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CHEMICAL & ENGINEERING NEWS
JULY 17, 2023

Organic chemistry in water?

To cut waste, chemists are taking the plunge into a new medium

P.20

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Cover story

Quote of the week

"Nobody talks about this, but we organic chemists obviously are contributing to climate change. We're generating CO_2 by burning that organic solvent."

—**Bruce Lipshutz,** organic chemist, University of California, Santa Barbara

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Illustration by Yang H. Ku/ C&EN/Shutterstock

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ACS News

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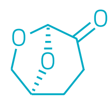
Editorial

The challenge of green chemistry

In 2019, I wrote a story about efforts by a start-up company and its corporate partners to launch a new solvent they called Cyrene. I was reminded of that article while reading Leigh Krietsch Boerner's cover story this week about efforts to expand the use of water as a solvent for organic chemistry reactions (see page 20).

As Boerner reports, dissolving compounds in a solution is the best way to get them to react, and organic molecules tend to dissolve in organic solvents. The trouble is that many organic solvents are safety or health hazards. They are typically disposed of by incineration, a process that creates greenhouse gases. Chemists would like nontoxic, renewable solvents, and it is in part the dearth of such solvents that causes them to turn to water.

That's where Cyrene is supposed to come in. Its chemical name is dihydrolevoglucosenone; it's made by hydrogenating levoglucosenone, a molecule that is derived from cellulose waste. But as is almost always the case for new chemicals and materials being developed by new companies, the road to market has been long.



Cyrene

Cyrene's origins go back over 15 years, to when the paper industry was confronting declining demand. An industry executive, Tony Duncan, identified levoglucosenone as a promising cellulose-derived molecule. He turned to James Clark, a University of York professor, who came up with the idea of hydrogenating it to create a solvent. The two figured it could replace nitrogen-containing dipolar aprotic solvents like *N*-methyl-2-pyrrolidone and dimethylformamide. To commercialize the product, Duncan helped form an Australian firm, Circa Group, in 2006 and became its CEO.

Circa is alive and well today, but large quantities of Cyrene cannot yet be found.

Circa and its solvent got a big vote of confidence in early 2021, when the company succeeded in raising about $60 million on the Euronext Growth Oslo stock exchange. Circa is now based in Norway.

The firm has since put some of the money into building a facility in northern France with the capacity to make 1,000 metric tons (t) per year of the solvent from sawdust and wood waste. When the plant was announced in 2020 it was expected to open in September 2023 at a cost of $25 million—half of that paid by the European Union's Horizon 2020 research and innovation program. The French government is contributing as well.

But these days, the target for opening the plant is late 2024. Moreover, in Circa's first-quarter financial report, published in May, the firm disclosed that "inflationary pressure across the project" is increasing costs and that it will need to raise more money to complete it.

Some investors are losing faith. Two years ago, Circa's shares traded for about 16 euros ($18 today). They are around 4 euros now. And output from the company's pilot facility in Australia is paltry: 588 kg in April.

I'm pretty sure the French plant will be built. The first-quarter report includes photos of demolition and preparation at the site, a former coal-fired power plant. And the EU and France are motivated to make it happen. But many stars will need to align for Circa to realize its plans for an even larger facility somewhere in the US or Europe and to be producing 80,000 t per year of Cyrene by 2030.

To be clear, I would like to see the company and its solvent succeed. Cyrene is a great example of how the chemical enterprise can make life on this planet more sustainable. And organic chemist Bruce Lipshutz told Boerner that chemists and the chemical industry can't keep doing things the way they do now. It's just very hard to find a new way.

Interim editor in chief

Views expressed on this page are those of the author and not necessarily those of ACS.

Concentrates

Chemistry news from the week

Highlights

GENE EDITING

Gene editing trees for sustainable fibers

CRISPR editing renders wood that may yield more cellulose, save processing energy

Cellulose fibers, often obtained from wood, are a key component in products like paper, packaging, tissues, and hygiene products. But within wood, another polymer called lignin is entangled with cellulose. In order to extract the cellulose from wood, the lignin is often broken down with harsh chemicals and separated from the cellulose. The more lignin in the wood, the harder it is to isolate the cellulose fibers.

Rather than just removing lignin from logs, researchers at North Carolina State University sought to lower the proportion of it from the outset. Using the gene-editing tool CRISPR on poplar trees, they modified some of the genes that produce the chemicals that eventually form lignin. Using seven gene-editing strategies, each modifying three to six genes, they were able to slash lignin content up to 35% compared with a nonedited poplar tree when measured after 6 months of growth (*Science* 2023, DOI: 10.1126/science.add4514).

The researchers started by modeling 69,123 combinations of edits to different genes. Of those, only 347 were predicted to match the team's required criteria, which included cutting lignin content, altering lignin and wood compositions, and being able to grow to a similar size as unedited trees. Ultimately, the researchers chose the seven editing strategies that they thought would yield the very best wood properties.

Wood edited to have lower lignin content could have several practical benefits, suggest corresponding authors and NC State professors Rodolphe Barrangou and Jack Wang. Lowering the amount of lignin means increasing the amount of cellulose in the wood, so less biomass is needed to yield the same amount of cellulose. Also, on top of requiring harsh chemicals, removing lignin from wood during the pulping process is energy intensive; wood with less lignin would allow savings of both energy and chemicals.

Having the ability to modifiy lignin in ways that make its removal easier and more efficent that require less of those hazardous chemicals "will bring really transformative benefits to the process of producing sustainable fibers," says Wang, a tree geneticist.

CRISPR-edited wood (red) and unedited wood (white)

CREDIT: CHENMIN YANG

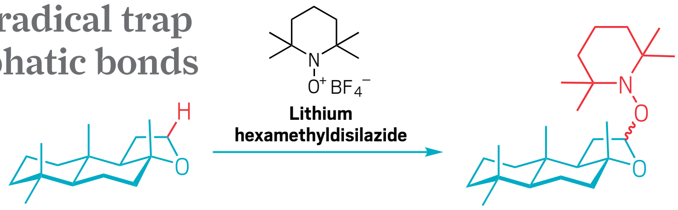
Steve Strauss, a forest biotechnologist at Oregon State University who was not involved in the study, says this work is "a good start." He praises the way the researchers used CRISPR to test a number of gene-editing combinations. But he says it will be important to see how the trees grow in the field rather than in the greenhouse and whether these modifications can be translated to tree species that are more important, such as pine or eucalyptus. Strauss also cautions that "if you cut lignin down too much, you get a tree that can't stand up or can't conduct water."

Wang and Barrangou say they didn't reduce the lignin content beyond what is found in other trees in nature, so they don't expect major adverse effects from the lower amounts. They also say the next step for the work will be to grow the trees in field trials and that they've already started working on tree types of more commercial interest.—GINA VITALE

C–H ACTIVATION

Frustrated radical pairs facilitate C–H activation

An H-atom acceptor and a radical trap work together to break aliphatic bonds



A radical new method has just been added to the C–H activation toolbox. In a new *Nature* paper, Song Lin and his group at Cornell University describe how frustrated radical pairs can make a handy team for activating C–H bonds on saturated carbon atoms (2023, DOI: 10.1038/s41586-023-06131-3). The reaction takes only half an hour, uses commercially available reagents, and opens up multiple functionalization options. “The simplicity of the system is really cool,” Lin says.

The researchers matched up hexamethyldisilazide or HMDS– (shown), which can be oxidized to make a nitrogen-centered radical, and the well-known oxidant and radical trap 2,2,6,6-tetramethyl-1-oxo-piperidinium (TEMPO+). The two radicals are too bulky to annihilate each other—hence the *frustrated* moniker—so they turn their pent-up reactivity on other molecules.

Lin says the research team initially set out to see what kinds of reactions the radical pair could accomplish, and were delighted to find it worked for C–H activation.

The HMDS radical snatches a hydrogen atom from the molecule to be functionalized. That molecule then becomes a carbon-centered radical and gets trapped by the TEMPO radical. The resulting adduct has relatively weak C–O and N–O bonds, which opens up numerous possibilities for installing new functional groups.

The researchers found that it’s possible to influence which hydrogen gets plucked off of the molecule by altering the size of the H-atom acceptor. A streamlined *tert*-butoxide radical can reach into crannies and pluck out tertiary hydrogens, while bulked-up hexaphenyldisilazide goes for less thermodynamically favored but easy-to-reach primary and secondary hydrogens.

In an email, Rebecca Melen of Cardiff University calls the method “an elegant way of achieving selective C–H functionalization without using transition-metal catalysts.” She praises the study for advancing scientists’ understanding of radical species in C–H activation.

Lin says the next steps include further investigating the relationship between H-atom acceptor choice and selectivity and exploring other radical traps that can provide different functionalization options.—BRIANNA BARBU

FORENSIC SCIENCE

Green ammo’s organic residues

Researchers use synthetic skin to analyze how organic particles behave on bodies and fabrics

A researcher evaluates the persistence of gunshot residue by exposing an artificial skin membrane to a washing process

CREDIT: WVU PHOTO/MATT SUNDAY

Firing a gun releases a burst of gases and microparticles that deposit on people and surfaces. Forensic scientists analyze this gunshot residue to investigate crimes. Today, this analysis relies mostly on heavy-metal particles used in ammunition, but the push to replace these metals with greener materials has recently led forensic scientists to study organic gunshot residues.

Researchers have now used both human skin and synthetic skin membranes to evaluate how long organic gunshot residues persist on skin and other surfaces and how they get transferred or lost (*Forensic Chem.* 2023, DOI: 10.1016/j.forc.2023.100498). “Very little is known about organics, which behave completely differently from heavy metals,” says Tatiana Trejos, a forensic chemist at West Virginia University.

Trejos, chemist Luis Arroyo, and colleagues developed a liquid chromatography/mass spectrometry (LC/MS) method to detect residues of organic compounds such as diphenylamine and nitroglycerine found in bullets. LC/MS requires large molecules, so the team used complexing agents that encapsulate the microparticles to form larger complexes for analysis.

The researchers used over 650 samples to study gunshot residues on human skin and synthetic skin, as well as on fabric onto which residue is transferred. They ran tests hours after firing and after tasks such as washing hands and running.

Organic residues persisted for a shorter time on fabric and skin than inorganic ones, the team found, but they were more likely to remain in their original location after washing or shaking hands.

The team has also developed a portable technology based on laser-induced breakdown spectroscopy and electrochemical sensors that detects inorganic gunshot residues with nearly 98% accuracy. While typical lab tests take hours, Trejos says, “this takes only 5 min and can be brought to the crime scene.”—PRACHI PATEL, special to C&EN

ART & ARTIFACTS

Chemical clues to ancient Egyptian redos

Over 3,000 years ago, artists adorned the walls of the Theban Necropolis with formal paintings and portraits. But they didn't always get it right the first time. Researchers analyzing works in two tombs with macro-X-ray fluorescence have found evidence of touch-ups and changes in design (*PLOS One* 2023, DOI: 10.1371/journal.pone.0287647).

The group, led by Philippe Walter at Sorbonne University, took portable equipment into the tombs and focused on two paintings in the complex. In the first, an alteration was already visible to the naked eye: an arm had been painted over and repositioned. But by measuring the chemical fingerprints, the researchers could show that the pigments used to paint the new arm differed from the original—the second arm employed an iron-containing ochre, whereas the first had an arsenic-containing pigment. In the tomb chapel of Nakhtamun, the team turned its attention to a portrait of Pharaoh Ramses II and uncovered hidden details. For example, levels of arsenic suggest that the collar and scepter originally had different shapes and were later adjusted to match other artworks.

Drawing conclusions from just two examples is unwise, the researchers say in their paper describing the work. But Egyptian art is often described as very formalized, with guidelines drawn out by more-skilled workers before the paint was laid down by a team of artisans. These corrections suggest that more investigation is needed to understand both the workflows used and the reasons changes were deemed necessary.—LAURA HOWES

SUSTAINABILITY

Podcast: Tires face yellow flags and pit stops on the way to sustainability

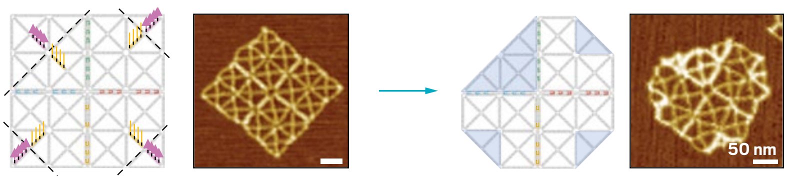
Be they powered by fossil fuels, batteries, or hydrogen, cars are here to stay. So what can be done to make tires greener? In this episode of *Stereo Chemistry*, C&EN reporters Alex Scott and Craig Bettenhausen look at where the rubber meets the road, literally. Scott's cover story about efforts to make tires more sustainable appeared in the May 29, 2023, issue of C&EN. He found people working on the movement and fate of tiny specks of tire-and-asphalt dust in the environment as well as large-scale efforts to shift to biobased and recycled raw materials when making new tires.

This conversation is part of C&EN Uncovered, a podcast project in which reporters share the most striking moments from their reporting, their biggest takeaways, and what got left on the cutting-room floor. Listen at cenm.ag/greentires.—CRAIG BETTENHAUSEN and MARK FEUER DITUSA

MATERIALS

DNA origami inspired by paper origami

If you've ever tried paper folding, perhaps you've run into a common challenge: the smaller the project, the harder it is to achieve a sharp fold. This was not an issue for researchers at Seoul National University led by Do-Nyun Kim, who reported in *Nature* the development of a DNA origami system that can, like regular origami, be folded into a panoply of shapes (2023, DOI: 10.1038/s41586-023-06181-7).



The researchers synthesized this origami "paper," a self-assembling DNA scaffold about 240 nm to a side, from four monomeric tiles. Each tile has what the researchers call a handle, two stretches of DNA (pink and yellow markings) on either side of a desired crease (dashed lines). They next added "glue" DNA molecules that can bind by base pairing to both halves of a handle, bringing them together and forcing the scaffold molecule to crease into a new configuration. The researchers confirmed successful folding using atomic force microscopy.

By combining monomers with different handles, the researchers generated scaffolds that can fold into a rectangle, a smaller square, an octagon, an envelope, and other irregular shapes. They also developed a way to unfold their origami: a releaser DNA sequence, which pairs with the glue DNA more strongly than the scaffold does, can restore a scaffold to its unfolded starting state.—LAUREL OLDACH

OUTSOURCING

Bain to acquire FIS

Family-owned drug chemical maker is the latest private equity target

The private equity firm Bain Capital will acquire Fabbrica Italiana Sintetici (FIS), a pharmaceutical chemical producer based in Montecchio Maggiore, Italy, for an undisclosed sum.

The seller is Nine Trees Group, the holding company of the Ferrari family, which started FIS in 1957. The group's holdings include Anemocyte, a biotech firm specializing in plasmids and messenger RNA.

In a related deal, the French company Minakem has acquired Delmar Chemicals, a Montreal-based drug chemical firm that FIS acquired in 2011.

The deal with Bain follows months of speculation about a possible purchase of FIS. A recent report in the Italian financial journal *Il Sole 24 Ore* said the Italian competitor Olon, in a partnership with the private equity firm Permira, was the lead contender in a field of several potential buyers that included Bain.

Industry observers have been anticipating an acquisition deal for FIS for at least 2 years. They point to the company's heavy debt load from a series of investments, including the Delmar purchase and the acquisition of a facility in Lonigo, Italy, from Zach System.

In addition, there is speculation that FIS, which generated sales of $770 million in 2022, has outgrown its family ownership. With three sites in Italy, FIS currently employs about 2,000 people, including 250 R&D scientists.

"What the family wanted most, probably, was to exit because of the debt situation," says Roger Laforce, an industry consultant who was general manager for commercial and R&D operations at FIS from 2004 until 2011. According to a 2022 balance statement, the company carries over $400 million in debt.

Using a rule of thumb for valuing an acquisition according to pretax earnings, Laforce estimates that Bain paid about $1 billion for FIS.

The acquisition is the latest in a yearslong trend of private equity firms' acquiring pharmaceutical chemical producers—several of them family owned. But it still took some industry watchers by surprise.

Fabbrica Italiana Sintetici says its labs employ about 250 R&D scientists.

"I thought for sure one of the chemical manufacturers was going to take it," says James Bruno, president of the consulting firm Chemical and Pharmaceutical Solutions. "Two years ago, I would have thought one of the Chinese groups would have come in and done something with it."

Bruno says Bain may invest in technology upgrades and will move to reduce costs. "And I think they are going to probably try to take advantage of the reshoring trend, putting investments into making intermediates and raw materials."

Bruno questions the logic of selling Delmar, however. "I would have kept this group," he says. "It was a good way to get projects into the company" that originate from North American biotech firms. Bruno says that Minakem has been on the lookout for a North American facility.—RICK MULLIN

ECONOMY

Outlook weakens for European industry

BASF, Evonik, Clariant, and Shell faced tough market conditions in the second quarter

Demand for chemicals dropped in the second quarter and shows no signs of improving, some European companies say.

BASF, in particular, has felt the effects of the weak market. According to the firm's preliminary financial results, its sales for the second quarter of the year were down 25% from the year-earlier period, to $18.9 billion. The German giant expects to report a 57% decline in its corresponding pretax profits before special items, to $1.1 billion. The firm has substantially downgraded its expected sales and pretax profits for the full year.

25%

Drop in sales BASF expects to report for the second quarter.

Evonik Industries has also revised its outlook for 2023 downward and says in a press release that it "no longer assumes any recovery in the second half of the year." In its preliminary financial results for the second quarter, the German firm says that its pretax profit was down about 40% from the year-earlier period and that sales fell 16%, to about $4.4 billion. Evonik plans to cut costs and reduce capital expenditures.

Evonik and its peers face common headwinds across the chemical sector, Sebastian Bray, a chemical stock analyst at Berenberg Bank, says in a financial note.

Clariant also downgraded its expectations for 2023. "The uncertainties and risks related to the economic environment, including the pace of a recovery in China, which we had indicated at the start of this year have unfortunately materialized and are weighing on the industry as a whole," Clariant CEO Conrad Keijzer says in a press release. On a positive note, the Swiss firm has a "strong order book" for its catalyst business.

Reporting preliminary financial results for the second quarter, Clariant estimates that pretax profits were down about 25%, to between $139 million and $148 million, and that sales dropped about 17%, to $970 million.

Shell also reported preliminary second-quarter results. The British firm expects to record a financial loss for its chemical business, despite improved profit margins.—ALEX SCOTT

CREDIT: FABBRICA ITALIANA SINTETICI

DRUG DISCOVERY

Generate opens cryo-EM lab

Generate Biomedicines, which uses artificial intelligence for protein design, recently opened a cryo-electron microscopy (cryo-EM) laboratory in Andover, Massachusetts, that it says will accelerate its efforts to discover new protein-based therapeutics for oncology, immunology, and infectious diseases.

Cryo-EM enables scientists to determine the structure of a protein without first crystallizing it, and has revolutionized structural biology in recent years. “What no one’s been able to crack though, yet, is just how do you scale this up?” says Generate cofounder and chief technical officer Gevorg Grigoryan, who says he envisions a future where determining a protein structure is as routine as sequencing a gene.

To acquire structural data around the clock, Generate spent about $15 million on four automated microscopes from Thermo Fisher Scientific and JEOL and roughly another $6 million on lab renovation. The company uses automated lab systems to help standardize production of AI-designed protein samples from DNA synthesis through imaging and is developing its own automated microfluidic lab systems to improve sample preparation.

While several pharmaceutical companies use machine learning for de novo protein design, JEOL sales account manager Jens Breffke says Generate is unique in its workflow: producing those proteins and confirming that they are shaped as expected. Its scientists hope that rapidly generating high resolution structures will both help fine-tune potential therapeutics and improve its models’ performance.

According to Melanie Adams-Cioaba, general manager of the pharmaceutical cryo-EM segment at Thermo Fisher Scientific, Generate “sits at the forefront of a lot of where both computation and experimentation are pushing.”—LAUREL OLDACH

ELECTRONIC MATERIALS

Gelest breaks ground on dry photoresist precursor plant

Facility will produce organometallic chemicals used in new lithography processes

The specialty chemical maker Gelest has broken ground in Morrisville, Pennsylvania, on a commercial-scale facility that will make organometallic photoresist precursors for advanced semiconductor manufacturing. The chemicals are used to pattern nanometer-scale lines on silicon wafers with a new technique involving extreme ultraviolet (EUV) light.

For Gelest, the investment represents not just an expansion but a change in business model, according to President Jonathan Goff. “Historically, Gelest has always interacted with the electronics and semiconductor industry as more of an R&D partner,” he said at a July 7 event. The project is “a big step into being not only a new product development house but also a long-term commercial supplier to that industry,” he said.

Goff credited Mitsubishi Chemical Group’s 2021 purchase of Gelest for giving the firm the confidence and business infrastructure it needed to make this move. After the acquisition, Gelest became the hub for Mitsubishi’s custom synthesis unit.

When the facility opens in late 2024, its first products will be precursors needed for a new dry photoresist–based lithography technology developed by Lam Research, according to Gelest executive vice president Edward Kimble. The technique replaces a wet, solvent-based method of applying patterning chemicals to the surface of a silicon wafer with a gas-phase method based on chemical vapor deposition.

Kimble and Goff said the precursors are discrete organometallic molecules, which are more responsive to the EUV laser light used in cutting-edge semiconductor fabrication than the polymers used in wet photoresist technology. They declined to go into chemical detail about the molecules.

Goff explained that the semiconductor industry often relies on trade secrets to protect its intellectual property because the patent system is slow. The rapid innovation cycle means that getting a product to market quickly is more important than securing long-term exclusivity.

“You know there’s going to be others that come along that are going to do something similar, so that the key is being first, and always moving forward,” Goff said. “Before we’ve even done generation one, we’re probably already working on generation two.”

Gelest already produces small-batch quantities of some chemicals, but a new plant will yield commercial volumes of certain electronic materials and other specialty chemicals.

After the dry resist precursors are shipping, Kimble said, Gelest will install production lines for other chemicals it sells for medical devices, vehicles, power electronics, thermal management, and specialty coatings. The firm owns an additional 3 hectares of land at the site, which leaves room for further expansions.

Lita Shon-Roy, CEO of the semiconductor supply chain consulting firm Techcet, cautions that the semiconductor industry’s move to dry photoresists is a few years off. Lam Research is facing a patent lawsuit over its technology from JSR, which bought the Lam competitor Inpria in 2021. Inpria’s main photoresist technology uses organometallic clusters with tin-oxide cores. And the equipment used to deposit and remove dry resist is currently slower than the corresponding wet resist machines.

“Perhaps pilot production in late 2024 at best, in my opinion,” Shon-Roy says.

At the same time, she says, the shift is inevitable because dry resist is shaping up to be an enabling technology to create more-powerful chips. The greater precision of dry resist will produce fewer patterning errors at tiny, sub-5 nm sizes, she adds.—CRAIG BETTENHAUSEN

CREDIT: GELEST

GREEN CHEMISTRY

Cepsa eyes first sustainable isopropyl alcohol plant

The Spanish oil and chemical firm Cepsa will spend $80 million to build at its site in Huelva, Spain, what it calls the world's first plant for producing sustainable isopropyl alcohol. Scheduled to be operational by 2025, the plant will use only renewable or biobased raw materials. Cepsa plans to make the plant carbon neutral by using renewable energy and green hydrogen, which it will produce locally through a partnership with the fertilizer producer Fertiberia. Isopropyl alcohol is a disinfectant in high demand for hand sanitizer gel and related applications. It is also used in cleaning products, electronics, cosmetics, and paints, and as a solvent. The sustainable nature of the product will also open doors to new uses, says José Maria Solana, Cepsa's vice president for chemicals, in a press release. In a related effort, Cepsa is substituting renewables for fossil fuel–derived materials in its production of linear alkylbenzene and phenol.—ALEX SCOTT

AGRICULTURE

▶ EuroChem threatens to close fertilizer plant

EuroChem Group says it may have to mothball a large phosphate fertilizer plant in Lithuania because of sanctions imposed by the country's government that the firm claims prevent profitable operation. EuroChem is based in Switzerland but is majority owned by Aleksandra Melnichenko, wife of the Russian billionaire Andrey Melnichenko. The European Union has imposed sanctions on the couple because of their ties to Russia's government. EuroChem says that the plant is one of the largest of its kind in Europe and that the closure would pressure regional farmers who are already suffering from sharp increases in fertilizer prices in recent months.—MICHAEL MCCOY

ENVIRONMENT

▶ Lhyfe plans green H_2 plant in Germany

The French green hydrogen producer Lhyfe has disclosed plans to build a 70 MW plant in Perl, Germany, that would deliver up to 30 metric tons per day of hydrogen. Lhyfe is due to start building the plant, which would deploy water electrolysis powered by renewable energy, in the first half of 2027. The plant would be connected to the planned mosaHYc hydrogen pipeline, which promises to supply Luxembourg, the German region of Saarland, and the northeast region of France.—ALEX SCOTT

BIOBASED CHEMICALS

▶ Syclus planning ethanol-to-ethylene

The start-up Syclus has chosen technology from the French engineering firm Axens for an ethanol-to-ethylene plant it is planning in Chemelot industrial park, in Geleen, the Netherlands. The plant will have capacity for about 100,000 metric tons per year of ethylene, the quality of which will be suitable for the region's ethylene pipeline network. CropEnergies, a German firm that owns a 50% stake in Syclus, will supply ethanol to the plant. Syclus estimates that the plant will cost $145 million to build and come on line in 2026.—ALEX TULLO

INVESTMENT

▶ BMW invests in NFW

Natural Fiber Welding (NFW), one of C&EN's 10 Start-Ups to Watch in 2021, is getting a big boost from BMW. The automaker says that NFW's Mirum is the first biobased leather alternative it has tested that stands up next to animal leather in terms of durability, cost, scalability, and environmental impact. BMW also made an undisclosed investment to help NFW scale up by switching from batch processing to roll-to-roll manufacturing.—CRAIG BETTENHAUSEN

Natural Fiber Welding's leather alternative has met BMW's material requirements for use in car seats.

MATERIALS

▶ CarbonCure raises funds for green concrete

The CO_2–consuming concrete maker CarbonCure has raised $80 million in equity investments led by Blue Earth Capital. Existing investors also participated, including Breakthrough Energy Ventures and venture capital funds from Microsoft, Amazon, and Samsung. CarbonCure says it will use the money to accelerate the deployment of its technology, which uses CO_2 as an ingredient in ready-mix concrete. The firm is active in 30 countries and says its process has sequestered 290,000 metric tons of CO_2 so far.—CRAIG BETTENHAUSEN

DRUG DISCOVERY

▶ AI developer Nvidia invests in Recursion

The graphics card designer and artificial intelligence developer Nvidia has invested $50 million in Recursion, an AI-based drug discovery company. The firms will also work together to optimize Recursion's AI models for biology and chemistry in drug discovery and distribute them via Nvidia's cloud services. Recursion recently acquired Cyclica and Valence Discovery, two chemistry-based AI developers, to broaden its biology-based drug discovery platform. The firm claims that it now has

CREDIT: NATURAL FIBER WELDING

a biological and chemical dataset exceeding 23 petabytes and 3 trillion searchable gene and compound relationships. Nvidia introduced a generative drug discovery AI cloud service called BioNeMo earlier this year.—RICK MULLIN

ONCOLOGY

▶ Crossbow draws $80 million in series A

Crossbow Therapeutics has landed $80 million in series A funding led by Pfizer Ventures and MPM BioImpact for the development of cancer immunotherapies. The company's pipeline consists of antibodies that mimic T-cell receptors and can recognize peptides bound to the major histocompatibility complex molecules on the surfaces of cancer cells. After binding, the antibodies rouse the immune system to attack the targeted tumors cells.—SHI EN KIM

MERGERS & ACQUISITIONS

▶ Nanobiotix partners with Janssen

The biotech firm Nanobiotix has entered a global licensing deal with the Johnson & Johnson subsidiary Janssen Pharmaceuticals. As part of the deal, Janssen will develop and commercialize NBTXR3, a radioenhancer for treating cancer currently in Phase 3 clinical trials. Nanobiotix will get $60 million, split evenly between up-front cash and in-kind support. The agreement also provides for up to $1.8 billion in milestone payments.—LAURA HOWES

NEUROSCIENCE

▶ BMS doubles down on neurodegeneration

In quick succession, Bristol Myers Squibb has entered global licensing agreements with both Evotec and Prothena for their neurodegenerative programs. A BMS partner since 2016, Evotec will receive $40 million for the rights to its late-stage discovery programs, plus milestone and royalty payments. BMS will pay Prothena $55 million for PRX005, an anti-tau antibody for treating Alzheimer's disease. Earlier this year, Prothena announced that PRX005 was well tolerated among participants in Phase 1 clinical studies.—SHI EN KIM

FOOD

▶ Corbion to expand sour-candy-coating capacity

The ingredient maker Corbion is adding a production line for sour-candy powders at its facility in Montmeló, Spain. The food-grade malic acid powders are a popular coating and ingredient for gummy and jelly candies, a sector the company says is worth more than $17 billion per year worldwide. Corbion says that sour varieties lead the gummy category in new product launches and overall growth and that acid-powder supplies are tightening.—CRAIG BETTENHAUSEN

The sour coating on gummy candies is often malic acid.

PHARMACEUTICALS

▶ Tenpoint launches to tackle vision loss

Tenpoint Therapeutics has launched with $70 million in series A investments to develop therapies that reverse vision loss. The company will pursue both ex vivo approaches, in which cells are manipulated outside the eye and then administered, and in vivo reprogramming, which acts on cells in place within the eye. "If we think of the eye . . . as a camera, it's easier to access certain parts of the camera depending on what part you need to exchange," says Tenpoint CEO Eddy Anglade. The firm says it aims to replace cell types in both inherited and age-related conditions.—GINA VITALE

Business Roundup

▶ **HF Sinclair**, a US oil company, has deployed technology developed by Topsoe to convert two crude oil refineries in Wyoming to make biodiesel from waste materials and biofeedstocks. The oil producer has also built a new refinery for making biodiesel with Topsoe technology in New Mexico.

▶ **JSR** has invested an undisclosed sum in Gaianixx, a 2021 spin-off from the University of Tokyo. Gaianixx is developing single-crystal interlayer films for semiconductor substrates.

▶ **Borealis** has agreed to acquire the polypropylene recycler Rialti. The Italian firm has the capacity to recycle 50,000 metric tons of polypropylene annually.

▶ **Biosynth** has acquired Celares, a developer and manufacturer of conjugate vaccines and bioconjugate drugs. The deal will add bioconjugation of antibodies, antigens, and peptides to Biosynth's current line of pharmaceutical and diagnostic raw materials for the life sciences industry.

▶ **Astellas Pharma** has licensed 4DMT's vector for gene therapies to treat eye disease for $20 million up front and milestones up to $943 million. Astellas says the deal fits with its focus on blindness and regeneration.

▶ **GSK** will collaborate with Elsie Biotechnologies on oligonucleotide therapeutics. The deal includes an undisclosed up-front payment, licensing fees, and milestones, and gives GSK access to a nonexclusive license for Elsie's technology.

▶ **BeiGene** has obtained an exclusive license from DualityBio for its preclinical antibody-drug conjugate for solid tumors. DualityBio will receive an up-front payment and milestones of up to $1.3 billion, plus royalties.

▶ **Septerna**, a small-molecule drug developer targeting G-protein-coupled receptors, has raised $150 million in series B financing. The firm was cofounded by chemistry Nobel laureate Robert Lefkowitz and launched early last year.

CREDIT: KWELSEY/FLICKR

PUBLISHING

Drug delivery journals publish more men than women as first and last author

The percentage of female last authors has not changed since 2017

Papers in drug delivery–related journals are one and a half times as likely to list a man as first author and three times as likely to list a man as last author as they are to list a woman in those positions, according to a recent study (*Mol. Pharmaceutics* 2023, DOI: 10.1021/acs.molpharmaceut.3c00328). The researchers also found that higher-impact journals disproportionately publish men over women.

Since hiring and promotion decisions typically consider an academic's publication record, this observed gender gap may help explain why women are underrepresented among faculty in drug delivery disciplines, such as chemistry, chemical engineering, and pharmaceutical science.

"If we're seeing structural differences by demographics in publication rates, it's something we should be paying attention to," Eden Tanner, a chemist at the University of Mississippi who wasn't involved in the research, says in an emailed comment.

To measure male and female authorship in the drug delivery space, the researchers collected data for papers published in 11 journals in 2021. They surmised whether the authors were men or women by comparing their first names with an online list. The study did not consider other genders.

39.5%
Percentage of women listed as first authors in 11 drug delivery journals in 2021

25.7%
Percentage of women listed as last authors

For the journals included in the analysis, women made up 39.5% of first authors and 25.7% of last authors. In these publications, first authors are typically graduate students and postdoctoral researchers, and last authors are usually the faculty that supervise and fund the research.

The study's senior author, Kristy Ainslie, a chemical engineer at the University of North Carolina at Chapel Hill, says that seeing such a low number of women in the last-author position is particularly concerning because the percentage of female professors in drug delivery–related disciplines is much higher—ranging from 35 to 50% internationally. Their percentages also haven't changed since 2017.

But the gender gap is slowly shrinking. The researchers estimate that women will make up 50% of first authors in drug delivery–related journals by 2030.

Still, journals need to do more to include women. Ainslie says that changes to the peer review process could help further reduce disparities.—KRYSTAL VASQUEZ

CHEMICAL REGULATION

Impurity in cleaning products poses risk

1,4-dioxane is a bigger health threat than previously thought, US EPA says

The chemical 1,4-dioxane poses more of a cancer risk to the general population and workers than previously thought, the US Environmental Protection Agency says in a draft analysis released July 7.

The analysis supplements a risk evaluation completed in late 2020 that was widely criticized for not considering risks to the general population from drinking water and from air. The EPA's initial evaluation also did not consider occupational exposures to by-product 1,4-dioxane generated during the synthesis of surfactants for soaps and detergents. The EPA found no unreasonable risks to the general population and the environment in its 2020 assessment, prompting environmental groups and states to sue the agency.

The draft analysis addresses those concerns. It finds an increased risk of cancer to the general population, including fenceline communities, from exposure to contaminated drinking water and air. It also finds an increased risk to workers from exposure to by-product 1,4-dioxane.

Exposure to 1,4-dioxane impurities in cleaning products poses unreasonable risks to workers but not to the general population, the US Environmental Protection Agency finds.

The EPA considers 1,4-dioxane a probable human carcinogen. The chemical is also associated with "adverse effects to the liver and nasal tissue," the agency says.

1,4-Dioxane is used to make other chemicals, including adhesives and sealants. It is also used as a processing aid and is found as an impurity in soaps and detergents. The chemical is a widespread drinking-water contaminant.

The EPA is accepting public comments on the draft analysis until Sept. 8. The agency says it is particularly interested in current practices for mitigating workplace exposure because the occupational monitoring data for 1,4-dioxane are several decades old.

The EPA plans to consider both the supplemental analysis and the 2020 risk evaluation in a revised risk determination for 1,4-dioxane to be released in the coming weeks.—BRITT ERICKSON

CREDIT: SHUTTERSTOCK

INDUSTRIAL SAFETY

CSB completes 2 more stalled accident reports

Runaway chemical reaction, huge Texas tank fire investigated in latest safety board reports

The US Chemical Safety and Hazard Investigation Board (CSB) has completed two more incident investigations, cutting the number of incomplete reports to six, one of its lowest backlogs in years. Altogether, the board has issued a dozen reports over the past year.

The two new reports present the root causes of a 2020 explosion at the Optima Chemical facility in Belle, West Virginia, and a 2019 tank farm fire at the Intercontinental Terminals Company (ITC) facility in Deer Park, Texas.

The Optima explosion occurred during production of a sanitizing compound for the pool chemical firm Clearon. A dryer at the facility was removing water from the compound and exploded, resulting in the death of an employee, $33 million in property damage, and a shelter-in-place order for the nearby community.

The CSB found the cause to be a runaway chemical reaction and overpressurization of the dryer. Optima did not adequately understand the potential for, or detect and mitigate, the self-accelerating reaction, the board says. Also contributing to the incident was the fact that Clearon, Optima's customer, did not transmit sufficient process safety information to Optima. Both companies also had ineffective process safety management systems, according to the report.

Optima was dehydrating sodium dichloroisocyanurate dihydrate, an isocyanurate, when the compound underwent a decomposition reaction, releasing gases that increased the dryer's internal pressure. The dryer exploded, the CSB says, releasing toxic chlorine gas and metal debris. Dryer fragments struck a pipe containing methanol that caught fire.

In a statement accompanying the report, CSB chairperson Steve Owens notes that the failure to control reactive chemicals has been a concern of the board for more than 20 years. The CSB has urged that reactive chemicals be included in Occupational Safety and Health Administration (OSHA) process safety management (PSM) programs and Environmental Protection Agency risk management program (RMP) rules, which neither agency has done.

Most recently, the CSB identified an incident involving another reactive isocyanurate, trichloroisocyanuric acid, at a BioLab facility in Westlake, Louisiana.

The fire at Intercontinental Terminals Company burned for 3 days.

The second report investigates the cause of a massive fire at ITC, a bulk liquid storage terminal. The fire burned for 3 days and caused $150 million in property damage, significantly impacting the environment and leading to several shelter-in-place orders.

More than 240 tanks at the site store petrochemical liquids and gases, fuel oil, bunker oil, and distillates. An accidental release of butane-enriched naphtha ignited near a large storage tank. The CSB found that a circulation pump connected to the tank failed, allowing the naphtha to escape for 30 min. The flammable vapors caught fire and spread to 14 other tanks and burned for days.

Among recommendations, the CSB urges ITC to establish a formal oversight program for mechanical integrity and a flammable gas detection system, as well as other means to recognize and mitigate releases. The board also recommends that both OSHA and the EPA begin a formal process to determine if PSM and RMP provisions should apply to tank farms.—JEFF JOHNSON, special to C&EN

CHEMICAL WEAPONS

Goodbye to chemical weapons stockpiles

The last chemical weapon from all stockpiles declared by parties to the Chemical Weapons Convention has been destroyed, the Organisation for the Prohibition of Chemical Weapons (OPCW) confirmed July 7. That last munition, which was part of the US stockpile, was a rocket containing the nerve agent sarin.

"The end of destruction of all declared chemical weapons stockpiles is an important milestone for the Organisation," OPCW director general Fernando Arias says in a statement. "It is a critical step towards achieving its mission to permanently eliminate all chemical weapons."

Preventing the reemergence of chemical weapons is now a priority for the OPCW. "Rapid developments in science and technology, new dangerous toxic chemicals, more sophisticated equipment and production methods, better means of delivery, and the interaction between chemistry, biology, and artificial intelligence present additional factors that will put the relevance of the Chemical Weapons Convention to the test," Arias says.

All but four countries have signed and ratified the disarmament treaty, which went into effect in 1997. Since then, the OPCW says, it has verified that 72,304.34 metric tons of stockpiled chemical weapons have been eliminated.

"I continue to encourage the remaining nations to join the Chemical Weapons Convention so that the global ban on chemical weapons can reach its fullest potential," President Joe Biden says in a statement. "Russia and Syria should return to compliance with the Chemical Weapons Convention and admit their undeclared programs, which have been used to commit brazen atrocities and attacks," he says.—BRITT ERICKSON

CREDIT: US CHEMICAL SAFETY AND HAZARD INVESTIGATION BOARD




Police thoroughly tested BM's house in Southampton after he was diagnosed with thallium poisoning in September 2012.

CREDIT: LUKE O'BRIEN

LAB SAFETY

Chemist who survived thallium poisoning speaks out

Thallium poisonings are infrequent, but they often involve chemists, as this man knows. Thallium and compounds containing it must be better controlled, he says

ANDY EXTANCE, SPECIAL TO C&EN

The first sign that something was wrong was numbness in his feet. Then things got rapidly and severely worse. It was August 2012, and soon, a chemistry PhD student in the UK would be fighting for his life. The cause eventually became clear: thallium.

On Friday, Aug. 17, that PhD student was a tall, muscular man in his 20s working in the chemistry laboratories at the University of Southampton. He was unaware that his life would soon change catastrophically. This article will refer to him by the pseudonym BM to protect his privacy.

After a full day at the lab, BM headed home. It was there he first noticed something amiss. The bottoms of his feet had started to go numb. Yet, as an outgoing man with many friends, including those he'd gained as a university-level athlete, he was in demand on a Friday night. So BM went out to a local pub. He mentioned the numbness to friends but thought little of it.

That night, BM slept badly. He woke on Saturday to numbness rising above his ankles. In the shower, he was disturbed to feel the numbness rising up his legs.

After calling the UK's health advice and information service, NHS Direct, BM went to Southampton General Hospital. There, doctors were just as confused as BM, and they admitted him to conduct further tests. He wouldn't leave the hospital for months.

Today, after a struggle lasting over a decade, BM has a somewhat normal life. Although he wishes to stay anonymous, he now wants to share his story. He wants to help raise awareness of the symptoms of thallium poisoning so that future victims won't suffer an equally long delay until diagnosis and will have a better chance of identifying their poisoners. It's very difficult to get thallium in the UK. Yet BM highlights that it can be less tightly controlled within chemistry departments than other poisons—such as mercury—that are less suited to malicious attacks. It's time that this changed, he says.

Thallium hallmarks

Acute thallium poisoning can cause many symptoms.

- ▶ **Stomach:** Diarrhea, nausea, and vomiting
- ▶ **Hands and feet:** Pain and nerve damage
- ▶ **Head:** Hair loss
- ▶ **Skin:** Various problems, including acne-like symptoms and scaling on the palms and soles of the feet
- ▶ **Nails:** White lines of discoloration known as Mees' lines

Sources: Atholl Johnston; Hayley Willacy, "Thallium Poisoning," Patient, last updated Oct. 27, 2021, https://patient.info/doctor/thallium-poisoning; *Br. J. Dermatol.* 1998, DOI: 10.1046/j.1365-2133.1998.02083.x.

Ominous signs

At about 9:00 p.m. on the Saturday he was admitted to Southampton General, BM's knees collapsed as he was walking around the ward. The numbness had risen above them without him realizing it. An hour later, BM's feet felt progressively more uncomfortable. Very soon, he was in excruciating pain. Even after he took morphine, he says, his feet felt as if they were being hit by "a red-hot hammer coated in needles."

The next morning, BM's housemate DC—also a pseudonym to protect BM's privacy—visited him in the hospital, expecting a minor illness. "What we found instead was him curled up on a bed," DC says. "I've never seen anyone in that amount of pain before. It was horrible. My girlfriend was in tears."

BM recalls, "At some points the entire surface of my skin felt like someone was blowtorching it, all the way up to the middle of my thighs."

On Monday, Aug. 20, a neurologist diagnosed BM with Guillain-Barré syndrome, a disorder in which a person's immune system attacks their nerves, and started treatment. It soon became clear that this was the wrong diagnosis. BM's pain continued, and his mobility worsened such that by Friday he became unable to walk even with support. BM's mother arrived from overseas on Sunday, Aug. 26. BM remembers almost nothing from the following 5 weeks. While he remained lucid and could answer simple queries during this time, he believes his mind didn't record the period to block out the pain.

A key clue to the true cause of BM's pain came during 2 weeks in late August and early September 2012, when his hair fell out.

His housemate DC recalls a visit to see BM on Sept. 11, when doctors asked DC to leave the room. "It was all very ominous," DC remembers. "Before they let me back in, they gave me an apron, gloves, a face mask. Then I went back in, and he croaked to me, as his voice was almost gone, that they'd found out that it was thallium."

From this point onward, things moved quickly. Within 12 h of blood tests confirming thallium's presence, doctors sent him to a specialist poison unit at University Hospital Llandough on the outskirts of Cardiff, Wales. Meanwhile, the Southampton chemistry department shut down for detailed forensic tests. The police also went to BM's house, extensively testing its contents and interviewing DC and BM's three other housemates about the poisoning.

BM seemingly dodged the most common initial symptoms of high-dose thallium poisoning, which are diarrhea and vomiting. That's according to Atholl Johnston, a forensic pharmacologist and toxicologist who works at Queen Mary University of London and St George's, University of London. Johnston is also the science director at Analytical Services International, a London-based toxicology laboratory. Nerve damage starts to develop next, followed by the most distinctive symptom, hair loss. Thallium has been used to remove people's hair "if they had a fungal infection like ringworm in their scalp," Johnston says. Few people will have seen such a set of symptoms because, while there are some well-known thallium poisonings, such cases are "not very common at all," Johnston says. But chemists are often the targets of the poisonings that do occur.

> "There will be an interchange between what's in your blood and what's in your body water, and you'll get the thallium distributed in all tissues of the body."
>
> **—Atholl Johnston,** forensic pharmacologist and toxicologist, Queen Mary University of London and St George's, University of London, and science director, Analytical Services International

The secret to thallium's toxicity is its ability to mimic a different and underappreciated element—potassium. We depend massively on potassium, Johnston says—for example, muscle power relies on potassium ions' coordinated movement in and out of cells. A thallium ion is similar in size to a potassium ion, Johnston notes. "It substitutes for potassium, but it doesn't do the same thing, so it stops the various bodily functions working," he says. "That's what causes the damage."

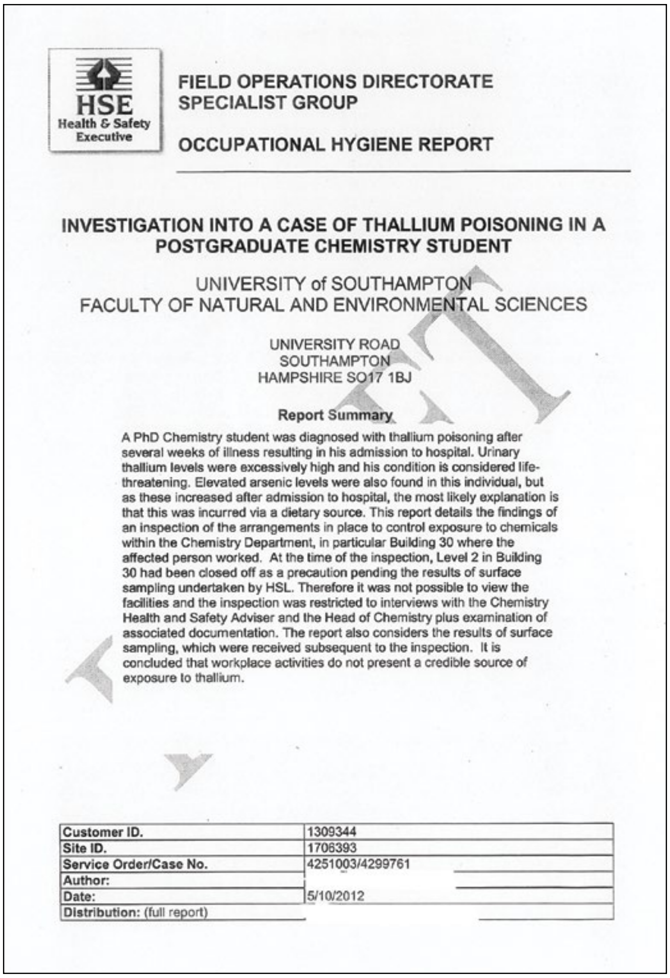
BM's resulting paralysis included his digestive system. Unable to absorb nutrition, his body instead digested itself. BM says he likely owes his survival to the size he'd developed doing sports to a high level. "I turned a quarter of my body weight into food," BM recalls. "If I hadn't had so much spare mass around my frame. . . to live off, I would have started to digest organs."

In Cardiff, doctors treated BM by giving him Prussian blue ($Fe_7(CN)_{18}$), the only known antidote to thallium poisoning. Prussian blue has a very high affinity for singly charged metal ions like thallium, a feature that increases thallium's elimination in feces. Gradually BM's body started to work better, including his memory, which began to return around the beginning of October. While he needed to have what happened to him explained several times, today he vividly recalls the bright green poop that his revived digestive system had started producing.

In mid-October, doctors moved BM out of the specialist toxicology ward, and he realized that he was going to live despite the fact that his blood was still toxic enough that it should have killed him, he says. His nerve damage and muscle loss made movement extremely difficult. For example, he was unable to actively straighten his hands or feet. By early

November, he returned to Southampton, to Western Community Hospital, for rehabilitative treatment lasting 5½ months.

The amount of thallium in BM's blood finally returned to normal levels in December 2012.



FIELD OPERATIONS DIRECTORATE
SPECIALIST GROUP

OCCUPATIONAL HYGIENE REPORT

INVESTIGATION INTO A CASE OF THALLIUM POISONING IN A POSTGRADUATE CHEMISTRY STUDENT

UNIVERSITY of SOUTHAMPTON
FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

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Report Summary

A PhD Chemistry student was diagnosed with thallium poisoning after several weeks of illness resulting in his admission to hospital. Urinary thallium levels were excessively high and his condition is considered life-threatening. Elevated arsenic levels were also found in this individual, but as these increased after admission to hospital, the most likely explanation is that this was incurred via a dietary source. This report details the findings of an inspection of the arrangements in place to control exposure to chemicals within the Chemistry Department, in particular Building 30 where the affected person worked. At the time of the inspection, Level 2 in Building 30 had been closed off as a precaution pending the results of surface sampling undertaken by HSL. Therefore it was not possible to view the facilities and the inspection was restricted to interviews with the Chemistry Health and Safety Adviser and the Head of Chemistry plus examination of associated documentation. The report also considers the results of surface sampling, which were received subsequent to the inspection. It is concluded that workplace activities do not present a credible source of exposure to thallium.

Customer ID.	1309344
Site ID.	1706393
Service Order/Case No.	4251003/4299761
Author:	
Date:	5/10/2012
Distribution: (full report)	

The UK Health and Safety Executive found that workplace activities were not a credible source of the thallium exposure.

No accident

While BM was in the hospital, the University of Southampton, the UK's Health and Safety Executive (HSE), the Health Protection Agency, and county police conducted a joint investigation into the poisoning. They found no evidence of contamination at the university or an accident.

BM himself had never worked with the metal. The HSE concluded in January 2013 that "workplace activities do not present a credible source of exposure to thallium".

The HSE report, obtained by C&EN under the UK Freedom of Information (FOI) Act, explores how someone might have obtained the thallium. It highlights that access to the lab building is secured by swipe cards and that extra security measures are taken outside normal work hours. While a secure chemical procurement system prevented private delivery of chemicals to the building, "not all thallium . . . is kept in locked cupboards," the report notes. It would "not be feasible" to keep all sources of substances as toxic as thallium under lock and key, the report adds. That comment alludes to the small amounts used in most applications in chemistry departments, particularly experimental samples.

The most common use of thallium salts in a chemistry laboratory would be in synthesizing coordination complexes, according to inorganic chemist Andrew Weller of the University of York. But they are not commonly used for this today because of their toxicity. Silver salts work equally well in this context. "In my lab we haven't used thallium salts in 15, 20 years," he says.

Currently, the UK's Control of Substances Hazardous to Health 2002 regulations don't specify how different substances should be handled. Instead, they require risk assessments that minimize workplace exposure. Organizations take the precautions they deem appropriate.

At York, thallium salt reagents are carefully stored in locked poison cupboards, Weller says. Anyone wanting to use them must sign them out, record the amount they have used, and sign them back in again afterward. Research samples produced on a milligram scale probably wouldn't be treated that way, Weller adds, but they would still be handled as toxic, with extreme care.

A key clue to how BM was poisoned comes from a set of lab reports that C&EN obtained through the FOI Act. They detail how the Health and Safety Laboratory in Buxton, England, tested various swabs taken from around the Southampton chemistry department. Inductively coupled plasma atomic emission spectroscopy data found that thallium was present in BM's mug and on three laboratory surfaces.

On the morning of Aug. 17, BM had filled his mug from a thermos containing coffee made at home, just as he always did. "I didn't wash it that day; I didn't bother looking in it," BM recalls.

Contamination would have been difficult to spot, Johnston says. He estimates that a lethal dose of a thallium salt would be just a sprinkling of a white powder, looking just like sugar. If thallium is swallowed, thallium ions would readily pass from your digestive system into your blood, Johnston explains. "There will be an interchange between what's in your blood and what's in your body water, and you'll get the thallium distributed in all tissues of the body."

Although doctors eventually solved the mystery of what was wrong with BM so that they could treat him, many questions remain unanswered. The most significant of them is, Who was responsible?

BM and his friends and family are adamant that he didn't do this to himself, and BM points to police psychological assessments to support this assertion. Meanwhile, county police investigations were unsuccessful. "There are currently no lines of enquiry. However, with any unsolved case, this is subject to change should we ever receive new information in the future," Detective Superintendent Justin Norris tells C&EN. "An offense remains undetected in this case, which means there is insufficient evidence to prove a crime has occurred." Norris says he'd like to hear any further accounts of the case, including from new witnesses.

The best form of revenge

With the time limit for BM to be able to bring a civil legal case having passed and the police stumped, the chances of prosecuting his poisoner are nearly zero. Instead, he's focusing on a different battle—getting his health back.

Despite the unusual cause of his nerve damage, BM received routine treatment, according to his doctor Caroline Hutchings, a consultant in rehabilitation medicine at Solent NHS Trust and University Hospital Southampton Foundation NHS Trust. "The effects on BM's nerves cause very predictable consequences,"

CREDIT: UK HEALTH AND SAFETY EXECUTIVE

Hutchings says, speaking to C&EN with BM's permission. "The signal that's arriving from his feet to his brain doesn't make sense to his brain. One of the few ways that the brain can make sense of it is that it hurts. People describe horrible pain." Hutchings and her colleagues frequently have to help people with such pain after nerve damage, she says.

Hutchings and her colleagues treated the pain and restored most of the feeling to BM's limbs. They also improved his mobility. By the time he left the hospital, he was using splints to keep his feet in place, crutches, and often a wheelchair.

On his release from the hospital, the university gave BM living accommodations adapted to his mobility needs. His rehabilitation owed a lot to his determination to get as much of his old life back as possible. When C&EN originally spoke to him in 2014, he said he wanted to "finish my PhD, get back to playing sport, and not have my splints and [not] use a wheelchair and crutches."

Completing his PhD meant first deciding how to type his thesis. At the time, BM's hands started to curl into fists when resting, so he often had to move them to reset them when typing. Eventually, he got "an old-style mechanical keyboard with spring-return keys on," he says, which made typing easier.

By his graduation ceremony in 2016, BM was well enough to climb onstage in front of many of his chemistry department colleagues—just. "You hear my name called out," BM recalls. "And there's a very short, shocked silence of 'Is he going to get up on the stage? Are they going to have to do some fancy trickery getting a wheelchair up there?' And I kind of hauled myself up the stairs at the side of the stage. Then there's this enormous round of applause from behind me. And I genuinely don't know if any of the staff knew I was still alive. The raw volume of it is something I'll remember for the rest of my life.

"I got someone to carry my crutches from one side of the stage to the other. . . . I was in splints. I could just about safely walk on a stable surface unsupported by anything."

Even after he had earned his PhD, BM was far from the athlete he had once been. Initially, he tried to remain involved with sports. But now he says that his mobility hasn't improved enough for him to participate. "It was making me miserable watching everyone else run around," BM explains. "There's always that niggling thought: 'You could have been playing.' And that really gets to me. So I don't really want to, as a protection method for my mental health."

BM's attitude toward working closely with chemicals has changed in the opposite direction. It was something he didn't want to do in the first years after being poisoned, but now it is something he does daily. In 2015, he told C&EN, "I don't honestly think I'd be able to trust anyone in that kind of environment ever again." Yet BM remained determined to get a job that used his chemistry qualifications, and in 2022 he finally managed to do so. He now works in hazardous waste management and is grateful for the support his employers and colleagues provide to accommodate his movement limitations.

Nevertheless, BM is still alarmed by the skull-and-crossbones symbols indicating toxic substances. "Anytime I see one of those, little hairs on the back of my neck stand up until I read the label and see that it's not thallium," he says.

BM is now relatively secure in his employment and life more broadly. He therefore wants to speak out to try to prevent others from being affected by thallium poisoning. For example, he hopes that if someone poisoned with thallium presents themselves to a doctor, his story will help them be diagnosed faster than he was. In his case, he feels the delay harmed the chances of finding out the truth of what happened and who was responsible. He also believes that the delay led to more nerve damage. A more rapid diagnosis might have given a better possibility that BM could walk without assistance, "maybe even run again," and be employable sooner, he says. He has no problems with how the University of Southampton chemistry department treated him but would have preferred that the university overall speak more openly about his case. "I'm of the opinion that they would rather it remain buried or forgotten or underinvestigated," BM says.

In an emailed response, a University of Southampton spokesperson says that it "cooperated fully with the extensive police and HSE investigations at the time, and no issues of workplace contamination were discovered."

BM also believes that health and safety standards should be tightened to require that thallium be locked up and treated with the highest levels of caution seen with other substances. BM would like the standard approach to be closely recording who has handled any thallium compounds, "to say that this person has taken this much out, like you have to do with mercury and radioactive compounds," he says.

"An independent internal review carried out shortly after the incident found that the university had robust safe working practices, and clear procedures in place, relating to potentially hazardous materials," the University of Southampton spokesperson says. "Our priority has always been the wellbeing and safety of our staff and students, and we therefore review all health and safety procedures on a regular basis."

That internal review, which C&EN obtained under the UK FOI Act, found that some supervisors did not keep the most hazardous substances under lock and key. The review found no evidence that this led to any safety issues. It did, however, recommend that the Southampton chemistry department ensure consistency in locking up a list of substances including thallium.

> "I'm of the opinion that they would rather it remain buried or forgotten or underinvestigated."
>
> **—BM,** survivor of thallium poisoning

"The University does not agree that errors were made by it in the first instance because none were found by the HSE or police," the University of Southampton spokesperson comments by email.

C&EN first spoke to BM in 2014, such a long time ago that the author of this article offered BM a drink from his own water bottle with little thought about infectious diseases like COVID-19 or any other contamination. BM turned the offer down, later pointing out his increased sense of caution and decreased trust. Those feelings are worse, he says, because whoever is responsible is still out there.

"I don't know why they did it; I don't know if they'll do it again to somebody else, and that's kind of scary," BM says. "I sometimes get upset and very angry about it. Then I remember that the best form of revenge is just overcoming it—to focus my rage towards that rather than something that I can't have, which is justice."

Andy Extance is a freelance writer based in Exeter, England.

Facing multiple calls for food additive bans, the US Food and Drug Administration is rethinking how it regulates food chemicals.

CREDIT: SHUTTERSTOCK

FOOD INGREDIENTS

Homing in on harmful chemicals in food

FDA seeks to overhaul food program with new emphasis on chemical risks

BRITT E. ERICKSON, C&EN STAFF

For decades, the US Food and Drug Administration has focused its food safety efforts on microbial pathogens that cause foodborne outbreaks. Preservatives, colors, and other chemicals that are added to food have taken a back seat.

But the agency is facing a flood of petitions to ban chemicals like titanium dioxide, Red No. 3 dye, phthalates, and per- and polyfluoroalkyl substances (PFAS) in food and food packaging. It's struggling to keep up with the requests from advocacy groups and Congress and wants to move away from this reaction-based approach to a more preventive way of addressing the health risks of food chemicals.

As part of a proposed reorganization of its Human Foods Program, the FDA is seeking to do more to manage the risks of the 10,000-plus chemicals added to food and food packaging. But that will require funds the agency doesn't currently have.

The proposed change comes during a particularly tough time for food safety at the FDA. Its top two food program directors stepped down earlier this year after a scathing report in December 2022 by an expert panel convened by the Reagan-Udall Foundation and criticism about the FDA's response to the national shortage of infant formula last year.

Both the Reagan-Udall evaluation, conducted at the request of FDA commissioner Robert Califf, and the agency's own internal review of the infant formula crisis pointed to serious shortcomings in its food safety culture and structure. The findings "also noted several areas of need, including modernizing data systems, providing more resources and authorities, improving emergency response systems, and building a more robust regulatory program," Califf said in late January, when he announced the agency's intent to overhaul the Human Foods Program.

Under the plan, the FDA will combine the Center for Food Safety and Applied Nutrition (CFSAN), the Office of Food Policy and Response, and parts of the Office of Regulatory Affairs under one leader, who will report directly to the commissioner.

The deputy commissioner for human foods will oversee all the FDA's nutrition and food safety programs, including inspections, laboratory testing, and efforts to get a better handle on chemical risks. Oversight of cosmetics and coloring agents will be moved under the Office of the Chief Scientist.

In an updated plan released June 27, the FDA proposes making microbial and food chemical safety separate offices; the vetting of dietary supplements and innovative food ingredients would be housed with food chemical safety. The agency also wants to create a specific office for risk prioritization and surveillance.

All this will require money and people, which the agency doesn't have a surplus of.

"One of the most eye-opening pieces of information that came out of the Reagan-Udall Foundation study was the relatively flat funding" for the FDA office that reviews food chemicals, Steven Musser, CFSAN's deputy center director for scientific operations, said in a keynote address at a June meeting of the Institute for the Advancement of Food and Nutrition Sciences (IAFNS).

The number of FDA employees reviewing the safety of food additives and food contact substances has not changed significantly in the past 40 years, despite a growing number of reviews, Musser pointed out. Agency staff now review biotechnology-based foods, recycled materials, a host of new food dyes, and an avalanche of citizen petitions to ban harmful chemicals in food, he said.

With limited staff and funding, the FDA is seeking to prioritize which of the thousands of chemicals in food and food packaging it should evaluate for potential safety risks. "We can't sample everything," Musser said. "We can't test everything."

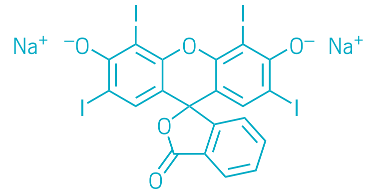
Artificial intelligence is likely to play a role in that prioritization process. The FDA hopes to get extra funding in fiscal 2024, which begins Oct. 1, to upgrade its information technology infrastructure. It is developing computer models to help sift through extensive amounts of data and prioritize chemicals as high, medium, or low risk. If the agency gets the additional funding, Musser said, "we're going to automate the whole system and hopefully make it available to the public to do their own analysis."

The big question is whether Congress will give the FDA extra money for food safety. A deal reached May 31 between President Joe Biden and Speaker of the House of Representatives Kevin McCarthy to raise the US debt limit essentially froze federal budgets for the next 2 years.

Industry-paid user fees are not an option unless Congress authorizes the FDA to collect them from food manufacturers, and congressional action doesn't appear to be on the table. Unlike other parts of the FDA, which rely heavily on user fees to review the safety of new drugs, medical devices, and tobacco products, the food side gets most of its resources from the federal budget.

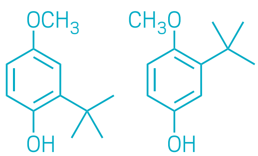
"Appropriations seem to be getting cut kind of across the board," says Melanie Benesh, vice president of government affairs at the Environmental Working Group (EWG), an advocacy organization. But the FDA has identified food safety as a priority, "and the food industry would like to see more funding go to the FDA foods program because they also suffer when the FDA lacks credibility."

The FDA is already actively reviewing the safety of about 10 chemicals, says Tom Neltner, senior director of safer chemicals at the Environmental Defense Fund (EDF). The agency should figure out how to fix the system for reevaluating those chemicals in a timely way "because the track record is not great," he says.

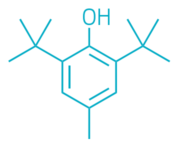


Red No. 3 dye

The FDA often misses deadlines to respond to petitions to ban chemicals in food or food packaging, Neltner says. The EDF is currently waiting for responses to its petitions to ban Red No. 3, titanium dioxide, bisphenol A, phthalates, lead, and PFAS in food or food contact materials, he says. Some of the petitions are more than a year old.



Butylated hydroxyanisole (BHA)

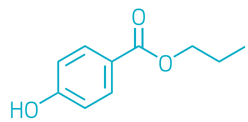


Butylated hydroxytoluene (BHT)

The EDF and other groups filed the phthalates petition in 2016, and the FDA denied it in 2022. The agency then agreed to reconsider the petition at the groups' request. That decision is pending.

The FDA has been evaluating the safety of the preservatives butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) for 33 years, Neltner says. The agency is also scrutinizing brominated vegetable oil and propylparaben, he adds.

Benesh at the EWG agrees that the FDA should not make prioritizing chemicals for reassessment overly complex. She and other environmental and consumer advocates are generally optimistic about the agency's intention to overhaul food safety related to chemicals, but they warn the FDA not to get too bogged down with fancy AI systems. "My understanding is that they're working on a very complicated decision tree and process," she says. "And I'm not sure that's necessary."



Propylparaben

Benesh points to five chemicals that would be banned under California legislation (A.B. 418) that passed the assembly in May and is now being considered in the state senate. Those five chemicals—brominated vegetable oil, potassium bromate, propylparaben, Red No. 3, and titanium dioxide—as well as chemicals banned in other countries and those subject to petitions would be a good place to start, she says.

Another place to look is the Food Chemical Reassessment Act of 2023—a bill reintroduced June 7 in the US House of Representatives by Reps. Jan Schakowsky and Rosa DeLauro, Benesh says. The bill would require the FDA to evaluate the safety of at least 10 chemicals in food or food packaging every 3 years, starting with *tert*-butylhydroquinone (TBHQ), titanium dioxide, potassium bromate, perchlorate, BHA, BHT, brominated vegetable oil, propylparaben, sodium nitrite, and sulfuric acid. The bill would also bring back an external food advisory committee to inform the FDA on evaluation methods.

The FDA reviewed the safety of many food chemicals decades ago, and it doesn't have a process to reassess them when new science arises. In addition, the agency has never reviewed thousands of chemicals in food because industry deems them generally recognized as safe (GRAS). Consumer advocacy groups are urging the FDA to revise the GRAS process.

"The FDA should be monitoring what's coming into the food supply," Benesh says. "And the FDA should have much more stringent controls rather than just letting industry self-refer whatever kind of chemical they want to as GRAS."

The FDA's Musser defended the GRAS process when asked at the IAFNS meeting whether the agency had plans to revise or eliminate the approach. "If there were a GRAS substance that we needed to take action on, given the current state of our legal framework for reviewing these, we could remove a GRAS substance very, very quickly, whereas a food additive could take decades," he said.

Advocacy groups are also pushing the FDA to consider all health effects, not just cancer. "The FDA theoretically looks at all of them," Neltner says. But it tends "to only look at things that are proven to cause harm in a demonstrable way," he says. The

Environmental groups are urging the US Food and Drug Administration to ban harmful per- and polyfluoroalkyl substances from food packaging.

CREDIT: SHUTTERSTOCK

agency also tends to dismiss epidemiology studies in favor of animal toxicology data, which aren't always available for reproductive, neurodevelopmental, immunological, and other noncancer effects, he says.

The FDA did begin looking beyond cancer about a decade ago when it examined the cardiovascular effects of trans fats. Trans fats, or partially hydrogenated oils, were a wake-up call, because the agency has traditionally looked at the cancer risks of food chemicals, Musser said. The FDA declared in 2013 that partially hydrogenated oils are not GRAS because of evidence linking consumption to an increased risk of heart disease. Two years later, after much pushback from the food industry, the agency finalized that determination.

Today, the FDA is grappling with the potential cardiovascular effects of another food chemical—the low-calorie sweetener erythritol, a sugar alcohol.

The agency is also concerned about early-life exposures and developmental toxicity, as those effects have the biggest impact on public health, Musser said at the IAFNS meeting. In 2021, after a congressional report revealed harmful levels of toxic heavy metals in many foods consumed by babies and young children, the FDA launched a program called Closer to Zero.

"The FDA should be monitoring what's coming into the food supply."

—Melanie Benesh, vice president of government affairs, Environmental Working Group

The effort aims to reduce levels of arsenic, cadmium, lead, and mercury as much as possible in foods consumed by children to address neurodevelopmental concerns.

Knowledge about the effects of chemicals on biochemical pathways that can lead to adverse health outcomes is growing rapidly. "We're moving into a very molecular approach to looking at the function of some of these chemicals, whether it be drugs, natural supplements, or food additives," Musser said at the IAFNS meeting. "Our understanding of those pathways is continually changing."

The food industry welcomes the FDA's move to unify its food safety efforts. Both industry and consumer advocacy groups criticized its initial plan for not giving the deputy commissioner complete authority over food safety. The FDA addresses that concern in its June 27 update.

"We are pleased the FDA is taking bolder action to make meaningful and lasting change by answering informed industry and stakeholder calls to unite and elevate the Human Foods Program and fully authorize the deputy commissioner with control over its strategic direction," Sarah Gallo, vice president of product policy at the Consumer Brands Association, says in a statement. The trade group represents food, beverage, and household product manufacturers.

The FDA plans to release final details on the proposed reorganization this fall, including an established budget. Congress will then have 30 days to raise any concerns. The FDA says it will continue to engage with stakeholders throughout the process.

The approach will be modeled after the Closer to Zero program, including frequent communication and engagement with industry and advocacy groups, Musser said. "Recently we've learned just how much misinformation is out there about the hazard of particular chemicals," he said. "Communicating risk here is going to be a challenge for the agency." ■

In brief

Making molecules makes a lot of organic-solvent waste, which can harm people's health and the environment. One solution might be switching to a more benign solvent: water. But how can chemists coax greasy organic compounds to go into polar water? Mimicking nature by using enzymes is one solution. Chemists have also developed a number of tricks to make organic compounds and water mix. Doing organic chemistry in water works for organic molecules that have some aqueous solubility. On-water reactions happen at the interface between water and an organic compound. And with-water reactions rely on additives such as surfactants to entice organic molecules and water to mingle.

CREDIT: SHUTTERSTOCK

Some organic chemists want to turn on the tap of a familiar solvent

Organic-solvent waste is a threat to the environment. Chemists think swapping in water might lighten the field's heavy carbon footprint

LEIGH KRIETSCH BOERNER, C&EN STAFF

Organic chemist Bruce Lipshutz had a bit of a rude awakening. It was around 2007, and the head of environmental health and safety (EH&S) at the University of California, Santa Barbara, sat Lipshutz down to deliver some sobering news.

"I was told, in no uncertain terms, . . . that my group was the number 1 polluter in all of Santa Barbara County," he says. "Not the campus, not the city, but in the entire county, we were number 1." The EH&S head, Dave Vandenberg, was in charge of collecting and disposing of the waste that came out of chemistry labs at the university. And Lipshutz's group, which focused on traditional organometallic synthesis, produced enough solvent waste to make Vandenberg notice. "I realized back then that this could not continue," Lipshutz says.

Organic solvents are organic compounds in the liquid state. To react, molecules need to bump into one another, and dissolving compounds in a liquid is the most common way to make that happen. With few exceptions, solvents are indispensable in organic chemistry. Chemists run reactions in solvents. They often have to purify the products, which means using more solvent in chromatography columns, separatory funnels, distillation equipment, or other lab tools.

"Nobody talks about this, but we organic chemists obviously are contributing to climate change," Lipshutz says. "We're generating CO_2 by burning that organic solvent."

Lipshutz realized that if just his group put out so much solvent waste, "just imagine how much waste was being created" worldwide, he says. "It's beyond our ken to even realize those numbers," Lipshutz says. "So that drove me to realize that there must be another way."

This other way can take a lot of forms. Chemists can switch to renewable and nontoxic solvents, such as supercritical carbon dioxide, a liquid-like pressurized form of the gas. Other options are solvents made from biomass or based on ionic liquids or molten salts. These all have safety or supply issues, though. Pressurized liquids such as supercritical CO_2 can be an explosion hazard, molten salts can be heat hazards, and solvents made from biomass and ionic liquids can be hard to source. There are other methods that don't use solvents at all, such as mechanochemistry in a ball mill. And although these methods are growing in popularity, they are not yet at a point that they can be used in a widespread way.

But there is another solvent that's very common, easily accessible, and nontoxic and definitely has a good safety profile. It's water.

"[Chemistry in water] isn't going to be a silver bullet that allows you to develop a sustainable process without putting in the work."

—**Dan Bailey,** sustainability scientist, Takeda Pharmaceuticals

But most organic solvents are safety and health hazards. Toluene, for example, is flammable, a skin irritant, and a health hazard. It's dangerous to inhale and touch. Repeated exposure can damage people's organs, cause fertility issues, harm unborn babies, and kill aquatic life. Other common organic solvents are carcinogenic, and overexposure can cause brain damage and death.

Using organic solvents calls for numerous safety measures, including working in a chemical fume hood, wearing personal protective equipment, and arranging special disposal. There are a number of ways to deal with solvent waste at scale, but EH&S agents typically send waste organic liquids to treatment facilities, where they are incinerated, sending greenhouse gases into the air.

The solvent all around us

Scientists estimate that RNA formed on Earth more than 4 billion years ago. Those reactions were probably happening in the oceans, which means organic reactions were happening in water. But how?

Anyone who's ever seen a lava lamp in action or tried to mix balsamic-and-olive-oil salad dressing knows that oil and water don't mix. When added together, organic and aqueous liquids tend to separate, forming distinct layers. Shake the mixture, and it may form blobs, with the oily, neutral parts retreating into themselves to get away from the incompatible polar water. But clearly, the two parts can be coerced together.

"The chemistry happening in the human body is not 100% in water," Lipshutz says. "And all the chemistry that happens in nature doesn't occur in organic solvents." This means that organic compounds and water can get together in some situations. In addition, chemists have developed tricks to wheedle organic compounds into aqueous solutions.

When first hearing about running synthetic chemistry reactions in water, most chemists express skepticism that it can work. But chemistry in water doesn't actually have a solubility problem, Lipshutz says. "Nature provided all the answers," he says. "Our contribution is to figure out how best to go about doing chemistry in water."

One way to do organic chemistry in water is to directly mimic nature. The human body is packed with enzymes. These proteins act as biological catalysts that speed up chemical reactions, and they work in an aqueous environment. Evolution has been fine-tuning enzymes for a very long time, says Dörte Rother, a biochemical engineer at RWTH Aachen University. So why not hijack enzymes to synthesize valuable compounds for you?

Cells are like tiny water balloons. Biocatalysis naturally lends itself to doing reactions in water because enzymes are produced in water-filled cells, Rother says. But to run reactions that are not specific to biology, scientists separate the enzymes and use them under different reaction conditions. The first step is finding an enzyme that makes a molecule similar to a desired molecule, Rother says. Through enzyme engineering, scientists can tune enzymes to make specific organic molecules not found in nature.

"The catalyst itself is really green," Rother says. Because enzymes are designed to work in our bodies, they operate at a neutral pH value and don't require the high temperatures and pressures often needed to activate catalysts for organic reactions. Enzymes are environmentally benign in other ways too. "They don't produce toxic waste," Rother says. "If you want to get rid of them at the end, you simply heat them. Then they are dead, and you can throw them away."

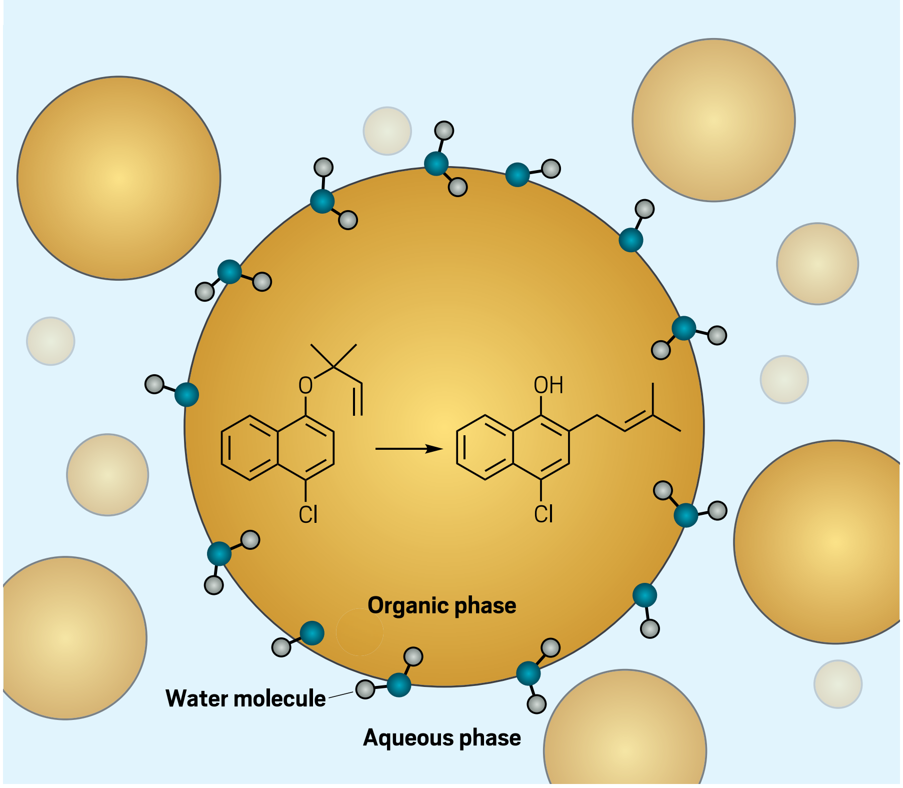
The catch is that biocatalysts tend to have a yield problem. Enzymes don't typically make large amounts of compounds; they make only what they need to fulfill their biological function. That's not ideal for industry, which strives to efficiently make large amounts of a compound, Rother says. And the answer to this challenge, counterintuitively, is putting enzymes in organic solvents.

Enzymatic biocatalysis reactions tend to give higher yields in organic solvents. And according to Rother's analysis, using organic solvents creates less organic waste than running the same reactions in water. Industry typically aims to use enzymes to make nonnatural compounds, such as drug molecules. These compounds tend to be very insoluble in water. As a result, researchers have to use large amounts of organic solvents to separate their products from the enzymes, Rother says, negating the benefits of using water in the first place.

Overall, running biocatalysis reactions in green organic solvents is more environmentally friendly, she says, because scientists can get higher yields that don't need as much workup and purification. This conclusion might surprise people, Rother says. "But you need to consider the complete process to look at the environmental factor," she says, even if water is the solvent.

Living on the edge

On-water reactions occur where an organic layer meets an aqueous layer. Researchers think that water molecules poke up into the organic bubble, lending H^+ and OH^- ions to the reaction. Along with creating hydrophobic effects, these ions may accelerate the organic reactions. The reaction shown is an example of the Claisen rearrangement.



In water, on water, with water

If using enzymes for biocatalysis is considered working with nature, then running organic reactions in water might be considered working against nature. But there are several ways chemists can coax organic molecules to react in water. Researchers separate these methods into various types but disagree on how many types there are. For simplicity's sake, this article presents three basic types: in water, on water, and with water.

In water basically means putting the compounds in water with no additives. For this method to work, the compounds have to be soluble in water, and the reactions happen in the water itself, says Fabrice Gallou, a scientist at the pharmaceutical company Novartis. Chemists tend to start with what they know, he says. And that means dissolving compounds in solution to react. Chemists like to put compounds in solution so they can analyze and control things, but that's an issue when the compound isn't very soluble in solvents, he says. One way to help reluctant organic molecules go into an aqueous solution is to change the pH of the water.

The pH of neutral water is 7. Tweaking it up or down can greatly affect reagents' solubility, says Dan Bailey, a sustainability scientist at Takeda Pharmaceuticals. Imagine the organic compound a chemist is trying to dissolve contains a carboxylic acid group, he says. Adding a base to this aqueous mixture will pull off a hydrogen ion, leaving a negative charge on the compound. A charged species is much more likely to go into the polar water solution than a neutral one, Bailey says. So in some cases, "you can get full dissolution of organic reaction components in water without really using any sort of surfactant or other solubilizing additive," he says.

The important word there is *some*. Manipulating the pH works only in cases in which the molecule has built-in ionizable groups, Bailey says. That's not the case for a high percentage of molecules, especially ones used in the pharmaceutical industry, Gallou says. Drugs have to contain very specific functional groups in exact places to be effective against a target in the body. Often, the required functional groups turn the compounds into "brick dust," Gallou says, organic chemistry slang for something that's hopelessly insoluble, especially in water. Pharmaceutical compounds that can work in pure water are "exceptional things," Gallou says.

Chemistry at the interface

Instead of fighting against the chemical unwillingness of organic molecules to dissolve in water, some chemists take advantage of this feature. *On water* refers to reactions that occur at the interface—where the organic blobs touch the water blobs. The compounds are clearly not soluble in water, Lipshutz says. "They usually sit on the surface in a neat state," he says.

Researchers have found that these

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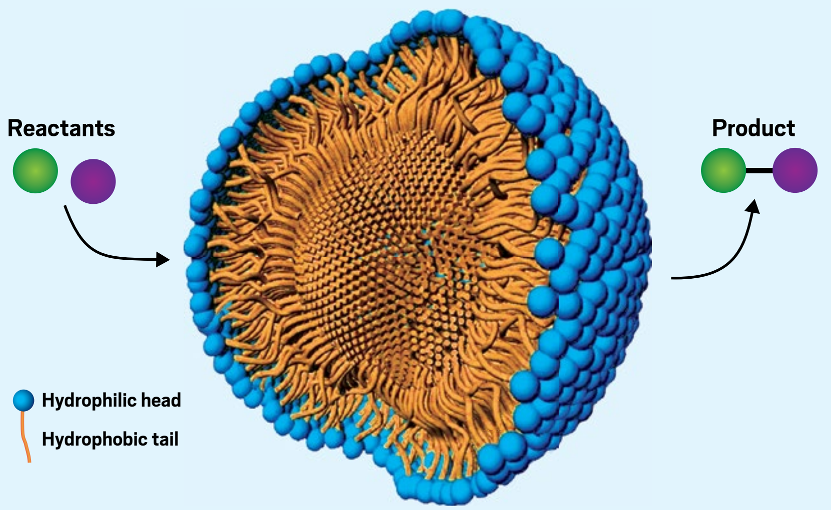
Micellar mechanism

To perform a micellar catalysis reaction, chemists first add surfactants to water. These molecules self-assemble into micelles, structures with hydrophilic heads facing out toward the water and hydrophobic tails facing in. That arrangement creates an organic-friendly pocket inside the micelle. Researchers then add organic reactants. These compounds migrate to the centers of the micelles, react, and form products that flow back out.



types of reactions have an unexpected boost: some chemical reactions run faster at the water-organic interface than they do in traditional organic solvents. This hydrophobic effect was first proposed by organic chemist Ronald Breslow, says C. J. Li, an organic chemist at McGill University. This reaction acceleration comes down to organic compounds forming blobs in water, he says. Water molecules form hydrogen bonds with one another, which pushes the organic molecules away, Li says.

"The organic molecules are squeezed together. And that internal pressure is extremely high," he says. High enough that even though the mixing occurs at room temperature and pressure, the reactions inside the organic blobs go faster than they would otherwise. Breslow found that on-water conditions accelerate the Diels-Alder reaction by as much as 700 times (*J. Am. Chem. Soc.* 1980, DOI: 10.1021/ja00546a048).

K. Barry Sharpless later developed the *on water* term and examined the effect in depth by showing that several other uni- and bimolecular reactions also get higher yields or faster reaction times than those performed in an organic solvent (*Angew. Chem., Int. Ed.* 2005, DOI: 10.1002/anie.200462883). Many scientists have also shown this reaction boost since then, and now the phenomenon is accepted as a given, Li says.

But one of the downsides of on-water reactions is that they are limited to the surface of the aqueous-organic divide. To address this limitation, chemists have had to come up with crafty ways to increase the organic-water surface area.

Back to the beginning

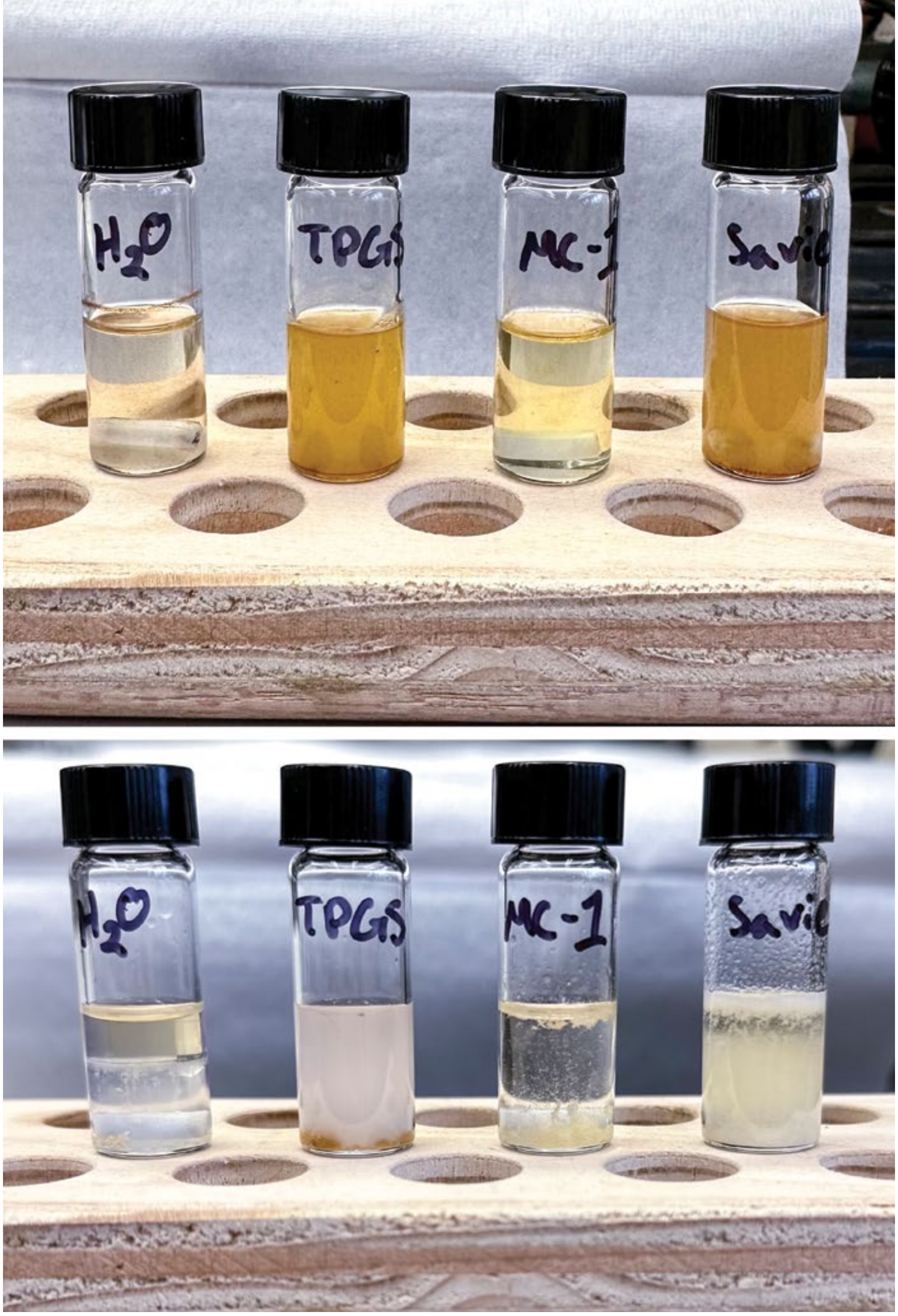
To figure out how to make organic compounds and water mix better, chemists need to once again look to the early days, Lipshutz says. Scientists don't know the

"Nobody talks about this, but we organic chemists obviously are contributing to climate change. We're generating CO_2 by burning that organic solvent."

—Bruce Lipshutz, organic chemist, University of California, Santa Barbara

CREDIT: BRUCE LIPSHUTZ/YANG H. KU/C&EN

Researchers in Bruce Lipshutz's lab ran palladium-catalyzed aminations in water to evaluate if various surfactants could be used in continuous-flow reactors. All vials contain water and reactants. The control vial (H_2O) contains no surfactant. TPGS is DL-α-tocopherol methoxypolyethylene glycol succinate; MC-1 is a sulfone-containing surfactant: Savie is a biodegradable surfactant based on vitamin E. The researchers took these photos at the beginning of the experiment (top) and after 20 minutes (bottom). Products show up as cloudy or chunky material in solution.



exact recipe for the primordial soup that gave rise to RNA, but they do know that it wasn't straight-up H_2O. "Clearly the water wasn't pristine. What was in the water that enabled chemistry to happen?" Lipshutz asks.

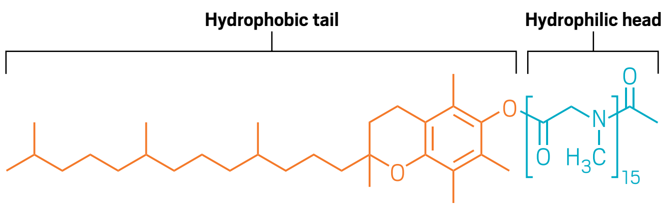
Adding another component, such as a surfactant, to help the water and organic layers mix is at the heart of with-water chemistry. Surfactants are molecules that have a hydrophilic, or water-loving, part connected to a lipophilic part, the greasy end of the molecule. "When you add surfactants to water, they self-assemble into structures known as micelles," Takeda's Bailey says. Micelles are essentially little bubbles in which the surfactant molecules line up such that the hydrophilic parts are pointing out toward the water and the hydrophobic parts face the inside. The idea is that these micelle bubbles act as sort of nanoreactors. The approach is known as micellar catalysis.

When chemists add oily organic molecules to mixtures with micelles, the compounds wiggle into the greasy spaces at the centers. "They come together and react, and then they can migrate back out into the surrounding water," Bailey says. "Because you have higher effective concentrations of reaction components inside these micelles, you tend to get faster reaction rates."

Micellar catalysis is one of the most active areas in with-water research, at least in part because Lipshutz has showed that it can be so successful. After the UC Santa Barbara EH&S specialist told Lipshutz about his waste output, the organic chemist threw all his synthetic efforts into finding ways to use water as a solvent.

In 2008, Lipshutz published his first research on micellar catalysis by showing it can work with olefin cross-metathesis reactions, which are typically performed in an organic solvent such as dichloromethane (*Org. Lett.* 2008, DOI: 10.1021/ol800028x). Since then he's ticked off a number of other common synthesis reactions, including Sonogashira couplings (*Org. Lett.* 2008, DOI: 10.1021/ol801471f), Suzuki-Miyaura cross-couplings (*Org. Lett.* 2008, DOI: 10.1021/ol801712e), and photocatalytic reactions (*Green Chem.* 2018, DOI: 10.1039/C7GC03866F).

Lipshutz has also produced an army of chemists doing further research in micellar catalysis. Former postdoctoral researcher Sachin Handa, now at the University of Louisville, stuck with the field, studying the application of micellar chemistry to Buchwald-Hartwig aminations (*ACS Catal.* 2019, DOI: 10.1021/acscatal.9b02622), carbanion intermediates (*ACS Catal.* 2020, DOI: 10.1021/acscatal.0c01196), and click chemistry (*ChemSusChem* 2022, DOI: 10.1002/cssc.202201826).



Savie

CREDIT: BRUCE LIPSHUTZ

> “Water is not our enemy. It’s actually our best friend.”
>
> **—Bruce Lipshutz,** organic chemist, University of California, Santa Barbara

In addition, Lipshutz’s group has teamed up with Gallou at Novartis to develop a biodegradable surfactant, derived from vitamin E and polysarcosine, called Savie (*J. Am. Chem. Soc.* 2023, DOI: 10.1021/jacs.2c13444).

Wilfried Braje, a chemist at the pharmaceutical company AbbVie, has done work in a similar vein, using a benign cellulose derivative as a surfactant. Hydroxypropyl methyl cellulose is often used in drugs and foods, including some kinds of ketchup. But instead of forming micelles, it makes structures with lipophilic pockets.

There is still work to be done to scale up these types of reactions for industry, Braje says. One problem is changing solubility over the course of the reaction, he says. The compound can sometimes come crashing out of solution, forming a blobby gumball around the stir bar.

“The reaction still works,” he says. But if this were to happen in a flow reactor that uses easily clogged tubes to deliver the solution to the next part of the reaction process, the entire operation might come to a screeching halt. “It’s not something that we could transfer to a large reactor,” Braje says.

It’s not a silver bullet

Scaling up organic reactions in water to the volumes that industry requires is only one of the challenges. Doing chemistry in water “isn’t going to be a silver bullet that allows you to develop a sustainable process without putting in the work,” Takeda’s Bailey says. “We often tend to focus on the reaction portion of a process because that’s where our expertise as chemists lies.” Chemists need to look at the entire process, which includes purification and isolation of the target compounds.

“We need to make sure we’re driving reductions not only in the reaction portion of the process but in those downstream unit operations as well,” Bailey says.

Another challenge is the pushback some chemists give these techniques. “The first thing you hear is, ‘Things have been done this way for centuries, literally. Why should I change now?’” Novartis’s Gallou says. “By design, especially in pharma, we are very much risk averse. We don’t like the changes.” People weigh the pros and cons of a change very carefully, Gallou says. “You really need to have significant benefits to induce that change.”

In addition, it’s difficult to change production techniques that have already been established and cleared by regulatory authorities. “It’s not easy to change, even if technically we can demonstrate the change is beneficial,” Gallou says. There’s so much at stake when a company makes compounds in large amounts, including changing protocols and the lengthy filing process required by regulatory agencies.

The problem of organic-solvent waste won’t be solved just by switching all organic chemistry to water. “I don’t think there’s a one-size-fits-all approach to solving this green chemistry problem,” Lipshutz says. “I think we need lots of alternatives.”

Bailey agrees. “I don’t think there will be a future point where we’re using 100% chemistry-in-water processes. I think there’ll be a variety of strategies, but I think this will be an extremely important component of that strategy,” he says.

Whatever those are, Lipshutz says he hopes changes are made soon. “I look at kids and I wonder what the future has in store for them because we have finite resources on the planet. And the evidence is that we are consuming these resources at an enormous rate.”

When are chemists going to reach the point of inflection where people start doing more environmentally friendly reactions? “We’re not there yet,” Lipshutz says. Part of the answer depends on what the driving force for this change is going to be, he says. “Is it going to be climate change? Is it going to be regulatory? Is it going to be costs? Or all the above?”

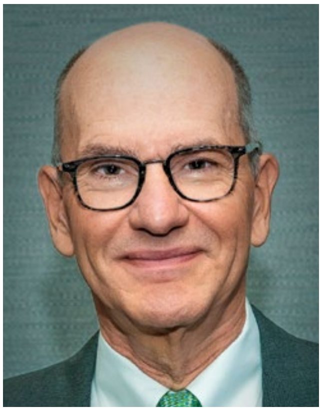
Lipshutz laments the slow pace of progress. “But the discoveries are there to be made,” he says. When scientists see the possibilities in doing chemistry in water—both the challenges and the excitement of making discoveries—more people will jump in, he says. “Water is not our enemy,” Lipshutz says. “It’s actually our best friend.” ■

COMMENT

Why corporations 'associate' with ACS

DON S. WARDIUS, CHAIR, ACS BOARD COMMITTEE ON CORPORATION ASSOCIATES

Corporation Associates (CA) is unique among the committees of the American Chemical Society, in that it is composed of legal entities rather than individuals. Companies that have chemistry at the core of their commerce may apply for membership and, once accepted, participate in the committee's work.



CREDIT: CHRISTINE BRENNAN SCHMIDT

Engagement with CA garners numerous advantages, including the opportunity to be involved in ACS decision-making and a road map to meaningful service. In return, CA provides ACS with a clear voice from industry.

The committee advises ACS on aligning with industry to grow in a mutually beneficial way as it seeks to responsibly address humanity's needs.

CA's strategic framework defines its priorities and guides its initiatives. The framework consists of six sections:

- Preparing for the changing face of industry
- Supporting industry initiatives
- Advancing public policy
- Fostering innovation
- Recruiting and retaining diverse and qualified talent
- Building the business case for sustainability

Joining CA gives your company the opportunity to work with ACS within this framework.

Awards that recognize the accomplishments of industrial chemists are an area of focus for CA. The committee conceived and helps administer the annual Heroes of Chemistry Awards. These high-profile awards recognize breakthrough contributions to societal welfare by the chemical enterprise. CA also sponsors two of the society's national awards: the ACS Award for Team Innovation and the ACS Award for Creative Invention. Both are intended to honor notable accomplishments for the greater good. More information about ACS industry awards can be found at http://cenm.ag/industry-awards.

Grants are another focus for CA. The committee offers seed grants to local sections, divisions, and international chapters with original new initiatives that support CA's goals. Projects the committee funds include those with an industrial emphasis, those aimed at improving public understanding of the industry, and those targeting enhanced professionalism or safety in the chemistry enterprise.

> Engagement with CA garners numerous advantages, including the opportunity to be involved in ACS decision-making and a road map to meaningful service.

Safety culture is an important aspect of working in industry, and safety is one of CA's core values. The committee helps communicate and advocate for safety excellence within ACS; it participated in the 2022 ACS Presidential Safety Summit and advises on other safety initiatives of the society as they arise.

There is more—even beyond CA's charge—that ACS should do to support industry and industrial members. This is why CA is enthusiastically supporting the board of director's newly formed Industry Member Advisory Board. Through this board, the value that ACS brings to industrial members is being articulated and extended. CA sees tremendous potential for this board to achieve results that help individual members from industry grow in their careers and contributions and their employers to derive value from engagement in ACS.

CA has 20 members and is continually looking to grow. Diversity is a strength, and the committee comprises members from companies large, small, and every size in between. Current member companies are in commerce related to agriculture, commodity and specialty chemicals, consulting, consumer and industrial goods, drug discovery, energy, knowledge, materials, pharmaceuticals, and polymers. We welcome companies engaged in any field of chemistry to join.

It is exciting to have an inside view of what's coming at ACS and a role in shaping it for the best outcome for industry and society. I hope you will consider what joining CA can do for your company and what the value of having such a position in the society means. If you have a question or see something to talk about, or to apply to join CA, I would be delighted to hear from you at industry@acs.org.

Views expressed are those of the author and not necessarily those of C&EN or ACS.

C&EN talks with Olivia Wilkins, a postdoc at NASA

The astrochemist explains how a chance sighting of a radio telescope led to a career studying molecules in space

NINA NOTMAN, SPECIAL TO C&EN

Olivia Wilkins presented her postdoc research on the SubLIME project at ACS Fall 2022.

CREDIT: COURTESY OF OLIVIA WILKINS (BOTH)

Olivia Wilkins is a space explorer who likes to keep her feet firmly on the ground. She is an astrochemistry postdoc at the NASA Goddard Space Flight Center in Maryland, where she is working to better understand the fundamental chemistry taking place on icy celestial objects, such as comets. To do this, she carries out lab experiments and compares results with data collected by radio telescopes such as the Atacama Large Millimeter/submillimeter Array (ALMA).

Nina Notman talks to Wilkins about her research, her dreams for the future, her passion for outreach, and her ACS service. This interview was edited for length and clarity.

What is astrochemistry, and why is it important that we study it?

Astrochemistry is the study of molecules in space. We look at what molecules are out there, how they form, and how they interact with one another. Studying interstellar space lets us look at the most fundamental chemical reactions in the universe, the chemistry that precedes life as we know it, and the chemistry that makes up our planet.

When did you first become interested in radio telescopes?

When I was 7, my family and I were on vacation in West Virginia, and I saw what looked like a giant satellite dish—which I later learned was the Green Bank Telescope—rising up above the trees in the mountains. The telescope is really cool: it's the largest movable object on land, it weighs 17 million pounds, you could fit two American football fields on the dish, and it's taller than the Statue of Liberty. The whole premise of radio astronomy is really cool too: you are exploring the invisible universe. I went on to do a summer research experience at the Green Bank Telescope while I was earning my undergraduate chemistry degree. This was when I first heard of the field of astrochemistry, during a talk from a visiting researcher. I was so excited because I learned that I could combine my background in chemistry with my passion for large radio telescopes into a career. This was what ultimately led me to pursue astrochemistry for my PhD.

Can you tell me about your postdoc research?

My research group at Goddard runs SubLIME, the Sublimation of Laboratory Ices Millimeter/submillimeter Experiment. The chemistry in space that we observe using radio telescopes is in the gas phase, but a lot of it is thought to have originated in cosmic ices. Our experiments complement these observations by looking at what is happening in the ice phase and connecting it directly to what is seen in the gas phase.

We make analogues of icy materials found in space, such as icy dust grains and comets, in the lab. Then, we irradiate them with ultraviolet light to simulate the starlight from an infant star as it's growing or the sun as a comet passes by on its orbit through the solar system. Next, we sublimate the ice and trap the resulting gas. We then use submillimeter spectroscopy, which is the same technique that radio telescopes use, to detect what gas-phase products are there. SubLIME is the first cosmic ice experiment to do this.

So far, about 300 molecules have been detected in interstellar and circumstellar space, but a lot of the chemical reaction networks for these molecules are unknown or are debated. Our experiment helps us understand the chemistry connecting cosmic ices, interstellar and solar radiation, and gas-phase molecules, which in turn can inform astrochemical models or contextualize telescope observations.

Your postdoc ends in January—what are your plans for the future?

Ultimately, I want to be an independent researcher. I'm currently hoping to stay at NASA for at least a little bit longer and am working on securing funding to do that.

I know that you do a lot of outreach. Can you share what you like to do and why?

One of the perks of being a NASA

Vitals

- **Hometown:** New Oxford, Pennsylvania
- **Current residence:** Annapolis, Maryland
- **Current position:** NASA Postdoctoral Program Fellow at NASA Goddard Space Flight Center
- **Education:** BS, chemistry and mathematics, Dickinson College, 2015; PhD, chemistry, California Institute of Technology, 2021
- **Favorite telescope:** Green Bank Telescope, West Virginia

postdoc is that I get NASA stickers and other swag to give out at events. I do disappoint a lot of kids though, because they think that because I'm from NASA, I must be an astronaut! I tell them, "I'm too scared to go to space. Even if I could go, I probably wouldn't."

I like going to career days, either virtually or in person, to talk to elementary school students about astrochemistry. I also like to visit and give seminars at primarily undergraduate institutions because I know—having gone through a chemistry program at a small liberal arts college—that astrochemistry is not something those students are likely learning about. Besides presenting at schools, I enjoy speaking at local libraries and observatories; the audiences at these events are mostly adults, but they are usually just as excited as kids to learn about space.

You're co-organizing an astrochemistry symposium at ACS Fall 2023. What are some details on that?

We are celebrating the 10-year anniversary of the Astrochemistry Subdivision of the Division of Physical Chemistry. We are holding a series of talks describing exciting research over the last decade, as well as panel discussions with an emphasis on the future of the field. The symposium is called "The Astrochemistry Subdivision: A Decade of Progress and Prospects for the Next Decade" and takes place on Sunday, Aug. 13 through Wednesday, Aug. 16. The sessions will cover experimental, theoretical, and observational work—the three main branches of astrochemistry research. It also happens to be 10 years since I first heard the word "astrochemistry" at Green Bank, so being able to co-organize this symposium is extra special to me.

What about your work with the Younger Chemists Committee?

I joined the National Younger Chemists Committee (YCC) in January as an affiliate because I wanted to meet other chemists at my career stage who work in different fields from me. We talk about the challenges that younger chemists are facing and share ideas for how to improve the chemistry community as a whole. I'm currently working on Meet the YCC posts for the YCC website that profiles a different committee member each month. It's important that other younger chemists know the people advocating for them within ACS and that people are recognized for the hard work that they put into these committees as volunteers.

Studying interstellar space lets us look at the most fundamental chemical reactions in the universe, the chemistry that precedes life as we know it, and the chemistry that makes up our planet.

What hats do you wear as an active member of the Maryland Section?

I am a member-at-large for the Maryland Section, and I have also been the chair of its Local Section Younger Chemists Committee (LSYCC) since April. Our LSYCC is being reinstated after being inactive for at least 10 years. I am planning for networking events, hopefully in partnership with LSYCCs from nearby local sections, and will be setting up an LSYCC award for the Maryland Section. I have other ideas for that committee, but nothing else is definite yet.

You were in the 2022 class of CAS Future Leaders. How did you find that experience?

I can't believe how much I enjoyed it. I recommend that everyone apply for it. The workshops that we attended were really insightful. They provided important skills that you typically don't learn about in graduate school, such as science communication, coaching, and mentoring. I met people who I never would have met otherwise, and now I have a cohort of people from across disciplines who I can meet up with at future ACS meetings. But honestly, the best part of that program was that it gave me a lot of confidence. The organizers constantly told us how great they thought we all were and that we were amazing, and by the end of the week, I believed them.

Nina Notman is a freelance writer based in Salisbury, England.

Olivia Wilkins (far right) and some of the 2022 CAS Future Leaders cohort.

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Newscripts

Curating quirky science since 1943

Bone songs

As Laurent Davin sorted through prehistoric bird bones, he did not expect to find musical instruments in the mix. Davin, an archeologist at the Hebrew University of Jerusalem and the French National Center for Scientific Research, and his colleagues are part of a team excavating Eynan-Mallaha, an ancient settlement in Galilee

Small yet mighty: This tiny flute made from bird bone recreates a raptor's cry.

that was once home to the Natufians. Davin was revisiting a collection of 1,112 bird bones from the site, all dated between 10,730 and 9,760 BCE, when he noticed one with a curious perforation. It was tiny and delicate, yet the holes were deliberately made and worn from use. It looked like a kind of notched flute, Davin tells Newscripts. The researchers scoured the collection and eventually found fragments of six flutes along with one complete instrument (*Sci. Rep.* 2023, DOI: 10.1038/s41598-023-35700-9).

All the specimens were made from the hollow wing bones of Eurasian coots (*Fulica atra*) and Eurasian teal (*Anas crecca*), small waterfowl that historically wintered at a nearby lake, Davin says. Because the Natufians also hunted larger animals, including meaty mallards, Davin wondered why they chose to craft with such dainty appendages. Perhaps the Natufians were after a particular pitch. "We didn't want it to blow in 12,000-year-old instruments, so we made replicas using the same techniques and tools," Davin says.

Though the instrument is difficult to play, Davin and his team were delighted to hear the bird bone resound with a clear, high-pitched whistle. They realized that this whistle bears a striking resemblance to the calls of the common kestrel (*Falco tinnunculus*) and Eurasian sparrowhawk (*Accipiter nisus*), two birds of prey whose bones have also been found in the Eynan-Mallaha archaeological site. The researchers can't be sure how the Natufians used these flutes. They could have imitated the raptor calls to help them hunt the birds or to hunt with the birds in the practice of falconry, Davin says. The instruments may have had symbolic importance as well, given that the Natufians incorporated the raptors' talons into personal ornaments.

Eurasian coots, Eurasian teal, common kestrels, and Eurasian sparrowhawks still abound seasonally at Eynan-Mallaha, where excavation is ongoing. This winter, Davin and his colleagues plan to play the flutes for visitors so they can enjoy the Natufian tune that's gone unheard for millennia.

Waste not, want not

In April, Erin Winick Anthony found herself in a bit of a tangle. As a science communicator and founder of STEAM Storytelling, Anthony has been to a lot of conferences that left her with a drawer full of commemorative lanyards. Many of them had sentimental value, and Anthony hoped she could use her crafting skills to reclaim some storage space. At the time, she was setting up a filming nook in her office, where she makes science communication videos. "I love putting maker projects in the background

Conference crafts: Eric Winick Anthony created a woven pillow by upcycling her favorite lanyards.

of my videos," Anthony tells Newscripts. So she chose a selection of her favorite lanyards and started weaving them together to make a small throw pillow.

Anthony encountered a couple of complications while constructing the cushion. "A lot of lanyards are really slick, which is not necessarily the ideal sewing material," she says. "Also, my cats were very fond of the many stringy pieces of material." Nevertheless, she continued to fantastic effect and later posted her creation on social media. Anthony was flattered by compliments from her followers, including one who made a lanyard pillow of their own. Anthony encourages fellow lanyard hoarders to try for themselves, noting that the woven pattern could be used for all sorts of applications.

Ariana Remmel wrote this week's column. Please send comments and suggestions to newscripts@acs.org.

CREDIT: LAURENT DAVIN (FLUTE); ERIN WINICK ANTHONY (PILLOW)

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