Countering the threat of Ricin

Contrer la menace de la ricine

SERB

Abstract

Ricin is one of the most toxic biological agents, classified as a level 1 chemical weapon and a category B bioterrorism agent. Easily accessible and requiring little technical expertise, the toxin can be used for malicious purposes, as illustrated by several hostile or terrorist acts in recent years. While several international expert reports have been highlighting the reality of the ricin risk for almost 10 years, the current geopolitical climate has also reinforced this risk. SERB Pharmaceuticals, looking to meet this unmet need and drawing on its expertise in polyclonal antibodies, is currently developing an antidote with promising preliminary results.

Key Words: ricin, threat, antidote, ovine polyclonal antibody, SERB

Résumé

La ricine est l'un des agents biologiques les plus toxiques, classé comme arme chimique de niveau 1 et agent de bioterrorisme de catégorie B. Facilement accessible et ne demandant pas de connaissances techniques très poussées, la toxine peut être utilisée à des fins malveillantes, comme l'illustrent plusieurs actes hostiles ou terroristes au cours des dernières années. Alors que plusieurs rapports d'experts internationaux soulignent la réalité du risque ricine depuis près de 10 ans, ce dernier se retrouve aussi renforcé par le climat géopolitique actuel. SERB Pharmaceuticals, cherchant à répondre à ce besoin non couvert et fort de son expertise en anticorps polyclonaux, développe actuellement un antidote avec des résultats préliminaires prometteurs.

Mot clés : ricine, menace, antidote, anticorps polyclonal ovin, SERB

Introduction

Ricin is one of the most toxic biological agents known to man; it's classified as a Schedule 1 chemical warfare agent under the Chemical Weapons Convention[1] and defined as a Category B bioterrorism agent by the US Centers for Disease Control[2]. The ingredients, equipment, and knowledge required to weaponize ricin are readily available. Although several governments are known to have funded research and development into potential medical countermeasures, as of today there are no prophylactic or post-exposure therapies for ricin toxin poisoning.

Easy to procure and weaponize

Ricin has several characteristics that set it apart from other weapons-grade chemical or biological agents, or even radiological or nuclear material, and make it a particularly serious threat.

- Materials are low cost and easy to acquire. Ricin is produced in the seeds of the castor plant (*Ricinus communis*). Castor beans are processed throughout the world to make castor oil for industrial or cosmetic applications, and ricin is present in the waste "mash" of this production process. The fast-growing plant can be grown in tropical and sub-tropical climates. Castor beans are also available for sale online.
- Weaponizing ricin requires no specialist chemistry or pharmaceutical knowledge, nor does it require expensive equipment or advanced technology.
- Information on how to design a ricin weapon is easily accessible with instructions available online.

In 2018 German police raided the home of a 29-year-old Tunisian jihadi in Cologne and found 1,000 castor beans purchased online, other chemicals needed to extract the poison, an electric grinder, and an ISIS guide on how to create a "ricin bomb."[3]
In fact, jihadi extremists have published several manuals for producing ricin. As recently as 2023 a Chechen jihadist group was seen discussing ricin production recipes on its Telegram channel, offering step-by-step instructions and recommending preferred extraction and delivery methods.[4]
Another terrorist plot was foiled in Germany last year when police detained an Iranian man who had procured ricin, as well as cyanide, and was suspected of having planned what investigators described as a "serious act of violence endangering the state." [5]

Ricin as a Bioweapon

Because there has never been a large-scale ricin attack, the threat from ricin is often associated with assassination and small-scale criminal activities. Many will be familiar with the use of ricin in the 1978 assassination of Bulgarian writer Georgi Markov, who was poisoned with a ricin pellet launched from a specially designed umbrella while walking across Waterloo bridge in London.
Last year a Canadian woman was sentenced to 22 years in prison for sending letters laced with ricin to Donald Trump in 2022. A man in Mississippi plead guilty in 2014 to sending letters containing ricin to Barrack Obama. Over the past two decades mainstream news outlets have reported on dozens of ricin incidents such as terror

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plots, poisonings and self-harm in Europe, the UK, and the US.

But how credible is ricin as a weapon for a terrorist group or hostile state actor?
Some assessments dismiss the likelihood and impact of a large-scale ricin attack, but these assessments may be based on exaggerated scenarios. For example, scenarios where several tonnes of ricin would need to be dispersed over a 100km^2 area, or scenarios involving the contamination of public reservoirs with several tons of ricin, have been challenged for being overly simplistic. Smaller scale operational attacks remain viable and with the wide availability of drone technology, far smaller volumes could still pose a credible threat to military installations or the public.
Other assessments take an out-dated view of the technical capabilities and equipment necessary to aerosolize ricin without damaging the protein that constitutes the poison. While overcoming this challenge may previously have required advanced technology, today the necessary equipment can be easily obtained, and at a moderate cost, even by non-state actors.
Clearly the threat landscape has advanced. A fair and up-to-date assessment of the likelihood and impact of a ricin attack casts into stark relief the need to develop medical countermeasures.

Assessing the Ricin Threat

Three independent, collaborative, international assessments have been published since 2016 by experts in the field of biological and chemical weapons highlighting ricin as one of the most likely agents to be used in a CBRN (Chemical, Biological, Radiological, Nuclear) attack.

- In 2016 a **NATO Task Group** lead by **Norwegian Defence Research** assessed the technical probability of biological agents being used by both state and non-state actors. They evaluated the ease of procurement, manufacture, weaponization and dissemination. They concluded that ricin is the 2nd most probable of all biological warfare agents to be used by a non-state actor (with anthrax ranked as most probable) and the 4th most probable to be used by a state actor.[6]
- In 2018 a team from the **US Department of Defence, Canada, the Netherlands, and NATO's Biomedical Advisory Council** assessed 33 biological agents using 12 key properties. They ranked ricin as the agent with the highest weaponization potential.[7]
- In 2020, the Director General of the Organisation for the Prohibition of Chemical Weapons (**OPCW**) requested that a Temporary Working Group (TWG) "review the science and technology relevant to the analysis of biotoxins and considerations that need to be taken into account in investigations of their alleged use". In a report published in 2023, the Temporary Working Group concluded that the focus of the OPCW will remain on ricin and saxitoxin for the foreseeable future.[8]

The current geopolitical climate, including the war in Ukraine, instability in the Middle East and challenges in the Indo-Pacific can only elevate concern surrounding chemical and biological threats. Perhaps chief among these concerns is Syria's 2014 declaration to the OPCW of the existence of a ricin programme, including production facilities and stockpiles of purified ricin. The destruction of all these assets in Syria has never been fully verified.[9,10]

Developing a Ricin Antidote

SERB Pharmaceuticals is uniquely positioned in the world of medical countermeasures to develop an antidote for ricin.
SERB is a global, specialty pharmaceutical company with operations across Europe, the US, Middle East, and Australia through 18 commercial affiliates and 3 manufacturing sites. The company provides the world's broadest portfolio of antidotes and essential medical countermeasures, partnering with health authorities, governments, and militaries. In fact, the company's portfolio is unique in that it includes products to counter each specific element of the CBRN threats.

Aerial view of SERB's biologic manufacturing site in Wales. **©SERB**

SERB is also one of the few companies in the world manufacturing polyclonal antibodies at a commercial scale—and to rigorous pharmaceutical quality standards—with a process robust enough to satisfy regulators in all territories. For more than 20 years, the company has used this polyclonal antibody technology to produce two commercially available medicines: CroFab® and DigiFab®. More recently, the company has begun to use this platform to develop novel biologic therapies against a wide range of toxins, drugs, and viruses for use around the world.
In 2022 SERB began a self-funded programme to develop a potential treatment for known or suspected ricin poisoning using its polyclonal antibody platform.
SERB produces antibodies by immunizing sheep at a dedicated facility in Australia with an antigen that the antibodies will be directed against. The antigen is specific to the toxin that the antidote is being developed for, in this case ricin. The animal's immune system responds to the antigen by producing a mixture of different antibodies, which are then collected from the animal's blood. In SERB's facility in Wales, the binding end of the fragmented antibody 'Fab is separated from the rest of the antibody, known as the Fc (fragment crystallizable) region, and purified. The lyophilized products can be delivered to hospitals or emergency stockpiles.
This polyclonal antibody infrastructure can be scaled up to manufacture up to 100,000 vials per year.

Production technicians inside a clean room at SERB's biologic manufacturing facility, **©SERB**
[CLEAN ROOM]

The advantage of Polyclonal Antibodies

Although polyclonal antibodies can be overshadowed by newer, easier to produce monoclonal antibody approaches, there are substantial advantages to polyclonal antibodies when designing antidotes for toxins.

These antibodies are called "polyclonal" because they are made by several different immune cells within the host. They all bind to the antigen, but they attach to different epitopes –varied molecular structures on the surface of the antigen. This differs from monoclonal antibodies, which are made using identical immune cells that are all clones of a specific parent cell and bind to a single epitope. The advantage is that polyclonal antibodies can recognize and target a wider range of variation in the target antigen, rather than just one specific type. For example, a polyclonal antibody may be more likely to bind to a virus or bacteria that has mutated, or where there are natural variations in a natural toxin, as with multiple strains of ricin.

For example, SERB conducted early phase development of an antibody for the corona virus. Data from binding studies show that these polyclonal antibodies performed similarly to monoclonal antibodies when binding to the Wuhan strain of the virus. However, as the virus mutated through the Delta and Omicron variants, monoclonal antibodies no longer attached to the virus, while the polyclonal continued to bind to these variants.

In addition to its ricin program, SERB is evaluating a wide range of targets that are suited to a polyclonal antibody solution, including additional toxins, infectious diseases, biological agents, and drug toxicities.

Production technicians inside a clean room at SERB's biologic manufacturing facility. **©SERB**

Early Results are Promising

SERB has published in-vitro neutralization data which showed strong efficacy at a low IC50 (inhibitory concentration) against two wholly different ricin strains. This demonstrates the potential for a relatively potent antibody that also offers a broad spectrum of efficacy.

The company has also conducted a dose range finding study using a mouse model. This data offers evidence of a consistent dose response, survival outcomes at an acceptable dose, and an adequate window of opportunity for treatment. This data is sufficient to allow the company to select a target dose and begin pivotal toxicology studies. The company plans to have its first GMP produced batch available in mid-2024.

Partnering with Governments, Militaries, and Healthcare Providers

Having published early in-vitro data, generated encouraging in-vivo data, and having received scientific advice from the FDA and EMA, the company is now meeting with governments and military organisations around the world to better understand their perception of the ricin threat, their doctrine for responding to it, and how best to work together to address it through meaningful partnerships.

Leveraging SERB's know-how in antibody development and long track record of commercial-stage manufacturing, there is an opportunity to close a significant gap in the field of biodefense and medical countermeasures. The company is eager to work with military forces, governments, and other emergency preparedness organisations to help protect soldiers and the general public.

References

1. https://www.opcw.org/chemical-weapons-convention/annexes/annex-chemicals/schedule-1
2. https://emergency.cdc.gov/agent/agentlist-category.asp
3. Brennan, D., 2018, Jihadist Made Ricin With Web-Bought Castor Bean Seeds, Police Say, Newsweek. Available at: https://www.newsweek.com/jihadist-made-ricin-web-boughtcastor-bean-seeds-police-say-977244
4. Arbel, S., 2023, Chechen Jihadist's Critical Analysis of a Ricin Poison Instructional Video, CBNW. Available at: https://nct-cbnw.com/chechen-jihadists-critical-analysis-of-a-ricin-poison-instructional-video/
5. https://www.reuters.com/world/europe/german-police-detain-iranian-suspected-planning-islamist-motivated-attack-2023-01-08/
6. NATO, 2016, STO Technical Report TR-HFM-186. Available at: doi:10.14339/STO-TR-HFM-186
7. Cieslak, T. et al, 2018, Beyond the Dirty Dozen: A Proposed Methodology for Assessing Future Bioweapon Threats', Military Medicine, Vol 183, Issue 1/2. Available at: doi:10.1093/milmed/usx004
8. OPCW, 2023, SAB/REP/1/23 – Analysis of Biotoxins. Report of the Scientific Advisory Board's Temporary Working Group. Available at: https://www.opcw.org/sites/default/files/documents/2023/04/Analysis%20of%20Biotoxins%20Final%20Report.pdf https://www.armscontrol.org/factsheets/syriaprofile
9. https://www.nti.org/countries/syria/