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Just Enough. What Amounts to Success for a Synthetic Opioid Antidote

Threats Lingering in the Open Air

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DEFENSE THREAT REDUCTION AGENCY

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Front cover: An Airman uses a nerve agent treatment on a simulated-infected Airman during a chemical, biological, radiological, nuclear, and explosive training exercise. Photo courtesy of the U.S. Air Force. Photo by Samuel King Jr.

Inside cover: Airmen intubate a simulated patient during an exercise. Photo courtesy of the U.S. Air Force. Photo by Staff Sgt. Kyle Brasier.

Back cover: Mitochondrial DNA technician readies a sample to amplify its target DNA. Photo courtesy of the Department of Defense. Photo by Fred W. Baker III.

Just Enough.

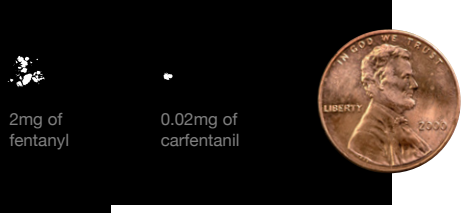
What amounts to success for a synthetic opioid antidote.

The first wave of deaths in the opioid epidemic began in 1999. By 2018, more than 450,000 Americans had died from opioid intoxication or overdoses[1,2] and synthetic opioids had established themselves as an emerging threat to warfighters and first responders. An antidote for an opioid overdose is naloxone, but the amount that reverses an overdose of a natural opioid, such as morphine, is not effective against synthetic opioids such as carfentanil, a fentanyl-based sedative used on elephants and other large mammals.

In the illustration above, the powdery dust next to the penny is 2mg of fentanyl. Just 2mg can be lethal to people.

Source: U.S. Drug Enforcement Administration (DEA). Fentanyl. DEA website. https://www.dea.gov/galleries/drug-images/fentanyl. Accessed May 26, 2020.

1. Centers for Disease Control and Prevention (CDC). Opioid data analysis and resources. CDC website. https://www.cdc.gov/drugoverdose/data/analysis.html. [Page last reviewed on March 19, 2020.] Accessed May 26, 2020.
2. Healthline. 2018. Opioid intoxication. Healthline website. https://www.healthline.com/health/opioid-intoxication. [Page last reviewed on September 7, 2018.] Accessed May 26, 2020.



The amount of carfentanil that is lethal to a person is 0.02mg, which is far less than the lethal dose of fentanyl. Source: Figueroa T. 2019. From January to June, fentanyl overdose deaths in county rose 68 percent over the first half of last year. San Diego Union Tribune website. https://www.sandiegouniontribune.com/news/public-safety/story/2019-12-22/medical-examiner-data-shows-fentanyl-overdose-deaths-in-county-up-68-percent-over-last-year. Accessed May 26, 2020.

Even an accidental exposure to microgram levels of carfentanil can lead to intoxication and the need for medical countermeasures that quickly reverse the adverse effects. But how much naloxone is an efficacious antidote? To answer this question, the Defense Threat Reduction Agency's Chemical and Biological Technologies Department (DTRA CB) is supporting research performed by the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD).

USAMRICD scientists conducted naloxone safety and efficacy studies using a combination of physiological and behavioral assessments in two animal models (small animal and a nonhuman primate). The physiological assessment evaluates respiratory rate, heart rate, blood pressure, etc., for the efficacy and safety of the naloxone doses given to the animals to counter their exposures to carfentanil.

Scientists have identified the therapeutic dose of naloxone that safely and effectively reverses the effects of carfentanil intoxication.

The behavioral assessment makes use of reward-based tasks to identify when the animal returns to 'normal' behavior after exposure to carfentanil and administration of naloxone. The research seeks to identify the safe and efficacious dose of naloxone, the frequency in which that dose must be administered, and the point in time when the animal is able to quickly and correctly perform a reward-based task. Reward-based testing in a nonhuman primate has relevance for human-based tasks as the testing measures changes in speed and accuracy in performing a trained task.

Based on study data, scientists have identified the therapeutic dose (for official use only) of naloxone that safely and effectively reverses the effects of carfentanil intoxication. In 2019, results from this research were transitioned to the Joint Program Executive Office Medical Countermeasure Systems through a signed Data Transition Agreement. The research finding has enabled the Department of Defense's Rapid Opioid Countermeasure System (ROCS) Program of Record to engage a pharmaceutical company to develop an autoinjector for administering the therapeutic dose of naloxone.

Through a separately funded effort, DTRA CB is also developing a higher concentration of naloxone that will be available in a larger, multidose vial. When taking care of warfighters and first responders exposed to carfentanil or an equally potent synthetic opioid, the availability of the vial of concentrated naloxone will enable the medic or clinician to prepare efficacious doses as needed and reduce the frequency of reaching for another vial of naloxone.

With the therapeutic dose of naloxone identified, research at USAMRICD continues, through DTRA CB's support, to learn how often the dose must be administered to effectively reverse a fentanyl-based intoxication. In 2022, a stronger dose of naloxone will become available to warfighters and first responders who will be on the frontlines to defend themselves and others against attacks of carfentanil and other fentanyl-based synthetic opioids. The stronger drug may also help prevent deaths due to intoxication from synthetic opioids. ●

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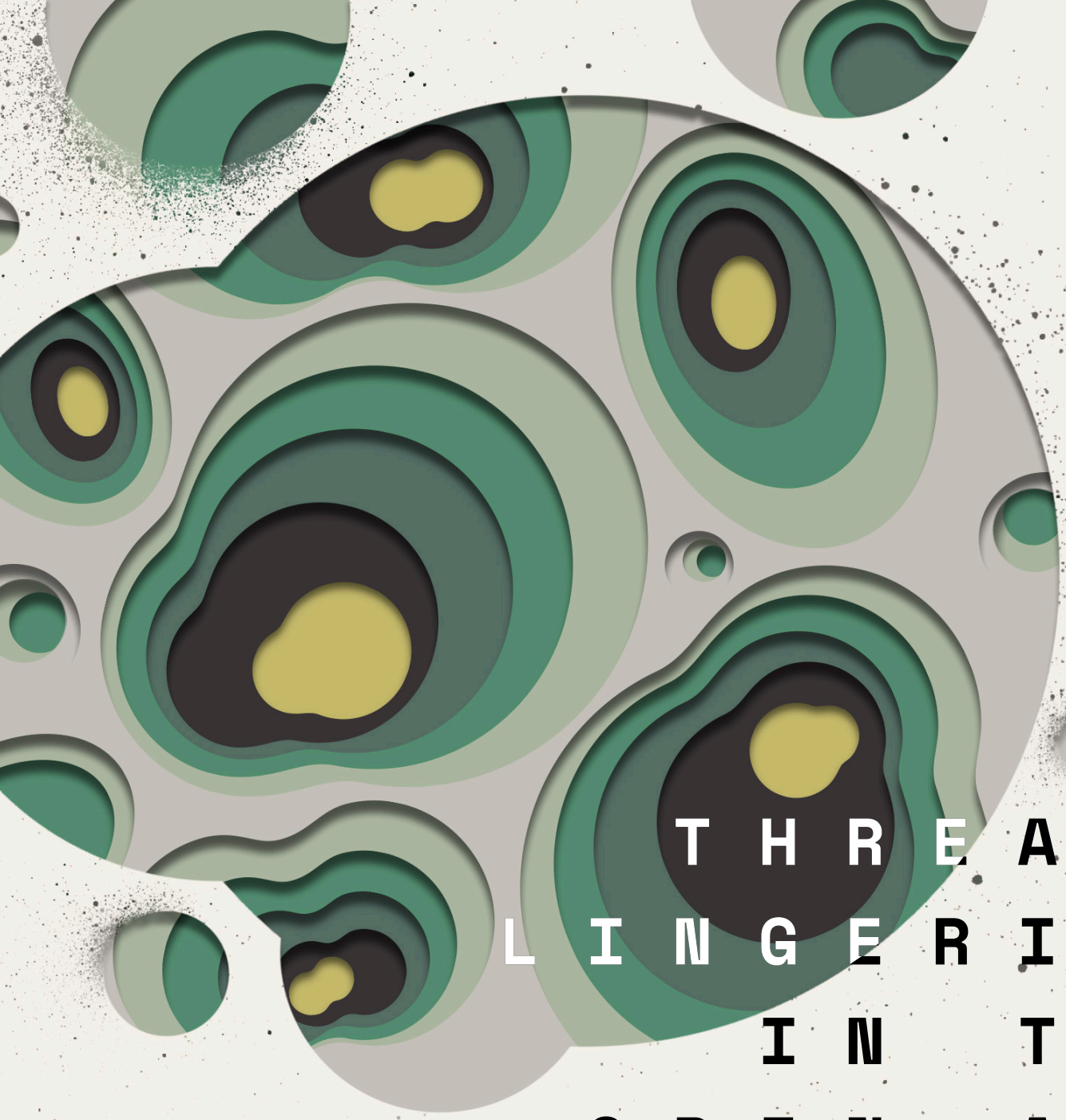
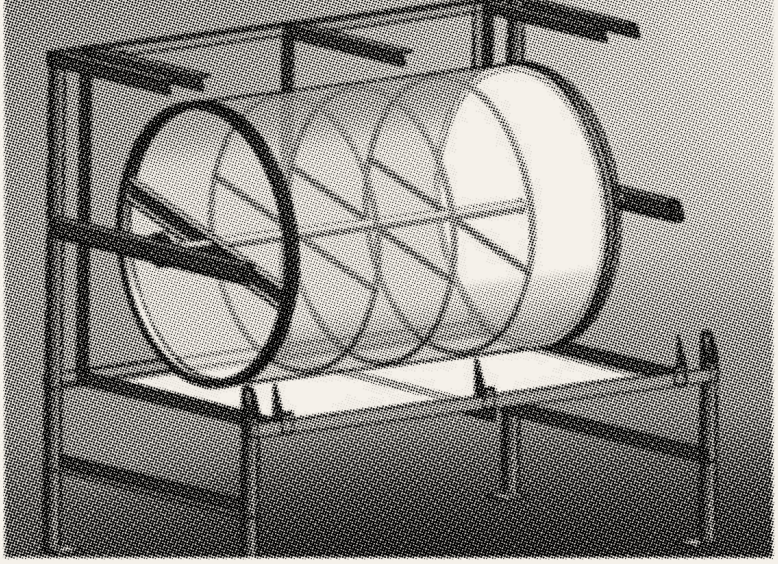


THREATS LINGERING IN THE OPEN AIR

A biological threat agent explodes out of a metal tube and travels toward a formation of warfighters. Thousands of aerosolized agents speed through the air. While some agents infect warfighters, others remain in transport or slam into rocks, trees, and the ground. Aerosolized agents that linger in the open-air environment, before decontamination efforts begin or even during that time when they are in transport, will age and decay. Until recently, because of challenges posed by outdoor testing of live biological threat agents, scientists empirically assumed that agents aged and decayed at similar rates indoors and outdoors. Yet laboratory measurements may not accurately predict — and even underestimate — the decomposition of agents released in the open air.



Sketch of a CAGES chamber. Photo courtesy of the Sandia National Laboratory.

To learn how biological threat agents decay upon interacting with variables in the open air, the Defense Threat Reduction Agency's Chemical and Biological Technologies Department (DTRA CB) funded research to evaluate the environmental stability of non–spore-forming simulants of biological threat agents. A new, state-of-the-art test apparatus, the Captive Aerosol Growth and Evolution System (CAGES), allows scientists to test this interaction. The research was performed at the Sandia National Laboratory, National Strategic Research Institute, and the Army Research Laboratory. Researchers evaluated the combination of open-air factors that most affect the rate of agent decay. They also compared data collected in laboratory studies to data collected in outdoor experiments.

The experiment took place in two locations: Albuquerque, New Mexico, and Houston, Texas. Houston has oil refineries, so it has many more air pollutants than Albuquerque does, which means that the differing air in the two cities offers differing volatile organic carbon (pollutant) levels that can interact with aerosolized biological agents. In both cities, researchers quantified how components of the atmosphere — ozone, ultraviolet light, and pollutants — would affect an agent's nucleic acids, surface protein chemistry, infectivity, detectability, and viability. For outdoor testing, researchers contained the simulants representing biological threat agents within the rotating drum chambers of CAGES, thereby exposing the simulants to the ambient atmosphere in which light intensity and gas composition mirror that of the surrounding air. After exposing the simulants to different atmospheric conditions, aerosol samples were taken from the chambers to study the physical and chemical properties of the aerosol that was contained. For the laboratory tests, researchers conducted indoor aerosol testing that mimicked real-world, aging conditions (including humidity, simulated solar light, ozone, and pollutants) to explore the degree to which outdoor decay data may be comparable to indoor decay data.

THE EXPERIMENTS REVEALED THAT IN OPEN AIR, SIMULANTS DECAYED 10 TO 1,000 TIMES FASTER IN CAGES CHAMBERS THAN IN LABORATORY SETTINGS.

The experiments revealed that in open air, simulants decayed 10 to 1,000 times faster in CAGES chambers than in laboratory settings. These data indicate that laboratory tests underestimate the rate of agent decay that occurs outdoors, and on their own, laboratory tests are not sufficient in understanding the decay process outdoors. This finding has implications for decision makers, such as in guiding agent detection and hazard mitigation efforts, decontamination efforts, promoting warfighter health in a contaminated space, and informing mission requirements.

Data gathered through laboratory- and CAGES-based experiments can transform the way DTRA CB examines the aging and decay of biological threat agents, and therefore, the atmospheric conditions within a contaminated environment. CAGES equipment provides unique opportunities to obtain more accurate outdoor agent decay data and further the understanding of chemical processes affecting biological agents released in the open air. With better data, DTRA CB can better detect and predict agent transport and persistence over time. Improved, fundamental knowledge of agent decay provides more accurate data to the modeling community, and ultimately, to the warfighter who needs to operate in a contaminated environment. ●

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Within the Defense Threat Reduction Agency's Research and Development Directorate resides the Chemical and Biological Technologies Department. This publication highlights the department's advancements in protecting warfighters and citizens through the innovative application of science and technology. DTRA.mil