



LAWRENCE
LIVERMORE
NATIONAL
LABORATORY

Recent advances in the chemistry of hydrometallurgical methods

G. Deblonde, A. Chagnes, G. Cote

January 7, 2022

Separation & Purification Reviews

Disclaimer

This document was prepared as an account of work sponsored by an agency of the United States government. Neither the United States government nor Lawrence Livermore National Security, LLC, nor any of their employees makes any warranty, expressed or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States government or Lawrence Livermore National Security, LLC. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States government or Lawrence Livermore National Security, LLC, and shall not be used for advertising or product endorsement purposes.

Recent advances in the chemistry of hydrometallurgical methods

Gauthier J.-P. Deblonde^{1*}, Alexandre Chagnes², Gérard Cote³

¹ *Glenn T. Seaborg Institute, Physical and Life Sciences Directorate, Lawrence Livermore National Laboratory, Livermore, California 94550, United States*

² *CNRS, GeoRessources, Université de Lorraine, 54000 Nancy, France*

³ *PSL Research University, Chimie ParisTech – CNRS, Institut de Recherche de Chimie Paris, 11 rue Pierre et Marie Curie, 75005 Paris, France*

**E-mail: Deblonde1@LLNL.gov*

Abstract

Producing pure substances has been the obsession of scientists for centuries and has defined chemistry as we know it. Nowadays, most of our economy still relies on the chemists' ability to extract and purify elements from raw or recycled materials, which, in most cases, is done partly or entirely via hydrometallurgical methods. Here, the authors present the critical aspects of this relatively overlooked, yet critical, chemistry discipline. This review article highlights the importance of hydrometallurgical processes for strategic industrial sectors, put in perspective traditional separation methods with emerging ones (new metal-binding chelators, ionic liquids, deep eutectic solvents, microfluidic devices, biomaterials, etc.), critically reviews progress made on separation methods over the past two decades, and highlights the challenges lying ahead for the hydrometallurgists in academia and the industry.

Introduction.

Science progress and the evolution of consumer habits have led us to a point where our economy, means of communications, transport infrastructures, energy production and storage, defense apparatus, and health care system depend heavily on advanced technologies which necessitate very elaborated supply chains. And, while the retail value of a final product or its benefits to society often come from the last few steps of the supply chain (manufacturing, marketing, branding, distribution, etc.), most items in our daily life stem from a common first step: extracting and purifying specific elements from raw sources or materials to recycle. For most metals, the first product that can be commercialized and enters the supply chain is a mineral concentrate or purified salt that is produced via hydrometallurgy (**Figure 1**). This often-overlooked chemistry discipline consists of starting from a feedstock (typically a mineral ore or spent materials that has been pre-concentrated by physical means like grinding, sieving, froth flotation, magnetic and eddy current separations, etc.) and extracting its valuable elements by dissolution in an aqueous media followed by multiple steps of selective solvent extraction, liquid-solid extraction, precipitation, crystallization, or a combination of these techniques. Hydrometallurgical methods leverage fundamental chemistry principles to achieve efficient separation such as differences in speciation, binding affinity, hydrodynamic size, solubility, aqueous/organic partition, redox properties, etc. Hydrometallurgy has been defined by opposition to pyrometallurgy, i.e., the historical route where raw materials are refined at high temperatures and without solvent. Hydrometallurgical processes present several advantages over pyrometallurgical ones: low energy consumption, low temperature, scalability, modularity, operations in continuous settings, and high and tunable purity for the final product(s). Hence, nowadays most elements are refined entirely or partially via hydrometallurgy methods (**Figure 1**). This review article underlines the importance of hydrometallurgical processes for strategic industrial sectors and research areas, contrast traditional

separation methods with emerging ones (new metal-binding chelators, ionic liquids, deep eutectic solvents, microfluidic devices, biomaterials, etc.), critically reviews progress made on separation methods and processes over the past two decades, and highlights the challenges lying ahead for the hydrometallurgists in academia and the industry.

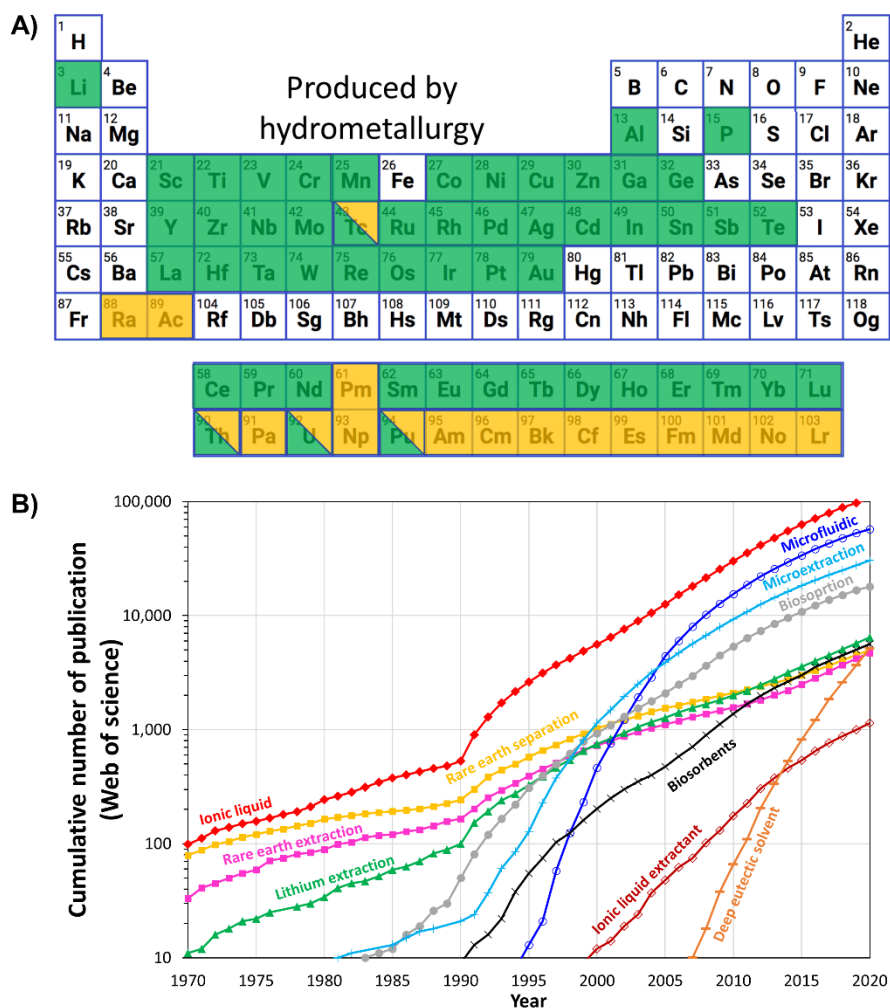


Figure 1. A) Periodic table of the elements with emphasis on economically important elements that are entirely or partially produced via hydrometallurgical methods (solvent extraction, selective precipitation, ion-exchange, electrowinning, electrolytic refining, etc.). This list is not meant to be exhaustive. Stable elements produced via hydrometallurgy and that have significant economic importance are highlighted in green. Hydrometallurgically-produced radioactive elements with significant economic and/or strategic importance are highlighted in both green and yellow. Radioactive elements used for research with minor economic importance are highlighted in yellow. For clarity, medical radioisotopes that also have stable isotopes (ex: ^{89}Zr , ^{177}Lu , ^{90}Y) are represented in green, even if the production of most radioisotopes involves hydrometallurgy methods; B) Cumulative number of publications listed in Web of Science for select topics related to hydrometallurgy (Source: Web of Science. Number of hits given for the expression listed on the graph, in the category “Topic”. Search updated on: April 5th, 2022).

Strategic sectors relying on hydrometallurgical methods.

Critical materials production and purification.

One of the most apparent changes that the hydrometallurgy field experienced within the past few decades is that it has been projected on the world's stage due to the rare earth elements (REEs) and associated geopolitical tensions between China (the current world's top producer) and countries that do not have a significant REE production and purification capacity. REEs (scandium, yttrium and the lanthanide elements) are so chemically similar that their separation at industrial scale can only be performed via hydrometallurgy, *i.e.* usually a multi-stage solvent extraction process^[1]. Given that REEs are used in numerous key applications (catalysts, hard drives, magnets, screen displays, electric engines, wind turbines, polishing, optics, etc.), hydrometallurgical methods capable of separating them from one another have become highly strategic, with both scientific and political implications. The REEs are part of a larger group of “critical materials” identified by western countries (mainly the United States and European Union) because of their economy strongly relies on the importation of these materials, hence creating a critical and fragile link in strategic supply chains (automobile, energy, defense sectors, etc.). Starting in 2011, the EU published its first list composed of 20 raw materials and has continued to update this list since then. In 2020, the EU published its 4th “*critical raw materials*” list, which has grown to 30 types of materials, including 16 that are mainly produced via hydrometallurgy: antimony, bismuth, cobalt, gallium, germanium, hafnium, heavy REEs, indium, light REEs, lithium, niobium, platinum group metals, scandium, tantalum, titanium, and tungsten. **Figure 2** gives an overview of the EU critical material list, in a 2D version of the typical critical material assessment framework (which initially had a 3rd dimension for “environmental implications”^[2, 3]). This kind of diagram is often cited to demonstrate the economic importance of REEs in western countries and the fragility of the REE supply chain. However, this representation also illustrates

that the REEs topic is only a fraction of a bigger issue as, for instance, ~10 other elements have higher economic importance than the REEs and are also subject to supply tensions in the EU.

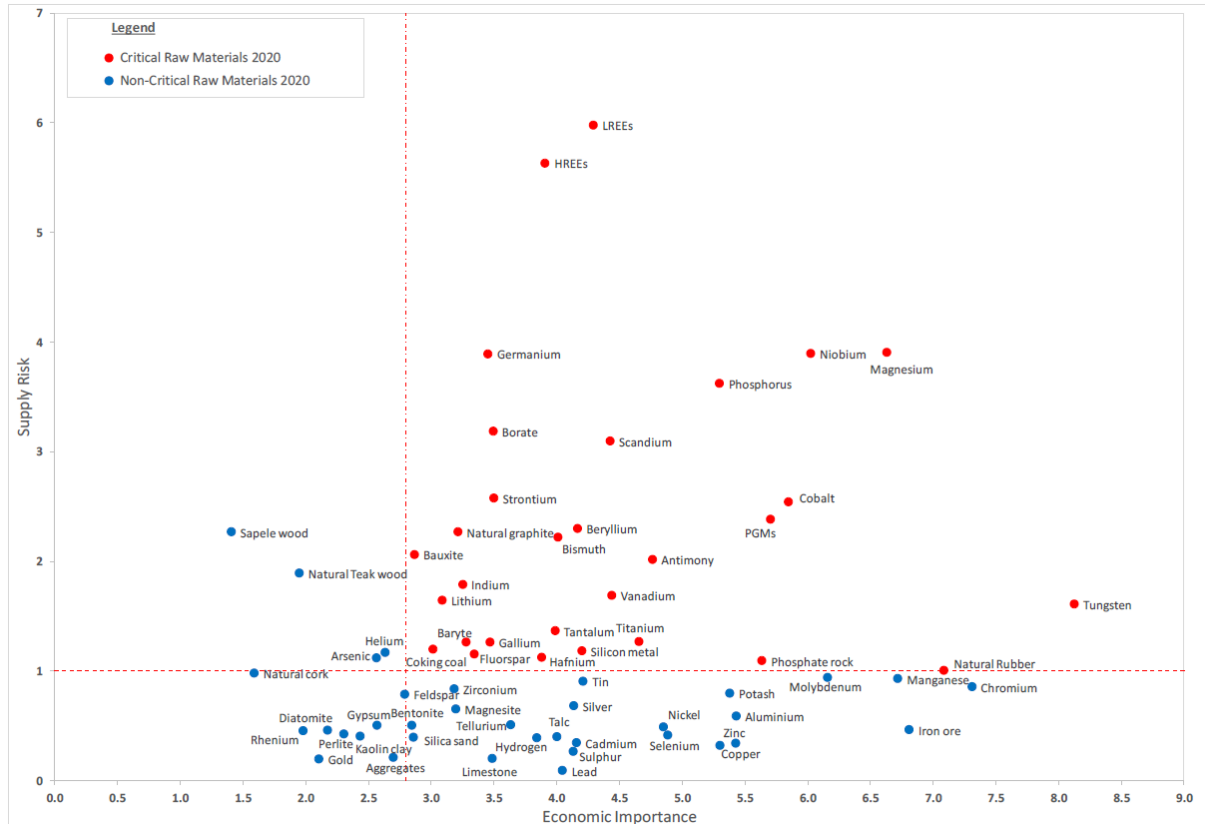


Figure 2. Raw materials considered as critical by the European Union, as of 2020. This plot was published by the European Commission in its detailed report entitled “Study on the EU’s list of critical raw materials (2020)”^[4].

Similar to the European Union, the United States strongly relies on importations for strategic elements that make them “critical” (**Figure 3**). In 2018, the US Department of interior released a list of 35 mineral commodities that it considers critical to the economy and national security of the US^[5–7]. The list includes the following: aluminum, antimony, arsenic, barite, beryllium, bismuth, cesium, chromium, cobalt, fluorspar, gallium, germanium, graphite, hafnium, helium, indium, lithium, magnesium, niobium, the platinum group metals, potash, the REEs (including scandium), rhenium, rubidium, strontium, tantalum, tellurium, tin, tungsten, uranium, vanadium, and zirconium. In late 2021, the USGS also published^[8] a proposed updated list of minerals to be

considered as critical in the US (**Figure 3**), and this draft list is largely consistent with the 2018 list with the addition of nickel and zinc to the list. The top five elements in terms of supply risk in the US are: gallium > niobium > cobalt > neodymium > ruthenium. One can note that most of the elements included in the US critical mineral list are produced via hydrometallurgy. Interestingly, Canada, which has an extensive mining industry, also has a list of minerals that are considered critical to the sustainable economic development of Canada and its allies. The most recent Canadian list of critical materials, released in early 2021^[9], is composed of 31 elements and is relatively similar to that of the 2018 US list, except for the inclusion of copper, molybdenum, nickel, and zinc, and the absence of arsenic, barite, beryllium, hafnium, rhenium, rubidium, strontium, and zirconium, relative to the 2018 US list of critical mineral commodities. This binary example highlights that material criticality is a truly relative term that mainly stems from the unequal distribution of natural resources around the globe, but that it can also be alleviated via international cooperation.

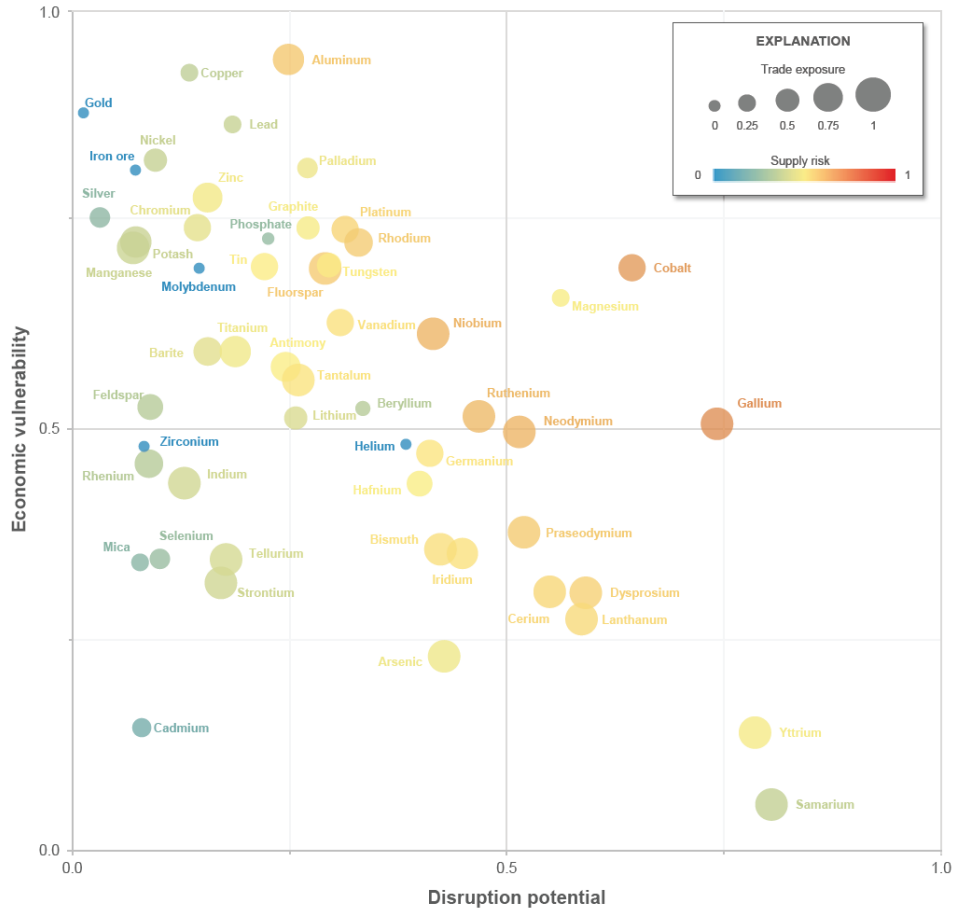


Figure 3. Evaluation of the supply risk for 54 mineral commodities in US. The economic vulnerability is plotted against the disruption potential. The point size corresponds to the trade exposure. The color of each point indicates the overall supply risk. This plot was published by U.S. Geological Survey in its 2021 report entitled “*Methodology and Technical Input for the 2021 Review and Revision of the U.S. Critical Minerals List*” [8]. The readers are also invited to read the prior report from the U.S. Geological Survey entitled “*Mineral commodity summaries 2020*”[10].

While China is often put under the spotlight for its monopolistic position on the REE production, it is often forgotten that China also relies on importations for other elements. **Figure 4** depicts the list of elements considered as critical for the Chinese economy. Unsurprisingly, the REEs are not considered as particularly critical in China (its supply risk being minimal since China is currently the world’s top producer) and the list is significantly different from those of the western countries. The Chinese economy particularly relies on importation for the platinum group metals (PGMs), niobium, and cobalt, and, to a lesser extent, for germanium, zirconium, selenium, and chromium.

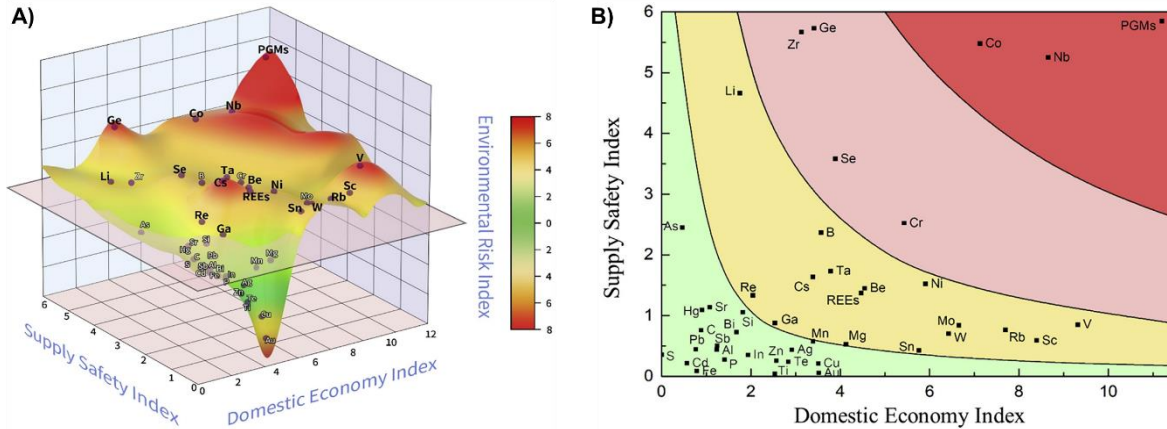


Figure 4. A) 3D criticality framework for raw materials in China. B) 2D version of the criticality matrix for raw materials in China. Graphs published by Yan et al. ^[11]. Copyright 2021 Cell Press.

The tensions related to critical materials has led to strong initiatives with the implementation of academic collaborations, industry-academia partnerships, and industrial hydrometallurgy networks that aim at creating domestic supply chains of critical materials. In the US, the Department of Energy’s Critical Materials Institute focuses on "critical" rare earths and "near-critical" materials (REEs, indium, gallium), as well as metals and graphite used in battery materials (lithium, cobalt, manganese) by “*diversifying supply, developing substitutes, driving reuse and recycling and crosscutting research*”. The European Commission launched in 2014 the “*Horizon 2020*” program dedicated to fund interdisciplinary research and innovation programs in order to address economic and societal challenges, including the sustainable supply of raw materials. The new research and innovation program “*Europe 2030*” has started in 2021 with the creation of the European Raw Material Alliance (ERMA), to make the “*EU more economically resilient by diversifying its supply chains, creating jobs, attracting investments to the raw materials value chain, fostering innovation, training young talents and contributing to the best enabling framework for raw materials and the circular economy worldwide with a special focus on the supply of raw materials for energy transition*”. These initiatives aim at securing a supply of critical elements for the energy transition and national security reasons but came with the immense

scientific challenge to rapidly develop separation processes that are tailored to domestic feedstocks, and it has greatly stimulated the research field over the past decade (*vide infra*).

While REEs routinely catch the media attention, other elements produced by hydrometallurgy are almost unknown to the general public but are nonetheless highly strategic and have nearly monopolistic supply chains. Notably, niobium and tantalum – two metals used in electronic components, optical lenses, supra-conducting magnets, magnets used for medical imaging devices, high-strength low-alloy steels for cars, airplanes and missiles – are produced by a very small number of countries: 88% Brazil, 10% Canada for niobium; 40% Congo, 20% Rwanda, 14% Brazil, 12% Nigeria for tantalum in 2019 ^[10]. **Figure 5** highlights the strategic importance of niobium and tantalum as both the United States and China rely entirely on importations for these two elements. The European Union also imports >99% of its niobium and tantalum^[4]. Likewise, hafnium is a highly strategic element as it is used in nuclear reactor control rods, cutting tools, and high-temperature alloys, but it is mostly produced in the USA and France. Hafnium is mainly recovered as a by-product of the production of high-purity zirconium, which is required for nuclear fuel claddings. The criticality of hafnium is therefore even higher than that of zirconium. The separation of these two elements is also not trivial, reminiscent of the separation of two adjacent REEs, since Hf and Zr are two elements of the same column and have nearly identical chemical properties (same +IV oxidation state, similar ionic radius, etc.). For these strategic but rather discreet metals, new hydrometallurgical processes for extraction from secondary sources or recycling from end-of-life products could become highly disruptive.

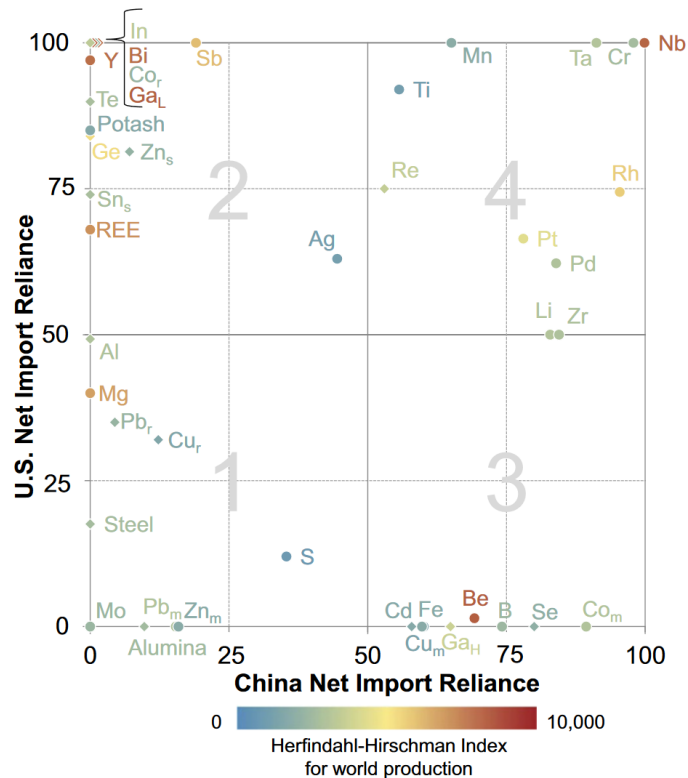


Figure 5. Comparison of the importation of 42 mineral commodities by the United States and by China. The data correspond to importations for the year 2014. Some of these materials are now considered as critical by the United States and/or China. This plot was originally published by Gulley et al. ^[12]. Copyright 2018, PNAS.

Materials for energy storage.

The storage of energy, especially in the form of electricity, is largely seen as an essential component of the energy transition. In particular, two emerging sectors will be particularly reliant on energy storage (*i.e.*, electric batteries): electric vehicles and storage of electricity from intermittent energy production (e.g., solar panels and wind turbines). In this context, lithium-ion batteries are of paramount importance. This technology is now mature although there are still many challenges to increase their energy density while ensuring the highest safety standards. As such, it is necessary to develop new electrode materials that can be cycled at higher voltages and electrolytes compatible with these materials. It also appears crucial to develop sustainable, cost-effective, and efficient Li extraction and purification processes to be able to meet the current lithium demand, respond to the growing market expansion, and establish reliable lithium supply

chains. Hydrometallurgical processes for Li production will be key to avoid a situation similar to that of the REEs. Moreover, these challenges are not limited to lithium since the production of Li-ion batteries also relies on other critical resources like nickel, manganese, and cobalt.

With regard to primary extraction, lithium is commercially produced from two main sources: (i) solid mineral ores containing spodumene ($\text{LiAlSi}_2\text{O}_6$) or petalite ($\text{LiAlSi}_4\text{O}_{10}$), and more recently Jadarite ($\text{LaNaSiB}_3\text{O}_7(\text{OH})$)^[13, 14]; (ii) subsurface brines which have become the dominant raw material for lithium carbonate production worldwide because of lower production costs compared to the mining and processing costs associated with hard-rock ores. The ores are processed by combining a thermal treatment and a hydrometallurgical process whereas the brine treatment involves solar evaporation for as long as 12-18 months to produce lithium chloride, followed by lithium chloride refining, and conversion stages to produce high-grade lithium salt via hydrometallurgical processing.

Among the different lithium ores, the mineral spodumene is one of the most potent and is relatively abundant, particularly in Australia. The main process used for lithium recovery from spodumene has been described in detail by Chagnes^[15] and Fosú et al. ^[16]. Briefly, it is based on a series of operations including beneficiation, roasting at 1070-1090 °C to convert spodumene to its beta form (this operation is accompanied by severe decrepitation, which leaves spodumene very finely pulverized), acid leaching with H_2SO_4 under at about 250°C under pressure, dilution with water, elimination of metallic impurities (Fe, Al, Mg, Ca...) by hydroxide precipitation at pH 12 by adding NaOH or by co-precipitation using limestone and, finally, recovery of lithium with ion exchange resins.

Production of battery-grade lithium salts from brines relies on natural evaporation followed by solvent and/or resin extraction steps. Solar evaporation is very inexpensive, but it requires >12

months from the start of the operation to the production of the lithium salt. Moreover, conventional lithium extraction processes which rely only on solar evaporation are only applicable to specific geographical areas (e.g., high altitude and dry weather). In order to circumvent the evaporation step and shorten the production time, two innovative industrial processes have been recently developed, as detailed below.

The ERAMET Process ^[18]: This mining and metal refining company started developing a lithium production project in order to extract lithium from brines located in the Andean cordillera area (Salta, north-western Argentina). The resources of the Centenario-Ratones deposit are significant and could yield 20,000 tonnes of lithium carbonate per year for several decades. The core innovation of this process is a sorption material selective towards lithium (general formula $\text{LiCl} \cdot 2\text{Al}(\text{OH})_3 \cdot n\text{H}_2\text{O}$) implemented in a solid-liquid extraction, and membrane stages. The brine is pumped from a depth of 200 m and is fed into the lithium extraction unit consisting of a solid/liquid extraction step using the Li^+ -selective sorbent^[18]. During this step, lithium is selectively extracted relative to calcium, magnesium, boron, and sulphates. The Li-depleted brine is then reinjected in the original field aquifer via infiltration so that the water balance of the brine field is not affected (unlike conventional solar evaporation processes which deplete the aquifers). After elution of the lithium-loaded sorbent, the solution is concentrated via reverse osmosis and the resulting concentrated solution is subsequently purified via solvent extraction (to remove boron traces) and ion exchange extraction (to remove traces of calcium and magnesium). A final addition of sodium carbonate produces high-purity lithium carbonate salts for use in glass, ceramic, and greases applications as well as lithium-ion batteries.

The Solvay-Tenova Process ^[19,20]: This new technology for lithium recovery from brine is based on Cyanex® 936— a phosphorus-based extractant specifically formulated for lithium, which

exhibits a good extraction efficiency for lithium (80% at pH 9) and high selectivity against potassium, sodium, and boron ions. This solvent extraction process is combined with membrane technologies and electrolysis. Calcium and magnesium are first removed from the brine by a membrane filtration. The brine without magnesium and calcium is then sent into an electrolysis cell to generate chlorine and then hydrochloric acid by-products (which is recycled as stripping reagent in the downstream solvent extraction step). The purified pregnant leaching solution containing lithium is sent to a solvent extraction stage that relies on the extractant Cyanex® 936. After scrubbing and stripping with hydrochloric acid, lithium chloride is directly produced, or the stream can be sent to a precipitation stage to produce lithium carbonate or to an electrolysis stage to produce hydrochloric acid and lithium hydroxide. This process is also advantageous as it allows for the extraction of lithium without affecting the water balance of the brine field, similar to the ERAMET process. Both processes avoid slow production kinetics inherent to solar evaporation. They are also more versatile than conventional evaporation-based processes since they can produce multiple products, at various grades, without significantly changing the process scheme. Processes circumventing the evaporation step may supplant traditional lithium extraction processes in the future as the growing lithium demand will inherently require mining companies to diversify their primary sources, outside conventional brines, such as geothermal brines or even second-hand materials to recycle.

Radiochemistry applications

The use of hydrometallurgy goes well beyond the bulk production of metal commodities, and it is also a convenient technique to refine materials for high-value elements. As such, the nuclear energy sector also depends heavily on hydrometallurgical methods throughout the nuclear fuel cycle, beginning with the mining and purification of natural uranium from mineral deposits, and ending with the reprocessing of spent nuclear fuel rods to recover their valuable components (U

and Pu isotopes) and isolate the most dangerous ones (fission products, activation products, heavy actinides). As such, one of the most iconic hydrometallurgical processes is the PUREX process (Plutonium Uranium Reduction and EXtraction process - also known as Plutonium and Uranium Recovery by EXtraction) which has been used in multiple countries since the 1950's and is still the harbinger of large-scale nuclear reprocessing plants at La Hague (France) and Ozersk (Mayak, Russia) which can treat a combined 2100 tones (expressed in tHM)^[21] of spent light-water reactor nuclear fuel per year, with an additional capacity of 800 tHM/year expected with the start of Rokkasho (Japan) in 2022. Detailed information about the hydrometallurgical processes in nuclear fuel processing, can be found in the three recent reviews from Taylor et al.^[22], Geist et al.^[23], and Baron et al.^[24].

On the fundamental research front, an international race to create new elements has been launched since the era of the Manhattan Project. Since then, the expansion of the periodic table as we know it has been driven by our ability to produce heavy actinide targets of high purity (e.g. ²⁴⁴Pu, ²⁴³Am, ²⁴⁸Cm, ²⁴⁹Bk, ²⁴⁹Cf, etc.) that are then bombarded with lighter elements (e.g. ²²Ne, ²⁶Mg, ⁴⁸Ca) to create synthetic “super-heavy elements” ($Z > 103$)^[25]. Milligram quantities of the heavy isotopes used in targets are extracted and purified from irradiated research nuclear fuels via hydrometallurgy and notably solvent extraction and ion-exchange^[26]. Over the past few decades, Oak Ridge National Laboratory (Tennessee, USA) has been at the forefront of these radio-hydrometallurgical purification processes^[27] and, interestingly, element 117 has been officially named “tennessine” in 2016, not to give credit the place where it was first synthesized (Dubna, Russia), but to acknowledge the place that produced and purified the target (made of ²⁴⁹Bk).

The hydrometallurgical production of very high-purity and high-value materials is also paramount to modern medicine. Over the past two decades, the medical imaging and nuclear medicine sectors

have experienced substantial growth^[28, 29]. Imaging techniques, such as MRI and PET scans are now considered routine and highly innovative cancer treatments like beta or targeted alpha therapies have emerged in the past two decades. This has led to the development of an entirely new hydrometallurgy sector that aims at producing and purifying minute quantities of very high-purity (and high-value) short-lived isotopes (^{44/47}Sc, ^{67/68}Ga, ⁸⁹Zr, ¹⁷⁷Lu, ²¹²Pb, ²¹³Bi, ²²³Ra, ²²⁷Th, ²²⁵Ac, etc.)^[29–31] that are crucial to medicine. Actinium chemistry has recently caught the most attention due the promising use of its short-lived isotope ²²⁵Ac ($t_{1/2} = 10$ days) in next-generation cancer therapies. Notably, resounding results have been obtained by Kratochwil et al.^[32] on the treatment of metastatic prostate cancer, and a flurry of initiatives have been launched by several countries to produce and hydrometallurgically purify actinium isotopes in order to fulfill future hospital needs and also to help studying actinium chemistry^[30, 33–44]. This growing field is at the crossroad of radiochemistry, pharmaceutical production, separation sciences and is adapting traditional hydrometallurgical methods to comply with the peculiarities and stringent specifications of radiopharmaceuticals.

Emerging technologies for hydrometallurgical separations

Novel super-selective extractants.

Despite remaining in the shadow of other chemistry disciplines, hydrometallurgy is nonetheless a very active field as it is continuously challenged by the evolving customer habits, sporadic consumption spikes and shortages for certain tech-metals^[45], geopolitical tensions, as well as decreasing natural resources. This drives the research efforts on the development of more efficient, selective, and cost-effective purification processes. At the heart of metal separation processes involving liquid-liquid extraction or chromatography are the molecules participating in the transfer of the metal ions between the two phases. A natural starting point for process optimization is therefore the extractant(s) present in the organic phase. Industrial solvent extraction processes

mostly rely on less than ten types of extractant molecules. **Table 1** gives an overview of the extractant molecules currently in use in the industry.

Table 1. List of the main extractants used in industrial hydrometallurgical processes. Additional information given in ref. ^[46]. a: initially commercialized by the company “Cytec Industries Inc.”, recently acquired by the “Solvay”.

Name of the extractant (company)		Composition	Targeted metals and comments
Oximes			
LIX (BASF)	LIX63	Alkyl-□-hydroxyoxime	Ge, Cu, U-Mo separation from H ₂ SO ₄
	LIX84-I	Ketoxime-based reagent without modifier	Cu from dilute H ₂ SO ₄ , nitrate, ammonical leach solutions Pd from acidic chloride solutions
	LIX 84-INS	Ketoxime-based reagent without modifier	Ni from ammoniacal solutions followed by acid stripping
	LIX 84-IT	Ketoxime based reagent+ester modifier	
	LIX 860N-I; LIX 860-I	Aldoxime based reagents (based on 5-nonylsalicylaldoxime for LIX 860-I and 5-dodecylsalicylaldoxime for LIX860N-I)	Cu extraction
Acorga (Solvay)^a	Acorga M5640, M5774, M5970	Aldoxime+modifier	Cu (mainly from Chile)
	Acorga M5850, M5050	Aldoxime+modifier	Cu
	Acorga NR10, NR20	Aldoxime+modifier	Cu (extraction solvent resistant towards nitration)
	Acorga OR15, OR25	Aldoxime+modifier	Cu (extraction solvent resistant towards oxidation)
	Acorga OPT	Mixture of aldoxime and ketoxime+modifier	Cu (mainly from Africa)
	Acorga PT5050, PT5050MD	Aldoxime+modifier	Cu (where plants are located at high altitude where temperature reaches 5 °C like in Chile)
Amines			
Alamine and Aliquat (BASF)	Alamine 308	Tri(<i>iso</i> -octyl)amine (branched alkyl chains)	Co-Ni separation from chloride Zn recovery from spent electrolyte solution
	Alamine 336	Tri(<i>n</i> -octyl/ <i>n</i> -decyl)amine (linear alkyl chains)	Recovery of U, Mo from acidic sulfate leach liquors Recovery of V(V), W from acidic leach liquors Separation of Mo and Rh Recovery of Au from acidic thiocyanate leach liquor Recovery of Ga from acidic chloride solution
	Alamine 304	Tri(<i>n</i> -dodecyl)amine (linear alkyl chains)	Recovery of Mo from acidic sulfate leach liquor

	Aliquat 336	Tri(<i>n</i> -octyl/ <i>n</i> -decyl) methyl ammonium choride	Recovery of Mo, V(V), rare earth from acidic sulfate leach liquor Removal of arsenic
LIX (BASF)	LIX 7820	Mixture of a quaternary amine and nonylphenol	Au extraction from cyanide solution, thiosulfate solution and cyanide recovery
Organophosphorus compounds			
Cyanex (Solvay) ^a	Cyanex 272	Bis(2,4,4-trimethylpentyl) phosphinic acid	Separation of cobalt and nickel from sulfate and chloride media
	Cyanex 301	Bis(2,4,4-trimethylpentyl)dithiophosphinic acid	Extraction of heavy metals vs. earth-alkali metals Extraction of Zn at low pH
	Cyanex 921	Tri- <i>n</i> -octyl phosphine oxide	U from wet phosphoric acid, Nb-Ta separation from HF/H ₂ SO ₄ solution
	Cyanex 923	Mixture of trialkylphosphine oxides (alkyl = normal, C6, C8)	Extraction of Rh, As, Cs; Li, Cd and more than 30 other metals by playing on the redox and the medium (chloride or sulfate).
PC-88A (Daihachi)	PC-88A	(2-Ethylhexyl)phosphonic acid mono-2-ethylhexyl ester	Cobalt extraction from sulfate acidic media Extraction and separation of rare earth Extraction of In, Mo and other metals
D2EHPA (Lanxess)	D2EHPA	Bis(2-ethylhexyl)phosphoric acid	Extraction of U, Zn, Fe, Ca, Be, Co, Mo
TBP (Daihachi and Lanxess)	TBP	Tri(<i>n</i> -butyl)phosphate	Separation of U and Pu from spent nuclear fuel Separation of rare-earth Extraction of As, Cr, PGM
Dialkylsulfides			
SFI (Daihachi)	SFI-6, SFI-6R	Dihexylsulfide	Separation of Pd from Pt Extraction of chloride complexes of Au, Ag, Cu, Hg and others

However, discovering the optimal extractant for a specific metal of interest is an incredibly challenging process, that usually goes from the selection of extracting functionalities and multiple molecule backbones leading to numerous potential combinations, the design of synthetic procedure for the new extractant (and oftentimes its precursors), performing the synthesis, purifying the compound (if successful synthesis), and testing it for extraction of the metal(s) of

interest and its potential impurities. Moreover, not all molecules are suitable for liquid-liquid extraction as the cost and physical properties of the extractant itself also impose strict constraints (e.g., solubility in the organic solvent versus aqueous phase, viscosity, solubility of its metal complexes). Reminiscent of a drug development process, most of the potential extractants that are considered in the beginning of the process do not meet the expected performance criteria. Additionally, even for the molecules suitable for liquid-liquid extraction, predicting their extraction efficiency and selectivity is nearly impossible as the phenomena involved are numerous, complex, and often correlated to each other (e.g., aqueous complexation, mass transfer between the two phases, metal coordination in the organic phase, co-extraction of water or salts, salting-out effects, long-range organization of the extractant, formation of micelles). A recent study from Stamberg et al.^[47] showed that even for a well-known REE extractant, called “TODGA” (trioctyldiglycolamide), subtle modifications of its alkyl sidechains, which at first sight do not take part in the metal extraction mechanism, can drastically influence the REE extraction efficiency and the selectivity of the extractant for the different REEs (**Figure 6**).

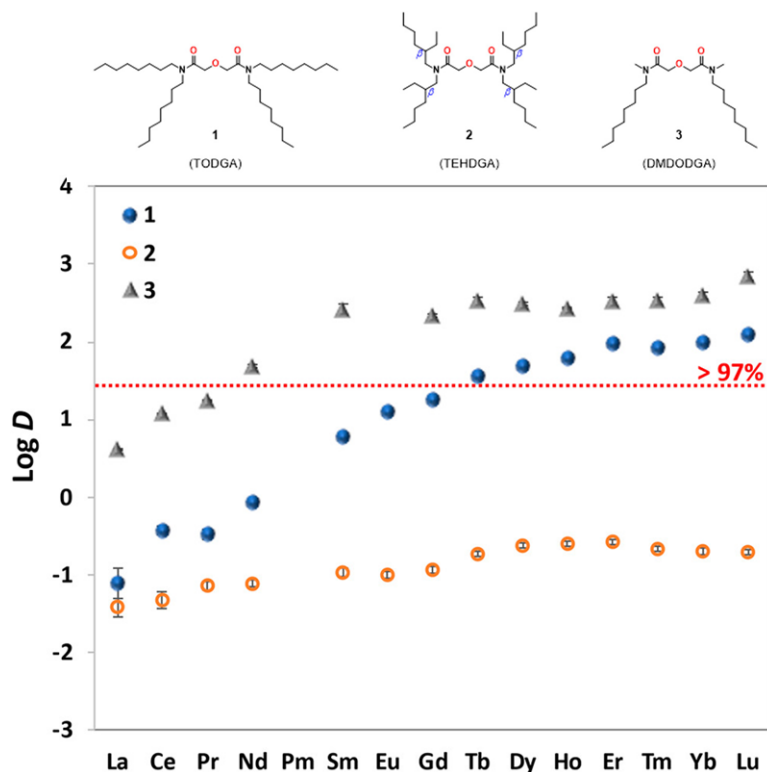


Figure 6. Impact on the modification of the alkyl chains (considered as non-coordinated to the extracted metal ions) of the diglycolamide extractant TODGA on the extraction coefficient and selectivity of the lanthanide ions. D represents the distribution ratio, *i.e.*, the ratio of the metal concentration in the organic phase and concentration in the aqueous phase. Adapted with permission from ref. ^[47]. Copyright 2020 American Chemical Society.

Another example illustrating the dramatic influence of subtle modifications of side alkyl chains on the extraction properties is given in **Table 2**, concerning the extraction of uranium(VI) and iron(III) from 5 M phosphoric acid using bi-functional carbamoylalkylphosphonate extractants recently reported by Turgis et al.^[48]. Indeed, the modified extractant bearing a methyl group between the carbamoyl and phosphonate functions exhibits a distribution ratio of uranium 10 times higher and a U(VI)/Fe(III) selectivity 80 times higher than the similar extractant without the methyl group. On the other hand, the replacement of the methyl group by a phenyl group decreases the distribution ratio of uranium by a factor of ~2 but doubles the selectivity uranium/iron. In a similar way, the mere branching of the C8 alkyl chains on the amide group leads to a U(VI)/Fe(III) selectivity 7 time higher, while the distribution ratio is kept constant^[48]. Such dramatic and non-

linear effects cannot be anticipated prior to experimental testing. These unforeseen effects are not only interesting from a fundamental point of view, but they also create intellectual property conundrums as the generalization of the properties of one extractant to its structural derivatives (as often claimed in patents) becomes questionable.

Table 2. Impact of the modification of the alkyl chains of the bis-functional liquid-liquid carbamoylalkylphosphonate extractant on its performances for the extraction of uranium(VI). The uranium distribution ratio (D_U) and the separation factor between iron(III) and uranyl ions ($SF_{U/Fe}$) are taken as the main indicators for the extractant performance. Table adapted from the results published by Turgis et al. [48]. Conditions: $[U] = 250$ mg/L. $[Fe(III)] = 2500$ mg/L. Aqueous phase: 5 M H_3PO_4 . Organic phase: 0.25 M extractant in dodecane. O/A = 1. For the sake of comparison $D_U = 3.8$ and $SF_{U/Fe} = 200$ for the mixture of HDEHP/TOPO in kerosene under the same experimental conditions.

Extractant :				Extraction performance	
$R_1 =$	$R_2 =$	$R_3 =$	$R_4 =$	D_U	$SF_{U/Fe}$
EtHex	EtHex	H	OH	2	1.5
EtHex	EtHex	CH ₃	OH	5.4	1
EtHex	EtHex	Ph	OH	8	80
EtHex	EtHex	H	OEt	12.2	10
EtHex	EtHex	CH ₃	OEt	120	800
EtHex	EtHex	Ph	OEt	65	1800
EtHex	EtHex	Oct	OEt	120	1900
EtHex	EtHex	H	OBu	24	10
EtHex	EtHex	Oct	OBu	117	2800
Oct	Oct	Oct	OBu	116	400

These examples^[47, 48], among others, illustrates the difficulty in developing solvent extraction systems, and the emergence of new extractants in hydrometallurgy has been hindered, not only because of the cost of associated with developing new molecules, but also because optimization studies are still largely based on labor-intensive laboratory tests, educated guesses, and trials and errors. In this regard, the hydrometallurgy field will likely benefit from future progress in molecular modeling and the increase in computing capabilities.

Novel super-selective aqueous chelators.

Another option for improving the selectivity of solvent extraction systems is to use a metal chelator in the aqueous phase (also called “hold-back reagents” or “masking agents”). This configuration is typically more expensive as it requires both a metal extractant and water-soluble metal chelator and it is therefore reserved for the most arduous metal-metal separations and for high-value elements. This configuration is also often used for chromatographic separations where the small scale of the process and low metal concentration allow for the addition of an aqueous chelator in the mobile phase without significantly increasing the overall cost of the separation. This approach is particularly useful for the analysis of REEs where the separation of all the lanthanides can be achieved by ion-exchange chromatography in the presence of simple carboxylic acids like oxalic, α -butyric, tartaric, and/or nitrilotriacetic acids^[49]. The use of hold-back reagent is also currently the most performant option for the separation of americium and curium, in the context of high-level nuclear waste recycling. The separation of these two actinides, which are adjacent in the periodic table, is reputedly one of the most challenging of the periodic table (even more demanding than separating two adjacent lanthanides) due to the radioactive nature of these elements and the very small size difference between their ions. The ionic radius of the nine-coordinated Cm^{3+} is 1.147 Å, which is just 0.9% smaller than Am^{3+} (1.157Å)^[50]. For comparison, the equivalent lanthanide ions, Gd^{3+} and Eu^{3+} , measure 1.101 Å and 1.116 Å, respectively, *i.e.*, the size difference is almost twice as big as that between Am^{3+} and Cm^{3+} .

One of the handful Am/Cm separation processes that has been validated using genuine nuclear spent fuel waste, is the so-called “ExAm” process (Extraction of Americium) developed by the French Atomic energy Commission (CEA) since the late 2000’s^[51–56]. While historical efforts on hold-back reagents have been limited to carboxylate ligands, aqueous chelators with new metal-binding functionalities have been investigated in recent years for the purpose of metal purification.

For instance, in this process, the water-soluble chelator “TEDGA”, a diglycoamide derivative, is used in combination with a mixture of two organic extractants (DMDOHEMA and HDEHP) (Figure 7). The presence of TEDGA in the aqueous phase decreases the overall extraction of both Cm^{3+} and Am^{3+} but the complexation of Cm^{3+} to TEDGA is stronger than that of Am^{3+} , yielding slightly higher extraction yields for Am^{3+} and separation of the two elements. The separation factor Am/Cm after a single bath extraction is about 2.3, which is low but enough to separate the two elements in a continuous flow setting. Despite its apparent complexity and low selectivity, this process has been tested and validated in hot cells on genuine high-level radioactive waste solutions (PUREX raffinate)^[56–58], using a 32-stage extraction unit for the $\text{Am}^{3+}/\text{Cm}^{3+}$ separation. The Am recovery was >99% and the overall decontamination factor Am/Cm was ~500.

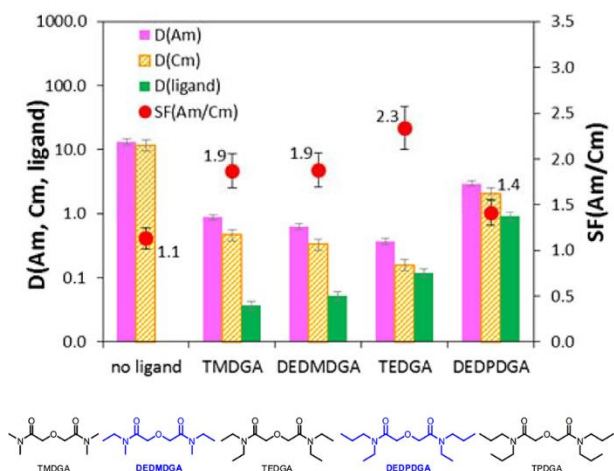


Figure 7. Distribution ratio Am^{3+} and Cm^{3+} and associated separation factor ($\text{SF}_{\text{Am}/\text{Cm}}$) obtained with the extraction system DMDOHEMA/HDEHP/aqueous diglycoamide-based ligand. The formula and names of the aqueous ligands are given at the bottom. Conditions: 0.6 M DMDOHEMA, 0.45 M HDEHP. Diluent = hydrogenated tetrapropylene. Aqueous phase: 6 M HNO_3 . $T = 25^\circ\text{C}$. 30 mM diglycolamide, trace amounts of ^{241}Am and ^{244}Cm . Adapted with permission from ref. ^[54]. Copyright 2016 Elsevier.

More recently, Jensen et al.^[59] obtained, in batch extraction tests, a record separation factor for a single extraction step of 4.1 between Am^{3+} and Cm^{3+} by using an aqueous chelator developed in-house called “bp18c6” (N,N’-bis[(6-carboxy-2-pyridyl)methyl]-1,10-diaza-18-crown-6) (Figure 8). Unlike TEDGA and its derivatives, the aqueous chelator bp18c6 displays higher affinity for

the larger cations ($\log \beta(\text{AmL}^+) = 15.5$ vs. $\log \beta(\text{CmL}^+) = 14.9$)^[59] so that it yields better separation if used in combination with common extractants like HDEHP which exhibits higher extraction efficiency for the smaller cations. Contrary to the ExAm process, this approach allows for the preferential extraction of Cm^{3+} in the organic phase while retaining the Am^{3+} complex(es) in the aqueous phase. While very promising for the treatment of nuclear waste and removal of Am, the ligand bp18c6 has only been tested at trace levels of Am and Cm isotopes and its performance would need to be tested in a continuous flow process and at concentrations close to what is expected in the treatment of nuclear waste.

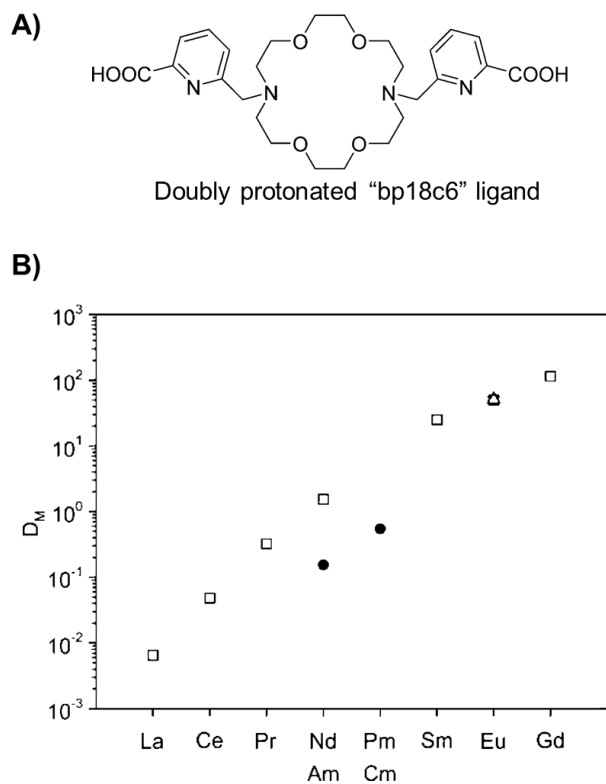


Figure 8. **A)** Formula of the water-soluble ligand “bp18c6” developed by Jensen et al.^[59] for the separation americium/curium. This ligand was later renamed “macropa”. **B)** Distribution ratio of trivalent americium, curium, and lanthanide ions using the $\text{H}_2\text{bp18c6}/\text{HDEHP}$ extraction system. Note that the higher extraction yield as the metal ion gets smaller (from La^{3+} to Gd^{3+}) is mainly due to the stronger complexation of $\text{H}_2\text{bp18c6}$ to the larger ions. Conditions: 0.05 M HDEHP in *o*-xylene/0.001 M $\text{H}_2\text{bp18c6}$ in 1 M NaNO_3 , 0.05 M lactate at pH 3.0 and 23 °C. Squares: lanthanides measured by ICP-MS. Triangles: $^{152/154}\text{Eu}$ radiotracer. Circles: ^{241}Am and ^{244}Cm radiotracers. Adapted with permission from ref.^[59]. Copyright 2016 American Chemical Society.

In line with the work from Jensen et al., the chelator bp18c6 has been further studied in recent years by Wilson and co-workers^[60, 61] for the separation of REEs due its unusual preference for the large cations over the small ones (*i.e.*, preference for the light REEs over the heavy REEs, due to the lanthanide contraction), which is the opposite of the trend observed for more classic metal chelators like the polyaminocarboxylates^[62, 63]. The name “bp18c6” was changed to “macropa” to reflect the presence of a macrocycle and picolinate arms in the molecule (**Figure 9**). Additional derivatives of macropa were synthesized (**Figure 9A**) and they also display unusual affinity trends along the REE series owing to different binding modes of the REE³⁺ ions to the aza-crown-ether macrocycles^[60]. For examples, the ligands “macrodiipa” and “macrotripa” exhibit a V-shape selectivity along the lanthanide series with minimal affinity around Er³⁺ and Gd³⁺, respectively (**Figure 9B**). This kind of ligands could be advantageous for next-generation REE or actinide separation processes if used in combination with an organic extractant, similar to the ExAm process. Another application taking advantage of the preference of the aza-crown-ether macrocycle ligands for the large cations is the use of macropa for the binding of the medically relevant actinium. The actinium ion, Ac³⁺, is the largest cation among the trivalent lanthanides and actinides^[39, 64]. Efficient chelators for Ac³⁺ are difficult to develop since classic ligands, like carboxylates, have a strong preference for the small cations, leading to weak Ac³⁺ complexes^[37, 41]. This is particular issue for the chemical purification of actinium isotopes as well as the production of ²²⁵Ac-radiolabeled drugs used in emerging cancer treatments^[32, 65]. However, Wilson et al. recently demonstrated^[66] the suitability of the macropa ligand for Ac³⁺ chelation and confirmed its *in vivo* stability, representing a significant step forward in this field of research. This example perfectly illustrates the far-reaching ramifications that can have hydrometallurgical studies, going from nuclear waste treatment^[59] to medicine^[66].

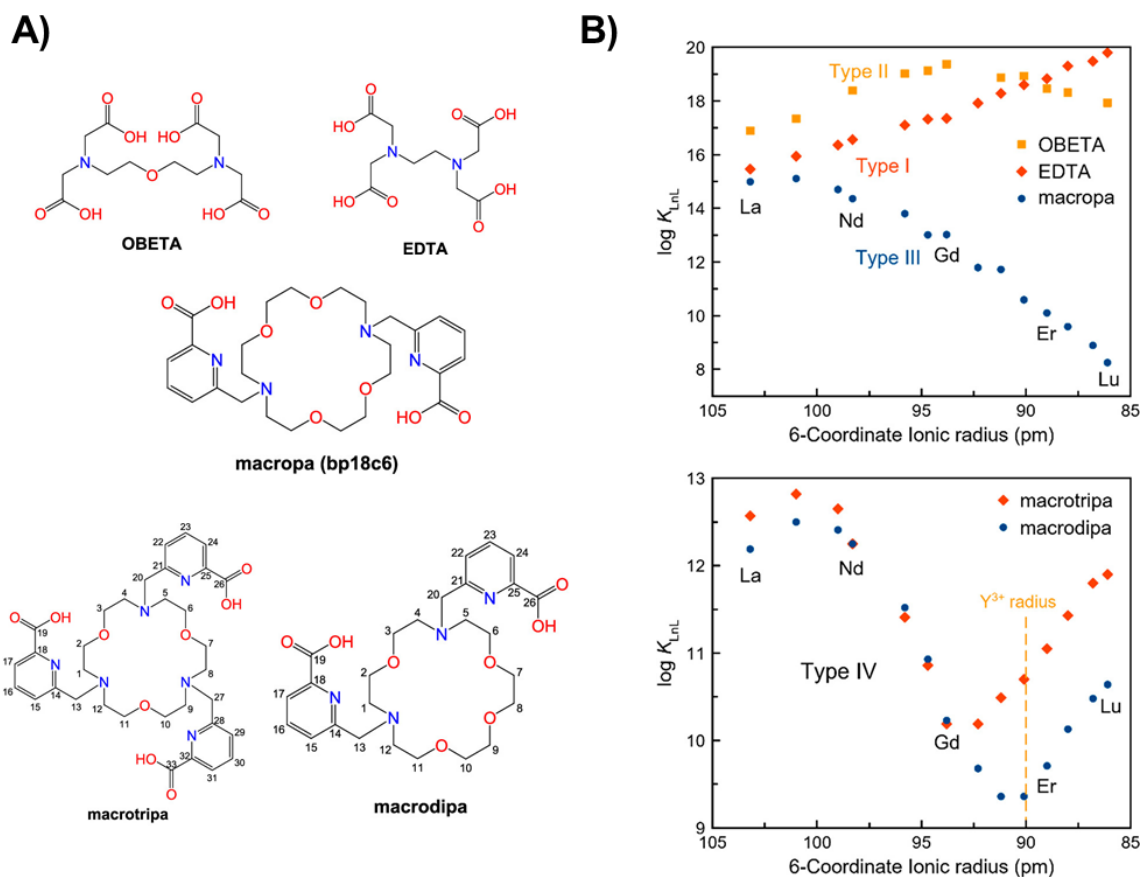


Figure 9. Recently developed aqueous chelators with a reverse selectivity for the lanthanide ions (i.e., higher affinity for the small lanthanides compared to the larger ones). **A)** Structures of the recently developed chelators macropa, macrodipa and macrotripa, and comparison with traditional carboxylic acid, EDTA and OBETA. **B)** Logarithm of the formation constants of 1:1 complexes (K_{LnLn}) formed with the aqueous chelators, plotted as a function of the ionic radii of the Ln^{3+} ions. Adapted with permission from ref. [60]. Copyright 2020 American Chemical Society.

In another recent example of the use of aqueous chelator to improve selectivity of extraction systems, it was demonstrated^[67] that the octadentate ligand hydroxypyridinonate (HOPO) ligand called “3,4,3-LI(1,2-HOPO)” (formula: $C_{34}H_{40}N_8O_{12}^{4-}$) yields ultra-selective separation systems for high-value actinides, such as actinium, plutonium, and berkelium. In this case, this particular molecule was selected for its strong preference toward the tetravalent ions over other cations (divalent, trivalent, and actinyl ions). This ligand is particularly suitable for the rare isotopes of berkelium as it is the only documented organic ligand that is capable of mediating the oxidation of Bk^{3+} (the regular oxidation state of Bk) and stabilizing it as Bk^{4+} , even in acidic solutions^[68, 69].

The use of 3,4,3-LI(1,2-HOPO) in the aqueous phase yields the total sequestration of the tetravalent ions (e.g., Th⁴⁺, Pu⁴⁺ or Bk⁴⁺) and therefore decouples their extraction behavior from that of the other cations. If a regular extractant like HDEHP, TBP, or TODGA is used in combination with 3,4,3-LI(1,2-HOPO), then the other cations can be extracted independently. This yields highly effective separations with separation factors Cf³⁺/Bk⁴⁺, Ln³⁺/Pu⁴⁺, An³⁺/Pu⁴⁺ >10⁺⁸ after a single step. Since 3,4,3-LI(1,2-HOPO) prefers cations with high Lewis acidity, it has very weak affinity for Ac³⁺ so that it also enables the purification of actinium under certain circumstances by retaining the other trivalent ions as well as the tetravalent actinides, with SF_{Ac3+/M3+} >1000 and SF_{Ac3+/M4+} >1,000,000. Moreover, the high selectivity of 3,4,3-LI(1,2-HOPO) for tetravalent actinides also allows for the separation of uranium and plutonium in a PUREX-like configuration ^[67] with separation factors UO₂²⁺/Pu⁴⁺ of ~5,000 and without the need for reducing Pu⁴⁺ to Pu³⁺, as required in the regular PUREX process. Despite the appealing and versatile performances of 3,4,3-LI(1,2-HOPO), it should be noted that the separations based on this ligand are only suitable for high-value elements, where not recycling the chelator (because it binds to the tetravalent ions so strongly that its recovery is arduous) does not impact the overall economy of the process. Additionally, since the HOPO binding groups are also efficient at binding Fe³⁺ (because HOPO chelators are part of the so-called siderophore family, *i.e.*, ferric iron binders), the abovementioned separation methods would be strongly impacted if iron is present in the process.

In another recent example^[70], Nelson et al. used another HOPO ligand, consisting of three 2,1-HOPO units attached to a tripodal linker, which forms neutral complexes [REE(HOPO)₃R] in order to perform REE separations via direct precipitation from aqueous solutions. The ligand-induced REE precipitation method exhibits separation factors similar to that of classic extractants

such as HDEHP and Cyanex® 572. This kind of approach could pave the way for REE separation processes that are free of organic solvent, but the scalability and economy of the method still needs to be investigated. In a related effort, led by Schelter et al.^[71, 72], a novel tripodal hydroxylaminate ligand [$\{(2\text{-tBuNO})\text{C}_6\text{H}_4\text{CH}_2\}_3\text{N}\}^{3-}$ (called TriNOx^{3-}), was also developed for REE separation by selective precipitation in organic solvents. While this approach necessitates the use of organic solvents like THF or benzene, it opens a potential new way for separating critical metals like the REEs. Despite the use of toxic organic solvents, the precipitation method using TriNOx^{3-} yields high separation factors, up to 359 between Nd and Dy after a single step. Interestingly, the same TriNOx^{3-} chelator can also be used for REE separation under a magnetic field (**Figure 10**). Schelter and co-workers observed^[73] the preferential crystallization of heavy REE complex of TriNOx^{3-} in chloroform when a magnetic field is present. This led the authors to perform efficient separation of light versus heavy REEs ($\text{SF}_{\text{Dy/La}} \approx 500$) by using a simple permanent magnet like $\text{Fe}_{14}\text{Nd}_2\text{B}$ (typically providing a magnetic field of $H = 1.1$ to 1.3 Tesla) to selectively precipitate the heavy REEs. While this kind of method is still in its infancy and not yet ready for industrialization, it could lead to future disruptive separation methods that would represent a hybrid between a precipitation process and a magnetic separation.

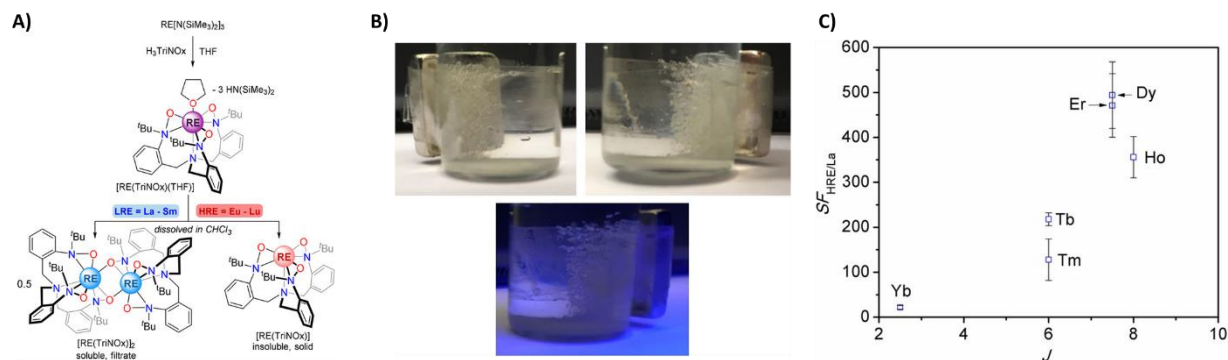


Figure 10. A) Synthesis and speciation of [REE(TriNOx)] complexes recently developed by Schelter et al. for the magnetic separation of REE complexes in solution.^[73] B) Photographs of [Tm(TriNOx)] crystals forming in the presence of a magnetic field, *i.e.*, a Fe₁₄Nd₂B permanent magnet. C) Separation factor as a function of heavy REE³⁺ free ion angular momentum, J, for La/RE(TriNOx) mixtures. Adapted with permission from ref. ^[73] Copyright 2020 Wiley.

Ionic liquids.

The need for more efficient and selective systems to process leaching solution produced from low-grade and polymetallic ores drives the development of new extractants. For instance, as already mentioned above, new organophosphorus compounds were recently developed for the selective recovery of uranium from phosphoric acid^[48]. Over the past two decades, many teams investigated the properties of ionic liquids (ILs) as an alternative to classical extractants for solvent extraction. As a reminder, ionic liquids are molten salts, mostly with organic cations and inorganic anions, exhibiting melting temperatures lower than 100 °C. Three reviews^[74–76] have recently been published on ILs and readers are invited to consult these studies for detailed information on ILs. Among the various IL systems previously considered, many studies concern imidazolium, pyridinium, pyrrolidinium, piperidinium, phosphonium, ammonium, and more recently triazolium cations combined with various anions such as chloride, bromide, PF₆⁻, BF₄⁻, bis(trifluoromethanesulfonyl)imide, etc.^[77]. However, in spite of the strong interest from the scientific community for ILs (**Figure 1B**), no industrial application has yet been implemented with this class of extractants in liquid-liquid extraction. On one side, ILs appear to have peerless physical characteristics such as low volatility, low melting point, and large electrochemical

window, which, in theory, offers many new opportunities for hydrometallurgical processes. On the other side, the high cost, high viscosity, often high water solubility, and possible toxicity of ILs narrow down their application potential under industrial conditions. Of note, many researchers claim the “green” properties and the low toxicity of ionic liquids whereas the lack of studies on their toxicity and ecotoxicity do not allow any conclusion yet, especially since their eventual toxicity can depend on both the choice of the anion and the size/functionality of the alkyl side chains of the cation^[78, 79]. The toxicity and environmental impact of ILs should also be considered for their full life cycle, from their synthesis to eventual disposal or recycling.

Likewise, the thermal stability of ILs is highly dependent on the nature of the anion and cation forming the ILs and therefore thermal stability should not be claimed as a general property of ILs. For example, a comprehensive study for Cao and Mu^[80] showed that the temperature at which ILs start to decompose can decrease by more than 200°C just by varying the anionic part of the ILs (e.g. replacing PF₆⁻ by a chloride or acetate anion). The long-term stability of ILs, or lack thereof, is also a major issue to resolve before they can eventually be employed in industrial processes. Comprehensive studies by Wang et al.^[81] and Xu et al.^[82] revealed that degradation of ILs occurs via many pathways, including hydrolysis, nucleophilic reactions, SN₂ reactions, acid-base reactions, Hofmann elimination, thermal degradation, and even radiolysis. Depending on the targeted process conditions and materials to be treated, the reactivity of ILs can readily limit their long-term stability and application potential. Furthermore, the current cost and high viscosity of ILs hinder their implementation in solvent extraction processes and future progress will be needed to render ILs compatible with applications at the industrial level. Nonetheless, the use of ILs in small-scale electrometallurgy, to target high-value metals, could be a more appropriate application in the short-term as ILs combine high electrochemical window and high ionic conductivity^[83].

Deep Eutectic Solvents.

More recently, Deep Eutectic Solvents (DES) emerged as a new class of solvents for hydrometallurgical processes. DES refers to a mixture a hydrogen bond donor(s) such as urea, and a hydrogen bond acceptor(s) such as choline chloride which has a lower melting point than the melting points of the individual compounds^[84, 85]. DES are generally liquid at <100 °C, and they exhibit physicochemical properties similar to traditional ILs, while being far less expensive (~ 2 €/kg) and potentially more eco-friendly^[86, 87]. Moreover, DES have several other advantages relative to ILs, such as their ease of preparation, and ease of production from relatively inexpensive and commercially available starting materials. These solvents could be used in leaching processes as extensive studies have already been reported on the solubility of metals in DES^[88–90]. They could also be used in electrometallurgy to refine, recover, or electroplate metals as they also exhibit wide electrochemical window^[88–93]. Furthermore, the recent synthesis of hydrophobic DES pave the way to their use as organic solvent in liquid-liquid extraction processes^[94–98].

Finally, both uses of DES in the leaching operation of ores or wastes and solvent extraction could contribute to the development of a new non-aqueous chemistry for the extraction and the purification of metals from raw materials. Such water-free processes in hydrometallurgy could be especially advantageous in arid regions and could lead to a significant reduction of the water consumption, which is often a major criticism against hydrometallurgical processes. For example, the work of Tersehatov et al.^[97] showed that certain DES have the ability to extract specific metals. The authors investigated the liquid-liquid extraction of indium from hydrochloric and oxalic acid media by quaternary ammonium- and menthol-based DES. This work demonstrated the ability of these DES to extract indium(III) via an ion-pair formation mechanism. In particular, the DES composed of DL-menthol and lauric acid extract indium(III) efficiently only from aqueous solution with low acidity (pH ≈ 3), and indium(III) stripping can occur by using 0.1 M diethylene

triamine pentaacetic acid. However, despite the recent keen interest for DES, this technology is still relatively new (**Figure 1B**) and far from ready for use in industrial processes. Similar to ILs, the thermal stability as well as long-term behavior of DES will have to be investigated in detail before this technology can be ready for applications beyond the laboratory scale.

Microfluidic devices.

As a general trend, an effort is made worldwide to design safer and more efficient hydrometallurgical processes with lower environmental impact. Within this context, a key approach is the intensification of the processes. A typical example in solvent extraction is the successive transitions from mixers-settlers to pulse columns and, more recently, to centrifuge extractors. The leading idea behind these technological transitions is to obtain higher mass transfer and smaller liquid-liquid contactors by increasing the surface/interface-to-volume ratios (**Figure 11**). A next technological leap is at reach with microfluidic and labs-on-chip devices.

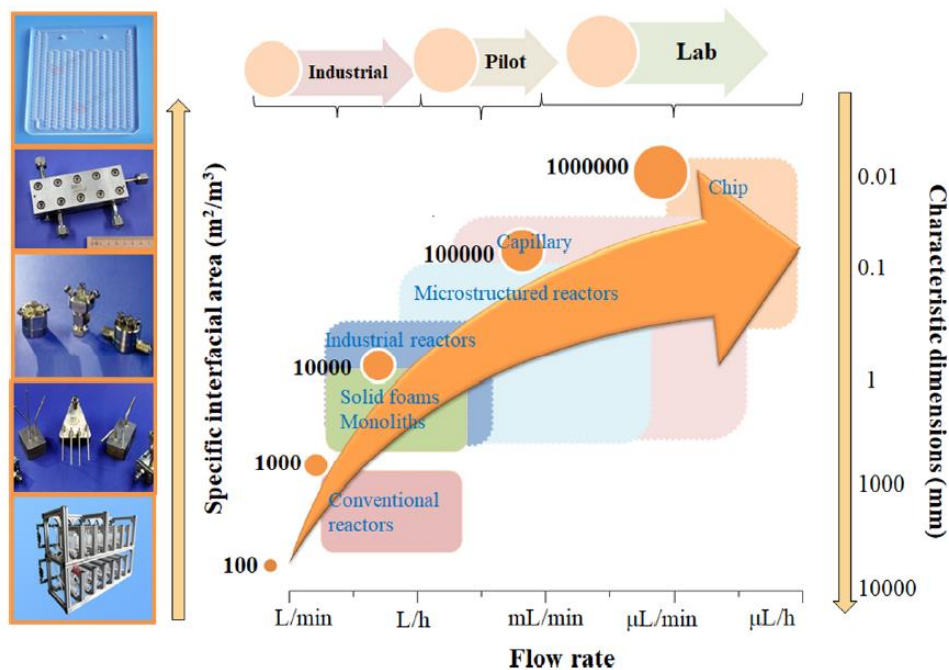


Figure 11. Comparison of different microreactors and conventional reactors (specific interfacial area, characteristic dimensions, and capacity ranges). From ref. ^[99], with permission. Copyright 2019 American Chemical Society.

Microfluidics refers to the manipulation of fluids at sub-millimeter scales, which exacerbates the surface forces compared to the volume forces. It should be pointed out that at the sub-millimeter scale (typically 1-100 μm) the behaviors are still mostly controlled by classical physics based on bulk solution chemistry, by opposition to what happens in nano-fluidics (typically 100 nm nanochannels) where specific fluid dynamic phenomena mainly driven by surface chemistry are predominant^[100]. Nano-fluidics is not relevant for hydrometallurgy and is therefore beyond the scope of the present article. Until now, most of the research dedicated to metal separation and recovery from feed solutions in micro-fluidic devices has been focused on liquid-liquid extraction^[101-104], however a few pioneering studies have also tentatively explored other unit operations of hydrometallurgy, such as precipitation^[105].

The primary advantages of operating at the sub-millimeter scale in microfluidic devices is the high surface-to-volume ratios that allow very fast heat and mass transfer, *i.e.*, rapid liquid-liquid extraction of the metal ions. **Figure 12** compares the volumetric mass transfer coefficients in different scaled contactors and unambiguously shows that the mass transfer rates in microflow extractors are 2 or 3 orders of magnitude higher than those in common extractors^[106]. In this regard, Kurniawan et al. have reported^[107] that complete Pb(II) extraction with N,N-diethylaminocarbonylmethoxy p-tertoctylcalix[4]arene derivative (EATOC) from 1.0 M HNO₃ was achieved in a droplet-based microfluidic reactor within 2 s, whereas 90 min are necessary to reach the equilibrium in batch. Advantages offered by microflow extractors are numerous: precise control of dispersion of one phase into the other one with subsequent well-characterized flow fields^[103, 104], easy on-line instrumentation to visualize flows and mass transfers (e.g., optical microscopes /digital cameras^[103, 104, 108], micro-Raman spectroscopy^[109]), possible intensification of liquid-liquid mass transfer by ultrasound irradiation^[110], reliable acquisition of kinetics data

otherwise difficult to obtain using the standard batch method^[111, 112], and possible enhancement of selectivity on a kinetic basis as a result of short residence times^[113].

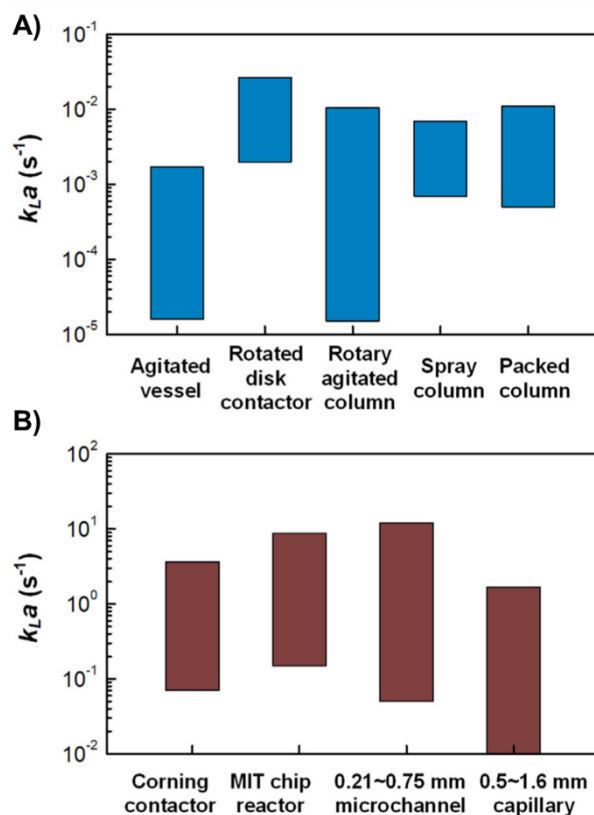


Figure 12. Volumetric mass transfer coefficients in different scaled contactors. **A)** Conventional liquid-liquid contactors; **B)** microflow extractors. From Wang and Luo^[106]. Copyright 2017, Elsevier.

Microfluidic reactors mostly exploit either stratified flows^[114] or segmented flows (droplet or slug flows)^[115, 116] generated with different types of junctions including T-junction, Y-junction, cross-shaped junction, cross flow T-junction, and concentric junction^[104]. These regimes depend on the relative flow rates of the two phases involved, their interaction at the interface and the wetting behavior on the wall of the microchannel. It should be pointed out that a given microsystem requires to be operated under specific hydrodynamic conditions to obtain/maintain appropriate flows as illustrated in **Figure 13**. For the ratio of the flowrates of aqueous and organic phases

$(Q_a/Q_o) > 1.18$, the droplets eventually coalesce, whereas for $Q_a/Q_o < 0.35$, no droplet are formed and back flow is observed in the to-be-dispersed phase^[115].

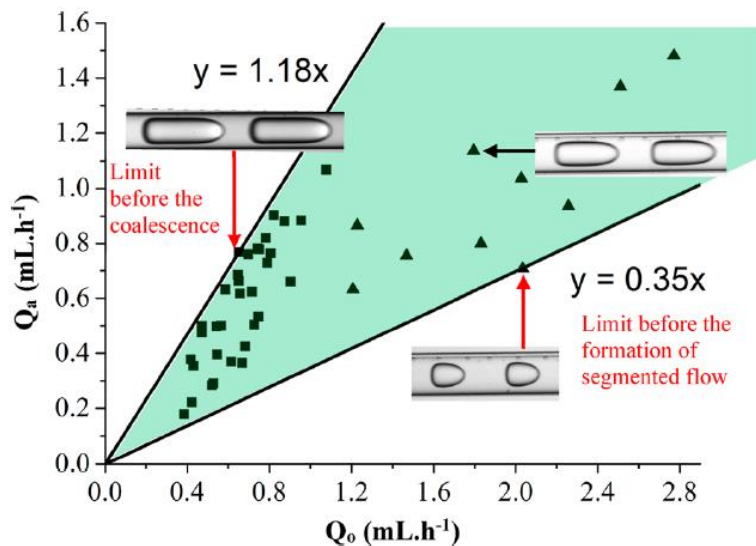


Figure 13. Domain of use (green area) of two T-junctions glass chips for the chemical system $[Eu(III)] = 10^{-2} M/[HNO_3] = 4 M / (\text{Dimethyl dibutyl tetradecyl malonamide}) = 1 M$ in n-dodecane. Squared symbols: Flow-rate couples reached within the T-junction chip with an extraction length of 27.8 cm. Triangular symbols: flow-rate couples reached within the T-junction chip with an extraction length of 1.125 cm. Reproduced with permission from ref. ^[115]. Copyright 2018 American Chemical Society.

In an attempt to expand the domain of application of microfluidic devices and increase the intensification of the separation processes, it has recently been proposed to take advantages of continuous flow membrane extraction with a 3D Printed Flat Sheet Supported Liquid Membrane (FS-SLM) to separate the feed and stripping channels of a microfluidic reactor ^[117]. The performance of such a microfluidic device was evaluated by quantifying uranium transport across a 15 v/v% tributyl phosphate (TBP) liquid membrane at flow rates between 5 and 60 $\mu\text{L}/\text{min}$. It was observed that the full recovery can be achieved in less than 10 min. By reducing the flowrate of the stripping solution, it was possible to increase the concentration in the sample. Several authors have reported studies on the liquid-liquid extraction, and sometimes the stripping, of metals in microfluidic devices. These studies clearly demonstrate that microfluidic reactors usually provide more efficient and more rapid extraction. Such observations often encourage the authors

to suggest the potential scale-up for applications at large scale, in particular in hydrometallurgy. However, such a leap from laboratory to industrial scale remains challenging from various points of view as discussed below.

The first point to consider for the potential implementation of microfluidics in industrial-scale hydrometallurgy, or even for the relatively small-scale production or recycling of high added-value metals (PGMs, REEs, Ta, radiometals, etc.) is that metals have to be recovered from volumes of leach solutions in the range of tens to hundreds of cubic meters. This necessarily implies to increase the overall output of the microfluidic devices to reach a total processing capacity compatible with an industrial production level. In principle, this can be obtained by deploying multiple microreactors in parallel or in stacks. However, the sheer number of microfluidic devices needed to reach the production level of classic hydrometallurgical processes still prevents their implementation in the industry. The adoption of microfluidics by industrials will likely start with the production of very high-value compounds or for analytical chemistry. For instance, Ahn et al. reported the production of about 31 g/hour of a commercial drug by copper catalysis with a numbering-up approach^[118]. With the same approach, Darekar et al.^[119] obtained a capacity of about 10 L/hour for the extraction of uranium(VI) from 1 M HNO₃ using 30% (v/v) tributyl phosphate (TBP) in dodecane and 20 parallel microbore tubes. Such results are encouraging, but the gap is still important to reach the throughput necessary for most metals produced via hydrometallurgy.

Another challenging aspect of microfluidics is the implementation of counter-current flowsheets. Indeed, most microreactors described in published studies are operated at co-current flows. In contrast, counter-current extractions are commonly used in chemical engineering as a method to increase the extraction efficiency. To overcome this difficulty, Kriel et al.^[120] have proposed to

assemble extraction chips in a counter-current circuit, but with co-current flow in each chip. More recently, Xie et al.^[121] have adopted an oscillating feedback microextractor to demonstrate how a co-current microextractor can be turned into a high-throughput counter-current microextractor. Here again, the transition between co-current to counter-current microreactors remains tantalizing and is not ready for industrial-scale processes. Potentially, the implementation of Flat Sheet Supported Liquid Membrane in microfluidic devices may allow for an easier operation in counter-current mode^[117]. In summary, microfluidic liquid-liquid extraction is a breakthrough technique for the recovery and separation of metals from various solutions, with convincing applications in the field of analysis, and possible implementation for on-line control of hydrometallurgical processes. On the opposite, its implementation as core technology for the primary production or recycling of metals is still challenging and further work is still needed for adoption of such technique at the industrial level.

Toward more sustainable processes.

The past few decades have seen a strong push to develop more sustainable hydrometallurgical processes, going from the use of less toxic chemicals to the advent of solvent-free solvent extraction methods, or the incorporation of biotechnologies in metal extraction processes. For example, the hydrometallurgy of niobium and tantalum is currently based on liquid-liquid extraction processes that operate with highly toxic fluoride media as the aqueous phase (typically HF or $\text{NH}_4\text{F} + \text{HNO}_3$) because Nb and Ta are insoluble in other mineral acids. The highly flammable extractant methylisobutyl ketone (MIBK) is also the gold standard in the current extraction processes for Nb and Ta, further increasing the environmental impact and operational risks. An alternative liquid-liquid extraction method that is fluoride-free has recently been proposed with notably the use of an alkaline solution as feed and an organic phase based on the extractant Aliquat 336.^[122–127] The alkaline route takes advantage of the formation of inorganic Nb

and Ta polyoxometalate ions, $H_xNb_6O_{19}^{x-8}$ and $H_xTa_6O_{19}^{x-8}$, and offers a greener approach contrasting with the harsh conditions of the current industrial processes.

Biomaterials could also be one solution for a more sustainable hydrometallurgy. Indeed, bio-based processes allow greener reagent production routes (e.g., bio cultures) and enable recovering metals from feedstocks that are too diluted to be economically processed via current hydrometallurgical techniques like liquid-liquid extraction. While bioleaching has been used for decades for the industrial-scale hydrometallurgy of copper, recent studies have showed promising results for the broader use of biomaterials (*i.e.*, biolixiviants, biosorbents, and bioextractants) in hydrometallurgy and extended its potential applications to other metals. A remarkable recent example is the development by Zhou et al. of a “super-uranyl-binding protein” (SUP) for extraction of uranium from seawater^[128]. This engineered protein has femtomolar affinity (Dissociation constant, K_d , of 7.4×10^{-15} M, at pH 8.9) for UO_2^{2+} and >10,000-fold selectivity over competing ions found in seawater, Na^+ , Ca^{2+} , Sr^{2+} , VO^{2+} , etc. Yuan et al. further modified the SUP protein to embed it into spidroin fibers, yielding selective and effective extraction of uranium from seawater at a capacity of ~12 mg U per g of sorbent^[129].

Similarly, the tensions in the REE sector could eventually be appeased by emerging bio-hydrometallurgical processes. Brewer et al.^[130, 131] recently developed microbead based on common and inoffensive microbes (*Escherichia coli* strain) that have been engineered to display lanthanide binding tags (short peptides with metal-binding moieties), allowing the selective recovery of REE from electronic waste (**Figure 14**). The use of biomaterials, like microbes, presents the unique advantage of unlocking the biological machinery to produce solid adsorbents, hence circumventing the tedious and non-sustainable production routes of the chemical extractants.

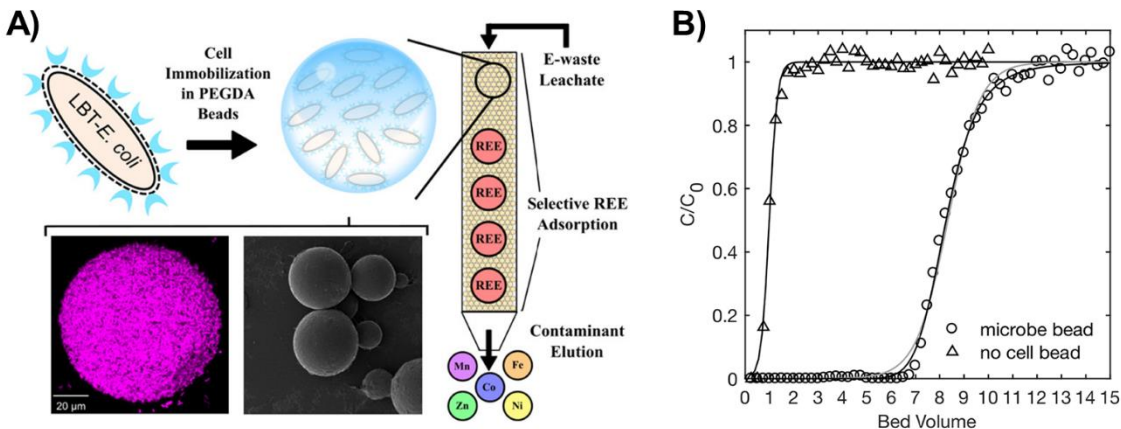


Figure 14. Biosorption process for REE extraction from secondary feedstocks such as electronic waste. **A)** General process strategy. **B)** Breakthrough curve for Nd with and without microbe-decorated microbeads. Adapted with permission from ref. ^[131]. Copyright 2019 American Chemical Society.

Even more recently, a natural protein that is particularly selective for REE, called “lanmodulin” (short for lanthanide-modulated protein), has been discovered by Cotruvo and co-workers^[132]. This small protein (only 12 kDa) has three binding pockets with picomolar affinity for the trivalent REE (K_d , of $\sim 1 \times 10^{-12}$ M, at pH 5.0) ions which is orders of magnitude stronger than any previously known biomacromolecular REE chelator. Lanmodulin also sustains acidic conditions^[133], complexing the REE³⁺ ions down to pH ~ 2.5 which is similar or better than manmade chelators like EDTA or DTPA. Additionally, lanmodulin exhibits exceptional selectivity for REE³⁺ ions over most competing ions (including Ca²⁺, Cu²⁺, Co²⁺, Ni²⁺, Zn²⁺, Al³⁺, etc.) allowing its use for the selective recovery of REE from electronic waste, or even from currently untapped sources like coal by-products (**Figure 15**)^[133]. Further development of this bio-based technology also recently led to column separations of REEs from non-REEs impurities, separations of REEs from one another, as well as the selective extraction of actinides for radiochemistry applications^[41, 134, 135].

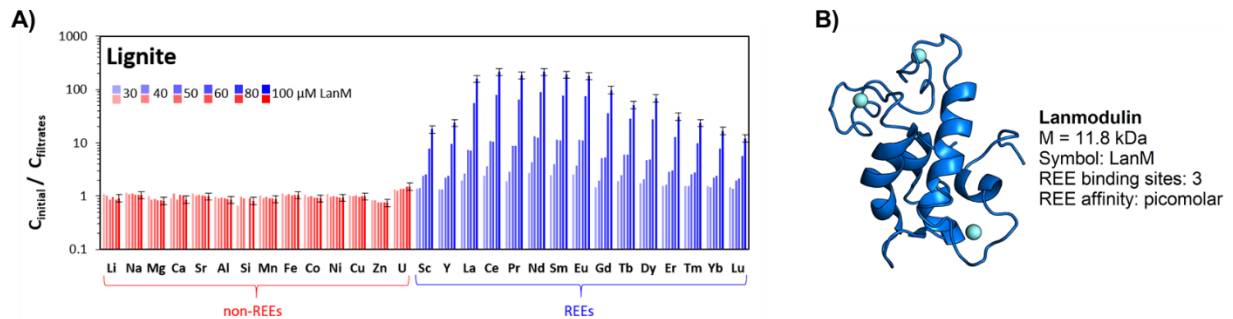


Figure 15. A) Lanmodulin-based selective recovery of REEs from coal leachate (Lignite). The concentration ratios between the initial lignite leachate solution and the filtrates are given. A ratio higher than 1 corresponds to an enrichment of the metal by the protein lanmodulin. **B)** Representation of lanmodulin (blue) bound to three REE ions (cyan). Adapted with permission from ref. ^[133]. Copyright 2020 American Chemical Society.

While bio-based technologies targeting critical metals like REE or uranium have only been developed recently and contrast with current chemical-based processes, external constraints such as the customer demand for more sustainable supply chains and fading natural resources will likely lead to a growing adoption of bio-based methods by the hydrometallurgy industry. Somehow similar to the microfluidic devices, the next challenge for the biohydrometallurgical methods will be to scale-up processes to meet the production goals of the industry. However, the development of new biohydrometallurgical methods for critical materials can build on the decades-long experience in the bioleaching processes and also on industrial-scale bioprocesses non-related to metal production. Hence, it seems likely that the adoption of biohydrometallurgical methods by the mining industry will be faster than that of microfluidic methods.

Outlook

Metal extraction and purification methods have continuously evolved to higher purity products, higher yields, and at a lower cost. However, decades of industrialization and growing consumption with little recycling created a situation where hydrometallurgists will have to refocus their efforts from concentrated natural resources to low-concentration deposits^[136] or urban feedstocks^[137] with high variability (in terms of valuable content, physicochemical form, nature, quantity of impurities,

etc.). The present and future generations of hydrometallurgists will also need to steer chemical-intensive processes toward more sustainable ones^[138, 139] since customers, brands, regulators, and investors, are more and more receptive to the way metals are extracted and produced before they enter the supply chain. Perhaps even more challenging is the question about the metals that will become critical in the short and long terms.^[140, 141] The recent innovative systems that emerged in the literature, such as microfluidic devices, biomaterials, new metal-binding chelators, ionic liquids, and deep eutectic solvents, could ease the difficulties related to our metal supply chains in the future. However, it is clear that these technologies need to be matured before industrial entities incorporate them in their business models. It is also evident that none of these solutions *alone* will replace the current hydrometallurgical processes in the near future. We posit that to address the challenges associated with the hydrometallurgical production of refined materials our best hope is to adopt a multi-prong approach combining, better utilization of natural resources, more efficient processes, substitution of critical metals by less critical ones (when possible), recycling, and a more responsible product consumption. Finally, given the sprawling influence of purified metals in our daily life, one could wonder if hydrometallurgy should be an integral part of the chemistry curriculum like other chemistry disciplines (organic chemistry, physical chemistry, inorganic chemistry, etc.). This last question remains open for debate.

References

- [1] Cheisson, T.; Schelter, E. J. Rare Earth Elements: Mendeleev's Bane, Modern Marvels. *Science*, **2019**, *363* (6426), 489–493. <https://doi.org/10.1126/science.aau7628>.
- [2] Graedel, T. E.; Barr, R.; Chandler, C.; Chase, T.; Choi, J.; Christoffersen, L.; Friedlander, E.; Henly, C.; Jun, C.; Nassar, N. T.; et al. Methodology of Metal Criticality Determination. *Environ. Sci. Technol.*, **2012**, *46* (2), 1063–1070. <https://doi.org/10.1021/es203534z>.
- [3] Graedel, T. E.; Harper, E. M.; Nassar, N. T.; Reck, B. K. On the Materials Basis of Modern Society. *PNAS*, **2015**, *112* (20), 6295–6300. <https://doi.org/10.1073/pnas.1312752110>.
- [4] Publications Office of the European. Study on the EU's list of critical raw materials (2020) : final report. <http://op.europa.eu/en/publication-detail/-/publication/c0d5292a-ee54-11ea-991b-01aa75ed71a1/language-en> (accessed Jun 6, 2021).

- [5] U.S. interior Department. *Final List of Critical Minerals 2018*; 83 FR 23295; Department of the Interior & Office of the Secretary, 2018; pp 23295–23296.
- [6] U.S. Geological Survey. Interior Releases 2018’s Final List of 35 Minerals Deemed Critical to U.S. National Security and the Economy <https://www.usgs.gov/news/interior-releases-2018-s-final-list-35-minerals-deemed-critical-us-national-security-and> (accessed Nov 7, 2021).
- [7] Fortier, S. M.; Nassar, N. T.; Lederer, G. W.; Brainard, J.; Gambogi, J.; McCullough, E. A. *Draft Critical Mineral List—Summary of Methodology and Background Information—U.S. Geological Survey Technical Input Document in Response to Secretarial Order No. 3359*; Open-File Report; USGS Numbered Series 2018–1021; U.S. Geological Survey: Reston, VA, 2018; p 26.
- [8] Nassar, N. T.; Fortier, S. M. *Methodology and Technical Input for the 2021 Review and Revision of the U.S. Critical Minerals List*; Open-File Report; USGS Numbered Series 2021–1045; U.S. Geological Survey: Reston, VA, 2021; p 31.
- [9] Government of Canada. Canada’s list of critical minerals 2021 <https://www.nrcan.gc.ca/our-natural-resources/minerals-mining/critical-minerals/23414> (accessed Nov 7, 2021).
- [10] *Mineral Commodity Summaries 2020*; Mineral Commodity Summaries; USGS Unnumbered Series; U.S. Geological Survey: Reston, VA, 2020; p 204.
- [11] Yan, W.; Wang, Z.; Cao, H.; Zhang, Y.; Sun, Z. Criticality Assessment of Metal Resources in China. *iScience*, **2021**, 24 (6), 102524. <https://doi.org/10.1016/j.isci.2021.102524>.
- [12] Gulley, A. L.; Nassar, N. T.; Xun, S. China, the United States, and Competition for Resources That Enable Emerging Technologies. *PNAS*, **2018**, 115 (16), 4111–4115. <https://doi.org/10.1073/pnas.1717152115>.
- [13] Mohr, S. H.; Mudd, G. M.; Giurco, D. Lithium Resources and Production: Critical Assessment and Global Projections. *Minerals*, **2012**, 2 (1), 65–84. <https://doi.org/10.3390/min2010065>.
- [14] Stanley, C. J.; Jones, G. C.; Rumsey, M. S.; Blake, C.; Roberts, A. C.; Stirling, J. A. R.; Carpenter, G. J. C.; Whitfield, P. S.; Grice, J. D.; Lepage, Y. Jadarite, LiNaSiB3O7(OH), a New Mineral Species from the Jadar Basin, Serbia. *ejm*, **2007**, 19 (4), 575–580. <https://doi.org/10.1127/0935-1221/2007/0019-1741>.
- [15] Chagnes, A. Chapter 5 - Lithium Battery Technologies: Electrolytes. In *Lithium Process Chemistry*; Chagnes, A., Światowska, J., Eds.; Elsevier: Amsterdam, 2015; pp 167–189. <https://doi.org/10.1016/B978-0-12-801417-2.00005-0>.
- [16] Fosu, A. Y.; Kanari, N.; Vaughan, J.; Chagnes, A. Literature Review and Thermodynamic Modelling of Roasting Processes for Lithium Extraction from Spodumene. *Metals*, **2020**, 10 (10), 1312. <https://doi.org/10.3390/met10101312>.
- [17] Gmar, S.; Chagnes, A. Recent Advances on Electrodialysis for the Recovery of Lithium from Primary and Secondary Resources. *Hydrometallurgy*, **2019**, 189, 105124. <https://doi.org/10.1016/j.hydromet.2019.105124>.
- [18] Boualleg, M.; BURDET, F. A. P.; SOULAIROL, R. C. J. R. Process for Preparing an Adsorbent Material in the Absence of Binder Comprising a Hydrothermal Treatment Step and Process for Extracting Lithium from Saline Solutions Using Said Material. WO2015162272A1, October 29, 2015.
- [19] Lipp, J. LISXTM A New SX Technology for Lithium Recovery. In *LISXTM A new SX Technology for Lithium Recovery*; Canadian Institute of Mining, Metallurgy and Petroleum, 2014; pp 395–402.
- [20] Cohen, L.; McCallum, T.; Tinkler, O.; Szolga, W. Technological Advances, Challenges and Opportunities in Solvent Extraction from Energy Storage Applications. In *Extraction 2018*; Davis, B. R., Moats, M. S., Wang, S., Gregurek, D., Kapusta, J., Battle, T. P., Schlesinger, M. E., Alvear Flores, G. R., Jak, E., Goodall, G., et al., Eds.; The Minerals, Metals & Materials Series; Springer International Publishing: Cham, 2018; pp 2033–2045. https://doi.org/10.1007/978-3-319-95022-8_170.

- [21] Processing of Used Nuclear Fuel - World Nuclear Association <https://world-nuclear.org/information-library/nuclear-fuel-cycle/fuel-recycling/processing-of-used-nuclear-fuel.aspx> (accessed Jun 5, 2021).
- [22] Lyseid Authen, T.; Adnet, J.-M.; Bourg, S.; Carrott, M.; Ekberg, C.; Galán, H.; Geist, A.; Guilbaud, P.; Miguiditchian, M.; Modolo, G.; et al. An Overview of Solvent Extraction Processes Developed in Europe for Advanced Nuclear Fuel Recycling, Part 2 — Homogeneous Recycling. *Separation Science and Technology*, **2021**, *0* (0), 1–21. <https://doi.org/10.1080/01496395.2021.2001531>.
- [23] Geist, A.; Adnet, J.-M.; Bourg, S.; Ekberg, C.; Galán, H.; Guilbaud, P.; Miguiditchian, M.; Modolo, G.; Rhodes, C.; Taylor, R. An Overview of Solvent Extraction Processes Developed in Europe for Advanced Nuclear Fuel Recycling, Part 1 — Heterogeneous Recycling. *Separation Science and Technology*, **2021**, *56* (11), 1866–1881. <https://doi.org/10.1080/01496395.2020.1795680>.
- [24] Baron, P.; Cornet, S. M.; Collins, E. D.; DeAngelis, G.; Del Cul, G.; Fedorov, Yu.; Glatz, J. P.; Ignatiev, V.; Inoue, T.; Khaperskaya, A.; et al. A Review of Separation Processes Proposed for Advanced Fuel Cycles Based on Technology Readiness Level Assessments. *Progress in Nuclear Energy*, **2019**, *117*, 103091. <https://doi.org/10.1016/j.pnucene.2019.103091>.
- [25] Despotopulos, J. D.; Gostic, J. M.; Bennett, M. E.; Gharibyan, N.; Henderson, R. A.; Moody, K. J.; Sudowe, R.; Shaughnessy, D. A. Characterization of Group 5 Dubnium Homologs on Diglycolamide Extraction Chromatography Resins from Nitric and Hydrofluoric Acid Matrices. *J Radioanal Nucl Chem*, **2015**, *303* (1), 485–494. <https://doi.org/10.1007/s10967-014-3398-1>.
- [26] Roberto, J. B.; Alexander, C. W.; Boll, R. A.; Burns, J. D.; Ezold, J. G.; Felker, L. K.; Hogle, S. L.; Rykaczewski, K. P. Actinide Targets for the Synthesis of Super-Heavy Elements. *Nuclear Physics A*, **2015**, *944*, 99–116. <https://doi.org/10.1016/j.nuclphysa.2015.06.009>.
- [27] Roberto, J. B.; Rykaczewski, K. P. Discovery of Element 117: Super-Heavy Elements and the “Island of Stability”*. *Separation Science and Technology*, **2018**, *53* (12), 1813–1819. <https://doi.org/10.1080/01496395.2017.1290658>.
- [28] Kostelnik, T. I.; Orvig, C. Radioactive Main Group and Rare Earth Metals for Imaging and Therapy. *Chemical Reviews*, **2019**, *119* (2), 902–956. <https://doi.org/10.1021/acs.chemrev.8b00294>.
- [29] Boros, E.; Packard, A. B. Radioactive Transition Metals for Imaging and Therapy. *Chem. Rev.*, **2019**, *119* (2), 870–901. <https://doi.org/10.1021/acs.chemrev.8b00281>.
- [30] Robertson, A. K. H.; McNeil, B. L.; Yang, H.; Gendron, D.; Perron, R.; Radchenko, V.; Zeisler, S.; Causey, P.; Schaffer, P. 232Th-Spallation-Produced 225Ac with Reduced 227Ac Content. *Inorg. Chem.*, **2020**, *59* (17), 12156–12165. <https://doi.org/10.1021/acs.inorgchem.0c01081>.
- [31] Brasse, D.; Nonat, A. Radiometals: Towards a New Success Story in Nuclear Imaging? *Dalton Trans.*, **2015**, *44* (11), 4845–4858. <https://doi.org/10.1039/C4DT02911A>.
- [32] Kratochwil, C.; Bruchertseifer, F.; Giesel, F. L.; Weis, M.; Verburg, F. A.; Mottaghy, F.; Kopka, K.; Apostolidis, C.; Haberkorn, U.; Morgenstern, A. 225Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer. *J Nucl Med*, **2016**, *57* (12), 1941–1944. <https://doi.org/10.2967/jnumed.116.178673>.
- [33] Radchenko, V.; Engle, J. W.; Wilson, J. J.; Maassen, J. R.; Nortier, F. M.; Taylor, W. A.; Birnbaum, E. R.; Hudston, L. A.; John, K. D.; Fassbender, M. E. Application of Ion Exchange and Extraction Chromatography to the Separation of Actinium from Proton-Irradiated Thorium Metal for Analytical Purposes. *Journal of Chromatography A*, **2015**, *1380*, 55–63. <https://doi.org/10.1016/j.chroma.2014.12.045>.
- [34] Boll, R. A.; Malkemus, D.; Mirzadeh, S. Production of Actinium-225 for Alpha Particle Mediated Radioimmunotherapy. *Applied Radiation and Isotopes*, **2005**, *62* (5), 667–679. <https://doi.org/10.1016/j.apradiso.2004.12.003>.
- [35] Borchardt, P. E.; Yuan, R. R.; Miederer, M.; McDevitt, M. R.; Scheinberg, D. A. Targeted Actinium-225 in Vivo Generators for Therapy of Ovarian Cancer. *Cancer Res*, **2003**, *63* (16), 5084–5090.

- [36] Grimm, T.; Grimm, A.; Peters, W.; Zamiara, M. High-Purity Actinium-225 Production from Radium-226 Using a Superconducting Electron Linac. *Journal of Medical Imaging and Radiation Sciences*, **2019**, *50* (1), S12–S13. <https://doi.org/10.1016/j.jmir.2019.03.040>.
- [37] Stein, B. W.; Morgenstern, A.; Batista, E. R.; Birnbaum, E. R.; Bone, S. E.; Cary, S. K.; Ferrier, M. G.; John, K. D.; Pacheco, J. L.; Kozimor, S. A.; et al. Advancing Chelation Chemistry for Actinium and Other +3 F-Elements, Am, Cm, and La. *J. Am. Chem. Soc.*, **2019**, *141* (49), 19404–19414. <https://doi.org/10.1021/jacs.9b10354>.
- [38] Abou, D. S.; Pickett, J.; Mattson, J. E.; Thorek, D. L. J. A Radium-223 Microgenerator from Cyclotron-Produced Trace Actinium-227. *Applied Radiation and Isotopes*, **2017**, *119*, 36–42. <https://doi.org/10.1016/j.apradiso.2016.10.015>.
- [39] Deblonde, G. J.-P.; Zavarin, M.; Kersting, A. B. The Coordination Properties and Ionic Radius of Actinium: A 120-Year-Old Enigma. *Coordination Chemistry Reviews*, **2021**, *446*, 214130. <https://doi.org/10.1016/j.ccr.2021.214130>.
- [40] Aldrich, K. E.; Lam, M. N.; Eiroa-Lledo, C.; Kozimor, S. A.; Lilley, L. M.; Mocko, V.; Stein, B. W. Preparation of an Actinium-228 Generator. *Inorg. Chem.*, **2020**, *59* (5), 3200–3206. <https://doi.org/10.1021/acs.inorgchem.9b03563>.
- [41] Deblonde, G. J.-P.; Mattocks, J. A.; Dong, Z.; Woody, P. T.; Cotruvo, J. A.; Zavarin, M. Capturing an Elusive but Critical Element: Natural Protein Enables Actinium Chemistry. *Science Advances*, **2021**, *7* (43), eabk0273. <https://doi.org/10.1126/sciadv.abk0273>.
- [42] Ferrier, M. G.; Batista, E. R.; Berg, J. M.; Birnbaum, E. R.; Cross, J. N.; Engle, J. W.; Pierre, H. S. L.; Kozimor, S. A.; Pacheco, J. S. L.; Stein, B. W.; et al. Spectroscopic and Computational Investigation of Actinium Coordination Chemistry. *Nat Commun*, **2016**, *7* (1), 1–8. <https://doi.org/10.1038/ncomms12312>.
- [43] Ferrier, M. G.; Stein, B. W.; Batista, E. R.; Berg, J. M.; Birnbaum, E. R.; Engle, J. W.; John, K. D.; Kozimor, S. A.; Lezama Pacheco, J. S.; Redman, L. N. Synthesis and Characterization of the Actinium Aquo Ion. *ACS Cent. Sci.*, **2017**, *3* (3), 176–185. <https://doi.org/10.1021/acscentsci.6b00356>.
- [44] Li, L.; Rousseau, J.; Jaraquemada-Peláez, M. de G.; Wang, X.; Robertson, A.; Radchenko, V.; Schaffer, P.; Lin, K.-S.; Bénard, F.; Orvig, C. 225Ac-H4py4pa for Targeted Alpha Therapy. *Bioconjugate Chem.*, **2021**, *32* (7), 1348–1363. <https://doi.org/10.1021/acs.bioconjchem.0c00171>.
- [45] Akcil, A.; Sun, Z.; Panda, S. COVID-19 Disruptions to Tech-Metals Supply Are a Wake-up Call. *Nature*, **2020**, *587* (7834), 365–367. <https://doi.org/10.1038/d41586-020-03190-8>.
- [46] Cote, G. Extraction liquide-liquide - Définition du procédé – Réactifs industriels. *Opérations unitaires. Génie de la réaction chimique*, **2016**. <https://doi.org/10.51257/a-v2-j2762>.
- [47] Stamberg, D.; Healy, M. R.; Bryantsev, V. S.; Albisser, C.; Karslyan, Y.; Reinhart, B.; Paulenova, A.; Foster, M.; Popovs, I.; Lyon, K.; et al. Structure Activity Relationship Approach toward the Improved Separation of Rare-Earth Elements Using Diglycolamides. *Inorg. Chem.*, **2020**, *59* (23), 17620–17630. <https://doi.org/10.1021/acs.inorgchem.0c02861>.
- [48] Turgis, R.; Leydier, A.; Arrachart, G.; Burdet, F.; Dourdain, S.; Bernier, G.; Miguiditchian, M.; Pellet-Rostaing, S. Carbamoylalkylphosphonates for Dramatic Enhancement of Uranium Extraction from Phosphates Ores. *Solvent Extraction and Ion Exchange*, **2014**, *32* (7), 685–702. <https://doi.org/10.1080/07366299.2014.951279>.
- [49] Chen, B.; He, M.; Zhang, H.; Jiang, Z.; Hu, B. Chromatographic Techniques for Rare Earth Elements Analysis. *Physical Sciences Reviews*, **2017**, *2* (4), 20160057. <https://doi.org/10.1515/psr-2016-0057>.

- [50] Lundberg, D.; Persson, I. The Size of Actinoid(III) Ions – Structural Analysis vs. Common Misinterpretations. *Coordination Chemistry Reviews*, **2016**, *318*, 131–134. <https://doi.org/10.1016/j.ccr.2016.04.003>.
- [51] Heres, X.; Baron, P. Increase in the Separation Factor between Americium and Curium and/or between Lanthanides in a Liquid-Liquid Extraction Process. WO2011012579A1, February 3, 2011.
- [52] Vanel, V.; Berthon, L.; Miguiditchian, J. M. M.; Burdet, F. Modelling of Americium Stripping in the EXAm Process. *Procedia Chemistry*, **2012**, *7*, 404–410. <https://doi.org/10.1016/j.proche.2012.10.063>.
- [53] Chapron, S.; Marie, C.; Arrachart, G.; Miguiditchian, M.; Pellet-Rostaing, S. New Insight into the Americium/Curium Separation by Solvent Extraction Using Diglycolamides. *Solvent Extraction and Ion Exchange*, **2015**, *33* (3), 236–248. <https://doi.org/10.1080/07366299.2014.1000792>.
- [54] Chapron, S.; Marie, C.; Pacary, V.; Duchesne, M.-T.; Arrachart, G.; Pellet-Rostaing, S.; Miguiditchian, M. Separation of Americium by Liquid-Liquid Extraction Using Diglycolamides Water-Soluble Complexing Agents. *Procedia Chemistry*, **2016**, *21*, 133–139. <https://doi.org/10.1016/j.proche.2016.10.019>.
- [55] Vanel, V.; Bollesteros, M.-J.; Marie, C.; Montuir, M.; Pacary, V.; Antégnard, F.; Costenoble, S.; Boyer-Deslys, V. Consolidation of the EXAm Process: Towards the Reprocessing of a Concentrated PUREX Raffinate. *Procedia Chemistry*, **2016**, *21*, 190–197. <https://doi.org/10.1016/j.proche.2016.10.027>.
- [56] Miguiditchian, M.; Vanel, V.; Marie, C.; Pacary, V.; Charbonnel, M.-C.; Berthon, L.; Hérès, X.; Montuir, M.; Sorel, C.; Bollesteros, M.-J.; et al. Americium Recovery from Highly Active PUREX Raffinate by Solvent Extraction: The EXAm Process. A Review of 10 Years of R&D. *Solvent Extraction and Ion Exchange*, **2020**, *38* (4), 365–387. <https://doi.org/10.1080/07366299.2020.1753922>.
- [57] Rostaing, C.; Poinssot, C.; Warin, D.; Baron, P.; Lorraina, B. Development and Validation of the EXAm Separation Process for Single Am Recycling. *Procedia Chemistry*, **2012**, *7*, 367–373. <https://doi.org/10.1016/j.proche.2012.10.057>.
- [58] Bollesteros, M.-J.; Calor, J.-N.; Costenoble, S.; Montuir, M.; Pacary, V.; Sorel, C.; Burdet, F.; Espinoux, D.; Hérès, X.; Eysseric, C. Implementation of Americium Separation from a PUREX Raffinate. *Procedia Chemistry*, **2012**, *7*, 178–183. <https://doi.org/10.1016/j.proche.2012.10.030>.
- [59] Jensen, M. P.; Chiarizia, R.; Shkrob, I. A.; Ulicki, J. S.; Spindler, B. D.; Murphy, D. J.; Hossain, M.; Roca-Sabio, A.; Platas-Iglesias, C.; de Blas, A.; et al. Aqueous Complexes for Efficient Size-Based Separation of Americium from Curium. *Inorg. Chem.*, **2014**, *53* (12), 6003–6012. <https://doi.org/10.1021/ic500244p>.
- [60] Hu, A.; MacMillan, S. N.; Wilson, J. J. Macrocyclic Ligands with an Unprecedented Size-Selectivity Pattern for the Lanthanide Ions. *J. Am. Chem. Soc.*, **2020**, *142* (31), 13500–13506. <https://doi.org/10.1021/jacs.0c05217>.
- [61] Thiele, N. A.; Fiszbein, D. J.; Woods, J. J.; Wilson, J. J. Tuning the Separation of Light Lanthanides Using a Reverse-Size Selective Aqueous Complexant. *Inorg. Chem.*, **2020**, *59* (22), 16522–16530. <https://doi.org/10.1021/acs.inorgchem.0c02413>.
- [62] Grimes, T. S.; Heathman, C. R.; Jansone-Popova, S.; Ivanov, A. S.; Roy, S.; Bryantsev, V. S.; Zalupski, P. R. Influence of a Heterocyclic Nitrogen-Donor Group on the Coordination of Trivalent Actinides and Lanthanides by Aminopolycarboxylate Complexants. *Inorg. Chem.*, **2018**, *57* (3), 1373–1385. <https://doi.org/10.1021/acs.inorgchem.7b02792>.
- [63] Grimes, T. S.; Heathman, C. R.; Jansone-Popova, S.; Bryantsev, V. S.; Goverapet Srinivasan, S.; Nakase, M.; Zalupski, P. R. Thermodynamic, Spectroscopic, and Computational Studies of f-Element Complexation by N-Hydroxyethyl-Diethylenetriamine-N,N',N'',N''-Tetraacetic Acid. *Inorg. Chem.*, **2017**, *56* (3), 1722–1733. <https://doi.org/10.1021/acs.inorgchem.6b02897>.

- [64] Shannon, R. D. Revised Effective Ionic Radii and Systematic Studies of Interatomic Distances in Halides and Chalcogenides. *Acta crystallographica*, **1976**, *A32*, 751–767.
- [65] McDevitt, M. R.; Thorek, D. L. J.; Hashimoto, T.; Gondo, T.; Veach, D. R.; Sharma, S. K.; Kalidindi, T. M.; Abou, D. S.; Watson, P. A.; Beattie, B. J.; et al. Feed-Forward Alpha Particle Radiotherapy Ablates Androgen Receptor-Addicted Prostate Cancer. *Nat Commun*, **2018**, *9* (1), 1–11. <https://doi.org/10.1038/s41467-018-04107-w>.
- [66] Thiele, N. A.; Brown, V.; Kelly, J. M.; Amor-Coarasa, A.; Jermilova, U.; MacMillan, S. N.; Nikolopoulou, A.; Ponnala, S.; Ramogida, C. F.; Robertson, A. K. H.; et al. An Eighteen-Membered Macrocyclic Ligand for Actinium-225 Targeted Alpha Therapy. *Angewandte Chemie International Edition*, **2017**, *56* (46), 14712–14717. <https://doi.org/10.1002/anie.201709532>.
- [67] Deblonde, G. J.-P.; Ricano, A.; Abergel, R. J. Ultra-Selective Ligand-Driven Separation of Strategic Actinides. *Nat Commun*, **2019**, *10* (1), 2438. <https://doi.org/10.1038/s41467-019-10240-x>.
- [68] Deblonde, G. J.-P.; Sturzbecher-Hoehne, M.; Rupert, P. B.; An, D. D.; Illy, M.-C.; Ralston, C. Y.; Brabec, J.; de Jong, W. A.; Strong, R. K.; Abergel, R. J. Chelation and Stabilization of Berkelium in Oxidation State +IV. *Nature Chemistry*, **2017**, *9* (9), 843–849. <https://doi.org/10.1038/nchem.2759>.
- [69] Deblonde, G. J.-P.; Lohrey, T. D.; Abergel, R. J. Inducing Selectivity and Chirality in Group IV Metal Coordination with High-Denticity Hydroxypyridinones. *Dalton Trans.*, **2019**, *48* (23), 8238–8247. <https://doi.org/10.1039/C9DT01031A>.
- [70] Nelson, J. J. M.; Cheisson, T.; Rugh, H. J.; Gau, M. R.; Carroll, P. J.; Schelter, E. J. High-Throughput Screening for Discovery of Benchtop Separations Systems for Selected Rare Earth Elements. *Commun Chem*, **2020**, *3* (1), 1–6. <https://doi.org/10.1038/s42004-019-0253-x>.
- [71] Bogart, J. A.; Cole, B. E.; Boreen, M. A.; Lippincott, C. A.; Manor, B. C.; Carroll, P. J.; Schelter, E. J. Accomplishing Simple, Solubility-Based Separations of Rare Earth Elements with Complexes Bearing Size-Sensitive Molecular Apertures. *PNAS*, **2016**, *113* (52), 14887–14892. <https://doi.org/10.1073/pnas.1612628113>.
- [72] Bogart, J. A.; Lippincott, C. A.; Carroll, P. J.; Schelter, E. J. An Operationally Simple Method for Separating the Rare-Earth Elements Neodymium and Dysprosium. *Angewandte Chemie International Edition*, **2015**, *54* (28), 8222–8225. <https://doi.org/10.1002/anie.201501659>.
- [73] Higgins, R. F.; Cheisson, T.; Cole, B. E.; Manor, B. C.; Carroll, P. J.; Schelter, E. J. Magnetic Field Directed Rare-Earth Separations. *Angewandte Chemie International Edition*, **2020**, *59* (5), 1851–1856. <https://doi.org/10.1002/anie.201911606>.
- [74] Wongsawa, T.; Traiwongsa, N.; Pancharoen, U.; Nootong, K. A Review of the Recovery of Precious Metals Using Ionic Liquid Extractants in Hydrometallurgical Processes. *Hydrometallurgy*, **2020**, *198*, 105488. <https://doi.org/10.1016/j.hydromet.2020.105488>.
- [75] Wang, L. Y.; Guo, Q. J.; Lee, M. S. Recent Advances in Metal Extraction Improvement: Mixture Systems Consisting of Ionic Liquid and Molecular Extractant. *Separation and Purification Technology*, **2019**, *210*, 292–303. <https://doi.org/10.1016/j.seppur.2018.08.016>.
- [76] Prusty, S.; Pradhan, S.; Mishra, S. Ionic Liquid as an Emerging Alternative for the Separation and Recovery of Nd, Sm and Eu Using Solvent Extraction Technique-A Review. *Sustainable Chemistry and Pharmacy*, **2021**, *21*, 100434. <https://doi.org/10.1016/j.scp.2021.100434>.
- [77] Dietz, M. L. Ionic Liquids as Extraction Solvents: Where Do We Stand? *null*, **2006**, *41* (10), 2047–2063. <https://doi.org/10.1080/01496390600743144>.
- [78] Costa, A. J. L.; Soromenho, M. R. C.; Shimizu, K.; Marrucho, I. M.; Esperança, J. M. S. S.; Lopes, J. N. C.; Rebelo, L. P. N. Density, Thermal Expansion and Viscosity of Cholinium-Derived Ionic Liquids. *ChemPhysChem*, **2012**, *13* (7), 1902–1909. <https://doi.org/10.1002/cphc.201100852>.

- [79] Wang, X.; Ohlin, C. A.; Lu, Q.; Fei, Z.; Hu, J.; Dyson, P. J. Cytotoxicity of Ionic Liquids and Precursor Compounds towards Human Cell Line HeLa. *Green Chem.*, **2007**, *9* (11), 1191–1197. <https://doi.org/10.1039/B704503D>.
- [80] Cao, Y.; Mu, T. Comprehensive Investigation on the Thermal Stability of 66 Ionic Liquids by Thermogravimetric Analysis. *Ind. Eng. Chem. Res.*, **2014**, *53* (20), 8651–8664. <https://doi.org/10.1021/ie5009597>.
- [81] Wang, B.; Qin, L.; Mu, T.; Xue, Z.; Gao, G. Are Ionic Liquids Chemically Stable? *Chem. Rev.*, **2017**, *117* (10), 7113–7131. <https://doi.org/10.1021/acs.chemrev.6b00594>.
- [82] Xue, Z.; Qin, L.; Jiang, J.; Mu, T.; Gao, G. Thermal, Electrochemical and Radiolytic Stabilities of Ionic Liquids. *Phys. Chem. Chem. Phys.*, **2018**, *20* (13), 8382–8402. <https://doi.org/10.1039/C7CP07483B>.
- [83] Matsumiya, M. Electrodeposition of Rare Earth Metal in Ionic Liquids. In *Application of Ionic Liquids on Rare Earth Green Separation and Utilization*; Chen, J., Ed.; Green Chemistry and Sustainable Technology; Springer: Berlin, Heidelberg, 2016; pp 117–153. https://doi.org/10.1007/978-3-662-47510-2_6.
- [84] Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel Solvent Properties of Choline Chloride/Urea Mixtures. *Chem. Commun.*, **2003**, No. 1, 70–71. <https://doi.org/10.1039/B210714G>.
- [85] Hammond, O. S.; Bowron, D. T.; Edler, K. J. Liquid Structure of the Choline Chloride-Urea Deep Eutectic Solvent (Reline) from Neutron Diffraction and Atomistic Modelling. *Green Chem.*, **2016**, *18* (9), 2736–2744. <https://doi.org/10.1039/C5GC02914G>.
- [86] Zhang, Q.; Vigier, K. D. O.; Royer, S.; Jérôme, F. Deep Eutectic Solvents: Syntheses, Properties and Applications. *Chem. Soc. Rev.*, **2012**, *41* (21), 7108–7146. <https://doi.org/10.1039/C2CS35178A>.
- [87] Bahadori, L.; Chakrabarti, M. H.; Mjalli, F. S.; AlNashef, I. M.; Manan, N. S. A.; Hashim, M. A. Physicochemical Properties of Ammonium-Based Deep Eutectic Solvents and Their Electrochemical Evaluation Using Organometallic Reference Redox Systems. *Electrochimica Acta*, **2013**, *113*, 205–211. <https://doi.org/10.1016/j.electacta.2013.09.102>.
- [88] Jenkin, G. R. T.; Al-Bassam, A. Z. M.; Harris, R. C.; Abbott, A. P.; Smith, D. J.; Holwell, D. A.; Chapman, R. J.; Stanley, C. J. The Application of Deep Eutectic Solvent Ionic Liquids for Environmentally-Friendly Dissolution and Recovery of Precious Metals. *Minerals Engineering*, **2016**, *87*, 18–24. <https://doi.org/10.1016/j.mineng.2015.09.026>.
- [89] Anggara, S.; Bevan, F.; Harris, R. C.; Hartley, J. M.; Frisch, G.; Jenkin, G. R. T.; Abbott, A. P. Direct Extraction of Copper from Copper Sulfide Minerals Using Deep Eutectic Solvents. *Green Chem.*, **2019**, *21* (23), 6502–6512. <https://doi.org/10.1039/C9GC03213D>.
- [90] Pateli, I. M.; Abbott, A. P.; Jenkin, G. R. T.; Hartley, J. M. Electrochemical Oxidation as Alternative for Dissolution of Metal Oxides in Deep Eutectic Solvents. *Green Chem.*, **2020**, *22* (23), 8360–8368. <https://doi.org/10.1039/D0GC03491F>.
- [91] Abbott, A. P.; Ballantyne, A.; Harris, R. C.; Juma, J. A.; Ryder, K. S. Bright Metal Coatings from Sustainable Electrolytes: The Effect of Molecular Additives on Electrodeposition of Nickel from a Deep Eutectic Solvent. *Phys. Chem. Chem. Phys.*, **2017**, *19* (4), 3219–3231. <https://doi.org/10.1039/C6CP08720E>.
- [92] Alesary, H. F.; Cihangir, S.; Ballantyne, A. D.; Harris, R. C.; Weston, D. P.; Abbott, A. P.; Ryder, K. S. Influence of Additives on the Electrodeposition of Zinc from a Deep Eutectic Solvent. *Electrochimica Acta*, **2019**, *304*, 118–130. <https://doi.org/10.1016/j.electacta.2019.02.090>.
- [93] Alesary, H. F.; Ismail, H. K.; Shiltagh, N. M.; Alattar, R. A.; Ahmed, L. M.; Watkins, M. J.; Ryder, K. S. Effects of Additives on the Electrodeposition of ZnSn Alloys from Choline Chloride/Ethylene Glycol-Based Deep Eutectic Solvent. *Journal of Electroanalytical Chemistry*, **2020**, *874*, 114517. <https://doi.org/10.1016/j.jelechem.2020.114517>.

- [94] Osch, D. J. G. P. van; Zubeir, L. F.; Bruinhorst, A. van den; Rocha, M. A. A.; Kroon, M. C. Hydrophobic Deep Eutectic Solvents as Water-Immiscible Extractants. *Green Chem.*, **2015**, *17* (9), 4518–4521. <https://doi.org/10.1039/C5GC01451D>.
- [95] Zante, G.; Boltoeva, M. Review on Hydrometallurgical Recovery of Metals with Deep Eutectic Solvents. *Sustainable Chemistry*, **2020**, *1* (3), 238–255. <https://doi.org/10.3390/suschem1030016>.
- [96] Dwamena, A. K. Recent Advances in Hydrophobic Deep Eutectic Solvents for Extraction. *Separations*, **2019**, *6* (1), 9. <https://doi.org/10.3390/separations6010009>.
- [97] Tereshatov, E. E.; Boltoeva, M. Y.; Folden, C. M. First Evidence of Metal Transfer into Hydrophobic Deep Eutectic and Low-Transition-Temperature Mixtures: Indium Extraction from Hydrochloric and Oxalic Acids. *Green Chem.*, **2016**, *18* (17), 4616–4622. <https://doi.org/10.1039/C5GC03080C>.
- [98] Volia, M. F.; Tereshatov, E. E.; Boltoeva, M.; Folden, C. M. Indium and Thallium Extraction into Betainium Bis(Trifluoromethylsulfonyl)Imide Ionic Liquid from Aqueous Hydrochloric Acid Media. *New J. Chem.*, **2020**, *44* (6), 2527–2537. <https://doi.org/10.1039/C9NJ04879K>.
- [99] He, Y.; Guo, S.; Chen, K.; Li, S.; Zhang, L.; Yin, S. Sustainable Green Production: A Review of Recent Development on Rare Earths Extraction and Separation Using Microreactors. *ACS Sustainable Chem. Eng.*, **2019**, *7* (21), 17616–17626. <https://doi.org/10.1021/acssuschemeng.9b03384>.
- [100] Zhong, J.; Alibakhshi, M. A.; Xie, Q.; Riordon, J.; Xu, Y.; Duan, C.; Sinton, D. Exploring Anomalous Fluid Behavior at the Nanoscale: Direct Visualization and Quantification via Nanofluidic Devices. *Acc. Chem. Res.*, **2020**, *53* (2), 347–357. <https://doi.org/10.1021/acs.accounts.9b00411>.
- [101] Santana, H. S.; Silva, J. L.; Aghel, B.; Ortega-Casanova, J. Review on Microfluidic Device Applications for Fluids Separation and Water Treatment Processes. *SN Appl. Sci.*, **2020**, *2* (3), 395. <https://doi.org/10.1007/s42452-020-2176-7>.
- [102] Maurice, A.; Theisen, J.; Gabriel, J.-C. P. Microfluidic Lab-on-Chip Advances for Liquid–Liquid Extraction Process Studies. *Current Opinion in Colloid & Interface Science*, **2020**, *46*, 20–35. <https://doi.org/10.1016/j.cocis.2020.03.001>.
- [103] Angeli, P.; Ortega, E. G.; Tsaoulidis, D.; Earle, M. Intensified Liquid-Liquid Extraction Technologies in Small Channels: A Review. *Johnson Matthey Technology Review*, **2019**, *63* (4), 299–310. <https://doi.org/10.1595/205651319X15669171624235>.
- [104] Sattari-Najafabadi, M.; Nasr Esfahany, M.; Wu, Z.; Sunden, B. Mass Transfer between Phases in Microchannels: A Review. *Chemical Engineering and Processing - Process Intensification*, **2018**, *127*, 213–237. <https://doi.org/10.1016/j.cep.2018.03.012>.
- [105] Sen, N.; Darekar, M.; Sirsat, P.; Singh, K. K.; Mukhopadhyay, S.; Shirsath, S. R.; Shenoy, K. T. Recovery of Uranium from Lean Streams by Extraction and Direct Precipitation in Microchannels. *Separation and Purification Technology*, **2019**, *227*, 115641. <https://doi.org/10.1016/j.seppur.2019.05.083>.
- [106] Wang, K.; Luo, G. Microflow Extraction: A Review of Recent Development. *Chemical Engineering Science*, **2017**, *169*, 18–33. <https://doi.org/10.1016/j.ces.2016.10.025>.
- [107] Kurniawan, Y. S.; Sathuluri, R. R.; Iwasaki, W.; Morisada, S.; Kawakita, H.; Ohto, K.; Miyazaki, M.; Jumina. Microfluidic Reactor for Pb(II) Ion Extraction and Removal with an Amide Derivative of Calix[4]Arene Supported by Spectroscopic Studies. *Microchemical Journal*, **2018**, *142*, 377–384. <https://doi.org/10.1016/j.microc.2018.07.001>.
- [108] Ciceri, D.; Perera, J. M.; Stevens, G. W. The Use of Microfluidic Devices in Solvent Extraction. *Journal of Chemical Technology & Biotechnology*, **2014**, *89* (6), 771–786. <https://doi.org/10.1002/jctb.4318>.
- [109] Nelson, G. L.; Asmussen, S. E.; Lines, A. M.; Casella, A. J.; Bottenus, D. R.; Clark, S. B.; Bryan, S. A. Micro-Raman Technology to Interrogate Two-Phase Extraction on a Microfluidic Device. *Anal. Chem.*, **2018**, *90* (14), 8345–8353. <https://doi.org/10.1021/acs.analchem.7b04330>.

- [110] Rahimi, M.; Jafari, O.; Mohammdifar, A. Intensification of Liquid-Liquid Mass Transfer in Micromixer Assisted by Ultrasound Irradiation and Fe₃O₄ Nanoparticles. *Chemical Engineering and Processing: Process Intensification*, **2017**, *111*, 79–88. <https://doi.org/10.1016/j.cep.2016.11.003>.
- [111] Corne, F.; Lélías, A.; Magnaldo, A.; Sorel, C.; Raimondi, N. D. M.; Prat, L. Experimental Methodology for Kinetic Acquisitions Using High Velocities in a Microfluidic Device. *Chemical Engineering & Technology*, **2019**, *42* (10), 2223–2230. <https://doi.org/10.1002/ceat.201900111>.
- [112] Nakajima, N.; Yamada, M.; Kakegawa, S.; Seki, M. Microfluidic System Enabling Multistep Tuning of Extraction Time Periods for Kinetic Analysis of Droplet-Based Liquid-Liquid Extraction. *Anal. Chem.*, **2016**, *88* (11), 5637–5643. <https://doi.org/10.1021/acs.analchem.6b00176>.
- [113] Liu, X.; Li, X.; Ju, S.; Gu, Y.; Tan, W.; Li, X.; Wang, S. Miniaturized Application of 3D-Printed Large-Flow Microreactor in Extraction and Separation of Platinum, Palladium and Rhodium. *Journal of Chemical Technology & Biotechnology*, **2021**, *96* (4), 1007–1015. <https://doi.org/10.1002/jctb.6611>.
- [114] Hellé, G.; Mariet, C.; Cote, G. Liquid-Liquid Microflow Patterns and Mass Transfer of Radionuclides in the Systems Eu(III)/HNO₃/DMDBTMA and U(VI)/HCl/Alquat® 336. *Microfluid Nanofluid*, **2014**, *17* (6), 1113–1128. <https://doi.org/10.1007/s10404-014-1403-1>.
- [115] Vansteene, A.; Jasmin, J.-P.; Cote, G.; Mariet, C. Segmented Microflows as a Tool for Optimization of Mass Transfer in Liquid-Liquid Extraction: Application at the Extraction of Europium(III) by a Malonamide. *Ind. Eng. Chem. Res.*, **2018**, *57* (34), 11572–11582. <https://doi.org/10.1021/acs.iecr.8b02079>.
- [116] Vansteene, A.; Jasmin, J.-P.; Cavadias, S.; Mariet, C.; Cote, G. Towards Chip Prototyping: A Model for Droplet Formation at Both T and X-Junctions in Dripping Regime. *Microfluid Nanofluid*, **2018**, *22* (6), 61. <https://doi.org/10.1007/s10404-018-2080-2>.
- [117] Servis, A. G.; Parsons-Davis, T.; Moody, K. J.; Gharibyan, N. 3D Printed Microfluidic Supported Liquid Membrane Module for Radionuclide Separations. *Ind. Eng. Chem. Res.*, **2021**, *60* (1), 629–638. <https://doi.org/10.1021/acs.iecr.0c05349>.
- [118] Ahn, G.-N.; Yu, T.; Lee, H.-J.; Gyak, K.-W.; Kang, J.-H.; You, D.; Kim, D.-P. A Numbering-up Metal Microreactor for the High-Throughput Production of a Commercial Drug by Copper Catalysis. *Lab Chip*, **2019**, *19* (20), 3535–3542. <https://doi.org/10.1039/C9LC00764D>.
- [119] Darekar, M.; Singh, K. K.; Sapkale, P.; Goswami, A. K.; Mukhopadhyay, S.; Shenoy, K. T. On Microfluidic Solvent Extraction of Uranium. *Chemical Engineering and Processing - Process Intensification*, **2018**, *132*, 65–74. <https://doi.org/10.1016/j.cep.2018.08.007>.
- [120] Kriel, F. H.; Binder, C.; Priest, C. A Multi-Stream Microchip for Process Intensification of Liquid-Liquid Extraction. *Chemical Engineering & Technology*, **2017**, *40* (6), 1184–1189. <https://doi.org/10.1002/ceat.201600728>.
- [121] Xie, T.; Jing, S.; Xu, C. Design Guideline for Passive Microextractors: From Cocurrent Flow to Countercurrent Flow. *Ind. Eng. Chem. Res.*, **2019**, *58* (20), 8750–8762. <https://doi.org/10.1021/acs.iecr.8b05639>.
- [122] Deblonde, G. J.-P.; Bengio, D.; Beltrami, D.; Bélair, S.; Cote, G.; Chagnes, A. Niobium and Tantalum Processing in Oxalic-Nitric Media: Nb₂O₅·nH₂O and Ta₂O₅·nH₂O Precipitation with Oxalates and Nitrates Recycling. *Separation and Purification Technology*, **2019**, *226*, 209–217. <https://doi.org/10.1016/j.seppur.2019.05.087>.
- [123] Deblonde, G. J.-P.; Bengio, D.; Beltrami, D.; Bélair, S.; Cote, G.; Chagnes, A. A Fluoride-Free Liquid-Liquid Extraction Process for the Recovery and Separation of Niobium and Tantalum from Alkaline Leach Solutions. *Separation and Purification Technology*, **2019**, *215*, 634–643. <https://doi.org/10.1016/j.seppur.2019.01.052>.

- [124] Wang, X.; Zheng, S.; Xu, H.; Zhang, Y. Leaching of Niobium and Tantalum from a Low-Grade Ore Using a KOH Roast–Water Leach System. *Hydrometallurgy*, **2009**, *98* (3), 219–223. <https://doi.org/10.1016/j.hydromet.2009.05.002>.
- [125] Zhou, H.; Zheng, S.; Zhang, Y. Leaching of a Low-Grade Niobium–Tantalum Ore by Highly Concentrated Caustic Potash Solution. *Hydrometallurgy*, **2005**, *80* (1), 83–89. <https://doi.org/10.1016/j.hydromet.2005.07.006>.
- [126] Zhou, H.; Yi, D.; Zhang, Y.; Zheng, S. The Dissolution Behavior of Nb₂O₅, Ta₂O₅ and Their Mixture in Highly Concentrated KOH Solution. *Hydrometallurgy*, **2005**, *80* (1), 126–131. <https://doi.org/10.1016/j.hydromet.2005.07.010>.
- [127] Zhou, H.; Zheng, S.; Zhang, Y.; Yi, D. A Kinetic Study of the Leaching of a Low-Grade Niobium–Tantalum Ore by Concentrated KOH Solution. *Hydrometallurgy*, **2005**, *80* (3), 170–178. <https://doi.org/10.1016/j.hydromet.2005.06.011>.
- [128] Zhou, L.; Bosscher, M.; Zhang, C.; Özçubukçu, S.; Zhang, L.; Zhang, W.; Li, C. J.; Liu, J.; Jensen, M. P.; Lai, L.; et al. A Protein Engineered to Bind Uranyl Selectively and with Femtomolar Affinity. *Nature Chemistry*, **2014**, *6* (3), 236–241. <https://doi.org/10.1038/nchem.1856>.
- [129] Yuan, Y.; Yu, Q.; Wen, J.; Li, C.; Guo, Z.; Wang, X.; Wang, N. Ultrafast and Highly Selective Uranium Extraction from Seawater by Hydrogel-like Spidroin-Based Protein Fiber. *Angewandte Chemie International Edition*, **2019**, *58* (34), 11785–11790. <https://doi.org/10.1002/anie.201906191>.
- [130] Brewer, A.; Chang, E.; Park, D. M.; Kou, T.; Li, Y.; Lammers, L. N.; Jiao, Y. Recovery of Rare Earth Elements from Geothermal Fluids through Bacterial Cell Surface Adsorption. *Environ. Sci. Technol.*, **2019**, *53* (13), 7714–7723. <https://doi.org/10.1021/acs.est.9b00301>.
- [131] Brewer, A.; Dohnalkova, A.; Shutthanandan, V.; Kovarik, L.; Chang, E.; Sawvel, A. M.; Mason, H. E.; Reed, D.; Ye, C.; Hynes, W. F.; et al. Microbe Encapsulation for Selective Rare-Earth Recovery from Electronic Waste Leachates. *Environ. Sci. Technol.*, **2019**, *53* (23), 13888–13897. <https://doi.org/10.1021/acs.est.9b04608>.
- [132] Cotruvo, J. A. Jr.; Featherston, E. R.; Mattocks, J. A.; Ho, J. V.; Laremore, T. N. Lanmodulin: A Highly Selective Lanthanide-Binding Protein from a Lanthanide-Utilizing Bacterium. *J. Am. Chem. Soc.*, **2018**, *140* (44), 15056–15061. <https://doi.org/10.1021/jacs.8b09842>.
- [133] Deblonde, G. J.-P.; Mattocks, J. A.; Park, D. M.; Reed, D. W.; Cotruvo, J. A.; Jiao, Y. Selective and Efficient Biomacromolecular Extraction of Rare-Earth Elements Using Lanmodulin. *Inorg. Chem.*, **2020**, *59* (17), 11855–11867. <https://doi.org/10.1021/acs.inorgchem.0c01303>.
- [134] Dong, Z.; Mattocks, J. A.; Deblonde, G. J.-P.; Hu, D.; Jiao, Y.; Cotruvo, J. A.; Park, D. M. Bridging Hydrometallurgy and Biochemistry: A Protein-Based Process for Recovery and Separation of Rare Earth Elements. *ACS Cent. Sci.*, **2021**, *7* (11), 1798–1808. <https://doi.org/10.1021/acscentsci.1c00724>.
- [135] Deblonde, G. J.-P.; Mattocks, J. A.; Wang, H.; Gale, E. M.; Kersting, A. B.; Zavarin, M.; Cotruvo, J. A. Characterization of Americium and Curium Complexes with the Protein Lanmodulin: A Potential Macromolecular Mechanism for Actinide Mobility in the Environment. *J. Am. Chem. Soc.*, **2021**, *143* (38), 15769–15783. <https://doi.org/10.1021/jacs.1c07103>.
- [136] Spooren, J.; Binnemans, K.; Björkmalm, J.; Breemersch, K.; Dams, Y.; Folens, K.; González-Moya, M.; Horckmans, L.; Komnitsas, K.; Kurylak, W.; et al. Near-Zero-Waste Processing of Low-Grade, Complex Primary Ores and Secondary Raw Materials in Europe: Technology Development Trends. *Resources, Conservation and Recycling*, **2020**, *160*, 104919. <https://doi.org/10.1016/j.resconrec.2020.104919>.
- [137] Boxall, N. J.; King, S.; Cheng, K. Y.; Gumulya, Y.; Bruckard, W.; Kaksonen, A. H. Urban Mining of Lithium-Ion Batteries in Australia: Current State and Future Trends. *Minerals Engineering*, **2018**, *128*, 45–55. <https://doi.org/10.1016/j.mineng.2018.08.030>.

- [138] Prodius, D.; Gandha, K.; Mudring, A.-V.; Nlebedim, I. C. Sustainable Urban Mining of Critical Elements from Magnet and Electronic Wastes. *ACS Sustainable Chem. Eng.*, **2020**, *8* (3), 1455–1463. <https://doi.org/10.1021/acssuschemeng.9b05741>.
- [139] Deng, B.; Luong, D. X.; Wang, Z.; Kittrell, C.; McHugh, E. A.; Tour, J. M. Urban Mining by Flash Joule Heating. *Nat Commun*, **2021**, *12* (1), 5794. <https://doi.org/10.1038/s41467-021-26038-9>.
- [140] Lusty, P. a. J.; Gunn, A. G. Challenges to Global Mineral Resource Security and Options for Future Supply. *Geological Society, London, Special Publications*, **2015**, *393* (1), 265–276. <https://doi.org/10.1144/SP393.13>.
- [141] Ali, S. H.; Giurco, D.; Arndt, N.; Nickless, E.; Brown, G.; Demetriades, A.; Durrheim, R.; Enriquez, M. A.; Kinnaird, J.; Littleboy, A.; et al. Mineral Supply for Sustainable Development Requires Resource Governance. *Nature*, **2017**, *543* (7645), 367–372. <https://doi.org/10.1038/nature21359>.

Acknowledgements

Lawrence Livermore National Laboratory is operated by Lawrence Livermore National Security, LLC, for the U.S. Department of Energy, National Nuclear Security Administration under Contract DE-AC52-07NA27344 (LLNL-JRNL- 830607).

Author Contributions

G.J-P.D., A.C., and G.C. carried out literature search, discussed ideas, and contributed to the writing of the manuscript.

ORCID numbers

Gauthier J.-P. Deblonde 0000-0002-0825-8714

Alexandre Chagnes 0000-0002-4345-6812

G rard Cote 0000-0002-6323-9487

Competing interests

The authors declare that there are no competing interests.