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# Emerging Technologies in Chemical Threat Reduction

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## Abstract

Emerging Artificial Intelligence (AI) applications and Machine-Learning (ML) technologies have changed the landscape of chemical threat mitigation. These technologies may enable production of novel threats and evasion of existing regulatory measures by bad actors. However, they can also be applied toward chemical threat mitigation in critical areas. Herein, we discuss the current state of global compliance with regard to chemical weapons norms and highlight applications of emerging technologies in three key areas of chemical threat mitigation: industrial verification, detection platforms, and medical counter measures.

**Keywords:** Countermeasures; Chemical weapons; Dual-use chemicals; Cheminformatics.

**Abbreviations:** AI: Artificial Intelligence; BARDA: Biomedical Advanced Research and Development Authority; CAS: Chemical Abstract Service; CWC: Chemical Weapons Convention; CWA: Chemical Warfare Agent; DEA: Drug Enforcement Administration; EDIS: Electronic Declaration Information System; DNA: Deoxyribonucleic acid; EBL: Endobronchial Lavage; FDA: Food and Drug Administration; GC: Gas Chromatography; HBV: Hepatitis B Virus; HPC: High-Performance Computing; IMS: Ion Mobility Spectrometry; LCMS: Liquid Chromatography Mass Spectrometry; MATCH: Monitoring and Tracking Chemicals; MIPs: Molecularly Imprinted Polymers; ML: Machine Learning; MPS: Microphysiological Systems; NPS: Novel Psychoactive Substances; OPCW: Organisation for the Prohibition of Chemical Weapons; PFAS: Per- and Polyfluoroalkyl Substances; REDIRECT: Repurposing Drugs for Chemical Threats; REMEDi4ALL: Rare and Emerging Diseases Initiative for All; RNA: Ribonucleic acid; SAB: Scientific Advisory Board; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ToxDromes: Diagnostic Toxicological Syndromes; UAVs: Uncrewed Aerial Vehicles; UGVs: Uncrewed Ground Vehicles; VX: Venomous agent X; WMD: Weapons of Mass Destruction.

## Introduction

Advances in new technologies such as Artificial Intelligence (AI) have sparked concern regarding their exploitation by bad actors for development of Weapons of Mass Destruction (WMDs) and other nefarious activities. In the area of chemical threats specifically, robust algorithms for toxicity prediction [1,2] and concurrent advances in retrosynthesis algorithms [3,4] have made it possible for bad actors to use AI technologies to not just identify new chemical weapons candidates but also to develop synthetic methods to access these molecules. During the 2022 Spiez Convergence Conference hosted by the Swiss government [5], experts from diverse fields including drug discovery, artificial intelligence, and disarmament met to identify enabling technologies that have implications for the Chemical and Biological Weapons Conventions and to develop strategies to effectively manage threats as an international community. At this conference, developers of a de novo molecule generator application called MegaSyn2 [6–8] demonstrated that an algorithm designed to make toxicity predictions for drug development could be repurposed to design new molecules with elevated toxicities [9]. In less than 6 hours, the algorithm suggested over 40,000 molecules with toxicities in the specified range, including known chemical warfare agents like VX [10], one of the most potent nerve agents identified to date. One alarming aspect of this result is that the datasets and models used at the conference are similar to open-source options [11]. This raises critical ethical questions for both researchers and regulatory bodies to consider when deciding how and what should be published and made freely available to the public. While it is true that producing these compounds in quantities and formulations necessary for weapons deployment may not be trivial [12], retrosynthesis algorithms have improved concurrently and are able to propose feasible synthetic strategies to access increasingly complex small molecules [4]. Further, these algorithms could be manipulated to prioritize scalable reactions and to use cheap precursor molecules that do not appear on lists of scheduled chemicals, the substances tightly regulated under the Chemical Weapons Convention (CWC) [13].

## Chemical Weapons Convention and Global Compliance

The findings of the above thought experiment underscore the imperative that national and international agencies evaluate current regulatory frameworks to minimize the risks of dangerous chemical research to public health and national security [14–17]. While new technologies, particularly AI, can be exploited by bad actors for




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nefarious ends, they can also be utilized by international agencies to mitigate chemical threats. To both appreciate the current applications of new technologies towards the mitigation of chemical threats and to evaluate opportunities in this space, it is worth reflecting first on the achievements of the CWC and the current state of global compliance.

The CWC, which opened for signature on January 13, 1993, and entered into force on April 29, 1997, was a response to the erosion of respect for international norms against chemical weapons use, which was made apparent in the conduct of the Iran-Iraq war [18–20]. The provisions of the CWC went farther than the previous Geneva Protocol in that it not only banned signatory states from employing chemical warfare agents on the battlefield, but also from developing, producing, acquiring, and retaining them [21,22]. Unlike the Geneva Protocol, the CWC specifies measures to ensure compliance and requires signatory states to disclose their chemical weapons stockpiles and production facilities [23]. The intergovernmental organization tasked with enforcing the CWC, the Organization for the Prohibition of Chemical Weapons (OPCW), has facilitated the destruction of over 72,000 metric tons of toxic chemical agents since the agreement was ratified. This was 100% of chemical weapons stockpiles declared by possessor states [24]. In July 2023, the United States completed the destruction of its chemical weapons stocks and was one of the final nations to do so [25]. In theory, with 193 states committed to the CWC, 98% of the world's population lives under the protection promised by the convention [26].

Unfortunately, despite these notable achievements, chemical risks still remain. Chemical warfare agents have been deployed by both sovereign states as well as by non-state actors on numerous occasions since the Iran-Iraq war. One well-documented example was the use of chemical weapons by the Assad Regime over 50 times during the Syrian civil war. One large-scale attack in 2013 involved the launch of rockets carrying sarin gas into the Ghouta region of Damascus, which resulted in the deaths of over 1,400 people [27,28]. As a result of these atrocities, Syria was pressured by the international community to join the CWC [29,30]. By January 2016, the OPCW verified the destruction of 100% of the Category 1 and Category 2 chemical weapons declared by the Syrian Arab Republic [31]. However, Syria has neither declared nor verifiably eliminated its chemical weapon's program [29,32]. Research conducted by the Global Public Policy Institute concluded that at least 336 chemical weapons attacks occurred during the Syrian civil war, with about 90% of them occurring after the infamous attack in the Ghouta region [33]. Furthermore, the Technical Secretariat of the OPCW issued a report in late 2023 citing 146 allegations of chemical weapons use by Syria between 2015 and 2023 [34]. Contention regarding these allegations hindered consensus on an outcome document at the 5th Chemical Weapons Review conference in May 2023, as Russia and Syria blocked adoption of drafts that mentioned Syria's chemical weapons use [35].

Syria's well-documented violations is just one example of how current geopolitical tensions strain cooperation in enforcement of longstanding nuclear, biological and chemical weapons conventions [36–39]. Both the 2024 annual threat assessment report issued by the US intelligence community and the annual report issued by the Department of State regarding compliance with the CWC mention two other states in noncompliance: Iran and Russia [28,40,41]. In these reports, Burma was cited for failure to disclose past activities, and compliance of the People's Republic of China also could not be verified [42]. One recent example of noncompliance is the battlefield use of traditional chemical weapons by the Russian military in its war of aggression against the Ukraine [43,44]. In May of 2024, the United States imposed sanctions on over 280 individuals and entities in Russia in response to the use of the chemical weapon chloropicrin against Ukrainian forces in violation of the CWC; this is in addition to previous allegations citing repeated Russian use of riot control agents as a method of warfare [45].

There are also recent instances in which new chemical agents have been deployed outside of the battlefield, indicating that the chemical threat landscape has evolved beyond the military use of known chemical warfare agents. Russia utilized Novichok nerve agents [46], organophosphorus compounds similar to sarin and VX, in multiple assassinations, including a failed attempt against Alexei Navaly in 2020 [47,48]. These reports, as well as evidence of laboratory research to develop aerosolized central nervous system agents in Iranian laboratories, suggests that some states may consider chemical agents to be strategic tools for targeted killings, crowd control, or suppression of domestic political dissent [28,49–53].

## Potential Use of Enabling Technologies for Chemical Threat Mitigation

Given the rising geopolitical tensions, increasing examples of noncompliance, apparent exploitation of dual-use chemicals for nefarious purposes, and the emergence of key enabling technologies like AI that could be used for nefarious purposes in the hands of bad actors, there is a clear need for improved monitoring of these three critical aspects of chemical threat mitigation: global chemical transfers, robust chemical detection platforms, and development of broadly applicable medical countermeasures. Each of these aspects are considered here for their beneficial applications in mitigating these threats.

## Digital technologies and AI in the regulation of global chemical transfers

Many chemical threat agents are produced by or are easily accessed by noncompliant states because they are considered dual-use chemicals. Thus, one important application of new technologies to chemical threat reduction is to enable the OPCW to better monitor international transfer of dual-use chemicals and to identify discrepancies in global chemical trade [54]. One distinguishing feature of chemical threats as compared to nuclear and biological threats is that these molecules are synthesized in a laboratory from building blocks made of a combination of multiple precursor chemicals. Increasing digitalization and advances in AI enable tighter regulation of industrial chemical transfers and identification of which precursor chemicals should be monitored. Effective application of these technologies could limit the ability of both state and non-state actors to develop or maintain chemical weapons programs or activities.

### Increasing Digitization Enables Efficient Monitoring of Chemical Transfers

The OPCW regulates trafficking of chemical building blocks by

maintaining lists of scheduled chemicals which include major classes of the chemical threats as well as common precursors used to make them [55]. However, monitoring the trade of precursor chemicals presents notable challenges, leaving space for bad actors to evade regulatory measures. First, the number of chemicals listed in the OPCW's inventory of Scheduled Chemicals represents only a small portion of the chemical space encompassed by "toxic families" of molecules. Second, toxic agents can be accessed by numerous synthetic routes, making it nearly impossible to regulate every possible precursor. The number of possible precursors which can be used is even higher if molecules structurally similar to known chemical threat agents are also considered. Finally, the sheer size of the chemical industry makes the logistics of verification and regulation far from simple. The global chemical industry accounts for about 5.7 trillion US dollars of global economic output, making it the fifth largest manufacturing sector in the world [56,57]. The impact of these challenges is evidenced by the inconsistencies in over 50% of annual declarations made by State parties regarding imports and exports of dual-use chemicals, many of which stem from unintentional human error [58,59].

Advances in AI and machine-learning (ML) technologies, along with increasing digitalization in manufacturing sectors offer the potential to mitigate these discrepancies by simplifying reporting of transfers and identifying anomalies in chemical trade. The significant investments made by the chemical industry in digitization because of "Industry 4.0" – a fourth wave of industrial transformation characterized by the incorporation of cloud systems, AI, and automation into manufacturing – offer significant potential to improve the OPCW's industrial verification scheme [58,60]. The Industry 4.0 movement has yielded numerous benefits for the chemical industry in general, including improved operational efficiency and worker safety; acceleration of innovation cycles; progress toward sustainability goals; and simplification of data sharing [58,61,62]. This same digital transformation provides an opportunity for the CWC's industry verification scheme to better track, back check, report chemical transfers, and minimize discrepancies [58,63]. The OPCW has already developed multiple platforms to enable quick and facile electronic reporting including SIX, a platform for transferring secure information between state parties and the secretariat through an electronic declaration system (referred to as EDIS) [64–66]. The Stimpson Center's Monitoring and Tracking Chemicals (MATCH) project goes beyond digital submission of declarations and seeks to apply block-chain technology to track trade records of individual dual-use chemicals and to reconcile discrepancies in the international imports and exports data [54]. A second iteration of the MATCH platform is in development and aims to increase the scale and transparency of the platform [67,68].

In addition to increasing the ease of reporting chemical transfers, AI and cheminformatics could be harnessed to better equip frontline officers responsible for border security to identify controlled chemicals. The current list of scheduled chemicals includes 63 specific chemicals, specified by name and Chemical Abstract Service (CAS) number as well as "families of molecules" that possess structural similarities to toxic classes of molecules. These families include 34,254 chemicals in the OPCW's scheduled chemical database; even this figure represents only a small fraction of the actual number of molecules possible in each toxic family [58,69]. A trained chemist, who can visually recognize common structural patterns among toxic molecules, may be able to intuitively distinguish between toxic and nontoxic precursors, but this is unlikely the case for an average border patrol officer. The task of discriminating toxic versus nontoxic chemicals is further complicated by the large number of synonyms associated with a single chemical. One project of the Stimpson Center, which is part of the Weapons Threat Reduction Program supported by Global Affairs Canada, aims to develop a database which processes large batches of chemical declarations and automatically matches chemicals against control lists. The cheminformatics tool envisioned would automatically match chemicals of concern to the appropriate toxic family on OPCWs list of scheduled chemicals, flagging them for special attention by customs [70]. Outreach to stakeholders is currently being conducted to further understand challenges frontline officers for border security face to better apply cheminformatics to simplify their work.

Beyond enabling robust monitoring of trade of scheduled chemicals, ML technologies could enable detection of illicit or unreported trade. One example of work in this space is the ATTENTION! project, a collaborative effort sponsored by Universität Bonn and several German and Singaporean industry partners that aims to analyze large databases of imports and exports to develop ML models which identify patterns of illicit trade [71]. While illicit trade is a massive problem costing the global economy approximately $2 trillion annually, there is currently a limited understanding of what patterns illicit transactions follow and few tools available to detect and trace them [71,72]. Similar algorithms could be applied to better detect anomalies in chemical trade and unreported transfers between states or between states and non-state actors. This could have transformative impact not only in mitigating the development of illicit drugs and chemical weapons, but also in preventing environmental and health effects caused by illegal trade of hazardous chemicals and pesticides that are restricted under the Rotterdam convention [73–77].

Increasing digitization of the chemical sector and concurrent advances in artificial intelligence offer potential to improve ease of reporting chemical transfers and thereby mitigate discrepancies and identify anomalies. While the technologies to accomplish these ends exist, efforts must be made to engage industrial partners and border control workers to ensure that these applications are developed in ways that are intuitive to use and are integrated within existing regulatory frameworks.

## Computer-Aided Synthesis Planning Algorithms Applied to Identify Chemical Warfare Agent (CWA) Precursors

Another application of ML technologies in regulation of industrial chemicals is to identify precursors that might be used to produce chemical threats, but which are neither structurally similar to scheduled chemicals nor toxic in and of themselves. For example, the chemical synthesis of opioids such as fentanyl can be achieved via hundreds of methods, utilizing otherwise benign precursors. This number is even higher when the large number of possible fentanyl derivatives are considered. It is no wonder that government regulations are frequently playing catchup with fentanyl producers as new iterations and methods of making these drugs are employed [13,78]. Identifying all possible routes is impossible for even an experienced, highly trained chemist but is achievable with advances in

computer-aided synthesis planning algorithms. Such algorithms have enabled the elucidation of synthetic strategies to access increasingly complex classes of natural products [3,4,79–81].

One challenge in applying ML algorithms to identify strategies employed by bad actors to produce illicit drugs or chemical weapons is that the existing algorithms are trained on reactions carried out on a small scale in research laboratories. Bad actors intending to produce illicit drugs or chemical weapons are more likely to use reactions that are robust, scalable, and importantly can be performed without complex equipment. Thus, these algorithms are of little use in predicting possible synthetic routes to chemical weapons and drugs unless they are retrained on chemical reactions performed at large scale. A recent study by the Grybowski lab overcame this challenge by curating thousands of large-scale industrial reactions that they then used to develop a model able to identify over 200 ways to synthesize fentanyl via scalable, simple reactions [13,82]. The algorithm, reassuringly, surfaced known routes [83], such as the Janssen method, which is comprised of precursors tightly regulated by both US Drug Enforcement Administration (DEA) and international regulatory bodies, [84,85]. But On a more somber note, the algorithm also revealed 166 synthetic routes that do not require any DEA-regulated intermediates – potentially exposing many regulatory holes that might be exploited in the illicit drug market.

While the notion that over 100 feasible synthetic routes exist to synthesize opioids and thereby evade surveillance is alarming, these algorithms offer enormous opportunity for identifying previously unregulated precursors and reagents whose distribution should be more tightly monitored [86].

The Grybowski study also identified several additional applications of ML technology beyond simply identifying unregulated precursors. ML algorithms could be applied to rank routes according to their practicality and to identify combinations of chemicals that are likely to indicate ill intent – even if the individual precursors are inert [87]. Another possibility is identifying the method by which a seized drug sample was produced using the trace presence of by-products and starting materials in experimental mass spectra of the sample [13]. Additionally, because these algorithms work not just in the backwards direction, but also in the forward direction, inputting substances suspected to be involved in illicit drug production could identify accessible derivatives [13,88]. Given the infinite size of chemical space, there are potentially infinite synthetic routes available to produce chemical threat agents while simultaneously evading detection. Computer-aided synthesis planning software offers a powerful tool for regulatory agencies to preemptively identify precursors being used for ill intent and to improve monitoring. When access to these algorithms is appropriately regulated, regulatory agencies could have a leg up on drug cartels and bad actors. However, it should be noted that these bad actors could easily query the same programs to identify an alternative production route [13,86]. This reinforces the importance of discussion within and between the scientific community and regulatory agencies about the regulation and safe dissemination of AI applications and ML technologies; while open access is certainly a plus for scientific innovation, restricting queries on certain classes of chemicals could safeguard from their use through these tools by bad actors [13,89].

## Emerging technologies in improved detection of chemical agents

In addition to applications in the regulation of chemical transfers, emerging AI/ML technologies can be utilized in the detection of chemical agents in the context of OPCW's routine verifications and investigations of chemical incidents [23,90]. Accurate and timely detection is critical both to conduct risk assessment and to hold member states accountable for their commitments under the CWC. Chemical forensics to investigate alleged violations of the CWC are carried out at 30 designated laboratories in 21 different nations; these laboratories are accredited by OPCW to perform analyses on biomedical or environmental samples collected from putative incident sites [91]. The analytical capacities of these laboratories were first leveraged to investigate violations of the CWC during the Syrian civil war, where evidence suggested that chlorine, sulfur mustard, and sarin gases were used as chemical weapons [92,93]. In order to ensure this network of laboratories remains able to rapidly and accurately investigate chemical incidents, a scientific advisory board (SAB), made up of twenty-five independent experts from member states, was established to ensure that detection and verification protocols remain in step with technological advances [94].

In May of 2024, the SAB's temporary working group on chemical forensics convened and noted several challenges hindering rapid and accurate detection of chemical agents. Two challenges particularly relevant in the investigation of chemical incidents were the limited access to incident sites and the limited access to reference standards [91]. With regards to the first issue, delayed access to incident sites can compromise the integrity of samples collected because the chemical agents being investigated are often reactive and degrade quickly, resulting in samples containing a complex mixture of different degradation products. For this reason, identifying the metabolites and degradation products of a chemical warfare agent are often more important than quantifying the chemical warfare agent itself. This task is more difficult and requires more sensitive analytical techniques because of the large number of distinct compounds and their lower concentrations in the sample [95]. One way to address the challenge posed by degradation of chemical agents, is to minimize logistical bottlenecks to ensure prompt access to incident sites and shortened time between sampling and off-site analysis of samples. In addition, the development of portable detection platforms and methods to identify degradation products are also critical to improve the integrity of incident investigations and routine verifications.

### Nanomaterials and Designer Proteins for Portable Testing Platforms

In OPCW accredited laboratories, samples are typically analyzed by Liquid Chromatography Mass Spectrometry (LCMS) or Gas Chromatography Mass Spectrometry (GCMS), both of which offer incredible sensitivity and can detect chemicals at sub-picomolar concentrations [96,97]. However, these large bench-top instruments are generally housed in specialized laboratories. Given the challenge of access to incident sites for sample collection, there is a need for more portable devices that can detect ultralow concentrations of chemical threat agents accurately and in real-time. Data obtained from portable devices would enable more rapid responses. Confirmatory data later obtained by LCMS or GCMS analysis of samples at OPCW

laboratories would enable a more comprehensive analysis of incidents and improved decision making by regulatory officials.

One approach to this challenge is to modify a gold standard analytical technique, LCMS, such that it is amenable for a field-deployable device. Increasingly portable devices equipped with LCMS-based detection have been developed for both military applications and for the detection of per- and Polyfluoroalkyl Substances (PFASs), common pollutants found in numerous consumer cleaning products, in soil samples [98–102]. Alternative methods that have been explored and used in the field include ion Mobility Spectrometry (IMS) [103], infrared spectroscopy [104], Surface Acoustic Wave (SAW) sensors [105], and spectrophotometric sensors and fluorescent probes based on color change reactions [106–108]. IMS is a particularly attractive analytical method as it offers both low limit of detection and instantaneous response and has been incorporated into numerous portable field detectors [103,107]. However, one drawback is that the IMS detector's response can be affected by humidity, temperature, and chemical interference in highly contaminated environments [103]. Chemical detection methods, which utilize a chemical reaction between a nucleophilic substrate on the sensor platform and the electrophilic chemical warfare agent of interest, have also been developed. Chemical methods often produce false positives stemming from the low specificity of the reaction itself [109].

Compared to LCMS, both IMS and chemical methods have historically suffered from poor sensitivity and selectivity. Recent advances in de novo protein synthesis, polymer design, and nanotechnology have substantial implications for addressing these dual challenges of specificity and sensitivity. A chemical sensor requires that selective binding or reaction of the chemical agent triggers a signal, often electrical, which can be quantified. Nontechnology enhances sensitivity by providing increased surface area for recognition elements, thereby increasing signal to noise ratio and generating a more robust signal on a smaller device [110]. Advances in de novo synthesis of designer proteins, RNA, and synthetic polymers provide an opportunity for enhanced selectivity of key chemical interactions.

Advances in technologies related to the bottom-up design of small molecule binding proteins have made it possible to develop sensitive and selective protein sensors that undergo a conformational change in response to binding specific chemical agents of choice [111–113]. Sensors have been developed which bind peptides including antibodies against viruses such as HBV and SARS-CoV-2, opioids, and the small molecule nerve agent VX [111,113,114]. In the case of the computationally designed VX-binding proteins, detection of VX was successful within seconds at concentrations three orders of magnitude lower than its toxicity in water, and without requiring additional signal-enhancing reagents [111]. Aptamers, single-stranded oligonucleotides (e.g., RNA and single-stranded DNA) that fold into defined architectures, possess binding affinities like those of proteins and have been utilized as recognition elements in sensors to detect arsenic and illicit drugs in wastewater [115–120]. Molecularly Imprinted Polymers (MIPs), which are tailor-made, synthetic polymers developed for molecular recognition of specific molecules, have also been used to improve selectivity of non-enzymatic sensors [121–123]. This approach has been used to successfully identify diazon, an organophosphorus pesticide, and nitrosodiphenylamine, a common carcinogen, in wastewater, as well as illicit drugs in plasma and urine [124–129]. The ability to custom design selective chemical recognition elements, be they proteins, aptamers, or polymers, accelerates the development of new sensors even for chemical threat agents which have emerged more recently.

More portable detection platforms made possible by advances in nanotechnology are already being deployed for on-site analysis and complement the LCMS or GCMS analyses that can be later confirmed by research or diagnostic laboratories in their ability to detect specific chemical agents at low concentrations in real time. Technologies underway may make it soon possible for such portable devices to be integrated into Uncrewed Aerial/Ground Vehicles (UAVs/UGVs) for remote sampling and sensing [58,130].

## Advances in Metabolomics Enable Deconvolution of Complex Samples

Portable and remote-detection platforms address challenges associated with access by providing an additional source of data to complement samples collected from incident sites and analyzed in OPCW-accredited laboratories. Advances in metabolomics, the high-throughput identification and quantification of small molecules in a biological sample, address this challenge from a different angle by allowing researchers to interpret complicated chemical signatures even after chemical threat agents have undergone significant metabolism or degradation, including uptake into humans, animals, or plants. For example, metabolomics can be used to identify exposure to chemical warfare agents or illicit drugs, such as the identification of chlorinated adducts of amino acids that result from exposure to chlorine gas or identification of metabolic products of specific fentanyl derivatives [131,132]. The sensitivity of metabolomic analysis has improved substantially such that many biomarkers can be identified via a dried blood spot, mitigating the need to collect larger plasma samples [133]. Plant samples can also be utilized for such analyses, and work initiated under the OPCW Plant Biomarker Challenge showed that biomarkers for exposure to chlorine gas and other CWAs including nerve agents are not plant-dependent and are stable in plant material up to three months post-exposure [134].

## Spectroscopic Prediction Algorithms Enable Identification of Threats in Absence of Reference Standards

Another challenge cited by the OPCW's working group is the identification of chemical threats without appropriate reference standards. Acquiring references for the full range of possible chemical threat agents is challenging not only because of the sheer number of possible agents, but also because of the sensitivity associated with sharing synthetic routes to these chemicals. The OPCW Centre for Chemistry and Technology includes a state-of-the-art microscale synthesis facility, where such reference standards may be produced in order to address this critical need [91].

Advances in AI could also be harnessed to predict spectral characteristics of chemicals based on their structure in the absence of suitable references. A generative ML model has been developed that is able to identify Novel Psychoactive Substances (NPS) from mass spectral analysis alone without reference materials [135–137].

Another notable example is the application of a molecular network to detect previously unknown novel per- and Polyfluoroalkyl Substances (PFAS) in wastewater samples [138]. The presence of common chemical motifs across classes of chemical warfare agents may enable a similar approach to identify previously unknown agents that bear structural similarity to existing threats. In addition, the application of ML algorithms that predict spectral patterns from structural data could be applied to fill data gaps in reference libraries and help identify unknown compounds.

In the field of chemical threat detection and investigation, limited access, resulting sample degradation and lack of reference compounds have at times impeded efficient chemical threat assessments. Increasingly portable detection platforms, the ability to deconvolute degraded samples, and reference free analysis methods could address these challenges.

## Applications of AI towards development of medical countermeasures

In circumstances where a bad actor does produce and deploy chemical threat agents, broadly applicable medical countermeasures are needed to counteract the toxic effects of these chemicals to ensure that harm to civilian or military personnel can be mitigated. In the past decade, advances in ML algorithms for protein structure and ligand prediction have accelerated the discovery of drug candidates. Improvements in High-Performance Computing (HPC)-based pharmacokinetics modelling [139], toxicity prediction algorithms [1], and organ-on-a-chip technology [140] offer promising means to reduce attrition rates during animal testing and clinical trials. These technologies are already impacting the drug discovery pipeline broadly and offer significant potential in the future development of medical countermeasures to treat exposure to chemical threats.

### Discovery of Medical Counter Measures via Drug Repurposing Campaigns and Ligand Prediction Platforms

One strategy being pursued by Biomedical Advanced Research and Development Authority (BARDA), a US government agency that focuses on research to promote health security, is to repurpose already FDA-approved drugs to treat exposure to toxic chemical agents [141]. The general approach, espoused by BARDA's REDIRECT initiative, is to treat five general classes of symptoms, termed diagnostic toxidromes, which are associated with exposure to certain types of chemical threat agents. If effective medical countermeasures are discovered that are already FDA-approved drugs, the need for lengthy and expensive clinical trials is alleviated. This approach is not new, and similar initiatives have been pursued to discover treatments for rare diseases through Harvard's BROAD Institute and the EU's REMEDi4ALL initiative. AI applications could also be utilized to identify candidates for repurposing, similar to what was attempted during COVID-19 [142–144]. Historically, numerous challenges have limited the effectiveness of this approach, including minimal funding mechanisms and bottlenecks in data access and integration, particularly for clinical data [145–149]. Nevertheless, the REDIRECT initiative has identified several new promising alternatives,, including the repurposing of the endobronchial lavage (EBL) procedure. Initially developed for lung cancer treatment, EBL was used as a drug-delivery method for the treatment of inhaled chemical threat agents. Another example is the FDA approval of the anti-inflammatory drug MN-166 (Ibudilast) for prevention of acute lung injury associated with chlorine gas exposure [150].

Another strategy to discover new therapeutics for those exposed to toxic chemicals is to harness improvements in ligand-prediction platforms and protein modeling. The quantity and quality of protein structural data enabled by multicomponent AI platforms such as Alphafold that use ML to predict protein structures based on amino acid sequence [151–153]; improvements in computing power [154]; and expansion of small molecule screening libraries [155,156] have significantly improved the ability to identify viable drug candidates. If the mechanism of toxicity is known for a given chemical agent, a suitable protein target and small molecule inhibitor can be quickly identified through these new powerful technologies. Recently, a neural network model was developed which predicts the binding behavior of thousands of small molecule fragments from fragment-based, drug-discovery screening libraries [157]. The authors of this study were able to develop promising inhibitors for three different protein targets of interest by using the hit fragments identified by the platform. This approach has been applied beyond small molecule fragments to larger macrocyclic peptides, illustrating the potential of this approach for molecules of increasing complexity [158].

To fully realize the potential of these new technologies, advances in automated iterative small molecule synthesis and autonomous closed-loop experimentation could be harnessed to address the persistent synthesis bottleneck associated with medicinal chemistry campaigns. Indeed, this approach has been successfully applied to discover new materials for organic lasers and to identify general chemical reaction conditions for Suzuki Miyaura cross-coupling reactions, but its potential in the drug discovery space remains untapped so far [159–161].

### Organ on a Chip Technology can Accelerate Preclinical Development

Another bottleneck in drug development is the large number of promising candidates that fail during animal testing and in human clinical trials. Drugs being repurposed for use as medical countermeasures avoid this hurdle, since safety tests have already been completed for most of these drug candidates. However, for new molecular entities, advances in ML models for prediction of pharmacokinetic properties and the emergence of organ-on-a-chip technology have the potential to streamline clinical testing by enabling earlier identification of toxicity [162]. These advances are in line with recent passage of the FDA Modernization Act 3.0, which aims to improve predictivity of nonclinical testing by reducing dependence on animal models and developing better human cell- and organoid-based assays [163–165]. Microphysiological Systems (MPS) or "tissue chips" are experimental, human cell-based platforms intended for screening drug candidates. BARDA's ImmuneChip+ Program is working to develop an MPS with a fully integrated immune system to reproduce pathology associated with exposure to chemical threats and to screen for new therapeutic candidates [166].

One daunting challenge associated with medial countermeasures research is the evolving nature of the chemical threat landscape. Advances in the drug discovery and clinical testing space enable

rapid development and testing, while also enabling treatments to be developed at a pace that remains in step with the constantly changing nature of threats. Another challenge is the diversity of chemical threats. The sheer number of possible chemical agents, all with unique modes of toxicity, makes the "one chemical, one treatment" approach nearly impossible to employ [167]. Research efforts need to continue to meet these challenges. It is also important to encourage public-private partnerships to prioritize treatments with broad utility across many types of chemical threat agents.

## Conclusion

Emerging technologies present a range of opportunities for improved chemical threat mitigation; however, implementation of these measures is not without its challenges. One challenge in effectively implementing these measures, particularly regarding the areas of verification and investigation, is the necessity for multilateral cooperation in a time when geopolitical tension and great power competition is heightened [168]. While many Western nations may believe that verification is a useful way to build confidence and trust, the traditional preference of many non-Western nations, particularly China, is that trust is an imperative precondition for cooperative verification [169].

Another challenge relates to the access of expertise in and experience with these cutting-edge technologies, datasets, and algorithms. On the one hand, public availability of AI algorithms, ML platforms, and toxicity datasets, as evidenced by the thought experiment carried out at the 2022 Spiez Convergence Conference, opens the opportunity and possible risk of these algorithms being employed by bad actors for nefarious ends [9]. Guardrails on access and the types of searches that can be queried could mitigate some of these risks while not hindering innovation. On the flip side, limited data access regarding proprietary compounds and the concentration of AI expertise in a relatively small number of corporations can hinder application of these technologies in the public sector – thus necessitating effective public private partnerships for maximum impact. Rapid advances in AI and biotechnology can complicate chemical threat mitigation strategies by enabling bad actors to develop new chemical weapons or evade surveillance. Yet, these same technologies when used effectively by government agencies have incredible potential to improve regulatory control, detection, and medical treatment in the event of exposure.

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