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EDWIN J. MEESE III CENTER FOR LEGAL AND JUDICIAL STUDIES

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Twenty-First Century Illicit Drugs and Their Discontents: The Challenges Posed by Novel Psychoactive Substances (NPSs)

Paul J. Larkin

Novel Psychoactive Substances multiply the difficulties involved in protecting ourselves and our families, friends, and neighbors from falling victim to illicit drug use. Ingenious chemists have used the Internet to research the chemical structure of existing psychoactive substances and use their skills to escape a strict reading of the controlled substances schedules. The result is to make extraordinarily difficult our long-standing strategy of relying primarily on an aggressive, supply-side, law enforcement–focused approach to reducing the availability of dangerous drugs. We can—and should—pursue each worthwhile option to combat this even though we know that we cannot immunize society against the pernicious effects of all NPSs, change hearts bent on evil, or save everyone who succumbs to drug abuse.

Introduction[1]

The United States and the international community regulate potentially dangerous drugs primarily through their controlled substances laws. The Controlled Substances Act of 1970 (CSA) created the basic federal regulatory system,[2] which most states follow.[3] Under the CSA, "hard" drugs like heroin that lack a legitimate medical use are altogether forbidden.[4] Drugs that have a legitimate therapeutic use are subject to lesser degrees of regulation based on their potential for abuse and their safety when taken under medical supervision.[5] International agreements to which the United States is a signatory[6] use the same basic scheme, which each nation separately enforces.[7]

Historically, those drugs were derived from agricultural products. A classic example is the opium poppy, from which chemists can synthesize (for example) morphine. Another opioid—diacetylmorphine, or heroin—is

a semi-synthetic drug because it is a derivative of morphine.[8] Opioids are a matter of particular, long-standing concern because their promise of bliss, like the Siren's call, entices a user down a path that leads to a short-term euphoria, but also to long-term addiction, misery, and death.[9]

Agricultural products, however, are not the only drugs of concern. Nineteenth and 20th century advances in organic and analytical chemistry enabled scientists to isolate and manipulate the psychoactive ingredients in plants ordinarily used for religious or medicinal purposes to create what are known as Novel Psychoactive Substances (NPSs) or, colloquially speaking, "designer drugs." Created in a laboratory from precursor chemicals, principally for recreational use, NPSs ordinarily are synthetically manufactured analogs of lawful or illegal drugs.[10] NPSs can be just as enticing—and dangerous—as the ones derived entirely from their botanical ancestors.[11] Sold in one or more formats—powder, pills, capsules, injectables, inhalants, vaping solutions, and so forth—they pose a variety of dangers.[12] Fentanyl (an analgesic) is one of the best-known examples,[13] but there are numerous others as well.[14]

The problem of NPSs has existed for some time, but the number of such compounds has increased in this century.[15] Over the past decade, they have assaulted America like the plagues that felled the Egyptians in the time of Moses.[16] The only promised land is avoidance.

The term "novel" does not mean that the drug was recently created, only that it has recently become available (or noticed) in the illicit market.[17] Some NPSs have existed for some time,[18] and some even have legitimate uses but are also unlawfully created and sold.[19] "[A] significant number of NPS were primarily developed for therapeutic purposes, but then started being misused and extensively abused for their euphoric effects, as legal alternatives to 'traditional' illicit psychoactive substances."[20] The number and types of NPSs available are large, and the task of regulating them has increasingly become an ongoing game of whack-a-mole.[21]

A designer's products might have a complicated structure, but his or her goal is quite simple: Create a new compound that mimics the psychoactive effects of a category of existing but illegal drugs that possesses a new chemical structure that is not clearly outlawed by federal or state controlled substances laws[22] or by international agreements to which the United States is a signatory.[23] NPS are designed to attract users who have their own goals: obtaining a "legal high,"[24] evading standard drug detection analyses,[25] or pursuing "novelty" in drug experiences.[26] A chemist's goal is not necessarily to create a product that will endure forever or monopolize the NPS market even for a short period, but rather to make a quick buck by synthesizing a

new compound that will attract "psychonauts" searching for "the ultimate high."[27] As explained below, however, a psychonaut's novel experience can also be his last.[28]

There is a growing literature discussing NPSs.[29] This *Special Report* seeks to add to that corpus by educating readers about the principal NPSs of concern in America, summarizing the problems they cause, and suggesting what we can do about them.

The Most Troubling NPSs

Although we have known about NPSs since the 1980s, the problem hibernated until the first decade of the new century. Since then, however, it has exploded.[30] More than 1,100 NPSs already exist, and additional ones are created every year. The number of potential synthetic opioids alone is in the thousands.[31] A lengthy discussion of each one is beyond the scope of this *Special Report*, but five merit discussion as our greatest challenges today: fentanyl, synthetic psychedelics, nitazenes, synthetic cannabinoids, and cathinones. I discussed the first two in earlier studies in this series.[32] The last three are summarized in the sections immediately below.

Nitazenes.[33] Nitazenes (known by chemists as 2-Benzylbenzimidazole opioids) are a class of analgesic drugs. First synthesized back when Elvis Presley released "Heartbreak Hotel" in the 1950s,[34] nitazenes were the product of an unsuccessful search for a more powerful but less addictive analgesic than morphine. The U.S. Food and Drug Administration (FDA), however, has never approved them as a human or veterinary medication.[35] Dormant for 50-plus years, nitazenes emerged in the illicit drug market in 2019. Nitazenes can be sold as powders, liquids, pills, or capsules under that name, or they can be disguised as (or admixed with) other drugs.[36] Some nitazenes are more than 10 times as potent as fentanyl, or 1,000 times more powerful than morphine.[37]

As of mid-2022, the U.S. Drug Enforcement Administration (DEA) concluded that nitazenes are sold less often than fentanyl, but that practice could change over time given the nation's focus on stopping illicit fentanyl's spread.[38] In fact, sales might already have increased without our knowledge, in part because medical examiners do not routinely test for NPSs.[39] The drug Naloxone (Narcan) can reverse a nitazene overdose, but its potency might require multiple doses to be effective.[40] Even then, it might not always be successful.[41]

Synthetic Cannabinoids.[42] In the 1970s, researchers created synthetic cannabinoids to understand the operation of the brain's cannabinoid

receptors, but their formula made its way into the hands of chemists who made synthetic cannabinoids available in the illicit market for recreational purposes.[43] The term "synthetic cannabinoids" applies to all synthetic compounds that bind to and activate the cannabinoid receptors (CB_1, found in the brain and spinal cord, and CB_2, found in the spleen and digestive tract), as well as structurally analogous drugs.[44]

Synthetic cannabinoids appeared in that market in this century, and their prevalence has increased steadily. More than 160 compounds have appeared since 2008 with new versions arising every two years.[45] "These compounds clearly are the result of mining the literature on cannabimimetics."[46] Their psychoactive ingredient differs from the delta-9-tetrahydrocannabinol (THC) found in botanical cannabis, and the synthetic versions can have a far bigger "kick." THC is only a partial agonist—that is, it does not fully activate receptors. By contrast, synthetic cannabinoids fully activate the brain's CB_1 receptors because they bind more readily with them than THC does, possibly by a factor of 100.[47] Moreover, synthetics lack the buffering compound—cannabidiol, or CBD—that can moderate the euphoric and dysphoric effects of THC.[48] For those reasons, the synthetic cannabinoids have "much more pronounced psychoactive effects."[49]

Marketed under the names Spice (the psychoactive ingredient of interest in Frank Herbert's *Dune* series) or K2 (the world's second highest mountain), synthetic cannabinoids are sold as powders, capsules, tablets, or plants sprayed with synthetic cannabinoids to look like old-fashioned "joints." They attract users by offering a more powerful but street-legal alternative to the mild high that comes from inhaling THC.[50] Used in low doses, "synthetic cannabinoids produce marijuana-like effects, including perceptual distortions and mood elevation."[51] But they can lead to more serious acute adverse effects than are seen with botanical cannabis[52]—among them being an "increased heart rate, uncontrolled vomiting, acute kidney injury, panic attacks, hallucinations, psychosis, and seizures"[53]—as well as a "30-fold" greater likelihood of needing emergency medical care.[54] Synthetic cannabinoids can also be contaminated with toxins or other drugs like brodifacoum.[55] Fatal overdoses from using synthetic cannabinoids have occurred (although they appear to be rare).[56]

Cathinones.[57] "In the beginning was the amphetamine."[58] Cathinones have a chemical structure similar to amphetamines and produce similar effects.[59] Cathinones are marketed as "bath salts," plant food, herbal blends incense, air freshener, insect repellant, or stain remover—as almost anything except drugs.[60] But, like the sign advertising a "Free Lunch for $5," that is "a marketing ploy," because they "have no value" in bathing, cleaning,

or any other advertised use.[61] Like traditional amphetamines, low doses of cathinones can increase energy and elevate mood, but high doses can lead to "hallucinations, psychosis, increased heart rate, high blood pressure and hyperthermia, often accompanied by combative or violent behaviors," as well as death.[62]

The Nature of the NPS Problem

Health Risks. Over thousands of years, humans discovered that some plants contained substances that could be used for medicinal or religious purposes because of their therapeutic or psychoactive properties.[63] White willow bark, for example, contains salicin, a chemical similar to acetylsalicylic acid, or aspirin, which has been used to treat inflammation or pain since the time of Hippocrates (400 B.C.).[64] Once organic chemistry developed as a modern science in the 19th century, however, the possibility arose of creating therapeutic drugs in a laboratory from precursor chemicals instead of botanical products. That process accelerated with 20th century advances in chemistry, communications, and creativity.[65]

Generally, those advances have benefited humanity. The 20th century synthesis of antibiotics, antivirals, and antineoplastics has saved millions of lives, while modern-day analgesics have reduced or eliminated the suffering that can accompany disease, injury, or surgery. Some discoveries, however, have created far more misery than they have alleviated, particularly when a new product is used for its recreational potential rather than its medicinal justifications. Just as a blade can be used as a surgical scalpel or a murder weapon, chemistry has been used to create some drugs that are far more dangerous than beneficial. NPSs belong to that category of drugs.

We have more to learn about NPS,[66] but we already know that users face severe physiological and psychological health risks.[67] Users can suffer from tachycardia, palpitations, chest pain, myocardial infarction, hyperthermia, hypertension (high blood pressure), seizures, immune thrombocytopenia (a low-level of platelets necessary for clotting), acute kidney injury, agitation, intracranial hemorrhage, strokes, panic attacks, neurocognitive deficits (e.g., memory loss and sleep disruption), paranoia, delirium, hallucinations, psychosis, and suicidal ideation.[68] NPSs can also trigger unpredictable and violent outbursts.[69] In the other direction, some new drugs—such as MPTP[70]—cause permanent symptoms of Parkinson's Disease by destroying dopamine-creating neurons, leaving users in an irreversibly frozen state,[71] creating real-life images of the fictional depiction of Han Solo frozen in carbonite in *The Empire Strikes Back*.[72]

And that's not the worst that can happen (although that judgment is debatable). NPS use has also led to fatal overdoses,[73] a problem that has recently grown.[74] NPSs, such as fentanyl analogs (e.g., carfentanil, an elephant tranquilizer), are so potent that only a miniscule amount is necessary to render someone unconscious and shut off his autonomic respiratory process.[75] Death can follow their use, or that of other NPSs, for any number of reasons. To start with, identifying the drugs consumed by someone who has overdosed can be a difficult undertaking. Some users do not know what they took (let alone its ingredients); they might have taken a combination of drugs (e.g., nitazenes mixed with heroin) that create peculiar or aggravated adverse reactions when consumed together;[76] and emergency departments can find it difficult to identify it (or them)[77] because NPSs are designed to evade standard recreational drug screening,[78] and not every emergency department has the sophisticated laboratory equipment[79] that is needed to test for the full range of NPSs.[80] Atop that, the body might quickly metabolize some NPSs, so if urine is used as the test matrix, it might be easier to identify the drug from a metabolite than from the drug itself (assuming that an emergency department knows the most common metabolite(s) of a newly introduced NPS).[81] Even if the emergency department can identify the relevant NPSs, there might be no way to eliminate it forcibly from the patient and no known antidote.[82] Even medical examiners, who do not act under the urgency of trying to save a life, might find it difficult to identify the specific cause of death.[83]

Aggravating those problems are these facts: Chemists can churn out new NPSs faster than we can find, identify, and outlaw them, creating a "virtually endless supply."[84] It can take six to eight months to perform the necessary laboratory analyses to identify a particular generation of a new NPS, and later generations could have appeared during that time as replacements for the just-analyzed drugs.[85] There is a possibility that NPSs can have unanticipated adverse effects that we will see only after their widespread, long-term use, which means that a large number of people might be harmed before emergency services, poison control centers,[86] or laboratories identify the drug, devise a response, and communicate their findings across the medical communities in different states or continents.[87] That delay might explain why there has been "an alarming spike" in the number of NPS-associated fatalities in some areas at different times.[88] Even working assiduously to identify the cause of an increase in overdose fatalities, medical examiners cannot identify the precise number of NPS-related deaths. That is true because medical examiners do not test for every NPS in every drug overdose fatality, particularly if the medical examiner discovers fentanyl in a victim's

lab tests.[89] The upshot is that even the dead might not be able to tell us why they died so that we can protect others.

Some drug policy scholars have argued that, despite the horrific damage that NPSs have inflicted on some individual users, they do not pose a major societal problem.[90] The reason is that many NPSs do not initially attract a large audience, while most of the ones that do quickly lose their appeal because of the informal spread across the Internet of adverse information about their risks by the community of NPS users.[91] "Few NPS achieve prominence beyond experimental use by psychonauts."[92] The overall, nationwide harm caused by those drugs, accordingly, has not been great. As a result, according to Peter Reuter and Bryce Pardo, the government might not need to schedule NPSs aggressively, perhaps because "the market self-regulates."[93]

That is a creative and intriguing suggestion. Ultimately, however, it is not a persuasive option for public policy implementation.

Reuter and Pardo are correct that we should focus our limited resources on the most dangerous drugs. The purposes of scheduling are to place out of bounds drugs that lack any legitimate medical use (which become listed on Schedule I) and to help law enforcement and regulatory agencies apportion their resources by identifying the relative risks of drugs that are both potentially useful and potentially dangerous (which are listed in Schedules II through V).[94] Those are worthwhile goals. The problem is that the initial scheduling decision must be made quickly and often without time to decide exactly where in the CSA's schedule of drugs a particular NPS best fits. Carolyn Coulson and Jonathan Caulkins do not see NPSs as a major societal problem, but they do acknowledge that initial classification decisions can be an all-or-nothing matter. The federal government can place a new, potentially dangerous drug into Schedules II–V only if there is an accepted medical use for it, and there may be no proof that it can be successfully used for treatment when it first emerges. If so, the only available slot is Schedule I, which prohibits a drug's use for any purpose, medical or recreational.[95] The solution to that timing problem, Coulson and Caulkins explain, is to create "a new 'Schedule IA' category for substances that should be prohibited from general recreational use, but for which absence of known medical applications is understood to mean 'not yet fully explored' rather than 'considered and found wanting'."[96]

Even if that were a satisfactory *legislative* answer to this matter, it would require Congress to amend the CSA. Yes, the critics are right to say that we should make rational drug-policy choices. Yes, the current regulatory scheme might "overregulat[e] substances in ways that strangle potential medical research," which no one wants to see.[97] Keep in mind that illicit

fentanyl is an NPS that has caused, according to the latest available federal figures, more than 70,000 overdose fatalities in one recent year.[98] Only the most diehard libertarian would leave fentanyl regulation to market forces. Nitazene might not yet have the visible fangs that fentanyl has, but it is dangerous to presume that it won't, and it certainly has at least the same venom. The number of people already killed through illicit fentanyl distribution, along with the number that might share that fate through increased trafficking in nitazenes, is sufficiently great to justify federal efforts to halt trafficking in both drugs. Consider also MPTP: It might not kill people, but the people whose brains it destroys, turning them into living statues, might wish that it had. And that does not take into account the as-yet-unknown worse NPSs that could pop up just around the corner.

Even if there were a good reason to assume that the market could do a better job than Congress, Congress has decided to prohibit trafficking in NPSs and other controlled substances by directing law enforcement agencies to use the criminal law to halt that conduct. Executive officials must respect that judgment until Congress changes its mind. Abandoning enforcement of the controlled substances laws in favor of market-based regulation is dereliction of duty. Congress has chosen a particular scheduling mechanism—a scheme that has only five schedules, not six—instead of leaving the matter to the discretion of executive agencies, and Congress expects law enforcement agencies to enforce the law. That is why Congress funds them.[99] Also, the DEA cannot independently create a new Schedule IA because Congress did not grant the agency such law-making authority.[100]

Congress's judgment, by the way, was and is not an irrational or outdated one. Psychonauts might keep up to speed on the potential highs from NPSs, but the market cannot prevent the spread of those drugs to people who do not surf the Web for news about the adverse effects of NPSs, particularly the ones that are sold locally. They will wind up using drugs contaminated with fentanyl or MPTP. Ironically, even though the penal code is not ordinarily characterized as a "consumer protection" device, use of the criminal law can be a sensible strategy to protect the unwary or ill-informed.

To be sure, not every NPS poses the same risks as fentanyl or nitazene. Perhaps the CSA's approach is overbroad in some instances, but it is not remotely irrational. Where to draw the line—distinguishing drugs that are appropriate for criminal prosecution from ones that are fit for only civil regulation or market control—is a classic matter of line-drawing, and Congress cannot be faulted for refusing to trust regulatory agencies or the "invisible hand" to deliver only "safe" illicit drugs. Besides, NPS traffickers can monitor the Internet for adverse reports on the compounds they

distribute, as NPS users do, and in response can fool users by constantly varying the names of their products. It has happened before; in the 1980s, some sellers claimed that their fentanyl was actually heroin to avoid the stigma associated with the former.[101] There is every reason to believe that it will happen again.[102] Besides, it is up to Congress to decide just how paternalistic it wants to be regarding the use of the criminal law to regulate illegal drug use. Education might not dissuade some current and potential users from taking NPSs, because they have heard the false cry of past drug scare campaigns.[103] (Does anyone remember the 1936 film *Reefer Madness*?) It is not irrational for Congress to decide that education and the criminal law work better than education alone.[104]

Unsafe, Disuniform NPS Contents. Not everyone who synthesizes NPSs was educated at the California Institute of Technology and trained at the Sandia National Laboratories.[105] Aside from making mistakes or being sloppy, they might be in over their heads when it comes to synthesizing NPSs that are both desirable and non-toxic. Underground laboratories also do not create NPSs in accordance with the "good manufacturing practices" that the FDA demands of modern-day public pharmaceutical companies.[106] Secret manufacture of NPSs keeps the synthetization facilities and processes hidden from regulatory authorities, preventing them from inspecting the laboratory production process or reporting their existence to law enforcement authorities.[107] Clandestine labs also lack quality control for their ingredients and products, and this allows impurities in, or dangerous combinations of, ingredients along with variances among the dosages in different batches of chemicals or within any one product such as a pill.[108] Open retail sale of those products misleads the public into believing that they are safe, which can have unfortunate consequences.[109]

There is limited data available on NPSs' effects on humans and even less on their potential cross-toxicity with other legal or illicit drugs,[110] combinations that might occur more often than we expect.[111] The lack of safety testing leaves unknown valuable information about NPSs' acute and chronic toxicity, including the difference between the maximum therapeutic dose and the minimum lethal one.[112] Atop that, there is a serious risk of toxicity due to contamination—whether accidental, negligent, or deliberate—with other drugs. One especially pernicious additive is the veterinary medicine xylazine, which goes by the street name "tranq."[113] Tranq is added to fentanyl to extend the latter's psychoactive effect,[114] but it causes abscesses and putrefying, necrotic tissue in the limbs of humans, potentially leading to amputation or sepsis.[115] The *New England Journal of Medicine* also has reported that some synthetic cannabinoids contain a derivative of the

anti-clotting compound warfarin, which resulted in severe, long-lasting coagulopathy (a condition that impairs the ability to form blood clots, which can lead to excessive bleeding).[116] Together, those factors pose a serious risk that toxic or hazardous compounds will wind up in NPSs and prove fatal to users.

NPSs put more than users at risk. Consider the risks to the chemists who synthesize NPSs. Twenty percent of the clandestine labs that law enforcement officers discover come to their attention as the result of a fire or explosion.[117] As one DEA agent put it, industrial labs focus on "safety and quality control," while clandestine labs focus on "secrecy," which exacerbates the risky nature of the business.[118] Keep in mind the risks that clandestine labs pose to the people who live in nearby areas, which include not only the release of toxic gases from the drug synthetization process,[119] but also insidious long-term environmental harms and chronic illnesses from a devil-may-care disposal of the manufacturing process's hazardous wastes.[120] Finally, clandestine labs pose extreme risks to the law enforcement officers who enter to search the premises and arrest the cooks. One such officer put it this way: "I've never worked anything with the dangers of clandestine labs. As far as I'm concerned, this is the most dangerous thing in law enforcement a guy can do."[121]

Ongoing Dangers. The dangers of NPSs are unlikely to abate in the coming years. On the contrary, the versions of NPSs available today are not the end of the line as far as development goes.[122] An increasingly large number of dangerous drugs can be synthesized in laboratories, and the people who succumb to "the lure of easy money" will not be put off by the risks noted above as long as they can continue to reap a steady stream of profits.[123]

NPSs offer several attractions that botanically based drugs cannot offer. The latter burden growers with the need to find uninhabited locations that can be easily guarded over a months-long growing season and that possess ideal climates in politically stable regions with dozens of laborers available at harvest time. Even then, botanical drugs remain hostage to droughts, blight, and labor availability and costs. By contrast, NPS traffickers can hire professional chemists, who can use scientific reports available on the Internet (including the Dark Web) or in patent literature to synthesize NPSs quickly in makeshift or top-flight laboratories.[124] As Jonathan Caulkins and Keith Humphreys have pointed out, the cost of ingredients or equipment is "trivial" when compared to a finished product's selling price.[125] "A modest investment in mixing equipment, a used pill-making machine, and a set of punch dies created to resemble the shapes and logos of popular drugs, are

all one needs to become a do-it-yourself—albeit unlawful—pharmaceutical manufacturer."[126] It takes only "competent synthetics chemists" to synthesize NPS, so there is a sizeable pool of available "cooks."[127] There also is no growing field that must be guarded or any climate, weather, or insect problem that might ruin a harvest.

Other production, transportation, and distribution costs are far lower for illicit businesses than for legitimate companies. NPS labs have materially lower operating costs than those that legitimate pharmaceutical companies must bear because clandestine labs are free of those "pesky" safety standards that legitimate pharmaceuticals must follow as well as the environmental costs of proper waste disposal. There are no employment antidiscrimination laws for clandestine labs to follow, nor are there human resources offices with rules that must be accommodated. There likely are no thousands-of-miles-long supply chains, subject to interference at multiple points, that must be traversed in secret before the final products of those plants make their way to our nation.[128] In short, illicit drug trafficking is unrestrained by any of the ordinary civil rules that every legitimate business must follow.

The Internet has changed the drug business by becoming "a primary base of operations for [NPSs], changing the dynamics of marketing, reducing risks to suppliers and buyers, and expanding markets globally without personal contacts."[129] The Dark Web makes it possible for sellers and buyers to transact business in relative secrecy without the need for a face-to-face meeting by using encrypted communications.[130] Payment can be done anonymously via cryptocurrency that is difficult to trace, certainly for most state and local law enforcement departments, and a private express service can deliver NPSs to purchasers. Those factors give NPS dealers a financial leg up over old-style traffickers in heroin.[131]

The Unknown Unknowns. One final problem must be noted: what we don't know. At a macro level, we do not know the likelihood that NPSs will replace traditional, agriculturally based drugs. The emergence of NPSs over the past few decades, however, gives us reason to be concerned that the illicit drug business might have branched out into a new path that makes it increasingly more difficult to protect the public against improvident decisions.[132] Or some of the same factors that increase the risk of the spread of NPSs—such as 21st century communications technologies and continued scientific advances—might help us to respond to this problem more effectively.[133] Only time will tell.

At a micro level, we also do not know the risk—and accompanying fear—that NPSs might fundamentally change a user's personality or create

Frankenstein-like monsters out of what previously were ordinary people.[134] Often present in (even if below the surface of) policy discussions about NPSs is the fear—something more than an anxiety but less than a terror—about a prospect that has not yet materialized but cannot be dismissed because it might exist just beyond the horizon: the odds that, in the search for new and not-yet-illegal compounds, chemists might synthesize drugs that entirely rejigger the human mind in a way that creates unmovably impassive or unstoppably violent personalities.[135] We already know that some clandestinely synthesized products can freeze unwitting users into statues by destroying regions of their brains that are responsible for communicating with the rest of their bodies.[136] What we don't know is how many yet-to-be-created NPSs might have either that effect or the opposite one of generating a propensity for uncontrollable violence. Some chemists—the ones acting merely to make a profit—might create such compounds unwittingly. Others—the ones working for nations that wish us harm—might do so quite purposefully. Either motivation could potentiate this fear.

The prospect that unregulated science would create a Frankenstein-like creature has been troubling ever since Mary Shelly wrote a book by that name in 1818.[137] The new science of genetic engineering makes that concern even more frightening.[138] Variations of whether and how such a bastardization of biology, biochemistry, medicine, and morality could arise has been the theme of more than a few books[139] and films[140] in popular culture. It is no exaggeration to say that NPSs pose a risk of permanent brain damage or transformation. An NPS might fundamentally and irreversibly change the brain, altering personality or mental health status on a life-long basis or creating zombie-like individuals that assume catatonic postures like some unfortunate souls on the streets of Philadelphia who mistakenly used MPTP-adulterated drugs.[141]

Remember: The FDA's mission is to protect the public against the potentially disastrous effects of new drugs like the incoming waves of NPSs. Congress created the FDA in 1938 to require an expert agency to review new drugs to be sure that they were safe before being publicly distributed.[142] Prompted by the Thalidomide disaster in Europe in the 1950s, Congress augmented the FDA's authority by passing the Drug Amendments of 1962, which vested the agency with the power and responsibility to refuse to approve any new drug until its sponsor has proved that it is not only safe, but also effective.[143] The FDA review process has worked well to date, and no one seriously argues that it should be eliminated. The FDA, however, cannot protect the public against distribution of a drug it never reviewed. Distribution of NPSs—"products never tested or without established human

use"—is tantamount to "experimenting 'on the fly' in human populations, with unpredictable results in popularity and toxicity."[144] That is precisely what the FDA exists to prevent, and for more than 85 years, the nation has endorsed that policy. The production and sale of NPSs flout that policy and endanger the public.

Potential Responses

Vigorous Intergovernmental Information Sharing. Knowledge might not be power, but it certainly is critical to sound public health decision-making.[145] In her 2012 article "Designer Drugs: An Escalating Public Health Challenge," Harvard Medical School Professor Bertha Madras proposed an excellent list of policy recommendations as to steps that we can take to address the challenges posed by NPSs.[146] One of her recommendations is to coordinate the national and international information-gathering and monitoring activities of health-care professionals, academic researchers, and law enforcement agencies to identify emerging NPSs, their source chemists, and their effects by using automated web-crawler bots to lessen the diversion of human resources. Another recommendation was to collate, categorize, and place all information regarding the hazards of NPSs and the sources of their precursor chemicals on a website accessible by relevant national and international public health and law enforcement agencies.[147]

To be sure, each nation's domestic statutes regulate how its law enforcement agencies can pursue criminal investigations, and differences among the controlled substances and criminal laws effective in foreign nations committed to battling NPSs make it difficult to adopt a uniform transnational response to NPS trafficking. Nonetheless, some version of Professor Madras's proposals has already been implemented to some extent and in some manner by the agencies involved in this battle, such as the U.S. Centers for Disease Control and Prevention (CDC), the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the European Medicine Agency, and each nation's national drug warning systems.[148] Any of her recommendations that have not yet been adopted deserve serious consideration.

Aggressive Scheduling of NPSs. Domestic and international laws use a scheduling process to list drugs that cannot be marketed or prescribed at all versus the ones that may be distributed but only as prescribed by a physician.[149] In the United States, federal law empowers the DEA to place an NPS into Schedule I on an expedited basis for a limited period.[150] That provision is useful, but it helps only so much.

The multi-step, complex, detailed, date-driven review process that the FDA has used for decades to determine whether a drug is "safe," "effective," and "uniform" establishes a rigorous regimen to avoid mistakenly approving new pharmaceuticals that could damage the public.[151] That process relies on a new drug's sponsor—ordinarily, a large corporate pharmaceutical company—to provide the agency with a wealth of information about its composition and effect on humans. Chemists operating out of clandestine laboratories, working to synthesize new, barely legal drugs, do not supply the FDA with the information that legitimate pharmaceutical companies do.[152] In fact, that would be the *last* thing that any of those chemists would even think of doing.[153]

One result is that the clandestine manufacture and underground distribution of NPSs make the emergency scheduling process a rather helter-skelter affair. Mexican Drug Trafficking Organizations (DTOs) likely have far larger research and development budgets and staffs than the DEA has in its emergency scheduling department, which means that the DEA is always playing catch-up. Use of a particular NPS might become widespread and prove often to be fatal before the DEA, even with the FDA's guidance, can acquire all of the relevant information needed to make an emergency scheduling decision.[154] The steps involved in this process include spotting a new drug; identifying its chemical structure and characteristics; understanding its pharmacodynamics (effect on the body) and pharmacokinetics (movement through the body); learning whether there is a safe, quick-acting "off switch" like Naloxone; determining what is the best emergency treatment for someone under its influence; and disseminating that information and treatment recommendations to ER physicians, emergency service personnel, poison control center officials, and law enforcement officers.[155] As a result, the cavalry might not arrive in time.[156]

For effective emergency scheduling to work, therefore, it is critical that information about new NPSs be disseminated immediately, completely, and regularly among the world's medical and public health agencies (e.g., the CDC, EMCDDA, and World Health Organization); established national medical organizations (e.g., the American and British Medical Associations); and the public health community (e.g., the American Public Health Association).[157] Information sharing likely will not allow government officials and physicians to get ahead of clandestine NPS operations—they and the rest of us will always be playing defense against NPSs—but it might enable them to lag just a step or two behind.[158]

One alternative is to place every new substance in Schedule I if it poses *any* potential risk to public health, regardless of its severity and despite

the medical profession's belief that it has legitimate therapeutic benefits.[159] That approach, however, is not cost-free.[160] First, it would deny physicians the ability to treat some seriously ill patients with the new drug.[161] Second, that approach might make it difficult to alter an initial scheduling decision. There is an inherent, strong regulatory bias toward restrictively scheduling any new compound. Senior regulatory officials face little risk of congressional or public outrage from being unduly cautious, but they could face a career-ending public relations nightmare from allowing a drug to be distributed even under Schedules II–V if it causes severe injury to a nontrivial number of patients, especially to pregnant women or children.[162] Finally, another harm from automatically placing every new NPS into Schedule I is that it might lead chemists to synthesize analogues that turn out to be more potent, and therefore more dangerous, than the parent drug—for example, acetylfentanyl and carfentanil are more potent than fentanyl—which would raise the stakes for each new round of whack-a-mole.[163]

Aggressive Criminal Enforcement. Our traditional response to unlawful drug trafficking has been to use the criminal justice system aggressively as a regulatory tool. The fact of imprisonment quarantines whoever conducts that business while also increasing a drug's street price.[164] The threat of imprisonment hopefully deters others from choosing that path. Nonetheless, that strategy is unlikely to be successful for NPSs.

Legal hurdles make the prosecution of NPS traffickers riskier for the government than is the case with regard to heroin or cocaine. One hurdle is that the CSA requires the government to prove that a compound is "substantially similar to the chemical structure of a" highly dangerous controlled substance and has a "substantially similar" effect on the human nervous system.[165] Ideally, the government would use a biochemist and physician to prove its case. Parties in the NPS business, however, have a powerful motivation to stay one step ahead of the law to become rich and remain free, so traffickers (particularly the Mexican DTOs) are able to hire expert chemists to generate products that fall just beyond the law's reach.[166] As a result, the government might not be able to prove its case against every defendant.

Congress cannot loosen the definition of a "controlled substance" too far or give the government the ability to redefine that term retroactively to cover materially different drug versions. The CSA requires proof that a party knew that (for example) a powder was a controlled substance (fentanyl, not talcum) in order to convict him of distributing a forbidden analogue (such as a new fentanyl variant).[167] That might be difficult to prove in some cases, given the complexity of the compounds at issue. NPSs do not advertise themselves as unlawful, and the average person does not hold a

PhD in chemistry. Consider that the Supreme Court of the United States has recognized that, while an average person might be able to identify a rifle, shotgun, or revolver as a "firearm," he or she might not know that it is capable of automatic firing.[168] So, too, the average person might know that a substance is a powder but not be aware that it is a *controlled* substance, let alone understand or even have ever heard the terms used to identify some NPSs, such as butonitazene.[169] Compounds like those make the *Federal Register* read more like a graduate school organic chemistry textbook—with terms like "salts, isomers, optical isomers, and salts of optical isomers" of any listed chemical—than what we would expect to find in the penal code.[170] Try asking an average person to understand those terms, and you can see why a prosecution might be dicey.

Organic chemists and the traffickers who employ them to produce NPSs doubtless know what those drugs are; no one could expect to make a living by selling legitimate "bath salts" for thousands of dollars for a one-ounce package. But those offenders are the most difficult ones to identify and prosecute. The government ordinarily begins an investigation by focusing on the retail dealers—the "little fish"—in the hope of persuading them to help the government step up the ladder to the "big fish" by an offer of charging or sentencing leniency. That might not be as easy in the case of NPSs as it is with regard to other illegal drugs. The criminal law requires that a criminal statute must be sufficiently clear to advise the average, reasonable person without a degree in biochemistry or law precisely what conduct is prohibited,[171] and the average person lacks any knowledge of exactly how a particular compound is structured or what its effects will be.[172] Together, those requirements might make more difficult the criminal prosecution of lower parties in the NPSs business whose testimony is necessary to prosecute their superiors, and without that testimony, the higher-level traffickers might skate. In sum, because of the difficulty involved in knowing whether a particular compound is an NPS, designer drug creators and suppliers are probably at a lesser risk than heroin traffickers of doing a long stretch in the hoosegow.

The bottom line is this: Several factors make impossible a complete reliance on an aggressive, supply-side, law enforcement–focused approach to halting or diminishing the availability of NPSs. That does not mean we should abandon law enforcement. To the contrary, we should continue to use it for what it does best: serve as a means of identifying and isolating the parties at every level of the process—from ingredient procurement to drug synthesis to NPS distribution and sales—who order or inflict violence as a means of doing business, as well as large-scale traffickers. That business

injures or kills individuals and degrades their communities. The government should not breach its end of the social covenant by abandoning NPSs' victims just because law enforcement alone will not make NPSs disappear everywhere, entirely, and eternally.

Aggressive Civil Enforcement. Some drug-policy scholars have suggested that, because NPSs are not marketed for medical-treatment purposes, governments might be able to use their civil laws governing alcohol, tobacco, ENDS (electronic nicotine delivery systems, or e-cigarettes), food, and consumer protection as NPS regulatory tools.[173] The responsible agencies should seize the drugs involved and fine everyone, from financiers to chemists to large-scale or medium-scale traffickers to street-level dealers, to sanction every party in the chain of production and distribution.[174]

The rationale for that approach is fourfold. First, that strategy invokes the "Precautionary Principle" that often guides decision-making in the environmental and consumer law fields: Potentially dangerous substances or actions should be prohibited or regulated unless and until their sponsor proves their safety under conditions of ordinary use.[175] Second, civil enforcement is also "more agile" than criminal enforcement, the argument goes, because the constitutional demands on its exercise are fewer. Third, civil enforcement carries a lesser punishment than the controlled substances laws, thereby avoiding the societal costs of imprisonment. Fourth, civil enforcement avoids criminalizing possession rather than distribution. By focusing on the more culpable parties, civil enforcement might not provoke a public backlash.[176] Here, that would leave the regulation of NPSs to the Commissioner of Food and Drugs (and his or her lieutenants) under the Federal Food, Drug, and Cosmetic Act and its implementing regulations.[177]

That strategy would be a potentially useful one in some cases. Civil penalties have some deterrent effect, albeit not as much as the risk of imprisonment.[178] But that difference might be important in this context. Because imprisonment is not a civil punishment, the civil law need not define unlawful conduct with the same rigorous precision that the criminal law demands. That explains why the "reasonable person" standard in tort law is not subject to challenge on the ground that the standard of care is unconstitutionally vague; forfeitures and fines are categorically less intrusive than imprisonment.[179] Civil sanctions might be one effective way to respond to companies selling borderline-legal but nonetheless dangerous products in well-known national package store chains.[180] A reason is that the notoriety of an FDA civil enforcement action could have such a damaging effect on a company's reputation and stock price that it and others will steer far clear of selling any similar compound.

Nonetheless, the civil law ultimately has only a limited usefulness in this context. Civil seizures might be a straightforward way to remove questionable NPS products from chain stores, but that tactic might just move sales from package stores to the streets or indoors. Moreover, businesses operating clandestinely will not provide open and obvious targets for seizures, and laboratories operating in other nations would be beyond the reach of our civil laws. Insofar as civil fines are viewed by the players in the drug trafficking chain as just a cost of business, they would have no material effect on the supply of NPSs. Finally, law enforcement officers radiate a nimbus that no civil inspector can generate because the former can make arrests, while the latter can only issue citations. That weakens the deterrent effect that civil inspectors and enforcement agents would have on people in the NPS business.[181]

Aggressive Border Protection. The smuggling of fentanyl from Mexico into the United States is not as immutable as the law of gravity. President Joe Biden could respond to it today by closing our Southwest Border with Mexico[182] from whence most fentanyl enters this country.[183] Yet he has proved unwilling to exercise that authority. So, even if Congress were to unite behind that policy (which won't happen during this presidential election year) or the nation were to demand that we close our border (which might happen this November), that result will not occur soon.

Trying to close the border, however, is not likely to be a complete solution even for a President who is willing to use that authority. As a historical matter, we have not been able to shield the nation against the smuggling of drugs like heroin, all of which comes from elsewhere. Even if we built a solid wall along the entire 2,000-mile border with Mexico and reinforced it by laying a mile of claymore land mines immediately behind it, the most that we could hope for is to reduce the amount of NPSs smuggled into America over land. Why? Where there's a will, there's a way.

The potency of drugs like fentanyl or nitazene simplifies a smuggler's job by multiplying his options. Since "a little dab'll do ya,"[184] a physical barrier would just prompt traffickers to switch to greater reliance on the U.S. Postal Service, private express mail companies, small planes, and drones to transport their merchandise into the United States.[185] Of course, that does *not* mean we should make no effort to stem the DTOs' reliance on NPS-carrying people to do their cross-border smuggling. On the contrary, we should make *every* effort. Increasing the costs of drug smuggling can lead to a reduction in demand and supply. More importantly, it can save lives. The Biden Administration's matador-like wave-them-by approach to illegal immigration has doubtless killed numerous Americans from smuggled fentanyl. My point is that immigration and law enforcement

alone cannot stop the death of thousands of people. We must pursue other approaches as well.

Enlisting International Cooperation. Should we seek assistance from foreign nations—particularly Mexico and China—to halt (or reduce) the quantities of NPSs produced in their homelands and smuggled into this nation? Perhaps, but enlisting their support to resolve what they see as America's drug problem is problematic at best. The current president of Mexico, Andrés Manuel López Obrador (AMLO), is competing with President Biden for the role of Ignorer-in-Chief as far as drug smuggling is concerned.[186] China certainly will not willingly help the United States to address this problem. Perhaps that is because China benefits militarily by addicting potential American servicemembers. Perhaps that is because China benefits financially by increasing the costs that illicit drugs inflict on our people. Perhaps that is because China sees our suffering as poetic justice for the Opium Wars that the West forced it to endure late in the 19th century. Or perhaps that is because *schadenfreude* is always a guilty pleasure, especially when it comes at the expense of an adversary. Whatever the explanation for its recalcitrance might be, China is not likely to assist the United States without receiving something in return so valuable that we would not find it in our interests to provide it.

Demand-Side Steps. With supply-side efforts and international assistance unlikely to halt NPS smuggling, we must also consider demand-side efforts. There are several options, though none is likely to be a home run.[187]

We should pursue the search for an effective long-term "off switch" for NPSs similar to methadone and buprenorphine. That is particularly important in connection with the new opioid-like drugs such as nitazenes. "Given the widespread availability of fentanyl and increasing presence of ultrapotent synthetic opioids,"[188] the failure to address this problem "[w]ithout innovative and effective treatments" could be quite devastating. "On the current trajectory, we can expect nearly a million deaths within the next decade."[189] That potential loss should prompt action.

No life-saving intervention, however, would be necessary for people who do not use NPSs. "The core of a prevention campaign is scientific evidence to document the potential consequences to users."[190] Education—of and by actual and potential users, public health officials, clinicians, medical examiners or coroners, laboratories, and legislators—is a critical life-saving tool.[191] Education could reduce the number of new drug users, and it has been a successful strategy in connection with smoking and alcohol-impaired driving. Those education campaigns have saved thousands of lives.[192]

Unfortunately, we have not witnessed the same effectiveness with our efforts to educate people against illicit drug use. In part, it has been difficult to persuade individuals to abandon their use of drugs or to dissuade potential new users from trying them. Hindering those efforts is the fact that, for the past 50-plus years, our culture has lauded drug use and lionized its champions. To change the mindset and conduct of the people at risk, we need to present truthful, factually accurate messages[193] with a strong visual component, particularly across social media, because the adolescent and young adult audiences we need to reach make great use of those platforms for news and play—as do NPS traffickers.[194] The political branches should attempt to persuade social media companies to broadcast messages explaining the physical and psychological suffering that drugs like fentanyl mete out to their users.[195]

Emphasizing an End to the Era of Drug Experimentation. One point that we do need to emphasize—everywhere and repeatedly—is that NPSs like fentanyl and their illegitimate offspring like the nitazenes have brought an end to the era of drug experimentation. Recreational drugs used in the 1960s, 1970s, and 1980s like marijuana could generate short-term and long-term harms but were not likely to produce immediate death, at least not on a widespread basis. Fentanyl can do so and has done so. "There is no safe amount of fentanyl, and unlike with heroin, no long-term users."[196] Fentanyl is sold as a stand-alone powder, as a secret ingredient in other illicit drugs, or sometimes in counterfeit pills.[197] That fact is a particularly important one to bring to the attention of people in their 20s and 30s because they are the primary clientele for NPS traffickers.[198] That generation might bewail the loss of their opportunity to pursue the same recreational drug experimentation as their fathers and grandfathers pursued. At the end of the day, however, Millennials and Generation Zers need to realize that more important than cursing the darkness is finding a light.

Conclusion

NPSs multiply the difficulties that our nation and others face in trying to protect ourselves and our families, friends, and neighbors from falling victim to illicit drug use. Ingenious chemists have used the Internet to research the chemical structure of existing psychoactive substances and use their skills to add new curlicues to those drugs in order to escape a strict reading of the controlled substances schedules. Because the criminal law must prospectively outlaw a substance in terms that the average person can understand, chemists and traffickers in NPSs have been able to stay

one step ahead of law enforcement, perhaps even laughing at us as they do. The result is to make extraordinarily difficult our long-standing strategy of relying primarily on an aggressive, supply-side, law enforcement–focused approach to reducing the availability of dangerous drugs. It is feckless to believe that Mexico will assist the United States while AMLO is in power, and China is not likely to help us to combat our drug use without receiving a massive bribe in return—perhaps even abandonment of our current willingness to support Taiwan's independence.

The remaining options are three.

- **At the wholesale level,** pursue and punish major illicit drug traffickers to prevent individuals and communities from being victimized and to show respect for the lives and communities they have already ruined.

- **At the retail level,** use law enforcement aggressively to reduce the violence associated with illicit drug trafficking by quarantining violent offenders.

- **At both levels,** continue and augment demand-side strategies by improving our educational efforts and making voluntary and compulsory drug treatment more available.

These three steps are necessary to protect parties not yet victimized, to provide justice to the ones who have already suffered that fate, and to demonstrate that the government is serious about protecting the public from drug trafficking and its violence while extending help to those who made a wrong choice.

These strategies are also legitimate and worthwhile. We can—and should—pursue each one even though we know that we cannot immunize society against the pernicious effects of all NPSs, change hearts bent on evil, or save everyone who succumbs to drug abuse. We can make a serious effort to do so, however, and in the process, we will save some. Consider these words by Robert Browning:

> Ah, but a man's reach should exceed his grasp,
> Or what's a heaven for?[199]

That's as good a game plan as any.

Endnotes

1. This is the ninth paper in The Heritage Foundation's *Twenty-First Century Illicit Drugs and Their Discontents* series. The earlier papers are Paul J. Larkin, *Driving Down the Psychedelic Highway*, Heritage Found., Special Report No. 279 (2024), https://www.heritage.org/sites/default/files/2024-03/SR279.pdf [hereafter Larkin, *Psychedelic Highway*]; Paul J. Larkin, *Methamphetamine—The Downs of Ups, or Tweaking the Night Away*, Heritage Found., Legal Memorandum No. 348 (2023), https://www.heritage.org/sites/default/files/2023-12/LM348.pdf; Paul J. Larkin, *Why the FDA Could Not Approve Raw Cannabis as a "Safe," "Effective," and Uniform" Drug*, Heritage Found., Special Report No. 275 (2023), https:/ www.heritage.org/sites/default/files/2023-08/SR275.pdf; Paul J. Larkin, *The Failure of Cannabis Legalization to Eliminate an Illicit Market*, Heritage Found., Legal Memorandum No. 326 (2023), https://www.heritage.org/sites/default/files/2023-04/LM326_0.pdf; Paul J. Larkin, *The Potential Risks that Cannabis Use by Pregnant and Nursing Women Poses to Their Children*, Heritage Found., Legal Memorandum No. 319 (2022), https://www.heritage.org/sites/default/files/2023-04/LM319.pdf; Paul J. Larkin, *The Troubling Potency of Twenty-First Century Cannabis*, Heritage Found., Legal Memorandum No. 317 (2022), https://www.heritage.org/sites/default/files/2022-12/LM317.pdf; Paul J. Larkin, *The Scourge of Illicit Fentanyl*, Heritage Found., Legal Memorandum No. 313 (2022), https://www.heritage.org/sites/default/files/2022-11/LM313.pdf [hereafter Larkin, *Fentanyl*]; and Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: An Introduction*, Heritage Found., Legal Memorandum No. 310 (2022), https://www.heritage.org/sites/default/files/2022-09/LM310_0.pdf.
2. The CSA was Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91-513, 84 Stat. 1242 (codified as amended at 21 U.S.C. §§ 801–904 (2018)). A "controlled substance" is "a drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of part B of this title," except for "distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1954." 21 U.S.C. § 802(6) (2018).
3. *See*, *e.g.*, S.C. Code § 44-53-110(6) (defining a "Controlled substance"), *id.* § 44-53-110(7) (same, a "Controlled substance analogue"), §§ 44-53-190, 44-53-210, 44-53-230, 44-53-250, and 44-53-270 (West 2024) (listing controlled substances in Schedules I–V).
4. *See*, *e.g.*, John Kaplan, The Hardest Drug: Heroin and Public Policy (1983).
5. *See*, *e.g.*, 21 U.S.C. § 812(b)(1) (providing that, to be flatly prohibited for any use, a drug must have the following characteristics: "Schedule I—(A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has no currently accepted medical use in treatment in the United States. (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision"), (c) Schedule I (listing such drugs). The CSA incorporates the definition of a "drug" from the Federal Food, Drug, and Cosmetic Act and assigns drugs to one of five schedules according to their potential benefits and risks. 21 U.S.C. §§ 201(g)(1), 812, 841 (2018). The CSA and its implementing regulations govern the lawful manufacture, transportation, and distribution of controlled substances. *See*, *e.g.*, 21 U.S.C. §§ 802(10), (11), (21) & (22), 822–823, 828, 829a, 831 (2018); 21 C.F.R. §§ 1306.01–1306.27 (2022). Category I is reserved for drugs that lack a legitimate medical use, lack an accepted safe use, and pose a serious risk of abuse. 21 U.S.C. § 812(b)(1). No physician may prescribe Schedule I drugs for any use.
6. *See*, *e.g.*, Single Convention on Narcotic Drugs, Mar. 30, 1961, 18 U.S.T. 1407, *amended by* 1972 Protocol, Mar. 25, 1972, 26 U.S.T. 1439; Convention on Psychotropic Substances, Feb. 21, 1971, 32 U.S.T. 543; United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Dec. 20, 1988, 28 I.L.M. 493 (1989), 1582 U.N.T.S. 95. For a concise treatment of the process for listing a controlled substance under those conventions, see Amy Peacock et al., *New Psychoactive Substances: Challengers for Drug Surveillance, Control, and Public Health*, 394 Lancet 1668, 1677 (2019); *see also* Int'l Narcotics Control Bd., United Nations, Psychotropic Substances 2022: Statistics for 2021 Assessments of Annual Medical Scientific Requirements for Substances for 2023, E/INCB/2022/3, at 59–61 (2023); Int'l Narcotics Control Bd., United Nations, List of Psychotropic Substances Under International Control (28th ed. 2017); Michael Evans-Brown et al., *Legal Classification and International Systems for Monitoring and Responding to Novel Psychoactive Substances*, *in* Novel Psychoactive Substances: Classification, Pharmacology, and Toxicology 3, 7–30 (Paul I. Dargan & David M. Wood eds., 2d ed. 2022). Whether those agreements are worth a tinker's dam is dubious. *See* Roy Gerona, Designer Drugs 22 (2024) ("As of March 2022, only 71 [NPSs] have been scheduled under the international conventions since the ECDD [World Health Organization Expert Committee on Drug Dependence] first examined NPS in 2014. This is less than 10% of the 1182 NPS that had been reported to UNODC [United Nations Office on Drugs and Crime] by the end of 2022, a testament to how out of sync international regulation is with evolution of the market."); Jose A. Cabranes, *International Law and Control of the Drug Traffic*, 7 Int'l Law. 761 (1973).
7. *See* European Monitoring Cntr. for Drugs & Drug Addiction, European Drug Report 2022: Trends and Developments 38–40 (2022) [hereafter European Monitoring Cntr. European Drug Report 2022]; United Nations Off. on Drugs & Crime, The Challenge of New Psychoactive Substances (2013); Christopher Humphries, *The United Kingdom's Psychoactive Substances Act of 2016. Where Are We Now?*, 8 Drug Sci., Pol'y & L. (2022). There are exceptions. For example, the United Kingdom has permitted heroin to be prescribed for individuals addicted to that substance. *See*, *e.g.,* 1 Heroin Addiction and the British System: Origins and Evolution (John Strang & Michael Gossop eds., 2004); 2 Heroin Addiction and the British System: Treatment and Policy Responses (John Strang & Michael Gossop eds., 2005).
8. Gerona, *supra* note 6, at 33.
9. *See* Kaplan, *supra* note 4.
10. Gerona, *supra* note 6, at 4.
11. Jonathan P. Caulkins & Keith Humphreys, *New Drugs, Old Misery: The Challenge of Fentanyl, Meth, and Other Synthetic Drugs*, Manhattan Inst., Issue Brief 1 (2023); Peter Reuter & Bryce Pardo, *New Psychoactive Substances: Are There Any Good Options for Regulating New Psychoactive Substances?*,

40 Int'l J. Drug Pol'y 117, 117 (2017) ("They have no claim to therapeutic purpose but are developed principally for recreational use, in contrast to the drugs (apart from cannabis) that dominate the illegal market.").

12. Gerona, *supra* note 6, at 1–2.

13. Fentanyl has several different analogs, some of which—such as carfentanil—are far more powerful than the basic version of the drug. Jolanta B. Zawilska, *An Expanding World of Novel Psychoactive Substances: Opioids*, 8 Frontiers of Psychiatry at 3 (2017), https://doi.org/10.3389/fpsyt.2017.00110 ("It is estimated that the clinical potency of carfentanil is 10,000 times that of morphine, 4,000 times that of heroin, and 100 times that of fentanyl[.]"); *id.* at 2 & 5 Tbls. 1 & 2 (listing examples of fentanyl analogs). There are also powerful new synthetic opioids with structures different from fentanyl, such as U-47700. *Id.* at 10–11 & Fig. 2. For a brief history of the origins of fentanyl, see G.L. Henderson, *Designer Drugs: Past History and Future Prospects*, 33 J. Forensic Sci. 569 (1988).

14. NPSs are heterogenous, with multiple types of, stimulants, synthetic cannabinoids, classic hallucinogens, synthetic opioids, sedatives or hypnotics, and dissociatives. Some synthetic drugs are created using the template (core structure) of botanical precursors: *e.g.*, mephedrone analogs, LSD from ergot, hallucinogens from methyltryptamines of plants, amphetamines from ephedrine found in the Ma Huang plant. Some others, such as fentanyl, are derived from earlier synthetic drugs (meperidine) with no analog in nature. *See*, *e.g.*, 6 United Nations Off. on Drugs & Crime, Current NPS Threats 1 & Fig. 3 (2023); Gerona, *supra* note 6; Bertha K. Madras, *The Growing Problem of New Psychoactive Substances*, *in* Neuropharmacology of New Scientific Substances 1, 3 (Michael H. Baumann et al. eds., 2017); Yu-Jang Su et al., *Clinical Characteristics in New Psychoactive Substance Users: A Single Center Study*, 102 Medicine 25, 25 (2023); Felix Zapata et al., *Chemical Classification of New Psychoactive Substances (NPS)*, 163 Microchemical J. 105877, at 2–11 (2021).

15. "Substances have been produced and marketed with the explicit aim of circumventing legislative restrictions for several decades. What has changed is an increase in their range, potency, profile and availability." Adam R. Winstock & John D. Ramsey, *Legal Highs and the Challenges for Policymakers*, 105 Addiction 1685, 1685 (2010).

16. *See*, *e.g.*, Commission on Combating Synthetic Opioid Trafficking, Final Report (2022); Sam Quinones, The Least of Us: True Tales of America and Hope in the Time of Fentanyl and Meth (2021); Ben Westhoff, Fentanyl, Inc.: How Rogue Chemists Are Creating the Deadliest Wave of the Opioid Epidemic (2019); John J. Coleman & Robert L. DuPont, *Fentanyl as Sentinel: The Deadly Threat of Illegal Synthetic and Counterfeit Drugs*, Heritage Found., Backgrounder No. 3436, at 2 (2019).

17. Zapata et al., *supra* note 14, at 1. For example, Merck Darmstadt first synthesized 3,4-methylenedioxymethamphetamine, or MDMA (an analogue of methamphetamine, as its technical name suggests) in 1912 for use as an appetite suppressant. It did not become a "party drug," known on the street as "ecstasy" or "Molly," until the 1980s. Gerona, *supra* note 6, at 3; Arie P. Francis & Silas W. Smith, *Availability and Supply of Novel Psychoactive Substances*, *in* Dargan & Wood, *supra* note 6, at 63.

18. For example, chemists synthesized nitazenes in the 1950s for potential use as painkillers, but the U.S. Food and Drug Administration has never approved their use for that or any other purpose. Novel Psychoactive Substances: Nitazenes, Legis. Analysis & Pub. Pol'y Assn. 1 (2023).

19. Such as fentanyl, which is used to treat post-surgical and end-stage cancer pain. *See* Cntrs for Disease Control & Prevention, Opioids, Fentanyl (June 1, 2022), https://www.cdc.gov/opioids/basics/fentanyl.html; Drug Enforcement Admin., *DEA Fact Sheet: Fentanyl* 1 (Apr. 2020).

20. Zapata et al., *supra* note 14, at 1.

21. "[L]egislation desperately and belatedly attempts to discover and control the large number of NPS that freely circulate on the drug market. In Europe, at least 50 substances are detected every year on the drug market, and more than 700 new substances are being monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) since 1997, through the EU Early Warning System (EWS)[.]" Zapata et al., *supra* note 14, at 1 (endnotes omitted). Yet that "legislation is often useless because for each specific substance that gets legally controlled, one or more structurally modified analogues are introduced into the legal market, becoming a never-ending process[.]" *Id.*; *see also*, *e.g.*, Giovanni Martinotti et al., Editorial, *Novel Psychoactive Substances and Behavioral Addictions*, 2014 Biomed. Research Int'l Article ID 534523, at 1, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290894/pdf/BMRI2014-534523.pdf ("The novel psychoactive substances, however, that began to spread after the millennium have fundamentally reorganized this apparently stable situation. Since then, new substances have constantly been appearing on the market. It is not rare that there is no time to even identify a new drug before another substance takes its place on the market and they might disappear a few days, weeks, or months later, while newer ones appear. This extremely rapidly changing situation concerning drug use and drug market set new challenges for professionals. We have to describe the use of drugs on which we have very limited knowledge. Not only is the chemical description of these substances often unavailable, but often we do not even know their street names. The effects of drugs should be explored while their name and nature are unknown to both the dealer and the user. We have to estimate the risks associated with substances without being familiar even with their most basic characteristics. We have to provide information to potential users of these drugs, and we hardly know anything about them or treat unknown side effects or overdoses.") (endnotes omitted); Marthe M. Vandeputte et al., PowerPoint, *Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylebenzimidazole Synthetic Opioids*, 7 ACT Chem. Neuroscience 1241 (2021) ("The depicted life cycles illustrate the persistent dynamic nature of the recreational synthetic opioid market. Once scheduling (and/or other factors) impedes one opioid's availability, the emergence of (legal) alternatives is inevitable.") (emphasis omitted); Zawilska, *supra* note 13, at 3 ("As in the case of other NPS groups, new designer opioids quickly replace the scheduled ones. For example, following the ban of acryloylfentanyl in 2016, four new fentanyls, i.e., 4-chloroisobutyrylfentanyl, 4-fluoroisobutyrylfentanyl, tetrahydrofuranylfentanyl, and cyclopentylfentanyl, appeared on the Swedish drug market[.]") endnotes omitted); *id.* at 6–7 (Tbl. 3), 12 ("While the majority of NPS are designer cannabinoids and psychostimulants, a range of different synthetic opioids have recently appeared on the illicit drug market, namely analogs of fentanyl and compounds with various chemical structures, such as AH-7921, U-47700, and MT-45.").

22. In addition to the CSA, several other federal statutes are relevant:

(1) *The Drug Enforcement Provisions of the Comprehensive Crime Control Act of 1984.* One law authorizes the U.S. Attorney General to schedule a controlled substance on an expedited but temporary basis if doing so is "necessary to avoid an imminent hazard to the public safety." The Comprehensive Crime Control Act of 1984, Title II of H.J. Res. No. 648, Pub. L. No. 98-473, 98 Stat. 2071, ch. V—Drug Enforcement Amendment, Pt. B—Diversion Control Amendment, §§ 508 & 509(a) (1984) (codified at 21 U.S.C. § 811(h)). For an example of the exercise of that authority, see U.S. Dep't of Justice, Drug Enforcement Admin., 87 Fed. Reg. 21,556, 21,556 (Apr. 12, 2022). ("Schedules of Controlled Substances: Temporary Placement of Butonitazene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, N-Pyrrolidino etonitazene, and Protonitazene in Schedule I… The [DEA] Administrator..is issuing this temporary order to schedule seven synthetic benzimidazole-opioid substances, as identified in this order, in schedule I of the Controlled Substances Act. This action is based on a finding by the Administrator that the placement of these seven substances in schedule I is necessary to avoid imminent hazard to the public safety. As a result of this order, the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances will be imposed on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess) or propose to handle these seven specified controlled substances."); *id*. at 21,557 ("The United States currently is experiencing an opioid overdose epidemic, and the presence of synthetic opioids on the illicit drug market threatens to exacerbate this. The trafficking, continued evolution, and abuse of new synthetic opioids are deadly trends posing imminent hazards to public safety."); *id*. at 21,557–21,561 (detailing the rationale for the designation).

(2) *The Controlled Substances Analogue Enforcement Act.* The second law is the Controlled Substances Analogue Enforcement Act (CSAEA), § 1202, Subtit. E, Tit. I, Pub. L. No. 99-570, 100 Stat. 3207, 3207-13 to 3207-14 (codified at 21 U.S.C. § 813 (2018)). It treats as a "controlled substance" any "controlled substance analogue," which the act defines as any drug, "to the extent intended for human consumption," whose chemical structure is "substantially similar to the chemical structure of a" Schedule I or II controlled substance and has a "stimulant, depressive, or hallucinogenic effect" on the central nervous system that is "similar to" the effect of such a controlled substance. 21 U.S.C. §§ 802 & 813(a). The CSAEA lists five factors that "may be considered" when determining whether a controlled substance analogue was intended for human consumption" but also permits "any other relevant factors" to be considered." *Id*. § 813(b).

(3) *The Chemical Diversion and Trafficking Act of 1988.* In 1988, Congress amended the CSA to address the precursor chemical used to synthesize drugs, as well as tableting and encapsulating machines, by imposing recordkeeping and reporting requirements on the purchase, sale, and import of such items. The Anti-Drug Abuse Act of 1988, Pub. L. No. 100-690, 102 Stat. 4181, §§ 6051–6061 (codified at various provisions of 21 U.S.C. ch. 13, subch. 1–3).

(4) *The Synthetic Drug Abuse Prevention Act of 2012.* Congress passed the Synthetic Drug Abuse Prevention Act of 2012, Subtit. D, Tit. XI of the Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993, to address the problem of "synthetic cannabinoids," compounds that were not analogous to the active ingredient in cannabis, delta-9-tetrahydrocannabinol. David E. Nichols & William E. Fantegrossi, *Emerging Designer Drugs*, *in* The Effects of Drug Abuse on the Human Nervous System 575, 593 (Bertha Madras & Michael Kuhar eds., 2014). The 2012 act directly added several particular synthetic substances to CSA Schedule I. 21 U.S.C. § 812(d)(1)–(2); Nichols & Fantegrossi, *supra*, at 593.

23. *See* Single Convention on Narcotic Drugs, Mar. 30, 1961, 18 U.S.T. 1407, *amended by* 1972 Protocol, Mar. 25, 1972, 26 U.S.T. 1439; Convention on Psychotropic Substances, Feb. 21, 1971, 32 U.S.T. 543; *see also* Int'l Narcotics Control Bd., United Nations, Psychotropic Substances 2022: Statistics for 2021 Assessments of Annual Medical Scientific Requirements for Substances for 2023, E/INCB/2022/3, at 59–61 (2023); Int'l Narcotics Control Bd., United Nations, List of Psychotropic Substances Under International Control (28th ed. 2017); Madras, *supra*, *in* Baumann et al., *supra* note 14, at 3.

24. While often used in connection with NPSs, the term "legal high" is inaccurate, misleading, and dangerous. Ornella Corazza et al., *"Legal Highs" an Inappropriate Term for "Novel Psychoactive Drugs" in Drug Prevention and Scientific Debate*, 24 Int'l J. Drug Pol'y 82, 82 (2013). The term is inaccurate because particular NPSs might be "legally ambiguous." Christophe Soussan et al., *The Diverse Reasons for Using Novel Psychoactive Substances: A Qualitative Study of the Users' Own Perspectives*, 40 Int'l J. Drug Pol'y 71, 71 (2018). Misleading because the term implies that the U.S. Food & Drug Administration has approved the drug as safe to use, which has not occurred. *See* Paul J. Larkin, Jr., *Reflexive Federalism*, 44 Harv. J.L. & Pub. Pol'y 523, 595 (2021) (noting that state cannabis legalization carries that implicit mark of legal approval); Peter H. Reuter & Bryce A. Pardo, *New Psychoactive Substances: The Regulatory Experience and Assessment of Options*, *in* Novel Psychoactive Substances: Policy, Economics, and Drug Regulation 165 (Ornella Corazza & Andres Roman-Urrestarazu eds., 2017) [hereafter Corazza & Roman-Urrestarazu, Policy] ("The fact that these products are distributed in a legal market provides false reassurance about government regulation. Approximately half of the Americans believe that the weight loss products are approved for safety and efficacy before they can be sold to the public.... The same ignorance held for young physicians: over a third of physicians in residency programs believed that these products needed to be approved by the FDA before they could be marketed."). Dangerous because NPSs can generate serious adverse physiological and psychological effects such as psychosis, stroke, and death. *See* Daniel Whiting, *Synthetic Cannabinoid Receptor Agonists: A Heterogeneous Class of Novel Psychoactive Substance with Emerging Risk of Psychosis*, 10 Forensic Psychiatry 110, 110 (2015); *infra notes* 50–59 and accompanying text. Thus, some scholars have recommended that the term "legal high" be abandoned. Corazza et al., *supra*, at 82.

25. *See* Samuele Naviglio et al., *An Adolescent with an Altered State of Mind*, 350 Brit. Med'l J. h299, h299 (2015) (noting "intoxication by emerging drugs of misuse, a vast class of chemically diverse psychoactive substances that go largely undetected by conventional immunoassay drug screen tests"); Peacock et al., *supra* note 6, at 1677 ("[T]raditional approaches to analysing illicit drugs might not be as effective for detecting some NPS. Firstly, laboratories need a certified sample of the molecule as a reference, which can be difficult to obtain when NPS are varied[,] and new substances are constantly emerging. Secondly, detecting high-potency substances present in low quantities in biological samples can be difficult, and these can degrade over time. Thirdly, data on the pharmacokinetics and pharmacodynamics of many NPS are lacking. This complicates detection of an NPS through its metabolites and interpretation of concentrations to infer toxicity levels when quantitative data can be obtained. Finally, testing for NPS

might require additional specialist analytical equipment and knowledge, which can place a substantial burden on analytical services.") (endnotes omitted); Su et al., supra note 14, at 25 ("Synthetic cannabinoids…cannot be detected by a simple urine toxicity test."); Zawilska, *supra* note 13, at 12 ("[C]onventional drug tests will not detect synthetic opioids.").

26. *See* Michael H. Baumann, *Preface*, *in* Baumann et al., *supra* note 14, at v ("In all cases, the substances are engineered to evade existing drug laws."); Madras, *supra*, *in* Baumann et al., *supra* note 14, at 3 (noting that NPS might elicit "psychoactive effects similar to the parent drug," an "amplified" effect, or "unique complex sensations"), 4 ("NPS tempt drug users who seek 'legal highs' to circumvent the legal consequences of using standard drugs, desire drugs to be undetected in drug screens, and attract substance users seeking novelty in drug experiences."); Soussan et al., *supra* note 24; Jenny L. Wiley et al., *Combination Chemistry: Structure—Activity Relationship of Novel Psychoactive Cannabinoids*, *in* Baumann et al., *supra* note 14, at 243 ("The recreational use of synthetic cannabinoids persists in an expanding variety of chemical forms and formulations, particularly in uninformed youth, 'psychonauts,' and individuals attempting to avoid drug testing (e.g., military, ex-convicts, and individuals involved in public transport.").

27. The term "psychonauts" has been defined as "individuals who explore altered states of consciousness, typically through hallucinatory drugs." Gerona, *supra* note 6, at 242.

28. *See*, *e.g.*, Alexandra Amaducci et al., *Naloxone Use in Potent Opioid and Fentanyl Overdoses in Emergency Department Patients*, 6 JAMA Network Open e32331264 (Aug. 29, 2023), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2808868?resultClick=1; Su et al., *supra* note 14, at 26 ("The use of illicit drugs and overdose is a serious problem in the United States and Europe. The age-adjusted rate of overdose deaths was 207 per million in 2018 in the United States and 23.7 per million in Europe.") (endnote omitted); Kosei Yonemitsu et al., *A Fatal Poisoning Case by Intravenous Injection of "Bath Salts" Containing Acetyl Fentanyl and 4-Methoxy PV8*, 267 Forensic Sci. Int'l e6 (2016). There is no antidote for most NPSs. Hege M. Krabseth et al., *Novel Psychoactive Substances*, 136 Tidsskr Nor Laegeforen [transl.: Journal of the Norwegian Medical Association] 714, 716 (2016).

29. Commission on Combatting Synthetic Opioid Trafficking: Final Report (2022); European Monitoring Centre for Drugs & Drug Addiction, New Psychoactive Substances—The Current Situation in Europe (2023); European Monitoring Centre for Drugs & Drug Addiction, New Psychoactive Substances: 25 Years of Early Warning and Response in Europe—An Update from the EU Early Warning System (2022); New Zealand Law Comm'n, Controlling and Regulating Drugs—A Review of the Misuse of Drugs Act of 1975, at 122 (2010); Stephen J. Hyde, Ketamine for Depression (2015); Torsten Passie, The History of MDMA (2023); Torsten Passie, Healing with Entactogens: Therapist and Patient Perspectives on MDMA Assisted Psychotherapy (2012); Bryce Pardo et al., The Future of Fentanyl and Other Synthetic Opioids (2019); Ben Westhoff, Fentanyl, Inc.: How Rogue Chemists Are Creating the Deadliest Wave of the Opioid Epidemic (2019); Sara Berg, *Physicians Recognize New Psychoactive Substances as Health Threa*t, Am. Medical Ass'n, June 12, 2017, https://www.ama-assn.org/delivering-care/public-health/physicians-recognize-new-psychoactive-substances-health-threat; Gary Bravo, *Ketamine*, *in* Handbook of Medical Hallucinogens 159 (Charles S. Grob & Jim Grigsby eds., 2021); Coleman & DuPont, *supra* note 16; Michael H. Baumann, *The Changing Face of Recreational Drug Use*, Cerebrum (Jan.–Feb. 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4938259/; Liana Fattore & Aviv M. Weinstein, Editorial, *Novel Psychoactive Substances*, 10 Frontiers of Psychiatry 3 (2019), https://doi.org/10.3389/fpsyt.2019.00119; Taylor Holborn et al., *Self-Medication with Novel Psychoactive Substances (NPS): A Systematic Review*, Int'l J. Mental Health & Addiction, Nov. 29, 2023, https://doi.org/10.1007/s11469-023-01195-8; Dino Luethi & Matthias E. Liechti, *Designer Drugs: Mechanism of Action and Adverse Effects*, 94 Archives of Toxicology 1085 (2020); Hawraa Sameer Sajwani, *The Dilemma of New Psychoactive Substances: A Growing Threat*, 31 Saudi Pharmaceutical J. 348 (2023); Abu Scafi et al., *New Psychoactive Substances: A Review and Updates*, 10 Therapeutic Advances in Psychopharmacology 1 (2020); Fabrizio Schifano et al., *Stimulant and Hallucinogenic Novel Psychoactive Substances: An Update*, 16 Expert Rev. Clinical Pharmacology 1109 (2023); Derek K. Tracy, *Novel Psychoactive Substances: Types, Mechanisms of Action, and Effects*, 356 Brit. Med'l J. i6848 (2017); Derek K. Tracy, *Novel Psychoactive Substances: Identifying and Managing Acute and Chronic Harmful Use*, 356 Brit. Med'l J. i6814 (2017).

30. Gerona, *supra* note 6, at 12.

31. *See id.* at 12–13; John R.H. Archer, *Novel Detection Methods and Data Triangulation for Novel Psychoactive Substances (NPS)*, *in* Dargan & Wood, *supra* note 6, at 131 ("Over the last decade [2012–2022,] there have been significant changes in the drugs that are available to users, both in terms of geography and temporal variation. This is particularly evidence for Novel Psychoactive Substances (NPS) where a large number of diverse substances exist within a rapidly changing and dynamic market. These substances represent a broad range of drugs and include cathinones and other NPS stimulants, synthetic cannabinoids, novel opioids and novel benzodiazepines. By the end of 2018, the European Monitoring Centre for Drugs and Drug Addiction…was monitoring more than 730 NPS, of which 55 were detected for the first time in Europe that year.") (endnotes omitted); Andrew C. Parrott, *Clinical and Medical Management of Conditions Caused by MDMA or "Ecstasy," in* Handbook of Novel Psychoactive Substances: What Clinicians Should Know About NPS 266 (Ornella Corazza & Andres Roman-Urrestarazu eds., 2019) [hereafter Corazza & Roman-Urrestarazu, Clinicians] (noting that in 2018, the United Nations Office on Drugs and Crime estimated that chemists were synthesizing one NPS every week); Peacock et al., *supra* note 6, at 1668 ("Dozens of new substances have been identified each year for longer than a decade.") (endnotes omitted). Not every NPS turns out to pose a material danger to individuals or the public, and the rate of creation might have slowed. *See* Peacock et al., *supra* note 6, at 1671; *see infra* notes 80–83 and accompanying text. The problem, however, is that we do not know whether that downward trend will continue or do an about-face, *id.* at 1679–80 (suggesting that the latter might occur, particularly in poorer nations), nor can we ever know in advance which NPSs will be duds and which ones, if any, will go nuclear.

32. Larkin, *Fentanyl*, *supra* note 1; Larkin, *Psychedelic Highway*, *supra* note 1.

33. *See generally* Gerona, *supra* note 6, at 10–11, 84–85; Vincenzo Abbate et al., *Novel Synthetic Opioids*, *in* Dargan & Wood, *supra* note 6, at 447–73.

34. *See* Marthe M. Vandeputte et al., *The Rise and Fall of Isotonitazene and Brorphine: Two Recent Stars in the Synthetic Opioid Firmament*, 46 J. Analytical Toxicology 115, 116 (2022) ("Isotonitazene…was first synthesized and patented in 1959 as part of research carried out by the Swiss pharmaceutical company CIBA[.] These studies showed that isotonitazene was around 500 times more potent as an analgesic than morphine.") (endnotes omitted).

35. Drug Enforcement Admin., *Benzimidazole-Opioids, Other Name: Nitazenes* (Nov. 2022); Zawilska, *supra* note 13, at 12.

36. Adam Holland et al., *Nitazenes—Heralding a Second Wave for the UK Drug-Related Death Crisis?*, 9 Lancet e71, e71 (2024) ("In the UK, nitazenes have been detected in substances sold as other opioids, benzodiazepines, and cannabis products. This means many consumers are using nitazenes inadvertently, unaware of the risks they face.... Other European countries, particularly the Baltic states, have also reported increasing numbers of deaths related to nitazenes.") (endnotes omitted).

37. *See* Amaducci et al., *supra* note 28, at 8; Michael DePeau-Wilson, *What to Know About Nitazenes, a Class of Potent Synthetic Opioids*, MedPageToday, Feb. 5, 2024, https://www.medpagetoday.com/special-reports/features/108578; R. Michael Krausz et al., *The Upcoming Synthetic Ultrapotent Opioid Wave as a Foreseeable Disaster*, 9 Lancet Psychiatry 699 (2022); *see also*, *e.g.*, Drug Enforcement Admin., *New, Dangerous Synthetic Opioid in D.C., Emerging in Tri-State Area* (June 1, 2022) [hereafter DEA, Nitazenes]; *see also* Cntrs for Disease Control & Prevention, *Notes from the Field*: Nitazene-Related Deaths—Tennessee, 2019–2021, 71 Morbidity & Mortality Weekly Report 1196 (Sept. 16, 2022); Grant C. Glatfelter et al., *Alkoxy Chain Length Governs the Potency of 2-Benzylbenzimidazole "Nitazene" Opioids Associated with Human Overdose*, 240 Psychopharmacology 2573 (2023); Ryan Marino, *Nitazenes Have Entered the Drug Scene. Now What?*, MedPageToday, Feb. 13, 2024, https://www.medpagetoday.com/opinion/second-opinions/108713; Eva Montarini et al., *Acute Intoxications and Fatalities Associated with Benzimidazole Opioid (Nitazene Analog) Use: A Systematic Review*, 44 Therapeutic Drug Monitoring 494 (2022); Joseph Pergolizzi, Jr., et al., *Old Drugs and New Challenges: A Narrative Review of Nitazenes*, 15 Cureus e40736 (2023).

    The potency of a drug matters even though, as noted earlier, a minute amount of some drugs can prove fatal. That is true for multiple reasons. First, the potency of a drug is measured by comparing its rate of attachment to receptors against its detachment. A highly potent drug such as fentanyl might associate rapidly and dissociate slowly. That means fentanyl can kill a user far more quickly than morphine by stopping respiration before a user can inject a full dose of fentanyl, which explains why some users are found dead with the needle still in their arm. It also means that rescue efforts with naloxone can fail because that drug is used too late to offset the association of fentanyl with the body or that the dose of naloxone needed to reverse a fentanyl overdose is much higher than what first responders have available. Second, a fentanyl "high" may be stronger than the euphoria produced by heroin because fentanyl attaches to receptors more quickly than heroin and sticks to them "like glue." Accordingly, people using fentanyl might never return to other opioids because their high doesn't match fentanyl's. *See* Karli R. Hochstatter et al., *Characteristics and Correlates of Fentanyl Preferences Among People with Opioid Use Disorder*, 240 Drug & Alcohol Dependence 109630, https://www.sciencedirect.com/science/article/abs/pii/S0376871622003672?via%3Dihub (noting that more than half (52 percent) of participants in a recent study preferred fentanyl alone (21.2 percent) and 30.8 percent preferred it to a heroin-fentanyl mix). Third, tolerance of fentanyl's effects may also be higher because of the drug's higher potency. Fourth, medications to assist in treating opioid addiction may need to be scaled up. *See* Laura C. Chambers et al., *Buprenorphine Dose and Time to Discontinuation Among Patients with Opioid Use Disorder in the Era of Fentanyl*, 6 JAMA Network Open, Sept. 5, 2023, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2809633. *Sixth*, individuals who intentionally use fentanyl have severe substance use patterns, precarious living situations, and extensive overdose history. In response to the increasing number of individuals who use fentanyl, alternative treatment approaches need to be developed for more effective management of withdrawal and opioid use disorder. *See* Vivian W.L. Tsang et al., *Systematic Review on Intentional Non-Medical Fentanyl Use Among People Who Use Drugs*, 15 Frontiers in Psychiatry 1347678, Feb. 12, 2024, https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2024.1347678/full.

38. DEA, Nitazenes, *supra* note 37; *see* Amaducci et al., *supra* note 28, at 2 (noting that "[t]he exact motivation to produce nitazenes and brorphine" is "unclear. The increased regulation of fentanyl and fentanyl analogues throughout the last decade may have led to a change in the chemical precursors required for clandestine laboratory production that were not yet regulated. This change in chemical precursors may have led to these newer and more potent opioids.") (footnote omitted); Vandeputte et al., *supra* note 34, at 115 ("[W]ith fentanyl analogues and synthesis precursors being increasingly controlled, we now observe a gradual shift toward a new generation of non-fentanyl-related synthetic opioids.").

39. Holland et al., *supra* note 36, at e71. A 2020–2022 study of patients admitted to emergency departments found that, of 537 patients with complete laboratory testing, 2 percent tested positive for only fentanyl (11) while 9 percent tested positive for what the study classified as Novel Potent Opioids (NPOs). Amaducci et al., *supra* note 28, at 1; *see also* Kerry Breen, *What Are Nitazenes? What to Know About the Drug That Can Be 10 Times as Potent as Fentanyl*, CBS News, Dec. 31, 2023, https://www.cbsnews.com/news/nitazenes-fentanyl-substance-use-drug-supply-opioid-death-colorado/ ("'I [viz., National Institute on Drug Abuse Deputy Director Compton] wouldn't be surprised if we see more and more nitazenes because they're still under the radar to a lot of America and it takes time to implement advisories for law enforcement to all get on the same page of what they need to look for[.]'"); *id.* (according to Claire Zagorski, a chemist, paramedic, and translational scientist, "'[i]t really is like Whack-a-Mole. Like they just keep coming and coming and coming,'...because of the way the drugs are developed. Now that stopping fentanyl is a national priority, she expects to see more nitazenes being developed by illicit manufacturers and used as authorities to catch up.").

40. *See* Amaducci et al., *supra* note 28, at 6–8 ("The NPO group [which includes nitazenes] was administered a statistically significantly higher number of in-hospital naloxone boluses compared with the fentanyl group, which corresponded to a moderately large effect size. While these findings were based on limited sample sizes, we detected a large effect size for the association between increased naloxone doses and NPO overdose. The majority of patients with ODs that involved NPO received 2 or more doses of naloxone, whereas most of the patients who OD from fentanyl only received 1 dose of naloxone. While this study was statistically underpowered to detect differences in naloxone administration in total cumulative dosage and clinical sequelae between patients with NPO and fentanyl only OD, this study provides important preliminary data on NPOs to inform clinicians and patients of the severity of ODs involving NPOs. Furthermore, this preliminary data underscores the urgent need to study NPOs in a larger, future cohort. These data suggest that NPOs may have higher potency than fentanyl and by extension heroin."). The study found further investigation necessary. *See id.* at 8.

41. DEA, Nitazenes, *supra* note 37 ("[Nitazenes are] being mixed into and marketed as other drugs to make drugs more potent and cheaper to produce. The major concern: This drug can [cause] and has caused deadly overdoses in unsuspecting victims.... DEA regional forensic laboratories have seen this drug mixed into heroin and/or fentanyl (and marketed as common street drugs) with deadly consequences. However, in other parts of the country, ISO has already been seen pressed into pills and falsely marketed as pharmaceutical medication (like Dilaudid 'M-8' tablets and oxycodone 'M30' tablets).... 'People have to keep in mind, with all the synthetic drugs out there, and the way they're being mixed together, you never know what you're actually buying,' says DEA Intelligence Analyst Maura Gaffney."); Breen, *supra* note 39 ("'Nitazenes being mixed with other illicit drugs emphasizes the increased risk of harm or death. Illicit drug suppliers often mix drugs to increase potency or lower costs,' the Boulder County coroner's office said. It's not clear if the man who died in Colorado knew he was ingesting N-Desethyl etonitazene. [¶] There also hasn't been much research into how nitazenes interact with other substances, so there may be unexpected side effects from mixing it with other drugs or alcohol, [Dr. Wilson M. Compton, deputy director of the National Institute on Drug Abuse (NIDA)] said."); DePeau-Wilson, *supra* note 37 ("'These are exceptionally dangerous molecules,' Andrew Kolodny, MD, an expert in opioid policy and addiction medicine at Brandeis University in Massachusetts, told *MedPage Today*. 'These drugs are entering the black market and they're being sold to people who are opioid addicted, and these individuals are losing their lives.'").

42. *See generally* Gerona, *supra* note 6, at 67–69; Martin F. Casey & Alex F. Manini, *Synthetic Cannabinoids (SC)*, *in* Dargan & Wood, *supra* note 6, at 415–46.

    The media created the term "synthetic cannabinoids," probably because the drug is often sprayed on plant material, smoked as if it were botanical cannabis, and can produce similar euphoric effects. Shane Darke et al., *"Synthetic Cannabis": A Dangerous Misnomer*, 98 Int'l J. Drug Pol'y 103396, at 1–2 (2021). The drugs so labeled, however, are not one uniform compound; they are not structurally similar to THC; they can be far less or far more potent than THC (sometimes between 10 and 100 times more powerful); they can have different and more severe effects than THC that can bring on dependence more quickly; and their "use is associated with..a more complex and severe withdrawal syndrome." *Id*. at 2, 3 ("One study of people using SCRAs or natural cannabis who sought emergency medical treatment following use of either drug found that the relative risk associated with SCRA use was 30 times greater that of cannabis, and that significantly more symptoms were reported by people using SCRAs seeking treatment... Of particular importance are documented cases of SCRA-related death, most frequently attributed to toxicity... It is likely that the most common mechanism in such cases is that there are toxic effects upon the cardiovascular system (e.g.[,] cardiac arrhythmia)...") (citations omitted), 4. Some scholars have argued that the term "synthetic cannabinoids" is a misnomer and that "this is a new drug class, with many effects similar to those of the psychostimulants, and an appropriate terminology should be used consistently: *synthetic cannabinoid receptor agonists (SCRAs)*."). *Id*. at 1. In short, the authors argue that SCRAs "are not benign cannabis substitutes." *Id*. at 4. They also maintain that the difference is not merely a terminological dispute. "We regard the term [synthetic cannabinoids] as a dangerous misnomer that has negative clinical and public health implications. Firstly, the term has the potential to misinform the perceived risk associated with these drugs. As has been stressed, there are no documented deaths from direct cannabis toxicity. The use of the term carries an implicit implication that the same may be true of SCRAs. In sharp contrast, deaths directly attributable to SCRA toxicity *do* occur, most likely due to acute cardiovascular events... Indeed, toxicity is the most frequently reported cause of SCRA-related death. [¶] Related to this confusion is the fact that people who use synthetic cannabis frequently may switch to SCRAs as cannabis *substitutes*, due to problems such as shortages in cannabis supply or as a quit strategy... Such people, however, are unwittingly transitioning from using THC to potent drugs with powerful cardiovascular effects. People who are relatively older, and thus arguably more likely to be attempting to quit cannabis or have a less stable supply, are at particular risk due to their higher rates of cardiovascular disease." *Id*. at 4. The authors make a persuasive case that botanical cannabis is an apple and synthetic cannabis is an orange. Nonetheless, their new terminology has not yet gained acceptance in the medical, scientific, or policy-making communities, so this *Special Report* uses the terminology found in the literature, however flawed it might be.

43. Baumann, *supra* note 29; Genevieve Lafaye et al., *Cannabis, Cannabinoids, and Health*, 19 Dialogues in Clinical Neuroscience 309, 310 (2017).

44. Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 418.

45. *See* Darke et al., *supra* note 42, at 1 ("The first reports of a legal herbal mixture that had cannabis-like effects emerged from Europe in 2004.... It was not, however, until 2008 that there was analytical confirmation of the substances present in these products such as the naphthoylindole JWH-018," which "was known to bind to the CB1 and CB2 receptors [to which THC binds]...and was therefore referred to as a synthetic cannabinoid, and more recently as a SCRA. Since then[,] the number of synthetic cannabinoids available on the non-pharmaceutical/illicit drug market has proliferated, with more than 280 unique substances identified between 2009 and 2019, and comprised 29% of new psychoactive substances first reported in 2019.") (citations omitted); *see also*, *e.g.*, Baumann, *supra* note 29 ("Marijuana-like NPS, also known as synthetic cannabinoids, appeared in the US recreational drug marketplace in the early 2000s, and by the end of the decade were being widely used."); Lafaye et al., *supra* note 43, at 310–11.

46. Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 586; *see also*, *e.g.*, Francis & Smith, *supra*, *in* Dargan & Wood, *supra* note 6, at 61 ("Early [synthetic cannabinoids] were procured from academic and industry research aimed at elucidating cannabinoid receptor properties and development of novel anti-inflammatories and analgesics."); Baumann, *supra* note 29 ("As governments have passed legislation to ban specific problematic NPS, chemists involved with the manufacture of these substances have consulted the scientific or patent literatures and quickly created novel 'replacement' drugs to stay one step ahead of law enforcement.").

47. Axel J. Adams et al., *"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York*, 376 New Eng. J. Med. 235, 240 (2017) (noting that the synthetic cannabinoid AMB-FUBINACA is 85 times more potent than THC); Baumann, *supra* note 29; Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 426; Darke et al., *supra* note 42, at 2; Fabrizio Schifano et al., *NPS: Medical Consequences Associated with Their Intake* [hereafter Schifano et al., *Medical Consequences*], *in* Baumann et al., *supra* note 14, at 354 (noting that, compared to botanical THC, the euphoria of synthetic cannabinoids can have a more rapid onset, be more intense, but have a shorter duration as well as generate more frequent and intense feelings of paranoia); Madras, *supra*, *in* Bauman et al., *supra* note 14, at 12.

48. THC can produce dysphoric effects such as "agitation, seizures, hypertension, nausea, and intractable vomiting." Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 426; Jenny L. Wiley et al., *Combination Chemistry: Structure—Activity Relationship of Novel Psychoactive Cannabinoids*, *in* Baumann et al., *supra* note 14, at 231 ("[W]hile their intoxicant effects may be similar to those of THC, use of synthetic cannabinoids may be accompanied by unpredicted and sometimes harmful effects."). CBD can dampen that dysphoria. "THC and CBD produce different, or possibly antagonistic molecular, neuropsychiatric, and pharmacological effects. The pharmacological effects that limit the therapeutic potential of THC in marijuana are addiction, anxiety, intoxication, impairment of cognition, amotivational syndrome, and psychosis. CBD not only has a wide safety margin, but also no evidence has emerged that it is addictive, produces euphoria or intoxication, or impairs cognition or precipitates psychosis. But with accumulating evidence, it is clear that CBD is not pharmacologically silent. High THC:CBD ratios in marijuana are associated with heightened euphoria, anxiety, and psychotic symptoms, whereas low THC:CBD ratios are linked to sedation and attenuation of THC-induced psychosis, anxiety, and cognitive deficits, leading to the conclusion, that CBD dampens the adverse effects of THC. . . . [W]e cannot yet say that CBD will reduce or eliminate all adverse effects of THC, but preliminary data indicate that CBD does attenuate specific THC-elicited neuroadaptations." Paul J. Larkin, Jr. & Bertha K. Madras, *Opioids, Overdoses, and Cannabis: Is Marijuana an Effective Therapeutic Response to the Opioid Crisis?*, 17 Geo. J. L. & Pub. Pol'y 555, 575–76 (2019) (footnotes omitted). CBD, however, is not present in synthetic cannabinoids.
49. Lafaye et al., *supra* note 43, at 311; *id*. ("The effects are comparable to those observed after high doses of THC, and the high efficacy—as well as differences from batch to batch—results in the risk of accidental overdosing.") (endnote omitted); *see also* Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 426 (noting that synthetic cannabinoids have "a markedly higher affinity" for the CB1 receptors in the brain and spinal cord and are "full agonists" for those receptors, instead of THC which is a partial CB1 agonist).
50. Darke et al., *supra* note 42, at 2; Lafaye et al., *supra* note 43, at 311; Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 587; Wiley et al., *supra*, *in* Baumann et al., *supra* note 14, at 234.
51. Baumann, *supra* note 29.
52. Lafaye et al., *supra* note 43, at 312 (endnotes omitted).
53. Baumann, *supra* note 29; Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 432 Tbl. 15.5 (listing the various possible adverse acute side effects).
54. Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 431 (noting that, in general, synthetic cannabis use is substantially more dangerous versus THC use and is "30-fold more likely to lead to utilization of emergency care when compared to traditional cannabis exposure").
55. A derivative of the anti-clotting drug warfarin, which can result in severe, long-lasting coagulopathy in users, as occurred in Illinois in 2018. *See infra* note 88.
56. Darke et al., *supra* note 42, at 3 (noting that there are "documented cases of SCRA-related death, most frequently attributed to toxicity.... Of primary importance, there are *no* documented deaths from THC toxicity, while drug toxicity is the most common diagnosis for SCRA-related death. Clinically significant adverse effects such as cardiac arrhythmia, haemorrhagic stroke, hyperthermia and acute kidney injury are not case profiles typically associated with acute cannabis intoxication.... They are, however, typical case presentations for a psychostimulant. While SCRAs are not psychostimulants, their general clinical toxicity profile is one more typically associated with a psychostimulant drug presentation.") (emphasis in original; citations omitted); *see* Baumann, *supra* note 29.
57. *See generally* Gerona, *supra* note 6, at 70–73; Kerry Layne et al., *Synthetic Cathinones*, *in* Dargan & Wood, *supra* note 6, at 333–79.
58. Philip Jenkins, Synthetic Panics: The Symbolic Politics of Designer Drugs 30 (1999).
59. *See*, *e.g.*, Su et al., *supra* note 14, at 26. "Like other stimulant drugs of abuse (e.g., cocaine and amphetamine), synthetic cathinones exert their effects by binding to 'transporter' proteins on the surface of nerve cells that synthesize the monoamine neurotransmitters dopamine, norepinephrine, and serotonin. These neurotransmitters are released from nerve cells and mediate cell-to-cell chemical signaling. The normal role of the transporters is to pull excess amounts of the released monoamine neurotransmitters from the 'extracellular' spaces around cells and move them back into the cells that made them (a process called 'reuptake'). Thus, monoamine transporters are critical for reducing extracellular concentrations of monoamine neurotransmitters." Baumann, *supra* note 29 (endnote omitted); *see id*. ("Elevations in extracellular dopamine are implicated in the pleasurable and addictive properties of stimulants, whereas elevations in norepinephrine are thought to mediate cardiovascular and autonomic effects."). Drugs such as cocaine slow the reuptake of neurotransmitters, while drugs like methamphetamine both slow the reuptake of neurotransmitters and stimulate neurons to release those compounds in greater quantities. Leslie Iversen, Speed, Ecstasy, Ritalin: The Science of Amphetamines 9, 12 ("[T]he ability of amphetamines to stimulate dopamine release in the brain...explains most, if not all, of their psychostimulant properties."), 85, 129 (2006); Ralph Weisheit & William L. White, Methamphetamine: Its History, Pharmacology, and Treatment 48 (2009); Baumann, *supra* note 29. For a depiction of the chemical structures of amphetamine and various cathinones, see Baumann, *supra* note 29 Fig. 1. There are several types of synthetic cathinones, including mephedrone, methylone, methylenedioxypyrovalerone (MDPV), and methcathinone. That last type is derived from khat, a plant found in Eastern Africa and the Arabian Peninsula. Many of methcathinone's effects parallel those of methamphetamine. Weisheit & White, *supra*, at 78–79; Baumann, *supra* note 29. One cathinone—MDPV—is 10 times as potent as cocaine. Baumann, supra note 29.
60. Madras, *supra*, at Bauman et al., *supra* note 14, at 11–12.
61. Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 585. Similar ploys are to market NPS as non-drug products, to use innocuous names for the drugs, or label them as "not for human consumption." Baumann, *supra* note 29.

62. Baumann, *supra* note 29.

    A potentially troublesome NPS that is not discussed in this *Special Report*— Captagon® —is an amphetamine analogue. It has not yet become a major social problem in America but nonetheless is a matter of concern, primarily because of geopolitical considerations. Captagon was created in 1961 as an alternative to amphetamine and methamphetamine for treatment of attention deficit-hyperactivity disorder and depression, but because of its potentially addictive properties, it was never approved by the FDA. Syria profits from its sales in Southwest Asia, and Iran indirectly benefits from the money going to its proxy Hezbollah. *See*, *e.g.*, *Captagon Trafficking and the Role of Europe*, European Monitoring Centre for Drugs & Drug Addiction, Technical Report (2023); United Nations Off. on Drugs & Crime, Global Assessment: Amphetamines and Ecstasy 45 (2011) ("The origin of the amphetamine sold as Captagon in the [Southwest Asia] region is unknown. Traditionally, the substance was believed to have been manufactured illicitly in South-East Europe, notably Bulgaria, and trafficked to the region, often transiting Turkey by air or sea. Some countries in the region, e.g.[,] the Syrian Arab Republic and Jordan, have named Turkey as a source. A recent report by the Turkish National Police concluded that criminal organizations have shifted Captagon manufacture to the Syrian Arab Republic. This shift which would appear to be consistent with the significant decline in the amount of seizures in Turkey, which have fallen from almost 20 million pills in 2006 to 2.8 million pills in 2009.") (footnotes omitted); Ahmed Allmam et al., *Captagon: Use and Trade in the Middle East*, 32 Human Psychopharmacology Clinical & Experimental e2548, at 4 (2017) ("The increasing trend of clandestine manufacture and use of amphetamine-type stimulants has become a major concern in countries such as Iran, Morocco and Pakistan. There is also a high demand for fenethylline (captagon) tablets in some countries of the region, especially in Syria, Lebanon and countries in the Arabian Peninsula. Captagon® was first introduced for its beneficial effects on hyperactivity, depression and narcolepsy, but it's addictive and hallucinogenic features made it a popular illegal psychoactive substance. Captagon® itself is no longer manufactured and counterfeit captagon tablets are mostly combined with amphetamine, caffeine, ephedrine, quinine, theophylline acetaminophen and diphenhydramine and may cause unpredictable complications. In Saudi Arabia, there are more treatment admissions registered as a result of captagon use than opioid use.") (endnotes omitted); Hossein Mohaddes Ardabili et al., *Tramadol, Captagon and Khat Ise in the Eastern Mediterranean Region: Opening Pandora's Box*, 19 Br. J. Psychiatry Int'l 58 (2022); Nicole Robinson, *Captagon, the New Cocaine of the Middle East?*, Heritage Found., Commentary (May 24, 2023), https://www.heritage.org/middle-east/commentary/captagon-the-new-cocaine-the-middle-east ("The $10 billion Captagon trade bankrolls Bashar al Assad's dictatorship in Syria and provides substantial resources to Lebanese Hezbollah, Iran's main proxy, to fund terror across the region."); Caroline Rose & Alexander Söderholm, *The Captagon Threat—A Profile of Illicit Trade, Consumption, and Regional Realities*, New Lines Inst. for Strategy & Pol'y, Intelligence Briefing (Apr. 4, 2022). Because captagon sales provide funds for terrorist groups, the federal government has identified steps that we can take to staunch that funding. *See* U.S. Dep't of State, Report to Congress: *A Written Strategy to Disrupt and Dismantle Narcotics Production and Trafficking and Affiliated Networks Linked to the Regime of Bashar al-Assad in Syria [Pursuant to] Sec. 1238(c) of the National Defense Authorization Act for Fiscal Year 2023, P.L. 117-263* (June 29, 2023). There also is no reason to assume that countries like Syria will never seek to tap into the seemingly unquenchable American thirst for illicit drugs and create a new source of injury to illicit drug users. *See* Robinson, *supra* ("Flush with cash, drug cartels tied to the Syrian regime and Iran will buy off more and more politicians, security forces, and other figures to secure drug routes and areas of control."). Accordingly, we need to keep an eye on captagon.

63. Bertha Madras, *Drug Use and Its Consequences*, *in* Madras & Kuhar, *supra* note 22, at 1.

64. Mount Sinai Health Library, Willow Bark (2024), https://www.mountsinai.org/health-library/herb/willow-bark.

65. Reuter & Pardo, *supra* note 11, at 117–18 ("Rapid advances in modern chemistry, technology, communications and globalization, as well as growing wealth and declining adherence to traditional values with respect to intoxication, have put pressures on existing national and international drug control mechanisms. Of note, late 20th century chemistry was advanced enough to produce a rapid flow of new psychoactive drugs that found their niches in recreational markets (e.g. ketamine and GHB [gamma hydroxybutyrate])…. Approximately 16 NPS were reported in 2005. Since then[,] approximately 560—more than double the number of substances controlled internationally—have been detected[.]"). In the seven years since the Reuter and Pardo paper was published, the number of NPS has doubled again. *See supra* p. 5.

66. *See* Gerona, *supra* note 6, at 17, 253; Brendan Hughes & Adam R. Winstock, *Controlling New Drugs Under Marketing Regulations*, 107 Addiction 1894 (2012); ("[D]etermining the most informed and effective policy response to today's untested synthetic psychoactive compounds is challenging, given the paucity of good-quality basic scientific and human experience data."); Marino, *supra* note 37; Abu Shafi et al., *New Psychoactive Substances: A Review and Updates*, 10 Therapeutic Advances in Psychopharmacology 1, 10 (2020) ("NPS comprise a diverse and ever-growing group of substances. There is much we still do not know, especially about the newest agents, and they can vary considerably in their desired effects and harms, even within drug classes.").

67. *See* Peacock et al., *supra* note 6, at 1675 Tbl. (listing "published case studies reporting NPS acute toxicity"); Sherrica Tai & William E. Fantegrossi, *Pharmacological and Toxicological Effects of Synthetic Cannabinoids and their Metabolites*, *in* Baumann et al., *supra* note 14, at 249, 251 ("[T]hese substances [synthetic cannabinoids] are not safe, have a greater toxicological profile than has been reported with marijuana, and should not be considered a legal alternative to cannabis."), 257; *see also*, *e.g.*, Madras, *supra*, *in* Baumann et al., *supra* note 14, at 7–8, 11, 12 ("'Spice' has been implicated in numerous medical emergencies and reports of toxicity . . . .") (endnotes omitted); Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 576–77; Schifano et al., *Medical Consequences*, *supra*, *in* Baumann et al., *supra* note 14, at 351, 356, 359.

68. *See*, *e.g.*, Gerona, *supra* note 6, at 66 Tbl. 3.1; Adams et al., *supra* note 47, at 236; Mariana Angoa-Perez et al., *Neurotoxicity of Synthetic Cathinone Analogs*, *in* Baumann et al., *supra* note 14, at 217 (discussing the risk of manganese poisoning causing Parkinson's-like symptoms); Baumann, *supra* note 29; Lafaye et al., *supra* note 43, at 312; Madras, *supra*, *in* Baumann et al., *supra* note 14, at 8 ("Another repugnant example of indifference to purity quality control, or safety, in clandestine production is manganese contamination of ephedrine used in its synthesis. Users can develop an ephedrine parkinsonism (EP) characterized by a complex, rapidly progressive, irreversible and leva dopa non-responsive parkinsonian and dystonic syndrome

due to manganese toxicity.") (endnote omitted); Parrott, *supra* note 31, at 268–69, 278–83; Schifano et al., *Medical Consequences*, *supra*, *in* Baumann et al., *supra* note 14, at 356; Su et al., *supra* note 14, at 25–26, 28 ("In our study, we observed that the heart rate of NPS users was 17.6 beats per minute faster than that of individuals who tested negative for toxicity. Synthetic cathinones, which are structurally similar to amphetamines, exhibit similar cardiovascular effects and complications, including tachycardia, myocardial infarction, and stroke. Furthermore, the INPS group, which comprised individuals using a combination of cathinone and ketamine, demonstrated an even higher heart rate (119.6 vs 93.5 beats, P < .05). Previous research has reported that ketamine can cause tachycardia.... Some NPS, such as synthetic cannabinoid compounds, have been associated with serious physical consequences like myocardial infarction, seizures, and renal damage.") (endnotes omitted); Valerie Wolff & Emilie Jouanjus, *Strokes Are Possible Complications of Cannabinoids Use*, 70 (Pt. B) Epilepsy & Behavior 355 (2017).

69. *See*, *e.g.*, Baumann, *supra* note 29; Mate Kapitany-Foveny et al., *NPS: Epidemiology, User Group Characteristics, Patterns, Motives, and Problems*, *in* Corazza & Roman-Urrestarazu, Clinicians, *supra* note 31, at 25 ("With regard to NPS-induced psychiatric symptoms and states, under the influence of synthetic cathinones, violent acts and unpredictable behavior are common consequences. Users lose touch with reality, and dissociative experiences and drug-induced psychotic states occur frequently.... Psychotic episodes or persistent psychosis may be present independently of either family or individual history of any psychiatric disorder....") (citations omitted); Carla Morganti et al., *NPS in Emergency Rooms: Dealing with Aggressiveness and Psychomotor Agitation*, *in* Corazza & Roman-Urrestarazu, Clinicians, *supra* note 31, at 93–94 (noting that in a study of a total of 5,529 patients admitted to 16 emergency departments in 10 European countries over one year, 1,467, or 26 percent, presented with symptoms of psychomotor agitation or aggressiveness).

70. MPTP is the acronym used to designate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Chemists can mistakenly produce MPTP when attempting to synthesize meperidine, a potent analgesic. MPTP is a precursor to the neurotoxin MPP+ (1-Methyl-4-phenylpyridinium). The toxin destroys the brain region known as the substantia nigra, which produces the neurotransmitter dopamine that is necessary for the brain to communicate with the rest of the body. Individuals still have an otherwise functioning brain but cannot move. *See* Nat'l Library of Med. (undated), https://pubchem.ncbi.nlm.nih.gov/compound/1-Methyl-4-phenyl-1_2_3_6-tetrahydropyridine ("[MPTP] is a neurotoxin that causes permanent symptoms of Parkinson's disease by killing certain neurons in the substantia nigra of the brain. While MPTP itself does not have opioid effects, it is related to MPPP, a synthetic opioid drug with effects similar to those of heroin and morphine. MPTP can be accidentally produced during the illicit manufacture of MPPP, and that is how its Parkinson-inducing effects were first discovered."); Michelle McCormick, Designer-Drug Abuse 21–29 (1989); Shasi V. Kalivendi et al., *1-Methyl-4-phenylpyridinium (MPP+)-Induced Apoptosis and Mitochondrial Oxidant Generation: Role of Transferrin-Receptor-Dependent Iron and Hydrogen Peroxide*, 371 Biochemistry J. (Pt. 1) 151, 151 (2023).

71. Jenkins, *supra* note 58, at 79; McCormick, *supra* note 70, at 33 (describing cases where MPTP caused irreversible Parkinson's-like symptoms).

72. *Star Wars: Episode V—The Empire Strikes Back* (Lucasfilm Ltd. & 20th Century Fox 1980), https://www.youtube.com/watch?v=wXrwWnu7agk.

73. Baumann, *supra* note 29.

74. "Clinical and public health responses to date have focused on acute toxicity from NPS. This attention has grown in previous years with the increased reportings of overdose associated with NPS in several countries. Current examples include rising mortality from benzodiazepine NPS in Scotland (etizolam implicated in 57% of all drug-related deaths in 2018); opioid NPS in North America (fentanyl analogues detected in 20.6% of opioid overdose deaths occurring between July, 2016, and June, 2017, in 10 US states); and from synthetic cannabinoids in New Zealand (reportedly in excess of 40 deaths linked to synthetic cannabinoids in 2017–18)." Peacock et al., *supra* note 6, at 1678 (endnotes omitted).

75. *See* M.M. Kirsch, Designer Drugs 14 (1986) ("A single dose of 3-methyl fentanyl"—which is 3,000 times as potent as morphine—"contains five to ten micrograms, or one quarter to one-half of a grain of salt."); Abbate et al., *supra*, *in* Dargan & Wood, *supra* note 6, at 451–52 ("A dose of only 20 µg of carfentanil is estimated to cause overdose, an amount that is barely visible to the naked eye.") (endnote omitted); Andrew Olivastro, *Fentanyl's Wake*, Am. Mind, May 25, 2022, https://americanmind.org/salvo/fentanyls-wake/ ("Only a miniscule amount of fentanyl is necessary for it to have its anaesthetic or analgesic effect. A smidgeon more and death follows like the Ghost of Christmas Yet to Come. 'It takes only 2 milligrams to be lethal. That's not even enough to cover the year on the front of the penny in your pocket.'") (endnote omitted); *see infra* note 134.

76. *See*, *e.g.*, Peacock et al., *supra* note 6, at 1669 ("NPS are increasingly manufactured and sold as, or mixed with, more established illicit substances, or sold as counterfeit prescription medicines—often unbeknown to consumers (and sometimes distributors).") (endnotes omitted); Chris Wilkins, *A Critical Assessment of the New Pre-Market Approval Regime for New Psychoactive Drugs in New Zealand*, 108 Addiction 1580, 1582 (2014) ("NPS are often used in combination with other legal and illegal psychoactive substances. A national [New Zealand] population survey of legal BZP [benzylpiperazine, a stimulant] use found that 86% of BZP users combined their use of BZP with another substance. The most popular combinations were alcohol (91%), tobacco (40%), cannabis (22%), 5-HTP (5-hydroxytryptophan) (9%) and ecstasy (5%).") (endnotes omitted).

77. *See*, *e.g.*, Naviglio et al., *supra* note 25, at 2 ("The most important step is to obtain a precise history, but this is not always possible because of the patient's conditions or reticence."); Justice N. Tettey & Sabrina Levissianos, *The Global Emergence of NPS: An Analysis of a New Drug Trend*, *in* Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 6 ("NPS users are often unaware of what they are actually consuming as substances contained within a product are not often listed on packages. This exposes the user to additional serious health risks since little to no scientific information is available to determine the psychoactive effects that these combinations may have.").

78. Gerona, *supra* note 6, at 20–21; *supra* note 24.

79. Which includes the new devices necessary to conduct high-resolution mass spectrometry (HRMS), such as liquid chromatography–quadruple time-of-flight mass spectrometry (LC–QTOF/MS), as well as the more traditional platforms such as liquid chromatography–tandem mass spectrometry

(LC–MS/MS), gas chromatography–mass spectrometry (GC–MS), nuclear magnetic resonance spectroscopy (NMR), Fourier transform infrared (FT-IR) spectroscopy, direct analysis in real time with thermal desorption mass spectrometer (DART-TD-MS), and surface-enhanced Raman scattering spectroscopy (SERS). *See* Gerona, *supra* note 6, at xii, 21; Martin M. Kimani et al., *Rapid Screening of 2-Benzylbenzimidazole Nitazene Analogs in Suspect Counterfeit Tablets Using Raman, SERS, DART-TD-MS, and FT-IR*, 15 Drug Testing & Analysis 539, 540 (2023).

80. *See* Gerona, *supra* note 6, at 253–54; Adams et al., *supra* note 47, at 241 ("The analysis of new psychoactive substances requires more than the typical targeted drug panels used in emergency departments and relies on more sophisticated analytic platforms that have the ability to rapidly identify previously unreported compounds."); Frank T. Peters & Marlins R. Meyer, *Analytical Techniques for the Detection of Novel Psychoactive Substances*, *in* Dargan & Wood, *supra* note 6, at 225–26 ("[M]ost of the new drugs may cause serious toxicity or impairment but their identification is not guaranteed by established analytical methods for several reasons"—e.g., the lab lacks the sophisticated equipment or the drugs are not yet listed in the refence libraries); Vandeputte et al., *supra* note 34, at 116–17 ("While timely updates to testing scopes and innovative approaches to new substance detection and identification can help ensure more timely recognition of new drugs…they are not consistently available to or implemented in all laboratories, resulting in a chronic underestimation of the overall life cycle and prevalence of each newly emerging drug…. [D]rug seizures or cases involving isotonitazene might have been underreported because laboratories were not actively screening for its presence, or [were unable] to do so due to unavailability of standard reference material. Hence, particularly in the early months of its emergence, the presence of isotonitazene on the illicit drug market was likely undetected.") (endnotes omitted); Kimani et al., *supra* note 79; Naviglio et al., *supra* note 25, at 2 ("Synthetic cannabinoids are not usually detected by conventional drug screening tests. In the absence of a positive history, advanced tests like liquid chromatography-tandem mass spectrometry may identify the substance, but these are not generally available in the acute setting…. [S]ome synthetic cannabinoids are not detected even with advanced testing because most laboratories have only a limited library of reference compounds, and newer molecules may not be included."); Sara E. Walton et al., *A Forward-Thinking Approach to Addressing the New Synthetic Opioid 2-Benzylbenzimidazole Nitazene Analogs by Liquid Chromatography–Tandem Quadrupole Mass Spectrometry (LC–QQQ-MS)*, 46 J. Analytical Toxicology 221 (2022).

81. Gerona, *supra* note 6, at 19.

82. *See*, *e.g.*, Anders Helander et al., *Intoxications Involving Acrylfentanyl and Other Novel Designer Fentanyls—Results from the Swedish STRIDA Project*, 55 Clinical Toxicology 589, 589 (2017) ("[T]he production is typically done in uncontrolled clandestine laboratories and the true content is not analytically confirmed. As a result, NPS-associated medical complications have become an increasing problem at emergency departments (ED) and intensive care units (ICU).") (endnotes omitted); Madras, *supra*, at Bauman et al., *supra* note 14, at 9 (quoted *supra* note 68; Shafi et al., *supra* note 66, at 910 ("[I]n clinical practice, patients are typically treated on the basis of the pattern of toxicity they present with, and the turn-around time for a standard and comprehensive NPS screen would often mean that the results are not available in a time-frame that would alter the clinical management of the patient. Test designs also need to take into account that users of NPS will be likely to use additional over-the-counter medication, other illicit drugs, and that NPS preparations themselves may be contaminated with other illicit drugs, or dissolved in diluents. [¶] The Novel Psychoactive Treatment UK Network (NEPTUNE) recognise the current limitations in the availability of timely clinical testing available during acute presentations of NPS toxicity, and currently recommend toxicity diagnoses are made primarily on clinical features rather than by testing.") (endnotes omitted); Naviglio et al., *supra* note 25, at 1–3; Su et al., *supra* note 14, at 28; Zapata et al., *supra* note 14, at 2.

83. As a result, sometimes a particular NPS is just one of several found in a particular batch, and the first one reported is treated as the cause of death. *See* Evans-Brown, *supra*, in Dargan & Wood, *supra* note 6, at 4.

84. *See* Vandeputte et al., *supra* note 34, at 118 ("As with prior patterns of NPS opioids, when they begin to wane in positivity, new (often related) substances invariably appear to fill the void. Recently, metonitazene…and flunitazene…(both structural analogues of isotonitazene) have appeared and began to increase in frequency of detection, as brorphine began to decline.") (endnotes omitted), 119 ("A virtually endless supply of drugs with opioid effects has been described in literature from the 1950s and from more recent times, and minor structural modifications quickly give rise to many closely related, yet unregulated, analogues. Hence, once scheduling (and/or other factors) impedes one opioid's availability, the emergence of various alternatives designed to evade previous restrictions appears inevitable—a phenomenon observed repeatedly in this review. In the case of isotonitazene and brorphine, increased awareness of their adverse effects, and the consequent national and international controls placed on them, ultimately appeared effective in reducing their availability and distribution.")

85. Gerona, *supra* note 6, at 19.

86. Which are often the first to spot a new NPS threat. Gerona, *supra* note 6, at xi, 231.

87. "[P]sychoactive drugs can be used in medicine for some time before their addictive properties are recognized" and "can lie dormant in a culture for many years if not decades before they break into widespread use and generate significant social problems. Both amphetamine and methamphetamine exhibited a long incubation period between their discovery and their emergence and association with addiction." Weisheit & White, *supra* note 59, at 28; *see* Reuter & Pardo, *supra* note 11, at 118 (noting that "enough users may have tried a substance before its harmful effects have been detected and publicized, leaving behind a substantial number of victims. The experience of Jamaica Ginger during Alcohol Prohibition in the US provides a good analogy…. [M]ore than 35,000 individuals experienced long-term paralysis as the result of drinking denatured alcohol.") (citation omitted).

Not to be forgotten is the very real threat posed by NPS-impaired driving. The United Nations Office on Drugs and Crime noted that problem in a 2023 report. *See* VI U.N. Off. on Drugs & Crime, Current NPS Threats 1–2 (2023) [hereafter U.N. Current NPS Threats] ("The following report presents the latest information on NPS that has been reported to UNODC and an analysis of over 1,200 cases submitted from toxicology laboratories within 12 Member States from the Americas, Europe, Asia and Oceania between December 2021 and May 2023… Drug-driving cases represented the

second largest group of toxicology cases during the current reporting period (n=234). By far the most commonly reported substances within this group were benzodiazepine-type NPS, accounting for 165 (71%) of reports followed by 25 (11%) reports of dissociatives and 19 (8%) cases involving kratom. 15 (6%) reports showed the detection of synthetic opioids and 10 drug-driving related cases involved stimulant NPS. The top four substances reported in DUID cases were etizolam (n=45), flubromazolam (n=39), flualprazolam (n=39), and bromazolam (n=23). The continuing persistence of benzodiazepine-type NPS in DUID, in addition to their predominance in PM cases continues to highlight the threat potential of this substance group.").

88. Baumann, *supra* note 29; *see*, *e.g.*, Jean M. Connors, *Hemorrhagic Highs from Synthetic Cannabinoids—A New Epidemic*, 379 New Eng. J. Med. 1275 (2018); Darke et al., *supra* note 42, at 3; Amar H. Kelkar et al., *An Outbreak of Synthetic Cannabinoid–Associated Coagulopathy in Illinois*, 379 New Eng. J. Med. 1216, 1222 (2018) ("Our data indicate that superwarfarin adulterants of synthetic cannabinoids can lead to clinically significant coagulopathy.").

89. *See* U.N. Current NPS Threats, *supra* note 87, at 3 ("The diversity in the types of substances identified in polydrug use cases associated with the use of NPS continues to highlight the complexity of analytical toxicology and the challenges faced by forensic toxicologists."); Breen, *supra* note 39 (noting that "[t]he illicit use of nitazenes remains rare, according to [NIDA Deputy Director] Compton," but since not every medical examiner tests for nitazenes in every overdose death, "'we don't actually know the complete universe of how many deaths are due to these potentially very toxic compounds.'"); Marino, *supra* note 37 ("[S]o far, nitazenes have primarily been detected in drug samples with fentanyl. While detection seems to be increasing, it remains unclear what their true prevalence is in the drug supply because testing for nitazenes is limited[,] and they are still not routinely tested for in overdose deaths."); Zapata et al., *supra* note 14, at 2.

90. *See* Carolyn Coulson & Jonathan P. Caulkins, *Scheduling of Newly Emerging Drugs: A Critical Review of Decisions Over 40 Years*, 107 Addiction 766, 771 (2011) ("Our overall conclusion is that the sky is not falling. That may seem anti-climactic, but given the strenuous criticisms the literature has leveled against scheduling decisions, we frankly expected to be decisively negative. In particular, the historical data are not consistent with the image of a system that has been overwhelmed by an ever-increasing onslaught of new substances."); Reuter & Pardo, *supra*, in Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 157 (noting that "nearly 98% of NPS disappear from the market within a few months of their introduction").

91. "What is striking is how narrow and/or ephemeral are the niches that these new drugs have occupied in the recreational market. Some simply lose popularity, either because that particular experience is unattractive to a new generation or because of fears about adverse effects, usually reflecting actual experience of recreational users, rather than government announcements [¶] Even those few NPS that gain a significant market share tend to fade fairly rapidly.... Though the development of new chemicals for the recreational market appears overwhelming, only a handful gain acceptance in popularity as unpleasant drugs lose popularity." Reuter & Pardo, *supra*, in Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 156 (citing Alexander T. Shulgin, *Drugs of Abuse in the Future*, 8 Clinical Toxicology 405 (1975)); *see also* Vandeputte, *supra* note 34, at 116 ("Overall, the life cycle of an NPS opioid can be very short (as little as 3–6 months), with an almost infinite number of other substances ready in line to replace it. This continuous cat-and-mouse game among illicit drug manufacturers, toxicology labs and law enforcement agencies renders the NPS market as a whole highly dynamic, with new drugs entering and leaving circulation rapidly.")

92. Reuter & Pardo, *supra*, in Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 157 (punctuation omitted).

93. *Id*. at 157.

94. "An immediate purpose is to provide guidance to the police and to the judiciary concerning the relative gravity of different drug-related offences with which they must deal. A broader purpose, as stated by the ACMD [*viz*., the U.K. Advisory Council on the Misuse of Drugs], is to identify those drugs responsible for the greatest degree of harm to the individual and to society, presumably for the purpose of directing efforts to reduce the total harm as much as possible. To that end, classification would have a variety of intended subpurposes, including decrease of availability and hence of use of certain drugs, education of the public concerning potential harms and shaping public attitudes in such a manner as to discourage harmful drug use." Harold Kalant, *Drug Classification: Science, Politics, Both or Neither?*, 105 Addiction 1146, 1146 (2010).

95. "[I]n order for a substance to be placed into any category other than Schedule I it needs to have an 'accepted medical use in treatment in the United States'. Because no emerging substance can already have an accepted medical use, the DEA may be faced effectively with the choice of placing the substance in Schedule I or not regulating it at all." Coulson & Caulkins, *supra* note 90, at 772 (endnote omitted).

96. *Id*.

97. *Id.*

98. *See* Mbabazi Kariisa et al., *Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine—United States, January 2019–June 2022*, Cntrs. for Disease Control & Prevention, 72 Morbidity & Mortality Weekly Rep. 731, 731 (2023) ("In 2022, provisional data indicated that more than two thirds (68%) of the reported 107,081 drug overdose deaths in the United States involved synthetic opioids other than methadone, principally illicitly manufactured fentanyls (IMFs).") (endnote omitted).

99. *See* TVA v. Hill, 437 U.S. 153, 189–91 (1978) (Congress assumes that the underlying substantive law will remain unchanged when it passes appropriations bills).

100. Executive agencies have only the authority that Congress has vested in them. *See*, *e.g.*, West Va. v. EPA, 577 U.S. 697, 723 (2022) ("Agencies have only those powers given to them by Congress, and enabling legislation" is generally not an "open book to which the agency [may] add pages and change the plot line.") (citations and punctuation omitted); Nat'l Fed'n of Indep. Business v. OSHA, 595 U.S. 109, 117 (2022); Ala. Ass'n of Realtors v. HHS, 141 S. Ct. 2485, 24790 (2021); Bowen v. Georgetown Univ. Hosp., 488 U.S. 204, 208 (1988) ("It is axiomatic that an administrative agency's power to promulgate legislative regulations is limited to the authority delegated by Congress."); La. Pub. Serv. Comm'n v. FCC, 476 U.S. 355, 374 (1986) ("[A]n agency literally has no power to act...unless and until Congress confers power upon it.").

101. McCormick, *supra* note 70, at 33 ("During the early 1980s, the fentanyls gained a reputation as a desirable drug of abuse and were actively sought and openly sold on the street. But as the dangers of designer drugs became apparent, users shunned them. In response, dealers began marketing them as heroin."). Technically speaking, that mislabeling might be a type of "fraud," which could be separately punished, but that possibility is beside the point. NPS traffickers are already at risk of receiving lengthy prison terms for synthesizing a compound that is covered by federal or state law, as well as the risk of an enhanced sentence if their product causes grave bodily injury or death. *See*, *e.g.*, 21 U.S.C. § 841(a)(1), (b)(1)(A)–(C) (2018) (authorizing an enhanced penalty for the distribution of a Schedule I or II drug when "death or serious bodily injury results from [its] use"). NPS dealers are unlikely to be deterred by the additional risk of being charged with fraud.

102. Ironically, to some extent the Biden Administration has adopted the Reuter–Pardo proposal without admitting it. One of the problems that follows from a refusal to enforce the law is the unimpeded smuggling of fentanyl across our border with Mexico. We don't know how many lives that policy has caused, but there is no reason to assume that the number is zero. A refusal to halt fentanyl smuggling also signals a disregard for the law and, especially, the people who suffer from fentanyl reaching our streets. Perhaps President Biden has bought into the view, held by some of his supporters. that enforcement of the drug laws is inherently racist. *See* Michelle Alexander, The New Jim Crow: Mass Incarceration in the Age of Colorblindness (2010). Perhaps he does not care for the people lost to fentanyl because they are the same "deplorables" that Hillary Clinton besmirched in 2016. *See* Katie Reilly, *Read Hillary Clinton's "Basket of Deplorables" Remarks About Donald Trump Supporters*, Time, Sept. 10, 2016, https://time.com/4486502/hillary-clinton-basket-of-deplorables-transcript/. Perhaps he does not want implicitly to criticize his son for the latter's drug use. Whatever the reason might be, his decision not to enforce the law against fentanyl smuggling is a marked departure from a tradition of enforcing those laws for the purpose of saving lives.

103. Kirsch, *supra* note 75, at ii ("[T]he likelihood of users paying heed to what sounds like one more 'drug scare' is slim; there have been too many drug scare campaigns in the past.").

104. *See The Untouchables* (Paramount Pictures 1987) ("[Al Capone:] I grew up in a tough neighborhood. And we used to say, 'You get further with a kind word and a gun than you can with just a kind word.'").

105. Unlike Walter White. *See Breaking Bad* (AMC 2008–2013). "'Statistically,' says one expert on illicit labs, 'we can even give a profile of an average methamphetamine manufacturer. He is a white male and may be well educated or has spent time learning techniques from an experienced cooker. Often, this chemistry lesson takes place in prison where formulas and techniques are passed around between inmates. He may have ties to outlaw motorcycle gangs who will provide him with necessary chemicals, protection, and a ready market for the finished product." McCormick, *supra* note 70, at 75. There are a few exceptions. *Id.* at 84 (describing the case of a DuPont Company chemist who tried to get into the fentanyl business: "[He] was 'a very sophisticated chemist' who 'had no idea how to be a criminal.'" (quoting Ray McKinnon, Chief of the DEA Dangerous Drugs Investigation Section); Kirsch, *supra* note 68, at 24–25 ("There are three type of clandestine chemists. First are the amateurs, who pick up expertise watching others cook. [Think Jesse Pinkman in *Breaking Bad*.] They usually start out synthesizing PCP because it's easy; they pick up new techniques and recipes from the street and in the prison system. [¶] The second type are the pros, chemists employed in the public and private sectors who enter the black market because they can't earn enough to satisfy themselves. They are most often college educated with a fund of laboratory experience and access to research material. [¶] The third type are the wizards—the designers of new drugs—who may or may not have any formal training.").

106. *See* 21 C.F.R. Pt. 210 (West 2024) (current good manufacturing practice in manufacturing, processing, packing, or holding of drugs), Pt. 211 (same for finished pharmaceuticals), Pt. 314 (2023) (requirements for FDA approval of a new drug); U.S. Food & Drug Admin., *Current Good Manufacturing Practice (CGMP) Regulations* (2023). For a description of the synthetization process at clandestine labs, see McCormick, *supra* note 70, at 78: "Clandestine labs bear little resemblance to the well-organized chemistry labs most students work in. Glass bottles, tubing, and cans of chemicals are strewn about. Large glass containers with narrow necks, known as reaction flasks, nestle into heating mantles resembling large, open crockpots. All kinds of tubes protrude from the reaction flasks and carry wastes away to glass jars or to drains. There is usually a jumble of chemical containers, electric wires strung everywhere, thermometers, and other tools. [¶] The cooks may have a bed or cot set up in their lab work area, so they can be constantly present while the reactions are going on. Windows may be painted black or boarded up to prevent detection. The lab may be in a kitchen, a garage, a laundry room, bathroom, or converted warehouse."

107. *See*, *e.g.*, 21 U.S.C. § 374(a)(1) (2023) (with identified exceptions, authorizing properly designated federal officials to "enter" and "inspect" any "factory, warehouse, or establishment in which…drugs…are manufactured, processed, packed, or held, for introduction into interstate commerce, or after such introduction," as well as any "vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein"); *id.* (providing that "the inspection shall extend to all records and other information" described elsewhere in Title 21); *id.* ("In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, devices, or tobacco products are manufactured, processed, packed, or held, the inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, devices, or tobacco products which are adulterated or misbranded within the meaning of this chapter, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this chapter."); Madras, *supra*, *in* Baumann et al., *supra* note 14, at 8. Often, a "cooker will pick an isolated area for his laboratory, where the threat from law enforcement is minimal." McCormick, *supra* note 70, at 76.

108. *See* Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 417 ("[NPS] monitoring in Europe revealed that active ingredients gradually became more potent, and 'exotic substitutes'…were increasingly introduced to products and available on the market.") (endnote omitted); *see also*, *e.g.*, Madras, *supra*, *in* Baumann et al., *supra* note 14, at 9 ("Without quality control and with deceptive labeling, compounds vary from product to product, batch to batch and even contain 'hot spots' within each packet. This array of untested polypharmaceuticals places users at risk of adverse health consequences,

and baffles emergency department physicians and staff who are powerless to identify the most significant threat to patient health and select effective antidotes."); Schifano et al., *Medical Consequences*, *supra*, in Baumann, *supra* note 14, at 354; Tai & Fantegrossi, *supra* note 67, at 257. For example, the solvents and precursor chemicals used to dissolve, synthesize, and purify the products may not be pharmaceutical grade, and this can introduce trace metals or other potentially toxic compounds into the final products. *See* Baumann, *supra* note 29; Su et al., *supra* note 14, at 25 ("Substances such as benzodiazepines and active metabolites of opioids are often added to synthetic cannabinoids, resulting in a wide range of unpredictable adverse effects."), 26 ("Reports from developed countries have revealed that NPS has been added to the existing classical illicit drugs.") (endnote omitted); Madras, *supra*, *in* Baumann et al., *supra* note 14, at 8; Zawilska, *supra* note 13, at 3 ("Recently, alarming reports from the USA and Canada show that carfentanil has been increasingly laced with or disguised as heroin.... Clandestine opioids are often up mixed with heroin ('fake heroin') to masquerade heroin, included in cocaine products or black tar heroin, or pressed into prescription pills[.]").

109. *See* Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 417 ("This accessibility has in turn led to a perception that synthetic cannabinoids are safe and legal alternatives to illicit controlled substances/drugs.") (endnote omitted); Janie Sheridan & Rachael Butler, *"They're Legal So They're Safe, Right?" What Did the Legal Status of BZP-Party Pills Mean to Young People in New Zealand*, 21 Int'l J. Drug Pol'y 77 (2010); *cf*. Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: Why the FDA Could Not Approve Raw Cannabis as a "Safe," "Effective," and "Uniform" Drug*, Heritage Found., Special Report No. 275, at 17–22 (2023) [hereafter Larkin, *FDA and Cannabis*] (arguing that people generally assume that state legalization of cannabis means that cannabis products are safe).

110. *See supra* note 37.

111. *See* DEA, Nitazenes, *supra* note 37; U.N. Current NPS Threats, *supra* note 87, at 3 ("Similar to previous Current NPS Threats Reports, the pattern of poly-drug use continued to be an important feature and consideration in NPS casework. Controlled drugs were found in the majority of PM [Post-Mortem] cases and for example in n=83 (62%) cases, between 2–6 other drugs were identified in combination with the particular NPS present. Cocaine was the substance most often reported, in 40% of poly-drug PM cases, followed by fentanyl and (non-NPS) benzodiazepines in 32% of cases, each. Collectively, the presence of multiple substances was most abundant in drug use cases, followed by DUID cases and PM cases."); Su et al., *supra* note 14, at 26 ("Polysubstance use is common among NPS users, including combinations of NPS and classical illicit drugs or a mixture of multiple NPS products.") (endnote omitted).

112. Zapata et al., *supra* note 14, at 1–2 (noting "the huge lack of knowledge about [NPSs'] toxicity, about the limit between a 'safe' dose and a fatal dose, and about the unknown adverse health effects they produce") (endnotes omitted).

113. *How Dangerous Is Tranq, the New Drug Sweeping America?*, Economist, Aug. 17, 2023, https://www.economist.com/the-economist-explains/2023/08/17/how-dangerous-is-tranq-the-new-drug-sweeping-america?utm_campaign=r.the-economist-today&utm_medium=email.internal-newsletter.np&utm_source=salesforce-marketing-cloud&utm_term=2/29/2024&utm_id=1856581 ("Tranq dope combines fentanyl, a synthetic opioid drug, with xylazine or 'tranq', a strong non-opioid tranquiliser used to sedate horses, deer and other large animals. It was first detected by drug authorities in the early 2000s in Puerto Rico and, in the years since, circulated there and in limited areas within the American north-east, such as Philadelphia. But the drug has now been detected in nearly every state in the country and, according to the [DEA] is probably being mixed by local dealers.... Many end users will not know whether they are buying fentanyl or tranq dope, though it is becoming increasingly risky to assume that the former has not been cut with xylazine. In March the DEA said that almost a quarter of American fentanyl powder contained it. In 2021 the proportion was above 90% in Philadelphia.... Perhaps more worrying still, Naloxone, the emergency treatment for a fentanyl overdose, is ineffective against non-opioids like xylazine.... [A]ddiction medics say that synthetic opioids remain their chief concern. They kill more and more Americans every year, claiming about 70,000 lives in 2021—in comparison, about 43,000 people died in car crashes that year. Yet those taking tranq dope are at greater risk of a fatal overdose. At a minimum its growing presence complicates America's already difficult battle against overdose deaths, and risks making drug users even more vulnerable").

114. *See* Jennifer Middleton, *Opioid Epidemic Updates: "Frankenstein Opioids" and Xylazine-Induced Skin Ulcers*, Am. Family Physician Found. Community Blog, Feb. 13, 2023, https://www.aafp.org/pubs/afp/afp-community-blog/entry/opioid-epidemic-updates-frankenstein-opioids-and-xylazine-induced-skin-ulcers.html ("Two new substances associated with illicit opioid use have been spreading in the United States and Canada, contributing to opioid use complications and overdoses. 'Frankenstein opioids,' or nitazenes, are Schedule I drugs; they are increasingly mixed with fentanyl or heroin. Xylazine, which goes by the street name 'Tranq,' is a non-opioid licensed for use in the United States in veterinary medicine as a sedative. Both substances have been injected or ingested, often unknowingly, by countless persons, worsening what is already a staggering epidemic.... Xylazine is added to fentanyl to prolong its euphoric effect."); Jacqueline Nunez et al., *Xylazine, a Veterinary Tranquilizer, Detected in 42 Accidental Fentanyl Intoxication Deaths*, 9 Am. J. Forensic Medicine & Pathology 11 (2021); *The Rise of "Tranq Dope" Is Making America's Opioid Crisis Worse*, Economist, Aug. 24, 2023, https://www.economist.com/united-states/2023/08/24/the-rise-of-tranq-dope-is-making-americas-opioid-crisis-worse ("Tranq dope is a combination of fentanyl, a powerful synthetic opioid, and xylazine, a veterinary tranquiliser. Adding xylazine to an opioid seems to make the high last longer.").

115. For gruesome, stomach-churning photographs of xylazine's work, see Rahul Gupta et al., *Xylazine—Medical and Public Health Imperatives*, 388 New Eng. J. Med. 2209, 2211 (2023); Srikrishna V. Malayala et al., *Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA*, 14 Cureus e28160, Aug. 19, 2022, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9482722/pdf/cureus-0014-00000028160.pdf.

116. *See* Connors, *supra* note 88, at 1275–76; *supra* note 65.

117. McCormick, *supra* note 70, at 71.

118. *Id*. at 72; *see id*. at 79–80: "Wherever the lab is located, and whatever the details of its setup, it is a dangerous place to be. The primary hazard is the presence of toxic chemicals, often improperly labeled, improperly handled, and stored without regard for safety precautions. Many of the chemicals

in the production of illicit synthetics pose hazards unrelated to the problems of drug abuse. [¶] The ether often used as a solvent is highly explosive, and acetone, another solvent, is extremely flammable. A random spark or cigarette ember will ignite either chemical in an instant. Lithium aluminum hydride, sometimes used in making crank [viz., meth], is also flammable—it explodes on contact with water. A drop of perspiration is enough to set it off.... Also, hydrofluoric acid, normally used in etching glass, has been found in labs. If spilled on the skin, it doesn't hurt because it anesthetizes the nerves as it eats through flesh to the bone. [¶] Even highly trained chemists can't predict what toxic fumes might result when certain drugs are combined. These unknown fumes are sometimes referred to as mutant chemical atmospheres.... Poisonous chemicals such as cyanide powder, mercury, or cancer-causing methylamine are routinely found in labs. 'We're talking about something that people could walk through and die,' says one drug agent."

119. *Id*. at 79: "The procedure for making PCP involves the use of two chemicals that if accidentally mixed form deadly cyanide gas."

120. *Id*. at 82: "As the illicit drugs are produced, many of the substances needed to complete the process are left over. Some of the chemicals, such as mercury or cyanide powder, may remain on the floors and counters long after the drug making is finished. These chemicals are not removed during normal cleaning.... They can remain viable and present, even in soil, for years. New occupants of buildings that have housed labs risk exposure to these poisons. Even people picnicking in areas where toxic materials have been dumped are in danger. [¶] Many cooks dispose of their dangerous wastes simply by pouring them down the toilet. But these powerful chemicals can disable a sewage processing plant.... In rural areas[,] the chemical wases can kill the bacteria necessary in septic systems. As a result, hazardous chemicals and raw sewage may leach out, contaminating aquifers and water sources. Buried in containers, they pose a threat to those who may accidentally come into contact with them where the containers decompose or are later uncovered."

121. *Id*. at 79–80; *id*. at 80: "For the police who seek out labs, the chemical dangers are only the beginning. Clandestine labs are often guarded by firearm-wielding cooks—and firearms are even more dangerous in a lab because the flash they produce when fired can ignite any one of the many explosive chemicals likely to be present. [¶] Cooks often set booby traps to protect them from unwanted intruders or from police. The booby trap may be a light fixture fixed with a chemical that will burst into flames when the switch is flipped, a refrigerator wired to explode when the door is opened, or something as simple as a can of powerful acid balanced on a partially open doorway."

122. *See*, *e.g*., Abbate et al., *supra*, *in* Dargan & Wood, *supra* note 6, at 447 ("Since 2009, 57 new synthetic opioids have been detected on Europe's drug market, including 11 in 2018 and 8 in 2019, some from entirely new groups of chemicals.") (endnotes omitted); Madras, *supra*, in Baumann et al., *supra* note 14, at 7–8; Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 576–77.

123. Glenn Fry, "Smuggler's Blues," on *The Allnighter* (MCA 1985).

124. *See*, *e.g*., Gerona, *supra* note 6, at 13; Baumann, *Preface*, *in* Baumann et al., *supra* note 14, at v ("The chemical structure of many NPS are based on compounds extracted from the biochemical or patent literature, whereas others are analogs of illicit drugs or prescribed medications."); Baumann, *supra* note 29 ("Scientific articles published in online databases (e.g., PubMed) provide step-by-step recipes for the syntheses of psychoactive compounds, most of which were originally developed as potential medicines or research tools."); Caulkins & Humphreys, *supra* note 11, at 2; German Lopez, *A New Kind of Drug*, N.Y. Times, May 20, 2022, https://www.nytimes.com/2022/05/20/briefing/synthetic-drugs-labs.html; Evans-Brown, *supra*, *in* Dargan & Wood, *supra* note 6, at 6; Vandeputte et al., *supra* note 34, at 115 ("Ingenious clandestine drug manufacturers carefully comb through early research papers and pharmaceutical patents that contain opioid drugs which, at some point in history, have been evaluated for their potential as analgesics. Very often, the development of these new opioids was eventually halted as side effects and/or adverse reactions became apparent, offering little (if any) advantage over the analgesic 'gold standard' set by morphine. These novel drugs (or closely related analogues) are now pirated from published works, synthesized clandestinely or industrially, and sold online or on the street in varying manners.") (endnote omitted), 117 ("Structurally related piperidine benzimidazoles...can be traced back to early patents and literature...[i]llustrating the in-depth monitoring of scientific literature by clandestine chemists."); Peacock et al., *supra* note 6, at 1669 ("The emergence of NPS is unique in the extent to which the scientific and patent literature has been used to rapidly identify, modify, synthesise, and bring new substances to market.") (endnotes omitted).

125. Caulkins & Humphreys, *supra* note 11, at 2 ("The cost advantages of synthetic drugs for traffickers are most dramatic for fentanyl. At higher market levels, producing fentanyl is up to 100 times cheaper than heroin, per dose. This economic logic is relentless. [¶] Meth's price advantage is also considerable. It often retails for less than half as much as cocaine per unit weight (e.g., $100–$200 per ounce vs. almost $1,000 for cocaine in Los Angeles), and although dose sizes are similar, the meth high lasts longer.") (endnotes omitted); Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 577.

126. Coleman & DuPont, *supra* note 16, at 10.

127. Nichols & Fantegrossi, *supra*, *in* Madras & Kuhar, *supra* note 22, at 577.

128. China, India, and Southeast Asia are the principal sources of NPSs. *See*, *e.g*., DEA, Nitazenes, *supra* note 37 (identifying China as a source of nitazenes); European Monitoring Cntr. European Drug Report 2022, *supra* note 7, at 38 (identifying China as "one of the main source countries"); United Nations Off. on Drugs & Crime, Synthetic Drugs in East and Southeast Asia, Latest Developments and Challenges 1 (2022) ("[O]rganised crime groups in East and Southeast Asia have taken advantage of the flexibility in manufacturing synthetic drugs to develop new products and substances, including new psychoactive substances, to appeal to drug users or try to circumvent legal controls.") (footnote omitted); *id*. at 20–23; Gerona, *supra* note 6, at 13; Baumann, *supra* note 14 ("Most NPS are manufactured by Asian laboratories and sold to consumers via the Internet or shipped to locations in Europe, the United States (US) and elsewhere, to be packaged for retail sale."); Baumann et al., *supra* note 14, at v ("The United Stations Office of Drugs and Crime (UNODC) reported that between 2008 and 2015, more than 600 NPS were identified by 102 countries and territories, and this number is expected to rise."); Lafaye et al., *supra* note 43, at 311; Madras, *supra*, at Bauman et al., *supra* note 14 at 11; Reuter & Pardo, *supra* note 11, at 117; Wiley et al., *supra*, *in* Baumann et al., *supra* note 14, at 234.

129. Madras, *supra*, in Baumann et al., *supra* note 14, at 9; *see also* Francis & Smith, *supra*, *in* Dargan & Wood, *supra* note 6, at 65 ("The Internet provides a key exchange platform for NPS information and NPD distribution. Numerous websites, chatrooms, forum, and instant messaging resources are devoted to drug-related information and experiences."); Peacock et al., *supra* note 6, at 1669 ("The connectivity offered by the internet facilitated access to methods of drug synthesis and raised awareness of new substances. It also enabled new substances to be sold online by multiple suppliers in countries with weak or differing regulatory frameworks.") (endnotes omitted).

130. *See*, *e.g.*, Francis & Smith, *supra*, in Dargan & Wood, *supra* note 6, at 60 ("By removing the requirement for personal interactions with drug dealers, the Internet emerged and succeeded as an alternative avenue for NPS acquisition.... The relative anonymity, personal safety, and novelty of purchasing psychoactive substances appealed to many."), 67 (noting that messages can be sent over encrypted networks); Raymond G. Hill, *Understanding the U.K. Psychoactive Substances Act*, 86 British J. Clinical Pharmacology 499, 499–500 (2020) ("It does not appear that the PSA [United Kingdom Psychoactive Substances Act] has significantly disrupted darknet sources for NPS activity and it appears that the emergence of new NPS in the UK has not ceased following the introduction of the PSA. Large amounts of synthetic cannabinoids remained available via the darknet in 2016 and 2017.") (endnotes omitted).

131. *See* Francis & Smith, *supra*, in Dargan & Wood, *supra* note 6, at 60 ("Some of these [NPS] markets account for billions of dollars in transactions since their creation.") (endnote omitted), 62 ("[F]rom 2013 to 2016, an individual who developed a multimillion dollar fentanyl drug ring could import 200 mg of fentanyl from the dark web for $3,500 and achieve an 85-fold return on investment.") (endnote omitted). To be sure, some NPSs have a very short half-life as consumer drugs, and the total number of NPSs appears to have decreased in recent years. *See id.* at 64. But "introduction of new structurally diverse substances such as fentanyl analogues and benzodiazepine derivatives have [*sic*] increased." *Id*. (endnote omitted).

132. "Regardless of the future emergence, availability, and use of new substances, several developments from the emergence of NPS might shape future drugs markets. First, the model of producing legal alternatives to controlled substances has already spread into the general area of synthetic drug production. Access to specialist knowledge, equipment, and necessary chemicals (facilitated through the internet) means that synthetic drugs could become increasingly important and represent a serious threat to existing drug control models. Second, this threat could be amplified by the synthesis of highly potent substances (including those not previously identified in scientific or patent literature) that are easy to conceal and transport, and which might carry greater adverse health risks because of unintended effects. Third, globalisation will probably facilitate exploitation of differences in regulatory frameworks between jurisdictions, particularly in an environment where goods can be internationally sourced and rapidly transported across borders. Fourth, the internet will continue to support rapid diffusion of substances into different settings in ways that are difficult to regulate and monitor." Peacock et al., *supra* note 6, at 1680.

133. "Globalisation, the internet, and information technology advances could also have positive effects on responding to emerging substances, enabling better means of proactively detecting new substances and exchanging information to set priorities for public health response and for research." *Id*.

134. *See* Jenkins, *supra* note 58, at 9 ("In more senses than one, synthetics arouse suspicion because they are unnatural. Two closely related concerns are at work: either these advances in science will supplant ideas and aspirations that are fundamental to humanity, or else the technologies will summon forth monstrous or demonic qualities hitherto latent in individuals.").

135. *See id.*

136. *See supra* text accompanying notes 70–72.

137. Mary Shelly, Frankenstein, or the Modern Prometheus (1818). That term is not an exaggeration on my part; politicians and physicians have used the term "Frankenstein" to describe the effects of NPSs. *See* Jenkins, *supra* note 58, at 1, 83, 201 n.1 (U.S. Senator Lawton Chiles used that term); Middleton, *supra* note 114 (a physician referred to nitazenes as "'Frankenstein opioids'").

138. *See*, *e.g.*, George M. Church & Ed Regis, Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves (2014); Jennifer Doudna & Samuel H. Sternberg, A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution (2017); Henry T. Greely, CRISPR People: The Science and Ethics of Editing Humans (2021); Jamie Wetzel, Hacking Darwin: Genetic Engineering and the Future of Humanity (2019).

139. *See*, *e.g.*, Michael Crichton, Jurassic Park (1990); Aldous Huxley, Brave New World (1932); Robert Louis Stevenson, Strange Case of Dr Jekyll and Mr Hyde (1886).

140. *See*, *e.g.*, *Altered States* (Warner Bros. 1980); *I Am Legend* (Warner Bros. Pictures 2007); *Serenity* (Universal Pictures 2005).

141. Want an example? Synthetic cannabinoid use also is increasingly associated with psychosis. *See* Brian O'Mahoney et al., *HHC-Induced Psychosis: A Case Series of Psychotic Illness Triggered by a Widely Available Semisynthetic Cannabinoid*, Irish J. Psychological Medicine, Feb. 14, 2024, online ahead of print, https://pubmed.ncbi.nlm.nih.gov/38351841/ (discussing two cases in which the legally purchased semisynthetic cannabinoid hexahydrocannabinol (HHC) appears to have precipitated psychosis).

142. *See*, *e.g.*, James Harvey Young, Pure Food: Securing the Federal Food and Drugs Act of 1906 (2016) (1989); James Harvey Young, The Toadstool Millionaires: A Social History of Patent Medicines in America Before Federal Regulation (2016) (1961); *Developments in the Law—The Federal Food, Drug, and Cosmetic Act*, 67 Harv. L. Rev. 632, 633–35, 638–40 (1954).

143. Pub. L. No. 87-781, 76 Stat. 780 (codified in part at 21 U.S.C. § 355(a) & (b)(1)(A)(i) (2023)).

144. Francis & Smith, *supra*, *in* Dargan & Wood, *supra* note 6, at 63–64.

145. *See* Winstock & Ramsey, *supra* note 15, at 1686 ("The capacity to detect and respond effectively to harm early can occur only when data from diverse sources are collected routinely, collated and acted upon. Longitudinal integrated monitoring systems incorporating international data from emergency departments, treatment services, toxicology services, police, sentinel groups and the internet are required. Such systems would also allow for the impact of legislation on the global burden of drug-related harm to be assessed, including the impact upon the appeal, price and purity of existing illicit markets.").

146. J. Global Drug Pol'y & Practice, at 31–33 (2012), www.dfaf.org/webinar/files/designer_drugs.pdf.

147. *Id*. at 31.

148. *See* Ornella Corazza & Andres Roman-Urrestarazu, Editorial Introduction, *The Proliferation of NPS as a "Game Changer" for Public Health Policy*, *in* Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at xiii–xviii; Tettey & Levissianos, *supra*, in Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 7–11; Reuter & Pardo, *supra*, *in* Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 155–77; Ute Stiegel, *Legislating NPS in the European Union*, in Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 13–21.

149. *See supra* notes 2 & 3.

150. *See* 21 U.S.C. § 811(h); *supra* note 22 (describing the expedited scheduling process).

151. *See*, *e.g.*, U.S. Dep't of Health & Human Servs., Food & Drug Admin., *New Drug Application* (NDA) (Jan. 21, 2022), www.fda.gov/drugs/types-applications/new-drug-application-nda (last visited Apr. 5, 2024); Lawrence T. Friedhoff, New Drugs (2009). For a summary of that process, see Larkin, *FDA and Cannabis*, *supra* note 109, at 5–6.

152. "The differences in the decision processes for therapeutic drugs and emerging psychoactive substances are more striking. An important distinction is the setting of the decisions. There is a well-financed and effective lobby for both sides of the regulatory decision debate for pharmaceuticals developed by pharmaceutical manufacturers. The manufacturers are often very large corporations, anxious to recoup investments that may run to the hundreds of millions of dollars. The consumer side is often represented by well[-]organized NGOs, provided with information from other government agencies that gather relevant data. Egregious errors are likely to generate effective protest by the injured party. [¶] In contrast[,] those who wish to prevent new backyard psychoactive drugs from being listed as prohibited drugs are marginal and poorly organized. Because the drug is new, they will not be able to enlist a large number of users to protest denying access to what they might see as a harmless (or less harmful) pleasure. Egregious errors on behalf of prohibition are unlikely to generate effective protest. The decision is weighted against approval in another sense, the most fundamental of all. No weight is given to the benefits of the substance to the user. At best the regulator might take into account that a substance is 'less bad' than the alternatives. Thus[,] the only benefits from not prohibiting the drug that are considered are precisely those, the benefits of not prohibiting. There is nothing within the process that allows the fact that, if the drug was allowed to enter the market, perhaps many users would gain pleasure without adverse consequences, to be taken into account." Peter Reuter, *Options for Regulating New Psychoactive Drugs: A Review of Recent Experiences*, UK Drug Pol'y Comm., Evidence Review 24 (2011).

153. Those chemists, unlike a drug's sponsor and consumer-oriented non-government organizations, also do not collect post-FDA approval data about the adverse effects of approved drugs on patients.

154. *See* Hughes & Winstock, *supra* note 66, at 1895 ("A study published in 2009 by EMCDDA [European Monitoring Centre for Drugs & Drug Abuse] found wide variation across Europe in both the times taken to control drugs (from a few weeks to more than a year) and the form of control adopted.") (endnote omitted).

155. *See* Martinotti et al., *supra* note 21 (describing the practical difficulties involved). For a summary of the questions that any regulatory agency would like to answer before making a classification decision, see Kalant, *supra* note 94, at 1146: "What are the quantities and frequencies of use of the various drugs? How are these quantities and frequencies of use distributed among the population? What are the physical, psychological, behavioural and demographic characteristics of those who are the heaviest users? What are the potential harms of all types—physical, psychological, developmental, social, economic and so forth—associated with different patterns of use of the various drugs? What are the actual numbers of individuals suffering these various harms in a given population at a given time? What are the costs to the affected individuals, to their families and associates, to society at large, both economic costs and costs in terms of wellbeing and effective function of individuals and of society as a whole? What have been the effects of variations in public attitudes and beliefs, social practices, disposable income and previous control policies on the extent of use and of adverse effects of drugs? What have been the adverse effects of previous control policies themselves?"

156. *See* Hill, *supra* note 130, at 499 ("Internet commerce has allowed NPS to be introduced to human use very rapidly and often multiple deaths occur in the user group before risks are identified."); Vandeputte et al., *supra* note 34, at 116 ("Importantly, the detection and identification of 'unknown' highly potent substances pose their own unique and specific challenges for forensic and research laboratories…which can result in significant delays between the start of a new drug's life cycle on the recreational market (i.e., 'patient zero') and laboratories' ability to detect and comprehensively report the drug.... [B]y the time the availability of a new drug (or a precursor needed for its manufacture) is impacted by national and/or international legislative controls, illicit drug manufacturers have already moved on to the next (legal) alternative, with hopes of avoiding the soon-to-be-regulated product altogether.") (endnotes omitted).

157. *See* Madras, *supra*, *in* Baumann et al., *supra* note 14, at 13.

158. Or, in the case of the international community, two or more years behind. The U.N. Commission on Narcotic Drugs (CND) plays an important role in the listing of controlled substances and precursor chemicals pursuant to the three relevant international conventions discussed above. The CND meets approximately every two years for just three–five days and considers only a small number of NPSs. Reuter, *supra* note 152, at 5.

159. *See* Gerona, *supra* note 6, at 264–65 (discussing such blanket bans).

160. Reuter, *supra* note 152, at 124. For example, Wellbutrin, an FDA-approved treatment for depression, is a synthetic cathinone. Gerona, *supra* note 6, at 23. Automatically placing every such drug into Schedule I could harm patients suffering from Major Depressive Disorder.

161. *Id.* at 2.

162. *See* Reuter, *supra* note 152, at 4 (discussing why that bias exists).

163. *See* Vandeputte et al., *supra* note 34, at 119 ("[A]s details on the toxicity and harm potential of new opioid NPS in humans are often lacking, it is important to note that any newly emerging opioid has the potential of being even more dangerous than the last one.").

164. As Jonathan Caulkins and Keith Humphreys have explained: "Sometimes law enforcement achieves the ideal of curtailing availability. Fentanyl was first synthesized in 1959, and its economic edge over heroin was recognized by the 1970s. But illegally manufactured fentanyl did not become a significant issue until around 2015, because several earlier outbreaks were swiftly curtailed by law enforcement. Likewise, it took decades for methamphetamine to spread from the Southwest to the rest of the country; appealing, cheap products with legal corporations behind them don't languish in regional pockets. The delayed spread of fentanyl and methamphetamine should be credited to prohibition and enforcement. More than a generation of Americans passed through their prime drug-using years with illegal fentanyl essentially unavailable and methamphetamine geographically limited. [¶] Unfortunately, once a drug market has become established, it is exceptionally difficult to uproot. The Communist Party in China all but eradicated opium addiction after 1949, and the Taliban has suppressed about 90% of Afghan opioid production, but the deprivation of civil liberties involved in such cases would be rightly intolerable to free societies. [¶] Often the best that law enforcement in a free society can do is to force traffickers to operate in inefficient ways. Historically, that translated into less drug use because prices were higher and access lower. Because synthetic drugs are so cheap to produce, law enforcement may now need to be content with relying relatively more on the latter. [¶] There is value in keeping drugs hidden and separated from Madison Avenue marketing budgets and expertise, for the same reasons that lead some people who eat healthily at home to struggle with restraint at all-you-can-eat buffets. Put differently, law enforcement can help someone who wants to avoid a drug not to be tempted by it daily, but it generally cannot stop someone who is determined to obtain the drug from finding it." Caulkins & Humphreys, *supra* note 11, at 4 (endnotes omitted); *see also* Lopez, *supra* note 124: "Regina LaBelle, the former acting drug czar for President Biden, told me [NPSs'] rise was her office's 'worst nightmare.' The traditional war on drugs largely focused on stopping the flow of drugs grown on farms. It did not work perfectly, but it had a significant effect: One expert estimated that prohibition increased the price of heroin and cocaine by 10 to 20 times, so users were less likely, or able, to buy them. [¶] The impact is likely smaller for synthetic drugs because they are easier to make and smuggle."

165. 21 U.S.C. §§ 802 & 813(a); *see supra* note 3.

166. *See* Vandeputte et al., *supra* note 34, at 119 ("It should be clear that, while legislations may be effective in reducing the availability of one (or several) opioid(s), even generic legislations (aiming to cover a wide range of analogues, e.g., the Chinese ban on fentanyl analogues) may spark the creativity of illicit drug manufacturers toward other (known or unknown) compounds, some of which have greater potential for public harm and deadly outcomes.") (footnote omitted).

167. *See* McFadden v. United States, 576 U.S. 186 (2015). But not always. *See id.* at 192–93 (footnote omitted): "That knowledge requirement may be met by showing that the defendant knew he possessed a substance listed on the schedules, even if he did not know which substance it was. Take, for example, a defendant whose role in a larger drug organization is to distribute a white powder to customers. The defendant may know that the white powder is listed on the schedules even if he does not know precisely what substance it is. And if so, he would be guilty of knowingly distributing 'a controlled substance.'... The knowledge requirement may also be met by showing that the defendant knew the identity of the substance he possessed. Take, for example, a defendant who knows he is distributing heroin but does not know that heroin is listed on the schedules, 21 CFR § 1308.11 (2014). Because ignorance of the law is typically no defense to criminal prosecution, *Bryan v. United States,* 524 U.S. 184, 196 (1998), this defendant would also be guilty of knowingly distributing 'a controlled substance.'"

168. *See* Staples v. United States, 511 U.S. 600, 608–19 (1994) (ruling that, to convict someone of unlawfully possessing an automatic weapon, "the Government should have been required to prove that petitioner knew of the features of his AR–15 that brought it within the scope of the Act").

169. Butonitazene is one of the NPSs that the DEA provisionally listed under CSA Schedule I in 2022. For others raising the same knowledge problem, see 87 Fed'l Register at 21,556 (identifying the NPSs provisionally listed as the following: "• 2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine (butonitazene), • 2-(2-(4-ethoxybenzyl)-1H-benzimidazol-1-yl)-N,N-diethylethan-1-amine (etodesnitazene; etazene), • N,N-diethyl-2-(2-(4-fluorobenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (flunitazene), • N,N-diethyl-2-(2-(4-methoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine (metodesnitazene), • N,N-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine(metonitazene), • 2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzimidazole (N-pyrrolidino etonitazene; etonitazepyne), and • N,N-diethyl-2-(5-nitro-2-(4-propoxybenzyl)-1H-benzimidazol-1-yl)ethan-1-amine (protonitazene)."). "[O]rdinary people"—the target audience to decide whether a criminal statute is decipherable, United States v. Davis, 588 U.S. 445,, 448 (2019)—would never have heard of those compounds before becoming jurors, and they would not have the faintest clue what they are.

170. Jenkins, *supra* note 58, at 84–85.

171. *See*, *e.g.*, Connally v. Gen. Constr. Co., 269 U.S. 385 (1926). *See generally* Anthony G. Amsterdam, *The Void-for-Vagueness Doctrine in the Supreme Court*, 109 U. Pa. L. Rev. 67 (1960). That standard is particularly appropriate when scientific knowledge is required to understand a law. As I explained two years ago: "That standard should focus the inquiry on how the average *lay person* would read a statute—*not* the average lawyer, geologist, hydrologist, botanist, or expert in some other field. Why? Because the advanced, specialized education and training those parties enjoy give them far more than 'common' or 'ordinary intelligence.' Physicians and nurses have more knowledge about medicine than medics or EMTs, and textbooks are

written with those different audiences in mind. Statutes, however, must focus on the last two groups, as well as people without any more knowledge of medicine than basic first-aid. Otherwise, we have made it a crime not to graduate from medical school. Demographics therefore matter when deciding if a law is understandable by the average person. [¶] If so, consider what Census Bureau statistics reveal. In the United States, the average person has only a high school diploma—*not* a college degree, let alone a professional degree in law or a graduate degree in science. Only 17 percent of U.S. residents hold a bachelor's degree (56 [million] of 331 million people) and only 10 percent hold an advanced degree (32 million). The American Bar Association reports that less than 0.4 percent of the population are practicing attorneys (roughly 1.3 million lawyers). Those facts are important when deciding whether the CWA is vague." Paul J. Larkin, *The Clean Water Act and the Void-for-Vagueness Doctrine*, 20 Geo. J. L. & Pub. Pol'y 639, 650–51 (2022) (footnotes omitted; emphasis in original).

172. *See* Larkin, *supra* note 171, at 650 ("As Justice Neil Gorsuch explained in *United States v. Davis*, '[in] our constitutional order, a vague law is no law at all.' To avoid that hamartia, a statute must afford 'ordinary people'—viz., people of 'common intelligence' or 'ordinary intelligence'—fair notice of what the law makes a crime. A criminal law is vague when its text 'either forbids or requires the doing of an act in terms so vague that men of common intelligence must necessarily guess at its meaning and differ as to its application' or its 'mandates are so uncertain that they will reasonably admit of different constructions.'... That standard should focus the inquiry on how the average *lay person* would read a statute—*not* the average lawyer, geologist, hydrologist, botanist, or expert in some other field. Why? Because the advanced, specialized education and training those parties enjoy give them far more than 'common' or 'ordinary intelligence.' Physicians and nurses have more knowledge about medicine than medics or EMTs, and textbooks are written with those different audiences in mind. Statutes, however, must focus on the last two groups, as well as people without any more knowledge of medicine than basic first-aid. Otherwise, we have made it a crime not to graduate from medical school. Demographics therefore matter when deciding if a law is understandable by the average person.... If so, consider what Census Bureau statistics reveal. In the United States, the average person has only a high school diploma—*not* a college degree, let alone a professional degree in law or a graduate degree in science. Only 17 percent of U.S. residents hold a bachelor's degree (56 of 331 million people) and only 10 percent hold an advanced degree (32 million). The American Bar Association reports that less than 0.4 percent of the population are practicing attorneys (roughly 1.3 million lawyers).") (footnotes omitted; emphasis in original).

173. There are four basic regulatory regimes that can be used for an NPS: regulating it as "food" or a food "additive," as a "temptation" or "disfavored" good such as alcohol or tobacco, as a therapeutic pharmaceutical, or as a controlled substance. Reuter, *supra* note 152, at 19 Tbl. 1.

174. *See* Winstock & Ramsey, *supra* note 15, at 1686 ("[S]ubstances called 'Instantly Smashed', 'X4 Ecstasy[,]' and 'Part E Pills' may be liable to control under the Medicines Act (which governs the manufacture and supply of medicines in the United Kingdom)."); *see also*, *e.g.*, Hughes & Winstock, *supra* note 66, at 1895–96; Reuter & Pardo, *supra*, *in* Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 164–69.

175. For a discussion of the precautionary principle focusing on environmental regulation, see Cass R. Sunstein, *Beyond the Precautionary Principle*, 151 U. Pa. L. Rev. 1003 (2003). For a discussion of that principle in the context of NPS regulation, see Reuter, *supra* note 152, at 19–24. For an alternative, multi-factor approach to NPS classification, see David J. Nutt et al., *Drug Harms in the UK: A Multicriteria Decision Analysis*, 376 Lancet 1558 (2010); David Nutt et al., *Development of a Rational Scale to Assess the Harm of Drugs of Potential Misuse*, 369 Lancet 1047 (2007).

176. Reuter & Pardo, *supra*, in Corazza & Roman-Urrestarazu, Policy, *supra* note 24, at 166–68.

177. For a discussion of how such rules could be applied, see Wilkins, *supra* note 76, at 1581–84. For a discussion of how the FDA could regulate cannabis and therefore NPSs, see Larkin, *FDA and Cannabis*, *supra* note 109; Paul J. Larkin, Jr., *Marijuana Edibles and "Gummy Bears*," 66 Buff. L. Rev. 313 (2018).

178. *See* Hudson v. United States, 522 U.S. 93, 102 (1997).

179. *See*, *e.g.*, Village of Hoffman Estates v. Flipside, Hoffman Estates, Inc., 455 U.S. 489, 498–99 (1982) ("The Court has also expressed greater tolerance of enactments with civil rather than criminal penalties because the consequences of imprecision are qualitatively less severe.").

180. *See* Casey & Manini, *supra*, *in* Dargan & Wood, *supra* note 6, at 416 ("SCs [synthetic cannabinoids] have been distributed as either incense or smoking mixtures in common settings such as convenience stores and gas stations.") (endnotes omitted); Winstock & Ramsey, *supra* note 15, at 1685 ("The application of the [United Kingdom] Medicines Act, for example, would require manufacturers to provide evidence of the safety of their products. Web sales and distribution could be banned and availability restricted though licensing of vendors, the establishment of legal requirements of sale (as with alcohol and tobacco products) and restricted advertising. Accurate information about product composition, standardization, quality control, dose recommendations and contraindications could be enforced under existing consumer protection legislation. Products could be taxed accordingly.") (endnotes omitted).

181. "Congress could create civil investigative arms for federal agencies and grant them the power to compel private parties to submit to on-site inspections. Civil compliance officers, however, lack the authority and respect given to federal agents. In comparison to civil inspectors, FBI agents wearing 'raid jackets' emblazoned with the Bureau's logo will receive far more deference from a judge, a corporation, and the public." Paul J. Larkin, Jr., *Public Choice Theory and Overcriminalization*, 36 Harv. J.L. & Pub. Pol'y 715, 738 (2013) (footnote omitted).

182. The Immigration and Nationality Act expressly empowers the President to suspend the entry of foreigners whenever he deems their entry "detrimental" to the national interest, as the Supreme Court has recognized. *See* 8 U.S.C. § 1182(f) (2018) ("Whenever the President finds that the entry of any aliens or of any class of aliens into the United States would be detrimental to the interests of the United States, he may by proclamation, and for such period as he shall deem necessary, suspend the entry of all aliens or any class of aliens as immigrants or nonimmigrants, or impose on the entry of aliens any restrictions he may deem to be appropriate."); Trump v. Hawaii, 585 U.S. 667, 684–97 (2018); *see also* 19 U.S.C. § 1318(a) (empowering the President to declare an "emergency" that requires closing the border "during the continuance of the emergency").

183. Larkin, *supra* note 32, at 9.

184. A 1950s jingle for Brylcreem hair pomade. *See* Jimmy Del Ponte, *And Now a Word from Our Sponsor*, Somerville Times, Feb. 3, 2010, https://www.thesomervilletimes.com/archives/18366. "Fentanyl is so potent that the total U.S. annual consumption is in the single-digit metric tons; it could fit comfortably into any one of the 7 million trucks or cargo containers that cross the southern border each year. One pure pound is enough to make 200,000 fentanyl-laced pills, which can simply be mailed to the U.S. from Mexico, China, or anywhere else." Caulkins & Humphreys, *supra* note 11, at 5 (endnotes omitted); *see* Henderson, *supra* note 13 ("A single gram of any very potent drug like 3-methylfentanyl could be…formulated (cut) into many thousand, perhaps a million, doses. Preventing the distribution of such small amounts of the pure drug will be exceedingly difficult."); Peacock et al., *supra* note 6, at 1669 ("The proliferation of chemical and pharmaceutical companies in emerging economies and growth in global trade enabled illicit drugs to be moved in small packages across legal jurisdictions with minimal risk of detection.") (endnote omitted).

185. *See* Gerona, *supra* note 6, at 13; *cf.* M.O. Dix et al., Crim. Just. Testing & Evaluation Consortium, Nat'l Inst. of Justice, *Contraband and Drones in Correctional Facilities: An Overview of Technologies and Issues Associated with Detection and Response* 1 (2022) ("The threat of contraband associated with drones is escalating with the evolution of the technology, which enables drone operators to carry larger payloads, fly faster and for longer distances, and operate at lower levels of investment. However, the extent of this threat is unknown because the capability to measure and detect drone incursions is an emerging field."); *id*. at 4 ("Human detection of drones has limitations. For example, many contraband deliveries occur in the evening hours or overnight when drones are less likely to be seen by human observers. In cases when drones are recovered by law enforcement, they have been found to be covered in tape to obscure their lights for camouflage and evade visual detection. Drones can [escape] and have escaped technology-based detection and/or may be able to fly above nets.") (footnotes omitted). The federal government has authority to deal with drones that the states and localities do not have. *Id*. at 2 ("Congress has exclusively authorized the Departments of Defense (DOD), Energy (DOE), Justice, and Homeland Security (DHS) to engage in limited UAS detection and mitigation activities to counter UAS presenting a credible threat to specified facilities or assets, notwithstanding certain other applicable federal laws that relate to surveillance.") (footnote omitted); Joe Russo et al., *Countering the Emerging Drone Threat to Correctional Security*, RAND (2024); *see* 6 U.S.C. § 124n (West 2024); 50 U.S.C. § 2661.

186. Larkin, *supra* note 32, at 9–10. Perhaps AMLO has looked the other way in the hope that the DTOs in return will reduce the number of kidnappings and murders of Mexicans. By contrast, President Biden has said that he lacks the authority to stop or slow the ceaseless and growing influx of what he now calls "newcomers" (who don't resemble Sam Francisco (played by Mandy Patinkin), see *Alien Nation* (20th Century Fox 1988)). Biden's claim is a lie. *See* 8 U.S.C. § 1182(f) (quoted *supra* note 182). Whatever the reason for his blinkered, irresponsible, and unlawful choice, President Biden clearly has no interest in performing the *Tercio de Muerte* on illegal immigration.

187. Treatment is also a natural demand-side step to take, but we seem to have more to learn. *See* Gerona, *supra* note 6, at 253 ("Unlike traditional recreational drugs, many NPS have been studied little if at all"); Peacock et al., *supra* note 6, at 1679 (endnotes omitted) ("Little is currently known about the chronic harms of NPS use. There is emerging evidence that synthetic cannabinoids might be associated with more rapid onset of dependence and a more complex withdrawal syndrome than is cannabis. Risk of dependence and withdrawal has also been noted with some stimulant NPS. When these features are evident, clinical guidelines recommend implementing the evidence-based interventions used in cases for the more established illicit drug counterpart. These usually comprise a stepped care approach, with low-intensity psychosocial interventions comprising first-line treatment, and withdrawal management, or inpatient or residential treatment for more severe problems.").

188. Krausz et al., *supra* note 37, at 699.

189. *Id*. (footnote omitted).

190. Madras, *supra*, *in* Baumann et al., *supra* note 14, at 14.

191. *See Metonitazene Begins Proliferation as Newest Synthetic Opioid Among Latest Cycle of Non-Fentanyl Related Drugs*, Cntr. for Forensic Scientific Educ. & Research, Alert FSRE (Jan. 2021). The Alert contains numerous recommendations worth debating: "Recommendations for Public Health • Implement surveillance for rapid identification of drug overdose outbreaks. • Engage local poison centers and clinicians to assist with treatment of affected patients. • Track and monitor geographical drug distribution and trends. • Track demographics and known risk factors for decedents and overdose patients. • Raise awareness about the risks and dangers associated with opioid use. • Make naloxone available to recreational drug users. Recommendations for Clinicians • Become familiar with the signs and symptoms associated with synthetic opioid use (e.g.[,] sedation, respiratory depression). • Naloxone should be administered to reverse critical respiratory depression and repeated naloxone administration may be necessary. Be aware that clinical conditions may change rapidly and unpredictably after naloxone administration due to precipitation of withdrawal. • Be mindful that illicit drugs have limited quality control, containing undeclared substances that impact the expected clinical effects or findings. • Counsel about the dangers of synthetic opioid products and other drugs. Recommendations for MEs & Coroners • Test for new synthetic opioids and their biomarkers in suspected opioid overdose cases. • Be aware that ELISA screening for synthetic opioids may not be specific or specialized for the newest generation of compounds; consider mass spectrometry-based screening. • Be aware that concentrations of synthetic opioids in biological specimens can vary and GC-MS sensitivity may not be adequate. Recommendations for Laboratories • Utilize analytical data available publicly for the identification of metonitazene and synthetic opioids if reference standards are not available. • Utilize previously developed non-targeted testing protocols or develop sensitive and up-to-date testing procedures for synthetic opioids. • Prioritize analytical testing of seized drug samples obtained from drug overdose scenes during death investigations. • Share data on synthetic opioid drug seizures with local health departments, medical examiners and coroners, and related communities." *Id*. (underlining omitted).

192. "Beginning in the 1980s…society resolutely chose to reduce what had previously become an increasing slaughter on our highways that had reached the astounding figures only heard of on the battlefield. The federal and state governments aggressively implemented multi-step programs to reduce that bloodshed. Among them were the following: legislation fixing the maximum blood-alcohol content (BAC) at 0.08 grams per deciliter (g/dL), mandatory license suspension penalties for conviction, more aggressive prosecution of drunk drivers, and public education and advocacy by organizations such as Mothers Against Drunk Driving (MADD) and Remove Intoxicated Drivers (RID). The result has been a tremendous success. Fatalities have decreased by nearly 50 percent, from more than 20,000 persons in 1982 to just above 10,000 in 2018. Scores of thousands of people are alive today because of our efforts to persuade individuals to follow the admonition Don't Drink and Drive." Paul J. Larkin, *Driving While Stoned in Virginia*, 59 Am. Crim. L. Rev. Online 1, 5 (2022) (footnotes and punctuation omitted).

193. There is wisdom in M.M. Kirsch's "scared-straight"-like recommendations in that regard: "Kids have a keen sense for dishonesty. The authentic earns their respect. Drug education programs will be effective the day educators stick to what is known and what is unknown—the simple, undisputed *facts*. The facts are sensational enough. What the public sees, hears, and experiences will then reaffirm rather than contradict what is being taught. [¶] That grade school and high school kids should be warned against experimenting with new drugs has never been more urgent than with the advent of these new synthetic narcotics. Let them hear not only from patents and counselors, but from the junkies, the narcs, and the emergency room doctors.... It's the neurologist treating victims crippled by the products of sloppy underground chemists who can share the tragedies in vivid living detail. It's the coroner who writes up the death certificate 'for unknown substance' one can chat with if still wondering just who the hell to believe." Kirsch, *supra* note 68, at ii–iii (emphasis in original).

194. *See* Francis & Smith, *supra*, *in* Dargan & Wood, *supra* note 6, at 65 ("The Internet provides a key exchange platform for NPS information and NPD distribution. Numerous websites, chatrooms, forum, and instant messaging resources are devoted to drug-related information and experiences.... Indeed, the Internet is the primary source of illicit drug information for 15–24 year-olds. 70 percent of American 12–17 year-olds visit social networking sites daily, a practice associated with a greater ease in obtaining illicit drugs and controlled prescription drugs.") (endnotes omitted), 67 ("NPS sales have extended to social networking sites, though the extent of market participation is difficult to completely assess."); Su et al., *supra* note 14, at 28.

195. The subject of "harm reduction" typically goes along with education as a demand-side strategy. That subject is far too large and complicated to address in this *Special Report*, but I can say this much: It is a mistake to deem stigmatization always and everywhere an ineffective and uncaring strategy. Stigmatization can deter illicit drug use. *See* Keith Humphreys & Jonathan Caulkins, *Destigmatizing Drug Use Has Been a Profound Mistake*, Atlantic, Dec. 12, 2023, https://www.theatlantic.com/ideas/archive/2023/12/destigmatizing-drug-use-mistake-opioid-crisis/676292/ ("Cultural disapproval of harmful behavior can be a potent force for protecting public health and safety—as the increased stigma against drunk driving and tobacco show."). The ultimate inquiry is whether the benefits of stigmatization outweigh their costs by, for example, deterring more drug use than it discourages users to seek entry into drug treatment. Moreover, while "[e]mpathy for people in the clutch of addiction is noble, and finding ways to help them is a moral necessity," harm reduction far too often focuses on reduction in the *consequences* of illicit drug use to the total exclusion of the *prevalence* of that activity. "The maxim 'Love the sinner, hate the sin' is apt when it comes to the use of new synthetic drugs flooding the U.S. At least in some parts of the country, we need more reflexive, more visible, and more consistent rejection of drug use, not less."). Also, stigmatization is not uncaring. It considers both the people currently using dangerous substances and the ones who have not yet done so. The latter group is of unknown size—no one knows how many people are deterred from drug use by any deterrent strategy, including stigmatization, because it is impossible to prove a negative—and their lives matter too. Finally, in what alternative universe is "laud[ing] many fentanyl *dealers* as 'harm reductionists' who should be respected and left alone by authorities (because the arrest of a trusted dealer might cause users to seek the drug from an unfamiliar source)" a worthwhile public policy? Humphreys & Caulkins, *supra* (emphasis in original) (disparaging that approach). Outside of cities like San Francisco, the American public will not endorse that strategy, so basing all or part of our drug policy on it will inevitably fail, tarnish the entire subject of harm reduction, and drive us toward complete reliance on a law-enforcement, supply-side approach.

196. Jeneen Interlandi, *48 Million Americans Live with Addiction. Here's How to Get Them Help That Works*, N.Y. Times, Dec. 13, 2023, https://www.nytimes.com/2023/12/13/opinion/addiction-policy-treatment-opioid.html.

197. *See*, *e.g.*, U.S. Cntrs. for Disease Control & Prevention, *Drug Overdose Deaths with Evidence of Counterfeit Pill Use—United States, July 2019–December 2021*, 72 Morbidity & Mortality Weekly Rep. 949, 949 (2023) ("The proliferation of counterfeit pills, which are not manufactured by pharmaceutical companies, but are typically made to look like legitimate pharmaceutical pills (frequently oxycodone or alprazolam), is complicating the illicit drug market and potentially contributing to these deaths. Counterfeit pills often contain illicitly manufactured fentanyls (IMFs), illicit benzodiazepines (e.g., bromazolam, etizolam, and flualprazolam), or other illicit drugs, and can increase overdose risk because the pills might expose persons to drugs they did not intend to use.") (footnote and endnote omitted), 954 ("[A]lthough the overall percentage of overdose deaths with evidence of counterfeit pill use remained below 6%, it more than doubled from July–September 2019 (2.0%) to October–December 2021 (4.7%); the percentage more than tripled in western jurisdictions. Second, the percentage of deaths with evidence of counterfeit pill use involving only IMFs was more than double the percentage among deaths without evidence of counterfeit pill use."); Gerona, *supra* note 6, at 14 (citations omitted)) ("In recent years, NPS have been incorporated in a variety of other products. Synthetic cannabinoids and NSO [novel synthetic opioids] are added to vaping liquids; fentanyl and its analogs are cut into inhalants and patches; synthetic cannabinoids are added to edibles. Dealers are also repackaging smaller quantities as 'rocks' or pressed into tablets or other forms that are then sold in the illicit market. Designer benzodiazepines and NSO, for example, are commonly compounded into tablets to produce counterfeit prescribed benzodiazepines or opioids. In the United States, they are often sold as fake Norco, Vicodin, Oxycontin, and Xanax."); Holland et al., *supra* note 36, at e71; Pol Quintana et al., *The Hidden Web and the Fentanyl Problem: Detection of Ocfentanil as an Adulterant in Heroin*, 40 Int'l J. Drug Pol'y 78 (2016); Vandeputte et al., *supra* note 34, at 116 ("Ultimately, in some cases, these 'new' synthetic

opioids end up in the street opioid supply, which was previously dominated by heroin, and sold as bindles, zip-bags or glassine bags. Nowadays, they also commonly appear in counterfeit tablets of registered drugs (e.g., hydromorphone (M-4's/M-8's), oxycodone (M-30's) or falsified Xanax bars).") (endnote omitted). As I explained in an earlier article: "'The people consuming many of these bastardized novel psychotic substances are not traditional hard-drug users.' Some are 'high school kids, college students, and recreational enthusiasts best described as drug nerds,' while others are 'psychonauts, thrill seekers who try brand-new drugs that have never been taken before.' [¶] Yet fentanyl is similar to heroin and cocaine in one important—and dangerous—respect: It is a white powder. Drug dealers can intentionally 'step on' drugs like heroin or cocaine by diluting it with less expensive fentanyl to reduce their costs or to give their product an extra 'kick' as a means of soliciting repeat business. Of course, a result is that there is no uniformity in how much fentanyl can be found in any package or pill. Fentanyl can also wind up unintentionally mixed into heroin and cocaine by dealers who are less than fastidious about how they package their wares. [¶] Many juvenile or young heroin or cocaine users purchase illegal drugs over social media, but they 'have no idea just how potent and dangerous these new drugs can be.' That ignorance can be costly; in fact, it already has been. Because one never knows how much fentanyl is in heroin or cocaine powder, or in counterfeit pills, using them is like playing Russian Roulette with more than one round in the chamber. Want proof? Fentanyl was present in the system of 40 percent of the people who overdosed and died from cocaine in 2016. [¶] There is an additional, more ominous aspect of illicit fentanyl sales. Americans are accustomed to and prefer taking drugs by swallowing pills rather than receiving or self-administering injections, so the cartels use commercial-grade presses to manufacture counterfeit pills containing fentanyl, either in part or entirely, creating look-alikes for legitimate prescription drugs such as OxyContin or Adderall. The machines allow the cartels to manufacture millions of pills. The goal is to attract new customers." Larkin, *supra* note 32, at 12 (footnotes omitted).

198. "Synthetic cannabinoid users are usually young, and demographic displacement was evident in studies of a 2011 student demographic, with usage rates of 8 percent or higher." Francis & Smith, *supra*, *in* Dargan & Wood, *supra* note 6, at 59 (endnote omitted); *see also* Hill, *supra* note 130, at 500 (noting that "young people" were one of the subgroups with "particularly high" NPS use); Carla Morganti et al., *supra*, *in* Corazza & Roman-Urrestarazu, Clinicians, *supra* note 31, at 94 (noting that, in a Swedish study of 183 biologic samples of patients admitted to an emergency department, "a widespread abuse of NPS by mostly male (79%) adolescents and young people (the median age was 20)" was found); Harry Sumnall & Amanda Atkinson, *Prevailing Use of Novel Psychoactive Substances*, *in* Dargan & Wood, *supra* note 6, at 93 (noting that 2011–2013 data from the Monitoring the Future study of drug use by 13- to 18-year-olds revealed that 10 percent of respondents had used synthetic cannabis within the past year). Consider the results of a study done at one Taiwanese hospital: "Regarding the analysis of age and gender, this study revealed that patients confirmed to have used NPS were significantly younger, with a mean age of 26.4 years, compared to those who tested negative (mean age: 37.5 years, $P < .05$). This finding aligns with a previous global review that indicated younger individuals have easier access to NPS. The review also highlighted the use of specific marketing strategies employed by drug dealers to target younger demographics, such as advertising through social media, offering free samples, and using colorful packaging. Another study conducted in Australia, which examined deaths related to NPS, reported a mean age of 30.7 years. These findings underscore the public health concern of NPS prevalence among younger populations." Su et al., *supra* note 14, at 28 (endnotes omitted).

199. *Andrea del Sarto*, in Robert Browning, Men and Women 184 (Oxford Univ. Press, 1972) (1855).

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