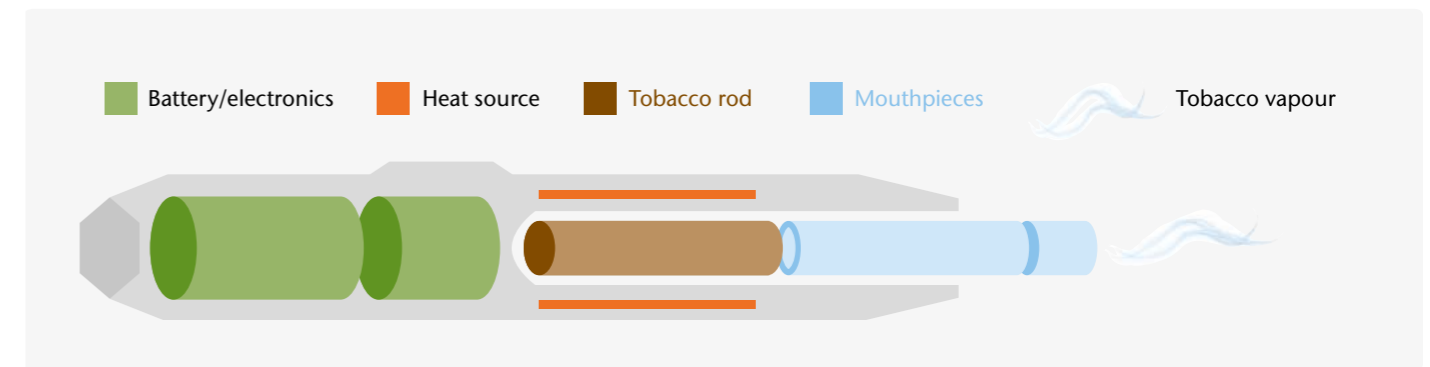


Figure 3. An illustration of how a rechargeable battery-powered tobacco heating product could function, where a tobacco rod is heated to a controlled temperature for aerosol generation.

THP aerosols, which are considerably less complex than cigarette smoke. In addition, research must focus on potential new toxicants as well as those already associated with smoking cigarettes. New sampling techniques and methodologies for chemical analyses are needed to thoroughly characterise these products and their potential to reduce the toxic effects of tobacco smoking.

At our Analytical Development Centre, we have already developed a range of sensitive methods for characterising emissions from THPs and used them to demonstrate that levels of known smoke toxicants are significantly lower than in cigarette smoke (Figure 2a). Using a smoking machine adapted to generate, dilute, and deliver THP aerosols to a bronchial epithelial-cell cytotoxicity model, we have shown significantly less cytotoxicity than with conventional cigarette smoke (Figure 2b). We have also developed a panel of *in vitro*

assays to measure oxidative stress, inflammation, and cytotoxicity in lung epithelial cells, and have shown that these models are suitably sensitive to compare different nicotine-delivery products. Studies using these models show that cellular responses indicative of oxidative stress are lower in cells exposed to THP aerosol than in cells exposed to cigarette smoke (Figure 2c).

However, there is still more to be done to fully characterise THP emissions, in particular to enable the use of these data in risk assessments. Further evaluation will require a series of multi-disciplinary studies that must also consider patterns of consumer use. Successful development will require tobacco science, portable electronics, and consumer insights to be combined in such a way that meets modern societal requirements for nicotine consumption. This novel category of tobacco product continues to present new challenges

requiring additional research into product science, stewardship, and substantiation of their potential for reduced risk. We are keen to engage with academic, industrial and entrepreneurial partners who can help us achieve the best possible THPs in terms of risk and satisfaction.

Aims for the future

- » Continue to evaluate how types of tobacco and processing and blending influence the chemical and sensory profiles of THP aerosols
- » Continue to develop our understanding of the THP category to ensure that our THP products are stewarded to meet state-of-the-art product safety assessments
- » Engage with regulators, policy makers and public-health advocates, and publish relevant, robust scientific data to ensure that THP regulation is appropriate and based on sound scientific evidence □

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RAPID EVOLUTION PRESENTS NEW CHALLENGES

T

he types of e-cigarettes sold, the science base examining their impact on users' health, the emergence of product standards and regulations have seen rapid developments over the last 12 months. Continuing innovation and commitment to product stewardship are needed to deliver on the public-health promise of e-cigarettes and provide consumers with the safest possible products.

We have previously described the emerging popularity of e-cigarettes as a potential tool for reducing the harm associated with cigarette smoking. Evidence to date suggests that, although their use may not be entirely safe, e-cigarettes have the potential to be substantially less risky than cigarettes.

Nevertheless, debate about e-cigarette safety continues, and we have seen a sharp rise in numbers of associated scientific studies published. Many have focused on contents of the aerosol, possible health effects associated with e-cigarette use, the potential of e-cigarettes to act as a gateway to cigarette smoking, and their effectiveness as smoking-cessation aids.

As researchers develop a deeper understanding of these issues, discrepancies between study findings are emerging. A recent example of this was the widely disseminated research purporting to show higher levels of formaldehyde and acetaldehyde in e-cigarette aerosol than in cigarette smoke¹. Those studies, however, have been strongly criticised by some e-cigarette and public health experts for their unrealistic heating conditions² and their failure to take into account likely consumer behaviour³.

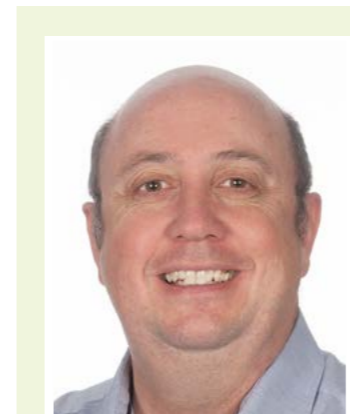
Research into the health effects of e-cigarette use is also providing contradictory

findings. For example, one study has shown that mice exposed to e-cigarette vapour display significantly impaired pulmonary bacterial clearance compared with mice exposed to air⁴, whereas a study conducted by our own scientists has found little cytotoxic response from e-cigarette aerosols in human reconstituted airway tissues⁵.

Essentially, all e-cigarettes are battery-powered devices that heat a liquid (e-liquid) to produce an inhalable aerosol. E-liquid usually contains excipient (glycerol, propylene glycol and/or water), flavourings, and, in many cases, nicotine, although nicotine-free preparations are available. The amount, content, and characteristics of the aerosol depend mainly on the power applied to the heating coil and the physical characteristics of the e-liquid formulation (such as composition, viscosity, and its specific heat capacity).

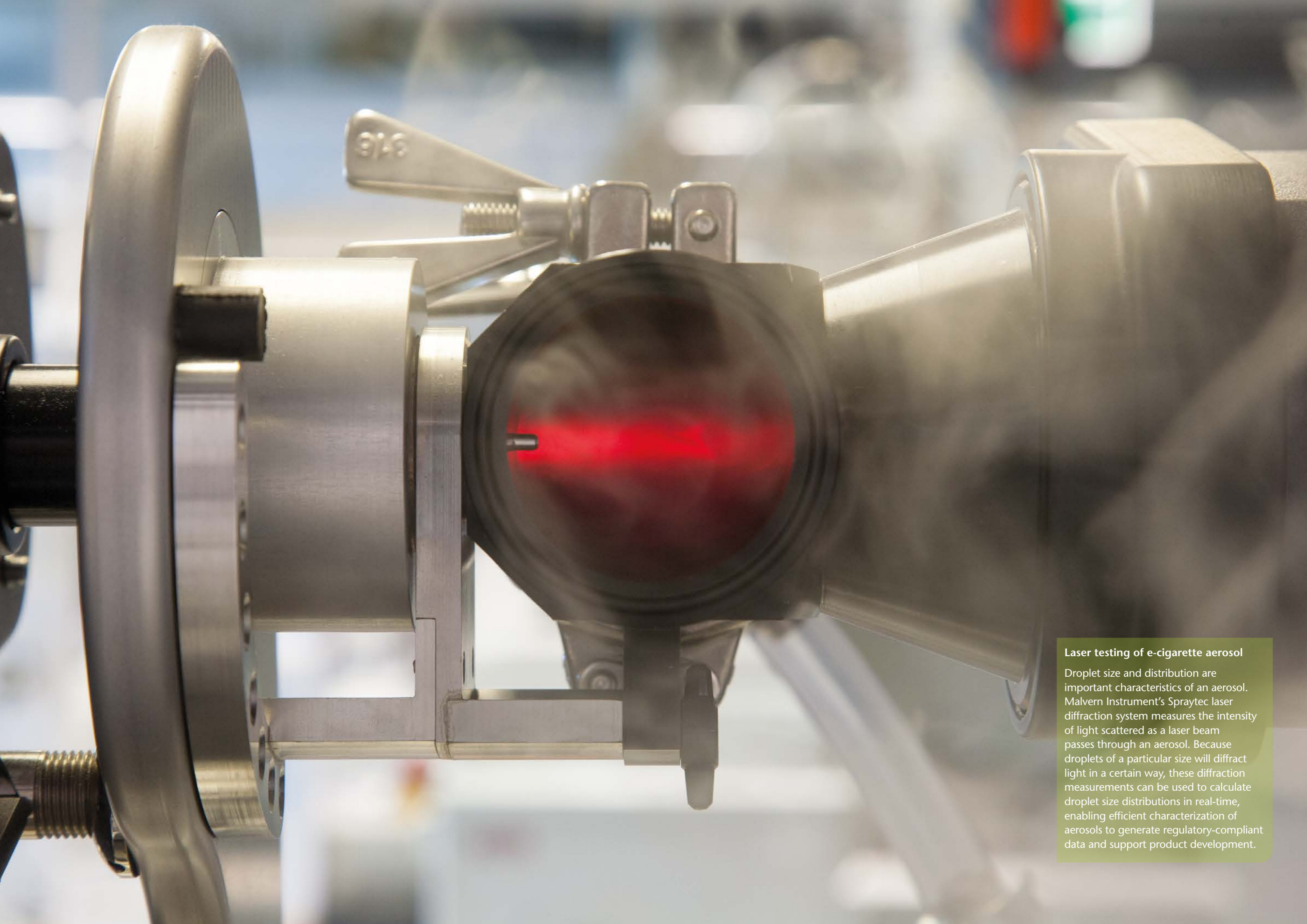
A huge variety of e-cigarettes is now available. These include disposable and rechargeable devices, many of which resemble conventional cigarettes in size and shape; larger, more-complex closed modular systems with replaceable flavour cartridges; open modular devices to which users add their own e-liquids; and dripping devices. A vast assortment of flavours (estimated at more than 7,000) is also sold worldwide.

With the range of devices and ways of customising them evolving rapidly, there is a real concern about the lack of product quality standards across the e-cigarette industry. Manufacturing methods, materials and device performance can differ greatly, and few devices are properly tested before sale. To safeguard consumers, we continue to advocate standardisation and ensure that our devices, e-liquids, and the vapour



DR KEVIN MCADAM
Head of Nicotvenues
Research

Kevin is an experienced chemist, who has spent the past 30 years researching tobacco harm reduction. Kevin specialised in combustion chemistry during his PhD and atmospheric pollution during his postdoctoral training. Kevin joined BAT in 1987, and has worked on the science underpinning tobacco harm reduction, including smokeless tobacco products, reduced-toxicant cigarettes, tobacco-heating products, and e-cigarettes. He now heads our Nicotvenues research programme.



Laser testing of e-cigarette aerosol

Droplet size and distribution are important characteristics of an aerosol. Malvern Instrument's Spraytec laser diffraction system measures the intensity of light scattered as a laser beam passes through an aerosol. Because droplets of a particular size will diffract light in a certain way, these diffraction measurements can be used to calculate droplet size distributions in real-time, enabling efficient characterization of aerosols to generate regulatory-compliant data and support product development.

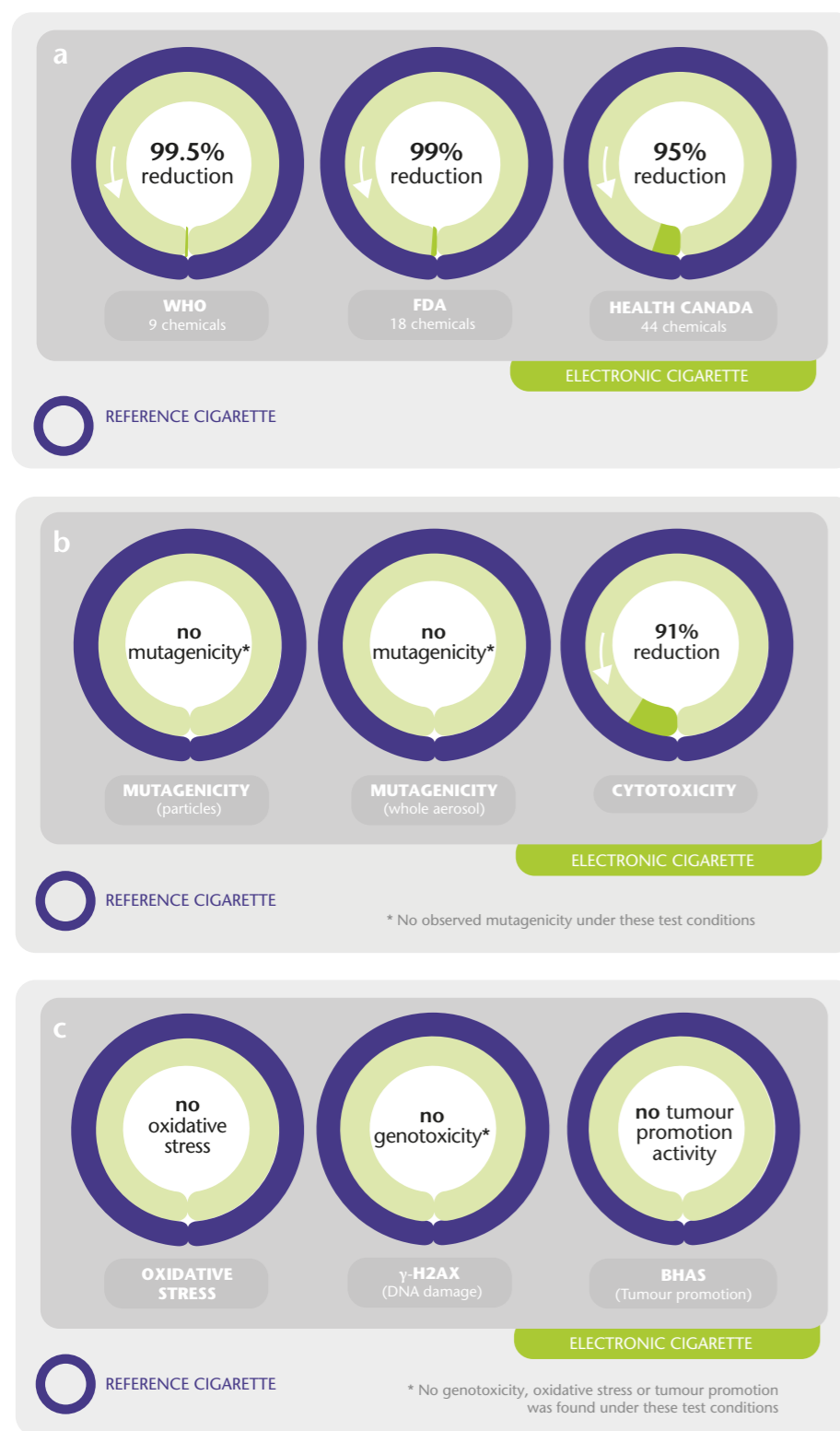


Figure 1. Testing of Vype ePen aerosols shows fewer toxicant emissions and substantially reduced mutagenicity, genotoxicity and oxidative stress compared with smoke from conventional cigarettes.

produced meet our high quality standards.

BAT's and Nicoventures' entire approach to e-cigarettes is underpinned by responsible product stewardship. We believe that it is vital to know and rigorously test exactly what each e-cigarette contains and produces. We carefully assess our

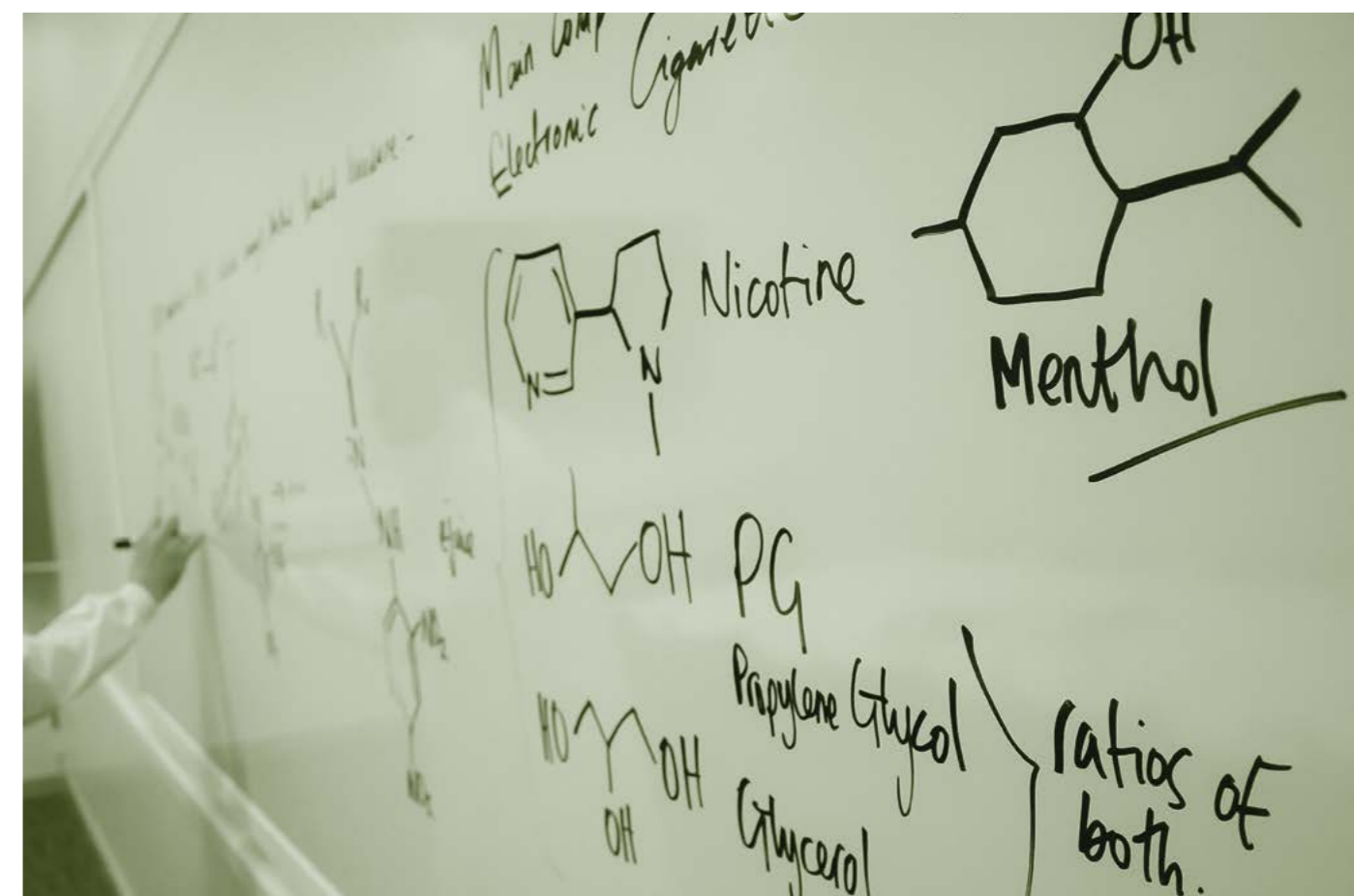
products, taking into account not only the device materials and e-liquid ingredients, but also compounds in the vapour that result from heating the e-liquid. We use a wide range of analytical techniques, specialised laboratory technology, and expertise to first develop and then conduct detailed tests of the vapour from the flavours and e-liquids we formulate, the products we manufacture, and the combinations in which they are sold. We also study the way consumers actually use e-cigarettes to make sure our risk assessments are based on and reflect consumers' behaviours. Only when we are fully satisfied that a product meets our high quality standards do we allow a product on the market.

Concerns over e-cigarettes has led to the development of a global regulatory divide, with some countries (eg Singapore) instigating bans on all e-cigarettes, others (eg Canada) restricting only those containing nicotine, and still others allowing free use of e-cigarettes. Recently, Wales announced a ban on e-cigarette use in public.

Recent successes

To promote good practice across the industry, we believe it is our responsibility to share our knowledge and contribute to the science of vaping. Our scientists have presented our scientific insights and approach to stewardship of e-cigarette flavours at major science conferences hosted by the US Food and Drug Administration (FDA), the Society for Research on Nicotine and Tobacco, and the Global Forum on Nicotine workshops. We also recently published the first practical guide on how to develop flavours responsibly, based on sound toxicological principles⁶. We have conducted a wide ranging comparison of the relative toxicology of e-cigarettes and a conventional cigarette (Figure 1). Measurement of a number of toxicants corresponding to toxicant lists identified by the WHO, FDA and Health Canada showed 95-99% lower levels of these toxicants in e-cigarette emissions than in cigarette smoke. Similarly, a series of *in vitro* toxicology tests examining a number of bioassays covering mutagenicity, cytotoxicity, oxidative stress, genotoxicity or tumour promotion activity, in which cigarette smoke gives clear responses, showed that e-cigarette aerosols were either inactive or 90% less active than cigarette smoke.

We continue to participate fully in the development of national and international standards aimed at phasing out poorly manufactured products and safeguarding



consumers. In April, 2015, for example, France's association for standardisation, AFNOR, published the world's first national standards for e-cigarettes and e-liquids⁷. We were active contributors and participants in the development of these rigorous product standards, which set out a series of voluntary safety and quality criteria for designing and testing products before they reach the market. The standards aim to improve the practices of all manufacturers, suppliers, test laboratories, and distributors with a view to minimising the risks of use to consumers by defining construction and performance criteria for e-cigarettes, identifying purity standards for authorised ingredients, and defining a list of banned substances in e-liquids. These standards were the result of work by close to 60 organisations, including consumer associations, test laboratories, health organisations, and manufacturers. A voluntary standard focused on characterising e-cigarette emissions is expected shortly.

The UK's British Standards Institution published similar e-cigarette guidelines in June 2015, and, once again, BAT and Nicoventures were strong contributors to the development of these standards.

Looking forward

We anticipate that the year ahead will see significant developments in the world of e-cigarettes. For example the national e-cigarette standards will serve as a roadmap for draft European product standards, on which the European Committee for Standardisation has begun work. In addition, voluntary global standards aimed at analytical laboratories are currently being developed by CORESTA and the International Organization for Standardization and are expected to be published over the next few years.

The FDA is working to finalise e-cigarette regulations and the European Tobacco Product Directive will be implemented fully in national laws in 2016. The first legally binding regulatory frameworks in Europe and the USA, therefore, will be clarified throughout 2016 and 2017.

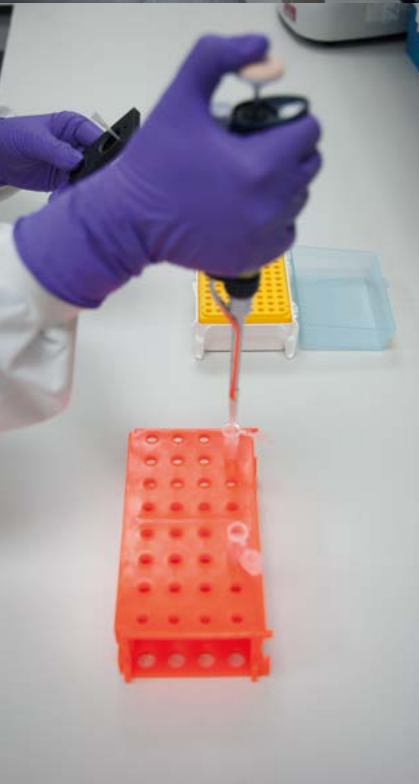
Aims for the future

- » Continue to understand what our consumers are seeking from our products and how they use them
- » Continue to research flavour and sensory science
- » Continue to refine and develop analytical approaches to characterise low-level

constituents of e-liquids and e-cigarette aerosols, as part of our commitment to effective product stewardship

- » Continue to publish our scientific research on e-cigarettes
- » As ever, we welcome the opportunity for collaborative research with external scientists in the field

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3. Farsalinos, KE *et al.* Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naïve users (smokers). *Sci. Rep.* 2015; **5**: 11269.
4. Sussan, TE *et al.*, Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *Plos One* 2015; **10**: e0116861.
5. Neilson, L *et al.*, Development of an *in vitro* cytotoxicity model for aerosol exposure using 3D reconstructed human airway tissue; application for assessment of e-cigarette aerosol. *Toxicol.* In *Vitro* 2015; **29**: 1952-1962.
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7. AFNOR. AFNOR publishes the world's first voluntary standards for electronic cigarettes and e-liquids. <http://www.afnor.org/en/news/news/2015/avril-2015/afnor-publishes-the-world-s-first-voluntary-standards-for-electronic-cigarettes-and-e-liquids> (accessed Aug 11, 2015).



BUILDING THE EVIDENCE BASE



We are using cutting-edge science and technology to develop both a range of innovative tobacco heating products (THPs) and nicotine products, such as electronic cigarettes (e-cigarettes) and the science to evaluate them. We are driving the science in characterisation of toxicants in smoke and aerosols, learning how exposure to these toxicants translates to risk of developing disease, and working on substantiating the reduced-risk potential of THPs and e-cigarettes compared with conventional cigarettes.

The risks of smoking conventional combustible cigarettes are well known. It is firmly established that the combustion of tobacco results in a smoke containing more than 6,000 different constituents, of which approximately 150 are known human toxicants. Most of the diseases associated with smoking, such as cardiovascular disease, chronic obstructive pulmonary disease, and cancer, are caused by inhaling this smoke.

In an effort to reduce the risks associated with tobacco use, we are focusing our research and development on new products such as THPs, e-cigarettes, and low-toxicant oral tobacco products (eg snus). These products deliver nicotine without the smoke that is generated by combustible cigarettes and, as such, are considered to hold potential for reducing the risks associated with tobacco use. If the reduced risk potential is substantiated, it will be important that it is supported by a robust body of evidence, both for consumer confidence in our products and for evidence-based regulation.

In 2014, we adopted McNeill and Munafò's¹ tobacco and nicotine risk continuum and adapted it for our use, ranking products by exposure of consumers to toxicants in the following

order: conventional cigarettes > THPs > smokeless tobacco > e-cigarettes > licensed medicinal products (Figure 1).

The aim of our research is to expand understanding of the science supporting the evaluation of next-generation products and a determination of whether their placement on a risk spectrum is justified.

To this end, and in line with likely regulatory requirements, BAT has established a framework for assessing new products for their potential for risk reduction by integrating chemical, toxicological, and human studies at the individual and population levels.

We have established a range of tools to characterise rigorously toxicant yields in next generation product emissions and to evaluate responses to these products in *in vitro* toxicity tests compared with results for conventional cigarettes. Our toxicity testing involves a battery of *in vitro* assays, including those already recommended by the Organisation for Economic Cooperation and Development (OECD), such as the Ames, *in vitro* micronucleus, and mouse lymphoma assays for genotoxicity the Neutral Red Uptake assay for cytotoxicity. We are also developing other *in vitro* assays to assess key tobacco-related disease endpoints in commercially available human tissue systems and models, including the use of primary cell types and three-dimensional reconstituted human tissue models, such as MucilAir™ and EpiAirway™.

Recent successes

Although some of the toxicity assays we employ are commonly used by the tobacco industry and the methodologies are consolidated through CORESTA (an association founded in 1956 to promote



DR MARIANNA GAÇA
Pre-Clinical Assessment
Manager

Marianna holds a PhD in cell and molecular medicine and did her postdoctoral work at Yale School of Medicine and University of Pennsylvania before joining us in 2004. She has held various roles investigating the biological effects of cigarette smoke, including the development of *in vitro* models of tobacco related-diseases and whole-smoke exposure systems. Marianna has also represented BAT (and the wider tobacco industry) at board level on many *in vitro* societies, including IVTIP and ASCCT. She is passionate about the development and application of *in vitro* models as alternatives to product assessment in animals.



Figure 1: Adapted tobacco and nicotine risk continuum.

international cooperation in scientific research relative to tobacco), our researchers are adapting them where necessary and applicable to assess next generation products more accurately. For example, we recently modified the Ames test to enable the assessment of aerosols and whole smoke^{2,3} and have applied existing irritancy testing standards to the testing of e-cigarette vapour in the EpiAirway™ model⁴, showing e-cigarette vapour producing results similar to those for air.

We have also started to participate in a new series of workshops initiated and moderated by independent organisations, such as the Institute for In Vitro Sciences (IIVS). This represents a good example of how public health, academic and industry scientists, and regulators, can come together with a view to debating potential science frameworks that could be used for evidence-based regulation of products across the risk continuum.

We have carried out a variety of tests on Vype ePen, one of our commercially available e-cigarettes, and a prototype THP, which is under development in R&D, and the results are encouraging. Initial studies published by other groups^{5,6} are contributing to the establishment of an evidence base with the potential to substantiate that THPs and e-cigarettes generate substantially lower levels of toxicant emissions than conventional cigarettes.

We have a strong heritage in scientific engagement, and to promote best practice we openly share and present our

research at many scientific conferences and welcome dialogue with other scientists. All material we have presented at scientific conferences can be accessed on our science website, bat-science.com.

Aims for the future

- » Publish the latest datasets on next generation products, including the science underpinning the chemical and biological tests that we are using
- » Do more to integrate *in silico* and *in vitro* toxicology assessments
- » Look at the scientific ways to bridge between datasets, facilitating the more efficient development of products by avoiding duplication of tests

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2. Kilford, J *et al.*, A method for assessment of the genotoxicity of mainstream cigarette-smoke by use of the bacterial reverse-mutation assay and an aerosol-based exposure system. *Mutat. Res.* 2014; **769**: 20–28.
3. Azzopardi, D *et al.*, Evaluation of an air-liquid interface cell culture model for studies on the inflammatory and cytotoxic responses to tobacco smoke aerosols. *Toxicol. in Vitro* 2015; **29**: 1720–1728.
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IMPROVED UNDERSTANDING OF TOXICANTS AND DISEASE



We have set out a framework of studies that we think need to be considered when trying to determine whether tobacco heating products or e-cigarettes could be described as reduced risk products in comparison with cigarettes (Figure 1). One part of this framework is computational toxicology.

We have for several years been using computational toxicology to try and prioritise toxicants found in tobacco smoke. Although aerosols from next generations products have fewer chemicals, there are still some toxicants present. As this is the case, improved understanding of the role and dose-response relationships between toxicants in aerosols and smoke from our products and tobacco-related diseases will help us focus the development of technologies for reducing the levels of those toxicants. It will also help us quantify residual risks as we continue to develop a range of new products aimed at reducing exposure to certain toxicants.

Our quantitative risk assessment approach (Figure 2) is based on integrating predictive and experimental models. Computer modelling approaches, including margin of exposure (MOE) calculations, mode of action (MOA) reviews, and physiologically based pharmacokinetic (PBPK) modelling, are supplemented where necessary with data from *in vitro* models of disease and conventional *in vitro* toxicology assays, as directed by the MOA.

Recent successes

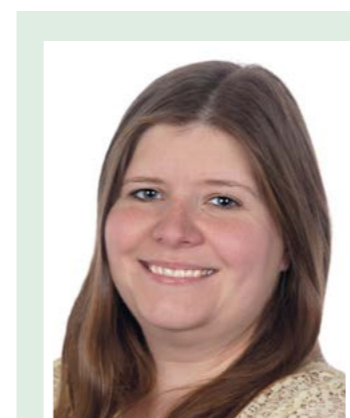
In 2011, we published a paper outlining our use of MOEs to segregate tobacco smoke toxicants and prioritise our research¹. This was followed by a presentation at the Tobacco Science Research Conference, in which we proposed the categorising of tobacco smoke toxicants according to the

calculated MOE and ascribing categories for toxicants with limited or insufficient data to generate a MOE². We also described the concept of calculating cumulative MOEs for groups of toxicants with similar toxicological properties, illustrated with aldehydes present in tobacco smoke³.

The World Health Organization (WHO) Study Group on Tobacco Product Regulation has proposed a list of 18 tobacco smoke toxicants for reduction and monitoring. Some of these toxicants are found in the vapour phase of tobacco smoke, others in the particulate phase, and the remainder in both phases. We have recently completed an assessment of all the particulate-phase toxicants with our suite of genotoxicity tests, which includes *in vitro* micronucleus, Ames, and mouse lymphoma assays. We have also evaluated a number of the particulate-phase toxicants with our *in vitro* models of disease. We have adapted the Ames mutagenicity and neutral red uptake cytotoxicity assays for analysing gases⁴, and we are currently using this methodology to assess the remainder of the WHO toxicant list with use of the appropriate genotoxicity tests and disease models.

Aims for the future

- » Identify tobacco smoke toxicants that are known to be present in the aerosol from next generation products and apply our computational tools to predict their likely impact on biological activity
- » Continue to generate and refine MOEs where possible for all toxicants of interest
- » Use the gaseous exposure system within R&D to test gaseous tobacco smoke toxicants in our *in vitro* models of disease
- » Use the MOA reviews to direct the assessment of individual tobacco smoke toxicants within relevant *in vitro* models



FIONA CUNNINGHAM
Combustible Toxicology
Scientist

Fiona joined our *in vitro* models team in 2005, with a BSc in chemistry, and has since completed an MSc in environmental toxicology and pollution monitoring. Recently Fiona's main focus has been prioritisation of tobacco smoke toxicants with use of several *in silico* techniques, and she has become one of the leading experts in this field within the tobacco industry.

	<i>In vitro</i> regulatory toxicology	<i>In vitro</i> models of disease		
	Chemical and physical characterisation	Exposure and pharmacokinetic study	Systems Science	Post market surveillance
TYPE OF STUDY	Product design stability	Computational Toxicology	Biomarker of effect study	Consumer perception study
PURPOSE	Stewardship science	Toxicant exposure reduction	Individual risk reduction	Population risk reduction

Figure 1: Studies required to substantiate reduced-risk potential of next generation tobacco and nicotine products.

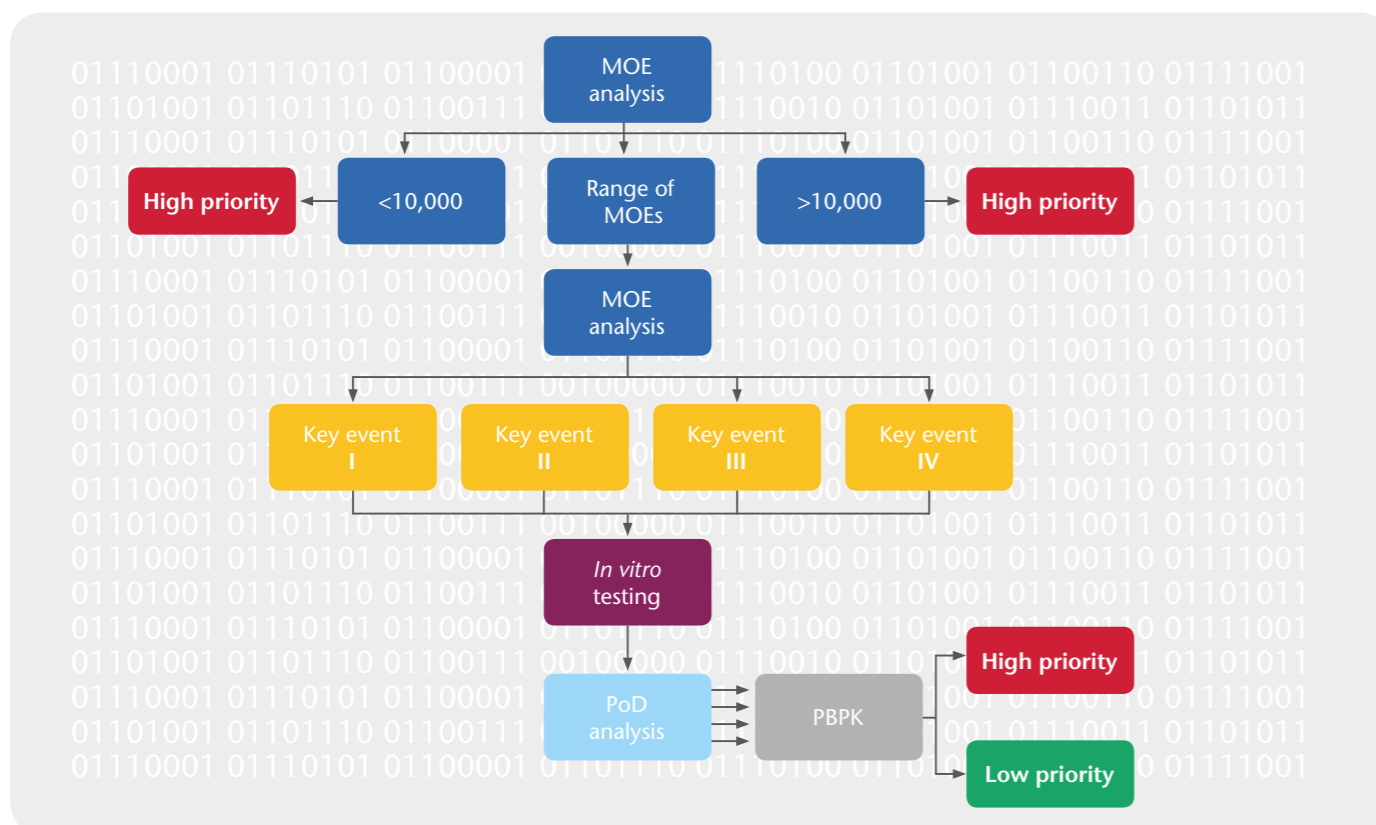


Figure 2: Our quantitative risk assessment approach.

- of disease and/or traditional genetic toxicology assays
- » Develop toxicokinetic and PBPK models, where possible, for all of the 18 WHO Study Group on Tobacco Product Regulation chemicals and adapt an established model for nicotine⁵ for use with nicotine delivery devices, such as e-cigarettes
 - » Develop an approach to the risk assessment of mixtures of toxicants present in smoke/aerosol □
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In vitro exposure machine syringes

In the smoking machine, these syringes generate and dilute cigarette, tobacco heating product or e-cigarette aerosols and deliver this to cell cultures located at the air-liquid interface. To avoid any cross-contamination of different aerosol types, each syringe is designated to one particular product.



UNDERSTANDING CONSUMER PRODUCT INTERACTION



etermining an appropriate and reproducible measurement of dose is an important step in gauging uptake of whole aerosol and individual components of aerosol by the consumer. Measurement helps us to understand nicotine delivery and enables analysis of the toxicological action of aerosol at cellular, organ, and whole body levels. We have focused on the development of real-time measurement tools to better define and replicate human puffing and inhalation behaviours, which allows equivalent doses to be assessed in laboratory-based biological assays. Through reassessing previously published data and the use of computational modelling, we are helping to improve sensitivity analyses, align laboratory findings with dose effects in humans, and characterise next-generation tobacco-heating products and e-cigarettes.

The size of particles in tobacco smoke and the partition of individual chemical components between particles and the vapour change constantly. Several chemicals have been identified by regulators and scientists as likely key toxicants that potentially influence disease risk owing to their observed biological actions in humans. Thus, it is important to identify the doses of smoke components, individually and in whole smoke, that are delivered to specific tissues and organs. Focusing mainly on the lungs, we assess the location of deposition, concentration, duration of exposure and mechanisms of removal. This characterisation is even more important with novel products, the aerosols of which might be quite different from cigarette smoke. To assess new products, we may need to develop new techniques and models that provide information on how the products are used and where in the respiratory system the aerosols are likely

to deposit. A broader understanding of nicotine delivery is also needed in order to support the production of novel alternatives to combustible cigarettes that are acceptable to and suitable for consumers.

Recent successes

We have undertaken collaborative work with external researchers to improve understanding of the physical processes in smoke, and have shown the overriding importance of coagulation and condensation (phase change) during the early puffing phase of smoking when the mouth fills with smoke^{1,2}. We have also shown that physical changes of the aerosol during subsequent inhalation into the lungs are dominated by hygroscopic growth (accretion of water on to the smoke droplet)³ in parallel with evaporation of soluble volatile and semi-volatile chemicals, including nicotine. Rapid droplet growth, effective dilution with water, and diffusion within the droplet all combine to slow the rate of nicotine release^{1,4}.

Additionally, we have measured the density of smoke droplets under steady-state and transient (puff-by-puff) sampling^{5,6}. Data from our experimental design confirms that smoke aerosol comprises spherical droplets with density that is unaffected by cigarette design parameters, such as format, filtration, yield, and ventilation. These findings are consistent with the dominance of early coagulation processes giving chemically homogenous droplets.

Through other collaborations we have investigated the relative deposition, uptake, and reactions of formaldehyde, acetaldehyde, and acrolein in the upper airways through hybrid computational fluid dynamic and physiologically based pharmacokinetic models⁷. We have compared the data with previously published non-adverse



JOHN MCAUGHEY
Principal (Aerosol) Scientist

John is a world-leading aerosol scientist with more than 30 years of experience. Early in his career, he moved to AEA Technology, where he researched and published in multiple fields of aerosol science, including tobacco smoke science, particulate air pollution, automotive emissions, pharmaceutical inhalers, radiation dosimetry, and occupational medicine.

John advocates effective science communication and has previously served on a number of UK Government scientific committees.



effect levels and confirmed a risk hierarchy of acrolein > formaldehyde > acetaldehyde. This sophisticated combination approach offers scope for aligning real-world exposures and doses of key chemicals at the cellular level when replicating these with doses delivered to *in vitro* disease models.

Recognising that detailed dose models covering all harmful and potentially harmful constituents of tobacco smoke requires significant resources, we have developed an initial empirical approach to separating particle deposition and vapour deposition. Particle deposition is significantly influenced by inhalation behaviour, such as depth and duration. Vapour deposition is generally independent of inhalation behaviour and increases with increasing vapour pressure of the compound. Deposition of semi-volatiles, such as polyaromatic hydrocarbons, lies between these extremes. Recognition of this range offers an effective screening and prioritisation approach to dosing that complements the margins of exposure approach we use in risk assessment^{8,9}.

Our real-time measurements of tobacco smoke aerosol have been cited on a number of occasions^{10,11} and adopted more broadly within the tobacco research community. We have adapted these systems for measuring e-cigarette aerosol, the droplets of which are larger than those in fresh cigarette smoke (150–250 nm), having a median diameter of approximately 500 nm. One consequence of this larger size is that the droplets become amenable to measurement by optical techniques, such as laser diffraction, and electrical mobility techniques, both of which demonstrate

excellent precision for size and concentration measurements on an individual-puff basis¹². Use of laser diffraction also allows alignment of our measurements with existing published standards, which enables us to validate our procedures for assessment of inhaled aerosol.

Aims for the future

- » Extend the measurement and modelling of specific processes that determine initial particle size, concentration, and chemical composition to tobacco heating products and e-cigarettes
- » Further characterise coagulation, condensation, evaporation, and hygroscopic growth processes to improve understanding of particle dynamics and partition in regional deposition
- » Extend regional deposition estimates to key toxicants in the vapour phase of inhaled smoke and exhaled breath to improve computational toxicology models
- » Support specific dosimetry assessments for key toxicants at the air-liquid interface for tobacco and novel nicotine products tested within *in vitro* models of disease □

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A SCIENTIFIC FRAMEWORK TO ASSESS NEXT GENERATION PRODUCTS

A framework for the assessment of novel tobacco and nicotine products with the potential to reduce health risks compared to cigarettes has been under discussion for over a decade, after the US Institute Of Medicine issued its report *Clearing the smoke – the scientific basis for tobacco harm reduction*. The US Food and Drug Administration (FDA), is the only national regulator to have provided a draft framework with which to assess novel tobacco and nicotine products for their harm reduction potential through their Modified Risk Tobacco Product application process. In addition to the FDA's proposed regulatory assessment framework, a recent publication from the Tobacco Product Assessment Consortium (TobPRAC) presented a four-stage model inclusive of: pre-market evaluation; pre-claims evaluation; post-market activities; and monitoring and re-evaluation. Their framework highlighted key tests and reference products that would be required to demonstrate reduction in risk and product stability by chemical, toxicological and human studies at the individual and population levels.

Our approach builds on those proposals and sets out an integrated framework using pre-clinical, clinical and population studies to assess the risk reduction potential of novel tobacco and nicotine products, including electronic cigarettes, at the individual and population level.

The key elements of the pre-clinical phase include the demonstration of the stability of the product and the toxicology of the emissions of the product. Analytical chemistry studies of the emissions of the product comprising both targeted measurement of the US FDA listed harmful and potentially harmful constituents, and untargeted analytical chemistry studies to ensure no unexpected compounds are formed.

A range of *in vitro* tests are required to assess the mutagenicity, genotoxicity and cytotoxicity of the emissions.

The clinical phase is comprised of studies that determine the potential of the product to reduce risk at the individual level and require data from human volunteers to show nicotine uptake and assess changes in biomarkers of exposure and biomarkers of biological effect. For the prediction of health-related outcomes an approach is proposed that uses systems science to integrate disease relevant *in vitro* biological and clinical responses.

It is likely that potentially reduced risk tobacco and nicotine products will continue to be upgraded as new technologies become available, as has been the case with electronic cigarettes. Scientific studies that bridge from a data set of pre-clinical and clinical studies for similar potentially reduced risk products should be sufficient to allow products with new technologies to be determined as potentially reduced risk.

A weight-of-evidence approach, based on the output of the pre-clinical and clinical studies would be used to determine whether the product had the potential to reduce risk. For a new-to-world product, reduced risk determination would require longer-term population-based studies.

To assess the impact of the product on the population as a whole, a Post Market Surveillance (PMS) plan would be agreed pre-marketing. A PMS programme could include information about product usage patterns, consumer perception; provide data with respect to the health risks, and the effect on morbidity and mortality as compared with using other products or quitting use of tobacco products. Specific information could also be collected such as health care visits, physiological measurements and adverse events. □



DR JAMES MURPHY
Head of Reduced Risk
Substantiation

James holds a PhD in polymer chemistry and joined us in 2005 after postdoctoral research at the Nara Institute of Science & Technology in Japan developing novel polymer-based drug delivery systems. He has held a variety of roles in R&D, including leading the development and assessment of a Reduced Toxicant Prototype cigarette, as well as development and commercialisation of Vype e-cigarettes. He now heads up our Reduced Risk Substantiation unit, overseeing all of our pre-clinical and clinical research programs. His group is working on research methodologies to substantiate the reduced-risk potential of next-generation products.



our
OPEN
 approach

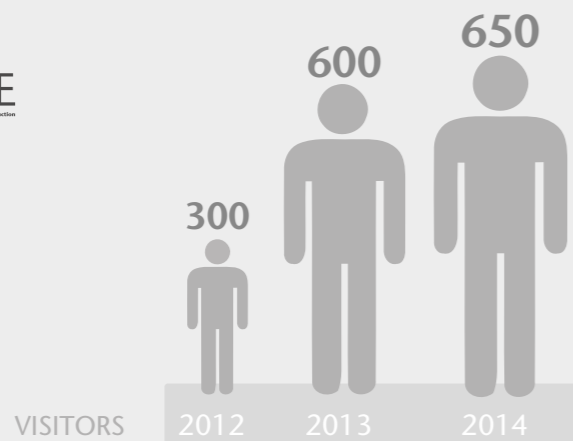
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Developing a scientific underpinning to tobacco harm reduction is too urgent and too important to be left to any one sector of the scientific community. We think that regulators, academia and industry all have roles to play. That is why, particularly over the past decade, we have tried to be open and transparent about the science we do, and have sought to develop scientific collaborations with a wide range of groups.

Tobacco and nicotine science is emerging as an exciting interdisciplinary field that encompasses subjects ranging from

materials science and electronics to advanced analytical chemistry, through to toxicology and risk assessment, clinical studies, and modelling of population effects, as well as genomics, metabolomics, and agriculture. Although the tobacco industry was not strong historically in many of these disciplines, the fact that several companies are now developing novel products that aim to be less risky than conventional cigarettes has required a multidisciplinary approach to innovating and assessing such products.

As you can see in this report, we are



Welcomed over 1500 visitors to our R&D Live Centre at Global R&D since 2011

Over 150 peer-reviewed articles published since 2008

Seven scientific conferences hosted at our world-class facilities on site

VISITORS

researching products across the risk spectrum, from electronic cigarettes (e-cigarettes) and medically licensed nicotine products, to oral products and tobacco-heating products. We also made a public commitment in 2007, as part of our duties as a responsible tobacco company, to a much more open and transparent approach that involves sharing information about our research into tobacco harm reduction.

In 2008, we launched our dedicated science website, www.bat.science.com, through which we share a great deal of information about the non-competitive aspects of our research programmes. In an effort to encourage genuine two-way engagement, we launched, in summer 2015, a Twitter handle (@BAT_Sci), which is allowing us to directly engage with scientists, policy-makers, and our consumers. By removing barriers to engagement, we have seen an overwhelmingly positive response; we have also been invited to participate in robust scientific discussion via Twitter. Both these tools have been welcomed by the scientific community as valuable sources of information.

Our scientists attend international scientific conferences to present our work and engage in dialogue with other scientists in the field, including academics, regulators, and public-health stakeholders. These conferences range from niche tobacco events (including the Society for Research in Nicotine and Tobacco and the Global Forum on Nicotine) to subject-specific meetings (Society of Toxicology, the Association of Inhalation Toxicologists, and the European Aerosol Conference), to mainstream fora (eg American Association for the Advancement of Science

(AAAS)). All our conference posters and presentations are available to download from the library section of bat-science.com.

We are publishing much of our work in peer-reviewed journals. More than 150 BAT-authored papers have been published in at least 50 different journals since 2008 (again, all the manuscripts can be found in the library on bat-science.com). It is heartening that the vast majority of journal editors and editorial boards continue to believe that good science speaks for itself and should be judged objectively by the peer-review process. Most journals today have straightforward processes that ensure that potential conflicts of interest are clearly disclosed.

In addition, our senior scientists have acted as peer reviewers for more than 40 different journals; this reflects an external recognition of the wealth of knowledge and expertise on tobacco and nicotine science that sits within the tobacco industry (and BAT in particular). We expect these requests to increase further over the next few years as the output from the growing tobacco regulatory science community also increases.

We were one of the first tobacco companies to allow external visitors to tour our R&D facilities in the UK (in Southampton and Cambridge), developing a science exhibition centre in 2011 that we updated in late 2015; here visitors spend time with our practicing scientists to learn about their areas of expertise. We have hosted visiting academics, journalists, scientists from standards bodies, scientists from consumer goods companies, regulatory scientists, learned societies, politicians, business people and many others. We have

seen steady growth in the number of visitors to the centre over the past few years.

We have also begun to host local business, national and international scientific conferences in a modern 300-seat auditorium at our Southampton site, including meetings of the Chromatography Society, the British Mass Spectrometry Society, the British Carbon Group, the Institute for Food Science & Technology, and the *In Vitro* Testing Industrial Platform.

Our first Science & Technology Report, published in early 2014, also marked an industry first. Available in both print and app versions, we gave an overview of BAT's progress and aspirations in 10 different areas of science.

We follow best practice regarding clinical studies, as established by the pharmaceutical industry, for instance obtaining ethics approval from the relevant geographical independent ethics committees, and registering our clinical studies on the International Standard Randomised Controlled Trial Number (ISRCTN; isrctn.com) or ClinicalTrials.gov databases before study initiation. It is well accepted (by the scientific community) that registration of a clinical trial in this way creates a commitment to publish the results of the study. Also, every academic who receives funding for fundamental research from BAT is encouraged to publish the results that arise from the project, irrespective of the findings, and to acknowledge the funding source.

These activities have given BAT a very strong heritage of scientific engagement in the tobacco industry. We are pleased to see that other tobacco companies

are also increasing their levels of openness and transparency by launching dedicated science websites and opening up their R&D facilities to visitors.

Recent successes

BAT senior scientists are regularly invited to contribute to the US Food and Drug Administration's Center for Tobacco Products workshops on tobacco regulatory science. We are also actively participating in the work of standards bodies, including the International Organization for Standardization, and, in the context of e-cigarettes, the British Standards Institute and the French organisation, AFNOR (see pages 24–25). Our senior staff have presented on tobacco harm reduction and e-cigarettes at mainstream scientific conferences including the AAAS and the EuroScience Open Forum (ESOF). We continue to regularly publish good manuscripts in high-quality peer-reviewed journals.

Our Chief Scientific Officer, Chris Proctor, was part of the American Chemical Society 2015 writing committee to revise the society's scientific integrity policy through his work with their Corporation Associates division.

Aims for the future

- » Refresh the bat-science.com website
- » Continue to explore new social media initiatives and further develop our presence on Twitter
- » Continue to present at mainstream and niche scientific conferences
- » Continue to host visitors and appropriate scientific conferences at our R&D site □

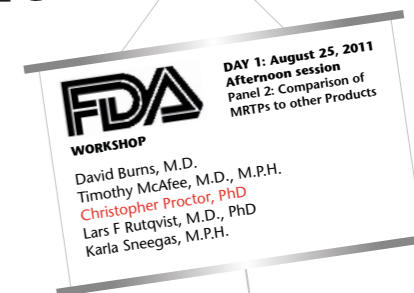


SARAH COONEY
Head of Scientific Collaboration & Communication

Sarah oversees BAT R&D's external scientific engagement strategy. She joined us in 2010 with over 10 years' experience in science publishing, ranging from editorial and production roles through to editorial director and new journal and web development. She holds an MSc in plant genetics, and her research has been published in *Science* and *Genetics*. Sarah has held positions at most of the world's leading publishers, including Nature Publishing Group, Elsevier, BioMed Central and Springer. She also managed the publishing programme of the Society of Chemical Industry in collaboration with Wiley-Blackwell.



bat-science.com



Bring your difference to BAT



Hi Chloe, first of all, could you tell us a bit about what you do at BAT?

I work in Product Stewardship as an evaluator. Our department conducts toxicological risk assessments of materials and additives that go into all our products, from commercially available combustibles to those in development, like e-cigarettes and tobacco-heating products (THPs).

How did you come to work for BAT?

After growing up in Qatar, I did a BSc in biological sciences at Birmingham University, followed by a lab-based MRes in toxicology at the University of Nottingham. Initially I had wanted to be an NHS pathologist but found it very difficult to gain the necessary experience. Through a recruitment agency looking for toxicology graduates, I discovered the toxicology job at BAT and a similar one at the Food Standards Agency. My granddad had worked for Ceylon Tobacco Company [a BAT subsidiary] a long time ago and said how great it was, and I also thought my quality of life would be better in Southampton than in central London, so I chose the position at BAT. That was in 2008 and I am still here 7 years later!

Overview of what you do

A project team will come to us with a new ingredient or material they'd like to use. It might be a new type of paper in a cigarette or a flavour for an e-liquid, for example. We then evaluate the ingredient based on how it is going to be used, what sort of product it is used in and the potential exposure of that ingredient is to the consumer. We use toxicology data and scientific evidence currently available to help us determine whether the ingredient is suitable for such use and, if so, the maximum

level at which it can be used. Although this might sound simple, a huge amount of work actually goes into making sure an ingredient doesn't add to the toxicological risk of any of our products. A typical risk assessment takes about 6 weeks, although we can do them sooner if necessary.

What does a typical day look like?

Although I am a toxicologist, my job is largely desk-based. A typical day depends on deadlines but usually involves a combination of commercial evaluations, work on novel projects (like e-cigarettes), some countersigning (when we double check each other's work), and providing some ad-hoc technical guidance to other team members on a particular assessment. I enjoy the variety of different challenges every day.

How has your role changed?

Technically I've been an evaluator in the same department for the 7 years, but my role has developed as I've become more experienced and I now also manage a small team. I started out on our more straightforward commercial cigarette portfolio; whether we can or can't support ingredients for these products is a lot more black and white. I then moved onto more novel products and now I lead on e-cigarettes. When a project comes in, I'm expected to know where to look for relevant data and evidence and draw from previous experience to find ways of contextualising exposure and supporting that ingredient by myself.

What experience have you gained in the job?

I've grown in confidence as my role has progressed, and am constantly trying to

Are you interested in working at BAT R&D? We have interviewed a member of R&D staff so that you can hear first-hand what motivates our world-class team, their backgrounds and how they feel about working here.

Chloe Winnington is a scientist in the Product Stewardship team. Chloe joined BAT fresh out of university and has progressed up the ranks over the past 6 years, developing into a highly valued and talented BAT scientist.

find creative solutions to problems and more efficient ways of working. In addition to the toxicology side of things, I've also learnt a lot about the products, including technical features that might change smoke chemistry and functionality.

Where do you see yourself in 5 years?

I'd like to continue developing into a more managerial and advisory role, but at the same time I'd never want to give up the science side of things as I enjoy the continuous learning I get from my from my job – I am never bored!

What is the biggest challenge you face in your job?

Not many people know that we're a global department, supporting products not just from R&D but from all over the company. Often we're seen as the people who slow progress down and put the brakes on ideas, but it's crucial that we take the time to rigorously risk assess everything that goes into our products to ensure that the ingredients we use are of the highest quality and do not add to the toxicological risk of the products, whether they're already commercially available or in development. Our department is the only one that knows every single detail about every product (tobacco, flavours, paper ingredients, filters etc) — that's why we're the only department that can deal with legal disclosures as well. Although we may sometimes seem to slow things down, we are actually working hard to protect consumers, product developers, and the company.

Is there anything that surprises you about working for BAT?

I was initially surprised by just how much care goes into assessment of the ingredients we use and making sure that they do not make our products more harmful, even when used in only tiny amounts. There is a lot of negativity around this industry and we're under a lot of scrutiny, but I can honestly say I'm proud of what I do.

Have you got any advice for someone following in your footsteps?

Certainly in my department, if you are interested and motivated there's a lot to understand and learn from experienced toxicologists as well as opportunities for career progression. As always, working here is what you make it. □

Focusing on practical solutions

T

he unseen heroes of R&D must be those in the Innovation Development Centre (IDC). This team has a dynamic, agile, and flexible manufacturing capability that can support R&D in launching new-to-world products, innovations, and technologies. These troubleshooters are the people who not only keep things running smoothly but can also turn ideas into reality, as such, they are vital to R&D.

IDC takes responsibility for the planning and deployment of all technical resources, aiming to increase capabilities and flexibility but without affecting the level of support and productivity it offers, to reduce its physical space footprint, and to increase space for new equipment.

Manufacturing innovation

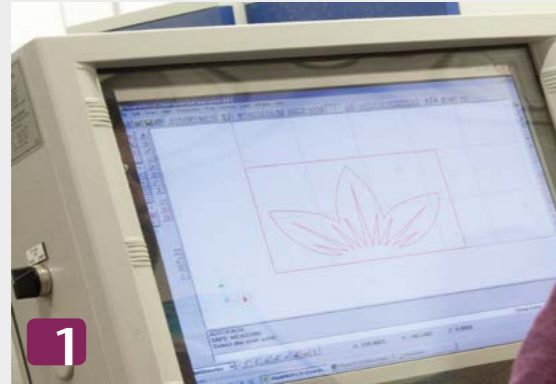
With an increasing focus on innovative technologies in recent years, the manufacturing facility has become ever more integral to R&D, helping project teams by setting up or evolving the processes that lead to new or improved products. Whether it is modifying equipment to manufacture a new product, adjusting machines to make

products in various formats, or developing methods to optimise a process, the team applies its engineering aptitude and technical expertise to drive innovation.

They have done a lot of work, for example, finding ways to manufacture reconstituted tobacco-sheet materials to improve the performance of tobacco heating products (THPs). They've supported the work to manage moisture levels, and have adapted standard processing for manufacturing THPs, shaping the future manufacturing demands of this emerging product category. "Good process control with flexibility helps support developing new products – it is critical to everything," says Richard Hepworth, Manufacturing Engineer.

Mark Goodeve, Senior Engineer, explained that often project managers come into IDC for an initial informal chat about an idea's potential. There will then be a more technical discussion and, once the engineer has given the project manager a steer on what can be manufactured, the department either adapts current equipment or procures what is necessary, dependent on the format and

How the Innovation Development Centre helped to design the cover of this report



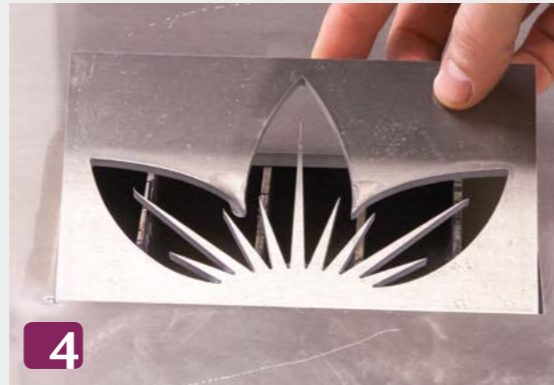
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1. Planned and drawn using computer-aided design
2. High-pressure water jets cut shape into aluminium sheet
3. Shape is cut
4. Shape is extracted from sheet
5. Final cover image created by shining light through metal shape and photographing

specification. “We like a challenge and everyone here has the same attitude – whatever we can do to help, we will,” he says. “We are very prototype-led here and can produce a machine-made sample that has the potential to be developed further or scaled up and commercialised.”

Engineering workshop

Gary Baker and Richard Vezey, both Senior Engineers, are in charge of work on the electrical, control, and mechanical sides of things. They are responsible for all machinery (mechanical, electrical, control systems, hardware, and software) associated

with manufacturing and processing of equipment. The work conducted by the Engineering Workshop ranges from conducting preventive maintenance, acceptance testing, fault finding, interfacing new pieces of kit with current equipment, and calibrating and testing devices, to manufacturing bespoke solutions.

These engineers really are the background problem solvers who support the entire business. As well as sorting machinery, the engineering workshop is the go-to place for a quick turnaround of custom-made parts for new products in development.

Their expertise has been vital in enabling the business to develop prototypes for exploratory work into e-cigarettes and THP devices, and continues to provide unique solutions for unique requirements.

“Anyone can come to us and talk through ideas,” says Gary. “We enjoy new challenges and try to bring even whimsical ideas to life and support them whenever we can.”

By actively seeking new solutions and embracing change, the IDC keeps the core business running and is able to provide innovative solutions that support the development of next-generation products. □



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