

A research project funded by BBSRC¹, the Technology Strategy Board² and EPSRC³ has resulted in the creation of valuable new 'natural' versions of savoury meat and vegetable, blackcurrant, coffee and sweetcorn flavour and fragrance compounds used by the US\$21.8Bn (£14.3Bn)⁴ global flavour and fragrance industry. They allow food manufacturers to create products containing no artificial flavours. Previously, the only way to produce these flavour and fragrance compounds was through chemical synthesis.

The research was carried out by scientists from Durham University, led by Professor Rob Edwards⁵, in partnership with Oxford Chemicals Ltd and Novacta Biosystems⁶. During the project, Oxford Chemicals was bought out by international flavour and fragrance company Frutarom Ltd⁷.

By developing processes which harness novel enzymes to manufacture the flavour and fragrance compounds, Oxford Chemicals was able to ensure the compounds met the requirements of EU regulations for natural products. "The output of the project was that we got four enzymes from Durham, one of which is now in full commercial production through a third party for ourselves. Of the other three, one will probably come through in the next year to that status as well," says Steven Jackson, Technical Manager at Frutarom Ltd.



Fine chemicals, including flavours and fragrances, are a multi-million pound industry in the UK.

The enzyme in commercial production is now being used by the company to manufacture a natural version of a flavour compound called methyl mercaptan. "It goes in all savoury bases for vegetables, noodles, crisps. Any vegetable or meat-based flavour will contain methyl mercaptan." Jackson explains.

Frutarom is now one of only two companies producing these natural flavour and fragrance compounds anywhere in the world.

"The project, which went on for three years, led to a number of products which are on their books as naturals. At the start of the project they were all synthetic," says Edwards, now Professor of Crop Protection at the University of York. "We also helped Oxford Chemicals establish a biotechnology facility on site, with a 100-litre fermenter." he adds.

The UK chemical industry is one of the UK's largest manufacturing sectors. For instance, in the north east of England the fine and speciality chemicals sector, which includes flavour and fragrance compounds, generates around £2.8Bn⁸ in annual sales. "Fine chemicals are something in which the UK has a strong industry profile, and strong technical profile," says Edwards.

Legislation drives innovation

The demand for natural versions of existing artificial flavour and fragrance ingredients came about as a result of new European legislation⁹. Previously, flavour compounds in Europe were categorised as 'natural', 'nature identical' or

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'artificial', depending on how they were manufactured. Food manufacturers could market products as containing no artificial flavours if they contained only compounds from the 'natural' or 'nature identical' category.

"Europe, as part of their big legislation change, wanted to get rid of this term 'nature identical' and move to purely 'natural' or 'flavouring'," says Jackson. "That 'flavouring' category would cover all artificial and all nature identical

IMPACT SUMMARY

Research by scientists from the University of Durham and commercial partners Oxford Chemicals Ltd (now Frutarom Ltd) and Novacta Biosystems has led to the creation of high-value natural flavour and fragrance compounds for the food industry.

The project developed the enzymes and processes required to produce natural versions of commonly-used flavour and fragrance compounds.

One the enzymes now in commercial production is being used by Frutarom Ltd to manufacture a natural version of a common flavour compound called methyl mercaptan, found in all savoury vegetable or meat-based flavours.

Frutarom is now one of only two companies producing natural versions of these flavour and fragrance compounds.

flavours. So there would be a price premium if you could manufacture something as 'natural' because companies that were focusing on 'no artificial flavours' would have to either take that tag line off or, if they wanted to still promote their product as true to nature, they would have to find alternative sources for some of their flavour components," he adds.

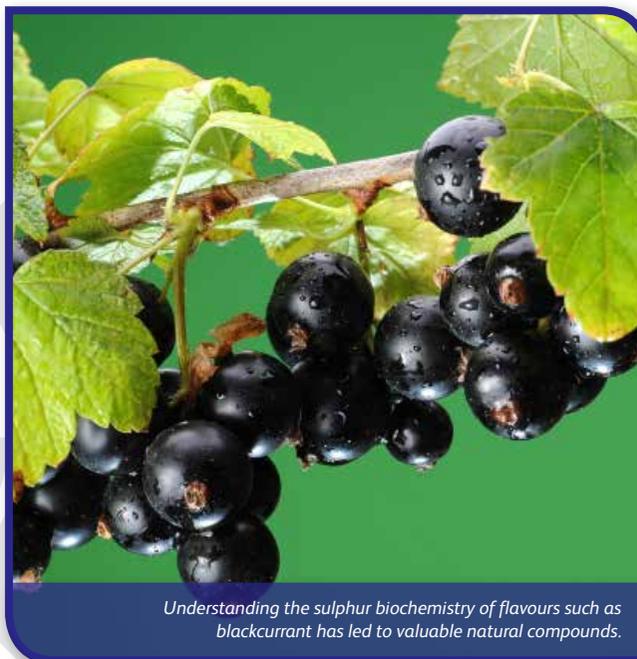
The new European legislation allowed products to be labelled as natural if they were either isolated from a natural source or manufactured via a biotechnology or fermentation processes. It meant that many of the aroma chemicals used by the European food manufacturing industry, which were produced by US companies, would no longer count as natural products. "Essentially some of the low volume but very high value products would be dropping out and there was no current technology in the business or in the whole industry to fill that void," Jackson explains.

This left a gap in the market that Oxford Chemicals, who already manufactured synthetic versions of many of these chemicals, sought to fill.

Developing a natural arsenal

The collaboration between Edwards' group at Durham and the team at Oxford Chemicals began in 2003. This project built on previous work at Durham into sulphur biochemistry, particularly in natural products, as well as their expertise in understanding the function of enzymes from microbes and plants. "When you put sulphur into a volatile aroma chemical you get a very pungent smell. So for example the smell of blackcurrant, thiomenthone, is a sulphur compound. The human nose can sense these down to a few parts per billion," says Edwards^{10,11}.

Initial funding through a Knowledge Transfer Partnership



Understanding the sulphur biochemistry of flavours such as blackcurrant has led to valuable natural compounds.

(KTP)¹² enabled Edwards' group to begin investigating the flavour and fragrance chemistry of pomegranates¹³. "As we were doing that we were talking about the sorts of products they [Oxford Chemicals] wanted to have in their natural arsenal, we came up with a list of chemicals they wanted to produce as naturals," Edwards explains.

Working with Oxford Chemicals, the researchers designed the metabolic pathways required to produce natural flavour and fragrance compounds and identified a list of three or four enzymes needed to produce the desired product. Subsequent funding, including a large co-funded Collaborative R&D¹⁴ grant from BBSRC, EPSRC and the Technology Strategy Board¹⁵, followed by a second, smaller Collaborative R&D grant from the Technology Strategy Board¹⁶, enabled the researchers to develop the enzymes

and the processes required to manufacture them.

The researchers then worked with Novacta Biosystems, the second industrial partner on the larger project, to scale-up the production processes. "Novacta helped us on the bulk production. They were particularly good at scaling up processes, so they would optimise fermentation conditions to produce more of the recombinant enzyme," Edwards explains.

During the project Oxford Chemicals was bought out by Frutarom Ltd, one of the largest global flavour and fragrance companies. "It was just as this project was starting up that Oxford Chemicals was bought by Frutarom. One of the reasons they were bought out was that Frutarom knew about the biotechnology programme we had initiated," says Edwards.

Leader of the technology

At the moment, Frutarom is using the new enzymes, developed to produce the valuable natural flavour compounds, to manufacture methyl mercaptan from a synthetic feedstock. This enables them to meet an industry need for the cheaper source of methyl mercaptan after other suppliers stopped providing the synthetic version in quantities appropriate for the food industry.

"That whole product bottomed out of the market – no-one could get the product. We'd already developed the natural version, using a natural precursor, but people wanted the cheaper synthetic version, which we can manufacture using the enzyme and make a good margin using the synthetic version of the precursor as the feedstock. We've been using that as the leader of the technology into the market while we've been working on the other products," says Jackson.



New European regulations provide an opportunity for innovative UK chemical companies.

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