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# Honey, I Shrunk the Lab: Emerging Microfluidics Technology and its Implications for Chemical, Biological, and Nuclear Weapons

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Imagine that a man dons a white lab coat and walks into a medical operations room, joining several others at a large window. It could be mistaken for a room in a hospital—because that is precisely what it once was—except for the Kalashnikov-wielding guards in the corner. The man in the lab coat watches as several hazmat suit-clad figures monitor what appear to be stacks of computer servers connected by a web of tubing. As he watches, a colorless liquid begins to flow out of the final tube and into a storage container. He walks to the wired phone behind him, picks up the receiver, and confirms the successful resumption of Syria's chemical weapons program.

As this hypothetical but plausible story illustrates, if Syria were to covertly restart the chemical weapons program it committed to abolishing in 2013[1]—though subsequent experience suggests that abolition was incomplete—it might take advantage of microfluidics, an emerging field with various national security implications. Microfluidic technologies could not only enable Syria's efforts, but also complicate international attempts to stop them, just as it could enable other states, and eventually terrorists, to produce their own chemical weapons. At the same time, these technologies also have the potential to aid efforts to defend against such threats.

Microfluidics and nanofluidics have various implications for both the offensive and defensive sides of chemical, biological, and nuclear threats. In recent years, industry and research laboratories have invested enormous resources in microfluidic technologies, and remarkable progress has been made in their development and integration. Despite

concerns by some specialists about potential nefarious uses of the technology,[2] microfluidics has received little attention from the national security policy community.

Microfluidics already has significant CBRN-related implications today, but it appears likely to have far greater consequences in the future. Although the offensive and defensive implications are most significant for the chemical weapons domain, both biological and nuclear weapons also require chemistry, indicating potential applications for microfluidics. Some can be projected with considerable confidence, while others are more speculative, contingent on technological developments that are difficult to predict. This paper explores both extant and potential implications.[3]

## WHAT IS MICROFLUIDICS AND WHY DOES IT MATTER?

Microfluidics refers to chip-scale chemistry, involving liquids flowing through and mixing via tiny channels that enable far greater control over reactions and their byproducts. Nanofluidics is similar, but orders of magnitude more microscopic. Before diving into an assessment of implications for chemical, biological, and nuclear weapons, we will provide a brief technical overview of the technology and its advantages as well as its accessibility, ease of use, global diffusion, and convergence with other emerging technologies.

### *Technical Overview*

Microfluidics involves the study and manipulation of small quantities of fluids, usually at or below the microliter level. A microreactor is a microfluidic device in which chemical reactions take place in a very small space, typically in microchannels with a width of less than one millimeter, or less than ten times the diameter of a human hair. At an even smaller scale, nanofluidics, an emerging sub-field of microfluidics, involves the study and manipulation of fluids at or below the nanoliter level. Nanoreactors are nanofluidic devices in which chemical reactions occur at or below the nano-scale, or less than 0.001 times the diameter of a human hair.

The emerging field of microfluidics was born out of the 1980s — a time when ancillary fields and technologies such as genomics and microelectronics boomed.[4] At the time, the study of genomics gripped the attention of many molecular biologists who endeavored to unlock the human genome. Experimentation with DNA required technologies capable of performing analysis at the molecular scale. Concurrently, advances in microelectronics, which required construction of circuit components on or below the scale of a few micrometers, inspired chemists and bioengineers to conceptually design devices capable of manipulating the flow of fluids on equivalent scales. Until the 21st century, the development of microfluidic devices had remained limited since cost-effective manufacturing capabilities for requisite materials had not yet evolved to meet the needs of researchers. Significant advances in manufacturing technologies over the past two decades have ushered in a widespread adoption of rapidly maturing microfluidic devices, also known as microreactors.

The best way to understand microreactors is to imagine a simple circuit board. In a standard circuit board, electricity flows along copper channels laid down on a plastic or fiberglass base, and interacts with the electronic components attached to the base. If you replaced those metal channels and

components with very small tubes, controllable connecting joints, and mixing areas, you would have a basic microreactor. Small, precise pumps send chemicals through those tubes, where they mix and react to form the desired product, which is then pumped out.[5] These flows are regulated by computer systems connected to the devices.

The small size of microreactors significantly changes how the chemicals flow, mix, and react compared to traditional bench or industrial-scale chemistry. They provide a much greater degree of temperature control than traditional lab and chemical plant equipment. As a result, reactions can be very precisely controlled, enabling the production of very pure substances while reducing both the inputs needed and waste produced at the back end. They can shorten the time needed for a given reaction from hours to minutes, even while increasing the total yield and purity of the product.[6] This quick reaction time means that chemicals can be continually pumped through microreactors, which could allow for on-demand production and the automation of much of the process. These methods—which can occur at various scales—are often called "flow chemistry".[7]

Unlike batch chemistry in which chemical reactions are conducted over multiple successive stages in different batch chambers or vessels, flow chemistry involves the continuous stream of chemicals through channels or tubes to conduct reactions.[8] This technique allows greater automation, control, and efficiency of the reactions than in larger batch chemical systems. Microfluidic devices amplify advantages in flow chemistry by changing the dynamics of fluids flowing through the system and creating the conditions for more controlled study or manipulation of chemicals.[9] The small size of tubes or channels within microreactors constrain fluids to flow in a laminar, instead of turbulent, manner. In a laminar dynamic, fluids flow alongside each other, and heat and mix in a more controlled manner. Though flow chemistry does not necessitate the use of microreactors, the fluid dynamic inherent to microreactors maximizes opportunities for reaction efficiency or safety in many cases that flow chemistry is judged an attractive alternative to batch chemistry.[10]

Nanofluidics, a sub-field of microfluidics, involves flow chemistry at even smaller scales whereby nanofluidic devices, known as nanoreactors, are used to more precisely study and manipulate fluids at the molecular scale. Reactions conducted in nanoreactors require far less inputs at the front end than do microreactors, and allow an even greater degree of control over reactions.[11] They are particularly useful when dealing with very limited quantities of inputs and fluids prone to extremely fast reaction times.

### *Accessibility and Ease of Use*

Though microfluidics and nanofluidics technologies offer significant benefits in chemical manipulation and synthesis, it is worth noting that their embrace by commercial industry and individual researchers continues to be somewhat constrained by challenges in accessibility and scalability. However, advances in related emerging technologies are trending to mitigate or bypass some of these hurdles.

Currently, many of the microfluidic and nanofluidic devices integrated in industrial platforms and distributed by commercial vendors require substantial investments of capital, time, and expertise by the user. Some

observers suggest that it is difficult to generalize costs and requirements for these technologies given their various applications and configurations.[12] A wide variety of microreactors and nanoreactors have been researched, designed, and produced, ranging from cheap and accessible paper-based, plastic or wax-coated devices costing less than fifty dollars, to sophisticated devices costing thousands of dollars.[13] But less than two dozen companies dominate the microfluidic sector.[14] And there is a relative consensus that most commercial microfluidic systems being integrated in industry today or used for advanced chemical synthesis and manipulation share similar barriers in accessibility and scalability.[15]

Though major commercial stakeholders in the microfluidic sector today benefit from manufacturing devices with increasingly cost-effective materials, the requirements in expertise, capital, and time for commercial microreactor fabrication remain challenging. Many types of microreactors have been researched and designed, and some simple types can even be made at home, but fabrication of the vast majority of devices handling complex chemical synthesis or hazardous high-throughput reactions requires chemical expertise beyond what is needed for traditional bench or industrial-scale chemistry. The theoretical underpinning of the benefits of microfluidic flow chemistry is based in an understanding of how surface-area-to-volume ratios in microreactors and nanoreactors affect fluid dynamics and reaction conditions. Thus, at a minimum, expertise in interfacial chemistry is additionally required to research, develop, and operate microfluidics.[16]

The cost requirements for additional expertise to create and use these devices currently limit their accessibility. On the producer side, vendors must allocate substantial resources to enlist and manage expert teams to construct microfluidic and nanofluidic devices for complex or hazardous experiments. Although over 280 microfluidic vendors exist internationally,[17] a comparatively smaller number of about 20 vendors are able to devote such resources to recruit and maintain a sizeable research and development team seeking to fabricate microreactors and nanoreactors at an industrial scale.[18] Moreover, clean room facilities needed for testing and development are expensive. Accessibility for industrial-scale fabrication is therefore limited to companies which can afford to build and service the needed clean room facilities.

On the consumer side, operation and upkeep of microreactors or nanoreactors designed specifically for complex or hazardous reactions also require sophisticated chemical and mechanical expertise and facilities. Furthermore, such devices, though reusable, often degrade over time due to the way in which high heat- and energy-producing reactions alter physical spaces and wear down the device.[19] While devices designed for strong exothermic reactions can be cleaned, the lifetimes of these devices appear unclear, and such pricing uncertainties may be an unwelcome addition to potential resource strains posed by already costly heat- or corrosion-resistant devices on consumers.[20]

Even if a consumer possesses the minimum expertise and resources needed to use or maintain these devices, customization is still very challenging, and producers face similar constraints in scalability. Currently, the size and design of microreactors and nanoreactors, and the manufacturing techniques used to

fabricate them, hinder horizontal and vertical scalability for industry. Industry has largely avoided "scale-out," which in this context means placing and operating microfluidic and nanofluidic devices in parallel, because of the difficulties in adapting flow chemical calculations of reaction conditions across multiple linked devices or purifying the products of those parallelized devices.[21] Additionally, consumers that desire to utilize such devices for complex or hazardous chemical reactions may face greater challenges to reusability in parallelized microfluidic platforms than they would otherwise experience with vertically scaled platforms. While microfluidic devices designed for these reactions are generally reusable, cleaning and eventually replacing horizontally aggregated devices may be more difficult and expensive.

Although parallelization has been widely demonstrated,[22] industry appears to appreciate the relative cost-effectiveness of customizing devices based on the volume of fluids involved.[23] This trend suggests that producers may prefer to "scale-up" devices by altering components of microreactors or nanoreactors themselves, rather than teaming them together. One example of how industry is addressing the need for scalability is through the prototyping of reactors with microchannels of higher interfacial areas, which increase flow rate.[24] Yet, these devices are only at the research and development stage, and "scale-up" of devices is generally slow because of the vast amount of expertise and time required at this stage in the production pipeline. Despite increasing advancements and opportunities in addressing hurdles to accessibility and scalability of flow chemical processes, and specifically microreactors and nanoreactors, these techniques and technologies may remain unsuitable for some chemical reactions for the long term. Currently, about five percent of the pharmaceutical sector has adopted flow chemical processing for the research, development, or production of drugs, some fraction of which involves microreactors.[25] The synthesis of many pharmaceutical and fine chemical compounds fails in continuous flow, as they require additional steps such as separation and purification, especially as precipitates or bubbles are formed which may impair the function of, plug, or permanently damage a microreactor.[26] For the synthesis of these organic compounds, batch processing is preferred and has long served as the industry standard.[27]

These challenges, however, could be at least partially overcome by integrating both continuous flow and batch processes into a multi-step synthesis.[28] Additionally, researchers are investigating ways of innovating microreactors to avoid clogging or accommodate solid or gaseous separation.[29] However, some reactions may remain either too complex or simply incompatible with continuous flow processes and microreactors. Nevertheless, experts have assessed that approximately 50 percent of known pharmaceutical and fine chemical reactions may benefit from continuous flow processes or microreactors.[30]

### *Global Diffusion*

Despite these challenges, microfluidics and nanofluidics technologies are already widespread and diffusing rapidly. Preference among major market players for "scale-up" of microreactors and nanoreactors may actually unlock further opportunities for niche producers to emerge. Smaller companies are focusing their assets on designing, prototyping,

and patenting various components of microreactors which can address the need for scalability. Demand for the production of these components and solutions is expanding the market for microfluidics and nanofluidics. At the same time, advances in emerging manufacturing techniques may help overcome some of the challenges in accessibility and scalability illustrated above.

A review of patent filings conducted a decade ago found that the primary patent assignees in microfluidics were in Germany, the United States, China, and Japan.[31] German academic centers and private industry paved the road for microfluidics research and development in the 1980s. Japan and the United States entered the market in the 1990s. China emerged as a primary patent filer in the early 2000s. A host of other nations are gaining ground as major market players, including Canada, France, India, Italy, Mexico, the Netherlands, South Korea, Switzerland, and the United Kingdom.[32] The global market for microfluidics is expected to reach 4.2 billion U.S. dollars by the end of fiscal year 2018-2019.[33] Demand is projected to surge within the next five years.

Much of the increased demand for microfluidics is driven by the many potential applications of chip-scale chemistry conceptualized or designed in academic centers and research institutes. In 2015, a team of analytic chemists from Oak Ridge National Laboratory, Kansas State University, and the Iranian Shahid Beheshti University examined over 2,500 papers on microfluidics.[34] Among their conclusions, the team forecasted that the number of papers related to microfluidics, and subsequent advances made in the production of microreactors and nanoreactors, will increase steadily for the foreseeable future.[35]

Private industry has also played a large part in facilitating the availability of microfluidic and nanofluidic devices for experimentation. Improvements in manufacturing have radically transformed the microfluidics market, making microreactor and nanoreactor fabrication quicker, cheaper, and more diverse. By further diversifying the types of materials and tools which can be used to fabricate microreactors and nanoreactors, manufacturing techniques have unlocked a wider range of potential applications of microfluidics.

### *Technological Convergence*

Specifically, a recent revolution in another emerging technology, additive manufacturing, commonly referred to as "3D printing," has unlocked new pathways for manipulating complex materials which can be used for microreactors and nanoreactors. Since the start of the 21st century, additive manufacturing (AM) technologies have rapidly matured from building small polymer-based 3D models to fabricating something as complex as metal components of rockets.[36] More recently, researchers have begun to fabricate micro- and even nano-scale metal devices through AM.[37] Scientists at the California Institute of Technology have demonstrated AM techniques for constructing nano-scale nickel structures.[38] Resistant materials such as these can make microreactors and nanoreactors capable of manipulating very volatile and harsh liquids and reactions, and AM makes experimentation with those materials and substances even cheaper.

### *Key Advantages*

Microreactors and nanoreactors are enabling quicker, cheaper, and more mobile chemical analysis and manipulation than traditional bench or industrial-scale chemistry, while

offering a wide array of new techniques for other engineering processes. According to a 2002 summary report compiled by the International Union of Pure and Applied Chemists (IUPAC) following a discussion on emerging technologies, a single microreactor capable of a 1-mL/second flow rate, operated 24 hours per day, could produce more than 1,000 pounds per week of a single, high-purity compound.[39] Unlike traditional chemical production methods, which would increase capacity not by adding more reactors but by increasing reactor size, adding more microreactors to this process increases the production rate in a close to linear way.[40] Although it is becoming more common to run reactors in parallel, the majority of reactors are still not run in parallel, and reactors are increasingly being designed to accommodate much higher flow rates, unlocking opportunities for even larger scale production.

A more recent report by the IUPAC assesses that teaming of microreactors is now less likely, and instead finds that individual microreactors are being scaled up to accommodate a spectrum of chemical studies or manipulations involving different fluid volumes or types.[41] Companies are designing various microreactors conducive to specific flow rates by altering the geometries of channels in the devices. Devices with lower flow rates enable the consumer to slow down very fast reactions, allowing more efficient mixing or study of the fluids. These conditions greatly benefit users with small sample sizes, at or below the gram scale.[42] Devices designed for higher flow rates make even larger scale production possible, and IUPAC concluded in 2012 that some devices designed at the time were being procured for campaigns intended to produce 100,000 pounds of a substance.[43]

The fast reaction times and potential for automation associated with microreactors could be used to quickly produce and test large numbers of high-quality chemical compounds. This involves mixing several reactive chemical building blocks together ("combinatorial chemistry") and analyzing all of the different combinations that they produced ("high-throughput assay"). Microfluidics entails various advantages in these processes, perhaps most importantly speed, so that many compounds can be rapidly produced and also tested quickly. The pharmaceutical industry is already using these techniques to analyze thousands of new chemicals for possible medicinal benefits and health risks.

Some of these improvements and techniques translate into other fields which require chemical analysis and manipulation, such as in biological and nuclear research and commercial processes. Microreactors and nanoreactors are already being studied and integrated in genomics and nuclear engineering.

The benefits offered by microfluidics and nanofluidics in chemical analysis and manipulation can be summed up as enabling chemistry either not feasible in other ways, or feasible but more expensive and/or time consuming in other ways. These tiny devices also take up less space, reducing the storage space needed to house equipment and making them potentially far more mobile compared to any traditional bench equipment.

Microreactors today are being used for applications that can be met in no other feasible way, such as studying some chemical reactions with extremely fast reaction times

that are highly exothermic (i.e., that generate large amounts of heat). With the much greater surface-area-to-volume ratio of a microreactor, the heat generated is more easily dissipated. For some types of chemical processing, microreactors are also perceived as preferable to other approaches, such as batch processing. While some highly exothermic reactions might today pose challenges to the integration of microfluidics in industrial scale processing, advances in microreactor fabrication with more heat-resistant material might unlock opportunities for microfluidics technologies to eventually overtake and displace the legacy way of processing highly exothermic or hazardous reactions.

Although microreactors presently require more sophistication than traditional bulk, batch chemistry equipment, microfluidics' rapid maturation and diffusion are likely to invert that dynamic. Consequently, advances in microfluidics technologies and their widespread adoption have potentially ominous implications for the production of chemical weapons agents, biological weapons agents, or nuclear weapons materials.

### Implications for Chemical, Biological, and Nuclear Proliferation

Because microfluidics and nanofluidics change what is possible in terms of chemistry, they have implications for efforts to both obtain chemical, biological, and nuclear weapons and to combat them. Microreactors have implications for proliferating known chemical weapons agents and synthesizing novel agents as well. As gene synthesis and targeting techniques and nanotechnologies evolve, nanoreactors might be used in pathways to synthesize threatening viruses. Microreactors might also enable countries to more easily, quickly, and covertly conduct reprocessing to extract weapons-usable material from spent nuclear reactor fuel.

Conversely, industry and state actors can utilize microreactors and nanoreactors for non-proliferation and counter-proliferation purposes. Experts in the chemical weapons domain have proposed using microreactors in field-deployable chemical weapons agent detection equipment, and the development of such devices is currently underway. Bio-defense programs are also seeking to develop nanofluidic genetic screening equipment to detect viral bioweapons, and unlock pathways to treatment for bioweapons exposure. Microreactors might be incorporated into nuclear reprocessing facilities to stream live or at least very timely data regarding ongoing reprocessing activities and nuclear materials recovered, potentially enabling "real-time" nuclear safeguard monitoring.

It is also worth noting that the cyber-physical interface of many microfluidics technologies may render these devices, and any of their chemical, biological, or nuclear applications discussed herein, susceptible to cyber risks.[44] More sophisticated applications of microfluidics technologies require computer control of such devices. In these types of systems, sensors, actuators, pumps, and control valves are connected to electronic systems such as computers to automate the processing of fluids.[45] Though not the focus of this paper, exploitation of cyber vulnerabilities related to microfluidics technologies and their applications may include digital information theft or sabotage, digital interference, or physical destruction.

***Offensive***

Actors intending to produce chemical, biological, or nuclear weapons materials can better evade detection using microreactors or nanoreactors than with traditional chemical equipment. The reactors require less input of the precursor material, yield less waste, and produce more pure materials at a quicker speed and with less hazard. These efficiencies pose challenges to intelligence services and WMD monitoring regimes attempting to uncover chemical weapons activities. Their small size also enables concealed trafficking for actors who aim to transfer the technology to others with malign intentions.

Though still constrained at the moment, the accessibility of microfluidics is increasing rapidly, and microreactors and nanoreactors can reach the hands of many current or would-be nefarious actors. As explained earlier, much of this vast diffusion is owed to advances in manufacturing, particularly AM processes. The exponential rate at which AM technology matures and spreads almost certainly multiplies the risk of misuse posed by microfluidics and nanofluidics.

Although AM is facing increasing scrutiny under strategic trade controls, microreactors are far less, if at all, regulated. In 2016 the National Defense University (NDU) performed a survey, supported by the Office of the Secretary of Defense, of subject matter experts' risk assessments of emerging technologies. Responding to questions on emerging AM applications, experts assessed "microreactor printing" as having the highest magnitude of potential harm of the choices given. Alarmingly, the study's participants seemed to fear that state and non-state actors could use AM to produce microreactors that might synthesize novel chemical compounds at the research and development stage of their quest for WMD.[46]

Should AM technology capable of metallic microreactor fabrication advance, nefarious actors may be capable of highly independent, covert analysis or synthesis of hazardous chemicals and WMD materials. Because of the very high degree of control over reaction rates and temperature that microreactors provide, they are very well suited for some reactions involving dangerous, volatile, corrosive, and even explosive compounds.[47] Thus, they would make the study or synthesis of certain WMD-related materials less dangerous and easier to control.[48] But the most significant applications of microfluidics may involve research and development; microfluidics is particularly suitable to finding, modifying, and studying substances that might be more readily produced at scale via more traditional processes.

*Chemical Weapons*

Countries or well-financed terrorist groups could potentially harness the capabilities of microreactors to establish clandestine chemical weapons agent research and production facilities. Microreactors might enable facilities to be smaller, more easily disguised, and harder to detect than traditional chemical plants.[49] They would, for example, be less likely to emit chemical signatures that could be detected by foreign intelligence services and alert them to the presence of a covert chemical weapons program. Furthermore, the production process would be far less messy, making the work less dangerous for personnel and easier to disguise or clean up.[50]

It is worrisome that a state might need only a few microreactors to conduct high-volume,

single-product or low-volume, multi-product synthesis. It is not difficult to see how high-throughput pharmaceutical processes such as combinatorial chemistry could be converted to identifying new chemical weapons agents. If new chemical agents and their precursors are kept secret, there would be no explicit restriction or tracking by the Chemical Weapons Convention (CWC), and intelligence services would be more likely to miss signs of their production.[51]

Fortunately, microreactor technology is unlikely to facilitate the acquisition of chemical weapons by non-state actors in the near term. There are two primary reasons for this. For now, microreactors and their associated equipment are difficult to obtain, and there is a fairly high level of expertise needed to use them. Microreactors can be purchased from chemical equipment companies, or they can be manufactured in-house.[52] Some companies sell pre-made microfluidics equipment capable of simple types of reactions, but these can be quite expensive. For more complex or dangerous reactions, interested parties would need to manufacture microreactors themselves, perhaps with the aid of a custom design from an established manufacturer. Both of these options would allow for customer screening and verification, helping to prevent proliferation to malicious actors. Fortunately, building a microreactor in-house would require advanced equipment and very in-depth experience and expertise.[53] Even if an actor managed to acquire one, they would need specific and high-level chemical engineering knowledge to effectively operate it.

Some experts have debated whether microreactors could more efficiently synthesize chemical warfare agents (CWAs) than traditional batch processes. Although synthesis of CWAs with microreactors has not been publicly demonstrated, relevant arms control and non-proliferation organizations and laboratories have discussed the potential threat. Spiez Laboratory, a nuclear, chemical, and biological threat investigative laboratory and one of five labs permanently working with the Organization for the Prohibition of Chemical Weapons (OPCW) to implement the CWC, investigated the threat and published its assessment in 2013.[54] Through its analysis of 81 chemical reactions related to CWAs, it determined that only 25 percent of the reactions could be facilitated through microreactors.[55] The remaining 75 percent of reactions formed solids, rendering them incompatible with microreactors.[56]

Still, microreactors were assessed by Spiez as capable of synthesizing a significant percentage of known CWAs, including some chemical precursors not controlled or monitored by the OPCW. According to the Spiez study, microreactors could synthesize sulfur mustard blister agent with almost the same purity, yield, and replicability and in near-equal time as batch processes.[57] Although it is surprising that microreactors do not offer significantly greater benefits in purity, yield, and time for this and other CWA-related reactions, these devices still offer other advantages such as small footprint. An actor could take advantage of the smaller and more unconventional nature of microreactors to synthesize CWAs with a significantly reduced signature to evade intelligence monitoring and arms control capabilities. Moreover, microreators can also synthesize a number of explosive, hazardous, and potentially toxic chemicals from uncontrolled chemicals.[58] Such demonstrations, if further researched and developed by academia, industry, or a determined and proficient nefarious actor,

could result in the optimized synthesis of known CWAs, or perhaps the synthesis of entirely new CWAs.

Over time, microreactor technology is likely to become more accessible and less challenging to operate. In the future, more turn-key capabilities are likely, i.e., "lab-on-a-chip" reactors that allow processes that would be more complex via traditional chemistry to be performed more simply.[59]

*Biological Weapons*

In the mid-term, microfluidics pose a high risk of misuse among state actors utilizing biological synthesis techniques and technologies for biological weapons research and development. Many security officials and experts have become concerned about recent advances in DNA synthesis and targeting, particularly with the emergence of an efficient and accessible biotechnology, known as CRISPR-Cas9. CRISPR is a technique for editing DNA sequences, and Cas-9 is a protein used in CRISPR to bind with a target DNA sequence to edit its code.[60]

Since CRISPR-Cas9's emergence as a gene editing tool in 2012, biodefense and national security experts have grown increasingly worried about the technology's rapid maturation and commercial diffusion.[61] The greatest concerns surrounding CRISPR are its wide accessibility, low cost, and potential for supporting the modification of harmful pathogens. Some nonproliferation experts hypothesize that the efficient gene-targeting technique allows state or non-state actors to make highly virulent bioweapons based on specific vulnerabilities that all humans, or all animals in a species, would share.[62] They suggest that state or non-state scientists with a greater understanding of genome sequences could use their expertise to create novel, weaponized viral or bacterial vectors, or to recreate those eradicated by vaccines.

Genomics is a sub-field of molecular genetics which studies the genome, or DNA, of an organism and related technologies which enhance understanding of the genome,[63] and microfluidics and nanofluidics are increasingly helping to advance genomics research. In order to understand the whole genome of a species of animal, plant, or microorganism, researchers use a high-throughput technique whereby DNA is extracted, broken down with chemicals, and analyzed many times to identify the order, or sequence, of the constituent bases (e.g., A's, C's, G's, and T's) that make up the genetic code. By corroborating analysis of these sequences with other known sequences, researchers can then identify where certain sequences of DNA code for mutations.[64] Understanding of the location of these codes for mutations helps researchers in the field of synthetic biology identify where to target DNA to manipulate the sequences which code for mutations.[65]

Considering that this chemical analysis and manipulation of DNA occurs at the molecular level, molecular biologists are increasingly embracing nanofluidics as a key tool to learn about genomes and potentially to alter them one day. Currently, some of the top genomics companies are acquiring nanoreactors and promoting them as a tool which could soon become standardized to enhance high-throughput screening.[66] This screening technique with nanoreactors has even been adopted recently by astronauts aboard the International Space Station.[67] Industry and governments have embraced nanofluidics with enough confidence to use these technologies in outer space. These techniques

will enable the field of synthetic biology by advancing scientists' understanding of an organism's molecular biology, and of proteins which may be able to manipulate the coding of mutations that cause disease.[68]

While many experts agree that advances in synthetic biological research threaten to expose genetic vulnerabilities and new opportunities for weaponization, many also contend that the threat of developing offensive biological weapons from the research catalyzed by microfluidics is remote or even infeasible in some cases. Chemical and biological weapons experts such as the late Ray Zilinskas and Jonathan Tucker argued that nefarious bioengineers are unlikely to synthesize novel pathogens because of various formidable complexities in designing an infectious, virulent, persistent, or stable organism.[69] These experts argued that a more viable option would be re-creating known viral pathogens,[70] which can still be helpful to an attacker since existing pathogen control regimes are largely based on securing access to physical stocks of pathogens. Recreating them from scratch would evade such controls. Still, synthesis of these known organisms requires great investments of time, resources for ensuring stability of the pathogen, and extensive training in molecular biology.[71] Experts assess that the primary threat of misuse rests in state-level biological warfare programs, and that advances in DNA synthesis techniques, such as CRISPR, will increase the risk of misuse.[72]

Although CRISPR requires scientific expertise and the ease of misuse remains relatively constrained to state actors with biological programs and industry in the near term,[73] nanoreactors are being used in combination with CRISPR platforms today, only heightening the magnitude of potential harm and risk of genetic screening technologies in the mid-term.[74] Nanoreactors allow higher throughput of DNA screening, conserve the required input of cell sample and comparison DNA pool, and allow the analysis and manipulation of chemical compounds such as synthesized DNA fragments at a much faster rate.[75] These enhanced techniques can be applied to the study, and eventually manipulation, of pathogens for malicious purposes. Nanoreactors make the study of potentially lethal viruses not only more cost-effective, but also quicker and therefore more concealed.

*Nuclear Weapons*

Microreactors[76] pose a mid-term threat for countries wishing to "break out" nuclear weapons from civil nuclear programs, or "sneak out" weapons-usable materials despite monitoring and verification regimes.[77] Plutonium, once reprocessed and recovered, is a weapons-usable byproduct of nuclear energy generation, and microfluidic-enabled reprocessing might come into play here.

Industry and government circles are studying microreactors for the research and development of more efficient ways of separating radioactive elements from other materials, particularly in the optimization of common reprocessing techniques. Nuclear reprocessing is a critical step in nuclear fuel cycles of some countries, whereby a nuclear reactor's spent fuel undergoes a chemical separation technique to recover valuable fission products such as uranium and plutonium.[78]

After chemical separation of desired elements from a solution of dissolved nuclear spent fuel rods, the solution is mixed with other chemical solutions to extract uranium and plutonium

liquid solutions, which then undergo a series of conversions into solid state products. This process, known as liquid-liquid extraction, can be enhanced by microfluidic devices. Countries with advanced nuclear reprocessing expertise have been researching and developing microfluidic platforms for such techniques.[79] For example, French scientists have developed and tested centrifugal microfluidic platforms for liquid-liquid extraction, which they termed "lab-on-a-disc," a nod to the "lab-on-a-chip" nickname for microreactors.[80] In a prototype design unveiled in 2013, scientists at the French Alternative Energies and Atomic Energy Commission embedded microreactors on a disc, which was mounted on a motor.[81] Engineers at the Institut Curie Research Center fabricated microreactors out of polymers capable of resisting corrosive chemicals as well as high temperature and pressure.[82] Simulating liquid-liquid separation of nuclear spent fuel materials, the motor spun the disc as liquids were pumped through the microreactors and mixed. The experiment demonstrated significant efficiency advantages in cost and time through the use of centrifugal microfluidic platforms, and prompted the researchers to speculate that such devices could benefit the nuclear industry with increased throughput and automation, as well as reduced generation of wastes.[83]

Microreactors may enable nefarious actors to utilize a smaller amount of nuclear material for the recovery of a greater amount of weapons-usable material, extract or recycle nuclear materials in a shorter amount of time, reduce footprints by integrating smaller reprocessing equipment, and test or operate microreactor devices for reprocessing with greater safety. Although currently microfluidic devices have not yet been integrated into active reprocessing platforms, utilizing them for the research and development of reprocessing technology remains unregulated and relatively accessible. A country interested in covertly studying ways of optimizing methods of liquid-liquid extraction of nuclear spent fuel products can rather easily acquire the materials involved in the experiment carried out by the French scientists, such as the motors, the polymer substrate material for manufacturing the microreactors, and materials with trace radioactive elements.[84] Additionally, these devices offer greater safety to engineers testing how to integrate the equipment, and to operators utilizing the equipment for reprocessing, because of the smaller volume of radioactive fluids traveling through the devices at a given time.

Reprocessing would still require other batch processing equipment for the purification and separation of materials. However, integrating microreactors such as the "labs-on-a-disc" into a multi-step batch and continuous flow reprocessing platform could reduce signatures and help evade inspectors or intelligence services conducting surveillance designed against conventional reprocessing techniques and equipment.

**Defensive**

Thankfully, microreactor technology may also provide benefits for efforts to inhibit or counter chemical, biological, and nuclear threats. One very promising application is the development of field-deployable chemical and biological analysis devices. The small size of microreactors and their associated equipment, along with their rapid reaction time and reduced need for solvents and reagents, could enable them to be used in a quick, efficient, and portable detection system.[85] Improvements in nanofluidic DNA sequencing could yield

greater opportunities for biodefense programs to identify, prevent, or degrade biological weapons agents such as viral vectors. Moreover, as centrifugal microfluidic platforms advance, nuclear industry and their ancillary monitoring and verification protocol and regimes could use data streams from connected software to observe nuclear reprocessing activities in real-time.

*Chemical Weapons*

Microreactors could be used to rapidly detect and identify chemical weapons agents in the field after use. In addition, many environmental samples would no longer have to be packaged and shipped to off-site laboratories. U.S. governmental interest in microfluidics spawned from research of microfluidic systems capable of detecting chemical or biological weapons threats, and the development of these systems is currently underway.[86]

In the 1990s, the U.S. Defense Advanced Research Projects Agency (DARPA) funded several programs aimed at developing field-deployable microfluidic equipment to detect chemical or biological warfare agents.[87] In the early 2000s, researchers proposed developing devices with microreactors that could quickly detect chemical weapons agents which did not persist in the environment once dispersed.[88] Within less than a decade, military research institutes reported the development of devices with microreactors used to detect nerve agent chemicals. They found that microreactors enabled the new sensors to detect chemicals three times faster than traditional detection device and techniques.[89] Their small size and increased sensitivity may allow them to one day be mounted on drones to perform remote intelligence, surveillance, or reconnaissance operations.[90]

*Biological Weapons*

Not only can states develop field-deployable microfluidic devices to detect biological agents, but they can also utilize microfluidic devices mimicking organs and employ advanced nanofluidic screening techniques to study and defend against biological weapons agents.

In the past year, scientists have demonstrated remarkable breakthroughs in the use of nanofluidics for biological and toxin weapons detection. One group of scientists used nanoreactors to perform DNA sequencing on samples of pathogenic agents.[91] With a portable nanoreactor-based kit, they were able to detect anthrax within five minutes and influenza within 10 minutes.[92] Designs for these devices were conceptualized less than two decades ago,[93] and they are already being developed and tested internationally.[94]

Additionally, microreactors and nanoreactors are being developed into organ-mimicking devices for synthetic biological studies. Academic and defense research institutions are increasingly testing genetic synthesis by lining microreactors with animal cells and exposing them to chemicals.[95] These devices, nicknamed “organs-on-a-chip,” offer higher fidelity and replicability than do animal organs, and allow a much greater degree of observation and data-gathering.[96] DARPA is investing in projects involving organs-on-a-chip that emulate human organs, such as the human lung.[97] Advances in studies of these devices will almost certainly improve understanding of cellular responses to disease, and can unlock pathways to developing countermeasures for biological and chemical warfare agents.

Gene therapy, aided by increasing integration of nanofluidics, is also demonstrating significant results in potentially countering biological weapons threats. In a study on ways to prevent or treat botulism, researchers performed gene therapy to protect against botulinum toxin using genes from an antibody known for its antitoxin capabilities.[98] They found that gene therapy treatments could treat and even prevent botulism for an extended period of time. As long as scientists continue to invest in high-throughput screening technologies which increasingly are being coupled with nanoreactors, their methods of gene therapy research will become more efficient. This may result in a variety of treatments and preventative medications for bioweapons agents in the mid-term.

*Nuclear Weapons*

The U.S. national labs have been experimenting with microfluidic devices in nuclear material reprocessing,[99] and their research could yield better ways of monitoring declared reprocessing sites and activities. As the U.S. Department of Energy continues to study innovations in the nuclear fuel cycle, it is funding the research and development of sensors which analyze extracted materials in nuclear reprocessing via microfluidic devices.[100] These research grants are awarded with the aim of not only improving the efficiency of nuclear fuel cycles, but also enhancing the management and monitoring of nuclear fuel cycles, which is consistent with the agenda of the International Atomic Energy Agency (IAEA).[101] If microfluidic devices combined with these sensors are eventually integrated into nuclear reprocessing equipment, nuclear regulators can more actively and precisely oversee the fuel cycle. These capabilities can potentially advance response time to irregular reprocessing activities, including malfunction, excess waste production, or hyperactive fissile material extraction.

## WHAT CAN BE DONE?

Microfluidics represents just one of a set of emerging technologies that pose new challenges for policymakers with responsibilities for countering WMD. These emerging technologies interact in ways that magnify their impacts. Restricting research is likely to be either undesirable or unfeasible, which makes nuanced strategies, which will require informal coordination, all the more imperative.

Greater dialogue among key stakeholders is needed to capitalize on the potential benefits of microfluidics and mitigate its relative risks. Nations have opportunities to collaborate to improve strategic trade control regimes, facilitate public-private sector partnerships to reduce the risk of nefarious use of microfluidics, and integrate microfluidics into counter-proliferation regimes and mechanisms.

### *Top-Down*

It may be premature to apply strategic trade controls to microfluidics and nanofluidics in the near term, but multilateral nonproliferation organizations can still begin to grapple with the implications. The OPCW has mentioned the chemical weapons implications posed by microreactors and nanotechnologies involved in nanoreactors with increasing frequency since 2008.[102] Within the OPCW's Scientific Advisory Board, States-Parties have increasingly raised the potential counter-proliferation applications of microfluidics and nanofluidics.[103] Given the far higher risk and greater imminence of misuse for chemical weapons produced by microfluidics than for biological or nuclear weapons, States-Parties

to the CWC face greater imperatives to grapple with microfluidics' implications and can also pave the way for efforts to address potential future biological and nuclear implications.

Perhaps, as microfluidics and nanofluidics technologies proliferate, countries may find the Australia Group (AG) control list an appropriate venue to begin regulating the dual-use item. Currently, the AG list for chemical weapons-related items requires accounting and licensing for reaction vessels or reactors with internal capacities greater than 100 liters volume.[104] The potential "macro" implications of microreactors complicate efforts to regulate them along similar lines, but precisely for that reason, it behooves States-Parties to begin thinking through these challenging issues.

Today, in most cases *more* sophistication is required to obtain and operate a microreactor as compared to traditional bulk, batch chemistry. Over time, microreactors are likely to become more accessible and less challenging to operate, and at some point the dynamic might actually inflect and microreactors might require less sophistication than traditional processes, as has been the case with many other technologies.[105] That inflection is at the heart of the challenge, but also the opportunity, that microfluidics poses.

***Bottom-Up***

Consistent with our explication above, today it is unlikely that actors who cannot already produce chemical, biological, and nuclear weapons would be able to do so with microreactors. However, microreactors already enable sophisticated actors in various ways. And as the technology develops and diffuses, it will empower a broader range of actors.

Therefore, it is imperative that policymakers and industry leaders discuss microreactor proliferation threats to get ahead of, or at least less behind, developments in microfluidics and nanofluidics.

The challenges outlined above essentially restrict the use of microreactor technology for WMD purposes to states in the near term, and even states would confront significant technical hurdles in integrating these technologies into WMD development pathways. Today, only states that have previous experience with chemical or biological weapons production or sizable chemical, biological, or nuclear industries would be able to use microreactors to quickly establish or accelerate WMD programs. But that is already a significant number of states. About 20 states are thought to either have had or presently have chemical weapons programs. A considerably larger number have robust chemical industries. Only a handful of states are thought to have had or presently have biological weapons, though many have biological industries of various kinds. And while the number of states with nuclear industries is smaller than those with chemical and biological-related industries, there are still about a dozen.

And over time, as with all emerging technologies, microreactors will become easier and cheaper to produce as they are developed and standardized. In fact, some recent research has focused on creating a limited number of standard microreactor types that can be interchangeably combined into unique systems able to perform a wide variety of complex reactions.[106]

In the mid-term, nations could be incentivized to implement regulations on microreactor

sales, and industry could be incentivized to screen customers and report to national authorities. But such actions cannot take place without an effective dialogue on microreactor and nanoreactor implications that currently appears largely lacking.

## CONCLUSION

Microreactors, miniature chemical plants that have been in development for over a decade, are still an emerging technology, and we are only beginning to understand their implications. They have significant potential to both enable and counter chemical, biological, and nuclear weapons threats. Their likely use for WMD purposes is currently limited to states that already possess sophisticated capabilities in the relevant chemical, biological, or nuclear domains, but down the road they are likely to have implications for both less sophisticated state and non-state actor threats. They already have implications for state efforts to defend against these threats. As this technology inevitably advances, the challenges and opportunities it entails will only grow. Policymakers and analysts have opportunities now to get ahead of, or at least less behind, the significant and growing implications of this emerging technology.

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## Emergence & Convergence Study

In its multi-year study entitled *Emergence and Convergence*, the WMD Center is exploring the risks, opportunities, and governance challenges for countering WMD introduced by a diverse range of emerging technologies. The WMD Center identified advanced robotics as one of several emerging technologies for deeper assessment. Toward this end, the WMD Center has developed an exploratory framework for first identifying the emerging technologies that will have greatest impact on the WMD space for state and non-state actors and then for evaluating the nature of that impact on the current tools and approaches for countering WMD.

Dr. Natasha E. Bajema, Senior Research Fellow and Dr. Diane DiEuliis, Senior Research Fellow are the co-principal investigators for the study. The Emergence and Convergence study is supported by several offices within the Office of Secretary of Defense (OSD) and receives its primary funding from the CWMD Systems Program Office within the Office of the Assistant Secretary of Defense for Nuclear, Chemical and Biological Defense Programs/Threat Reduction and Arms Control (NCB/TRAC/CWMD Systems). The support by Mr. Jim Stokes, Director, CWMD Systems Program, has been critical to the project's success.

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[3] Both of the authors have mostly non-technical, policy backgrounds, and we have approached this project as policy analysts deeply curious to unpack the extant and potential policy implications of a fascinating emerging technology. This project benefited from the counsel of many colleagues with relevant scientific and technical expertise.

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