Commentary on the addition of substance categories to the Dutch drug law (Opium Act)

Dr. rer. nat. Leonid Pevzner

LP-Chemadvies lp-chemadvies@protonmail.com

Abstract

The emergence of an increasing number of novel psychoactive substances (NPS) and their wide availability has led to public health concerns, which in turn have prompted many countries to pass laws prohibiting whole classes of compounds, or psychoactive substances in general (Great Britain). While it seems like the obvious answer to the quick emergence of great numbers of largely unstudied new psychoactive compounds, this approach is in many ways problematic. The main issues are difficulties in understanding and enforcement of the new laws, inhibitive effects on the work of scientific institutions and the chemical industry, as well as the general ineffectiveness of prohibition as a public health tool. Additionally, some of the arguments made by the Dutch government in favor of passing this law are not very solid, as will be elaborated later.

The new law will place a burden of understanding the legal status of a substance on the owner of said substance. However, understanding the definition by chemical structure requires a significant level of chemical knowledge, far more than can be expected from an average (even educated) person, or even enforcement agent. Since the new law also targets possession, it will leave end users of NPS in an ambiguous situation. Also, enforcement of the law will require every seized drug sample to be fully analyzed and reviewed by an expert, rather than just compared against a list of scheduled substances. This would increase the workload for forensic labs and prolong drug offense cases, most of which would be as usual just possession of small amount and thus of minor public interest.

The categories to be scheduled contain a considerable number of already known and used pharmaceuticals, with the potential of yielding even more. Despite the lawmakers' efforts to protect the scientific work by creating various possibilities of exemptions, prohibition has proven to be a major stumbling block when it came to doing research. The bureaucratic load imposed on the researchers, as well as the lack of legal sources for the substance of interest have hampered drug research for decades.

Perhaps the most important issue with scheduling whole categories is that it means joining or continuing the race of prohibition against the clandestine drug industry. While the lawmakers claim that making drug illegal will be understood as a warning sign about how dangerous they are, this is not what has been observed to happen. In recent years it became increasingly clear that prohibition as a preventive measure for public health has not led to expected results. In many cases countries with the most restrictive drug policies are among those with the highest drug mortalities and widespread problematic drug use. In contrast, countries that have adopted modern, science-based approaches, have managed to reduce drug-related deaths and problematic drug use. Those new policies are meant to reduce harm done by inevitable drug use by treating addiction as a medical rather than a criminal issue. The measures taken include but are not limited to decriminalization of possession, spreading of trustworthy information about drugs and drug use, as well as offering help to addicts and allowing drug checking. In such an environment people can be better educated about the potential risks of the particular drugs they use, rather than a general and highly ineffective "(illegal) drugs are bad" warning.

The Dutch lawmakers also claim that the new law would be effective in fighting organized drug crime by giving police and state attorneys the chance to prosecute the manufacturers and vendors of NPS. This argument is flawed because the NPS market is much smaller in volume and largely separate from the black market for well-established drugs (e.g. cocaine and MDMA). While most NPS vendors have some form of quality control for their products and put in efforts to resemble legit chemical suppliers, there is nothing of that sort when it comes to black market drugs. Especially with heroin and other opioids, fluctuations in the active ingredient content are a known factor causing potentially lethal overdoses. A broad NPS ban would likely push the same drugs into the black market to cover the existing demand, thus strengthening organized crime. Therefore, the still legal status of NPS can be viewed as a chance to try a new approach and regulate NPS production and sales in a similar fashion as the alcohol and tobacco industry.

1. Introduction

Starting from the second half of the 20st century, there was constant research into new psychoactive substances (NPS), both in official, scientific or industrial institution and by private persons. Alexander Shulgin alone discovered more than 200 NPS, both as an industry chemist and as a self-funded scientist.[1–5] A majority of those compounds belonged to the β-phenylethylamine (PEA) class, which is one of the categories proposed to be added to the Dutch drug law ("*Opiumwet*", Opium Act) in list 1A.[6] From a pharmacological point of view, PEA are a rich and diverse group of substances. It contains many serotonin (particularly $5HT_{2A}$ and $5HT_{2C}$) receptor agonists,[1,7–11] monoamine releasing agents (MRA)[12–15] and monoamine reuptake inhibitors (MRI).[16–19] Psychopharmacologically, $5HT_{2A}$ agonists usually act as so-called psychedelics. The term means "soul-manifesting" (Greek) and was coined in 1956 by British psychiatrist Humphry Osmond.[20] Both MRI and MRA can be broadly characterized as psychostimulants, although there are considerable differences between their biological activities and therefore potential uses, depending mostly on the ratios of activity on the three monoamine neurotransmitter systems (norepinephrine, dopamine and serotonin).[14,21] Both psychedelics and psychostimulants are known to be used recreationally, with especially the latter being of some concern due to their addictive and reinforcing properties.[22,23] Despite their abuse potential, those substances or their close analogues are still widely used medically or studied for potential future applications. MRA and MRI of the PEA category are used to treat such conditions as attention deficit hyperactivity disorder (ADHD),[15,24,25] narcolepsy,[26,27] obesity,[28,29] depression[19,21,30,31] and asthma,[32,33] as well as to alleviate the symptoms of the common cold.[34] Additionally, empathogens, a subclass PEA-based MRA, have shown big promise in treating PTSD and other currently hard to treat mental health conditions.[35-39] In recent years, psychedelics have come increasingly into focus of psychiatric research.[40] After being extensively studied in the middle of the 20th century for various applications,[1,41-43] they are now being investigated as potential treatments of depression,[40,44] alcoholism[45–47] and anxiety in terminally sick patients.[48] Additionally, some psychedelics have shown considerable promise in treating cluster headaches[49–51] and are now in phase II clinical trials.[52]

Synthetic cannabinoids are another category targeted in the proposed update to the Opium Act. They are defined by their agonistic activity on cannabinoid receptors, particularly the CB1 receptor.[53,54] Synthetic cannabinoids were developed to study the cannabinoid receptor system because of legal restriction and limited availability of natural cannabinoids.[55] While those substances are currently not used therapeutically, there is a conceivable potential of medical application to treat the same conditions that can be treated with cannabis.[56,57] In recent years synthetic cannabinoids became popular among recreational users as a cheap and legal substitute for cannabis.[58,59] However, most synthetic cannabinoids are more potent and more acutely toxic than THC, leading to increasing public health concerns as their use became more widespread.[53,59–61]

The third category targeted in the proposed update to the Opium Act are 4-aminopiperidine derivatives, which contain many potent opioid analgesics, derived from the well-known drug fentanyl.[62,63] While essential for medical and veterinary use,[64] those substances pose a high risk if sold

on the black market due to their high potency and the life-threatening character of opioid overdoses.[65,66]

Since the early phases of psychopharmacological research, new synthetic, psychoactive substances have appeared on the black market from time to time.[67] This was mostly a sporadic process which was often limited to a country or region and lasted a limited amount of time, with 3,4-Methylenedioxymethamphetamine (MDMA) being the major exception and becoming a globally used party drug.[68] The term “designer drugs” was coined to describe those emerging synthetic psychoactive drugs. Around the year 2000 the internet became widespread and fast enough to make a noticeable impact on society. The world became increasingly connected, information became more accessible and the trade started to shift more and more from classical ways to ordering online. This led to the emergence of online shops selling NPS that were legal at the time. The vendors called their products “research chemicals” (RC) and usually labeled them as “not for human consumption” to protect themselves from legal liability.[69] While the NPS trade starting out as a niche market, the number and sale volume of those online vendors grew with an increasing rate over the course of the next years.[69] The increased availability of NPS also led to a proliferation of so-called “legal highs” mostly sold in local headshops.[70] In contrast to research chemicals sold online, legal highs were marketed under brand names without displaying the identity or amount of active ingredients, which could even vary within the same product.[59] Many RC online vendors tried to avoid drawing attention of the general public, but some vendors still marketed their shops and products aggressively. This was especially true for the multitude of scammer websites, which claimed to sell the same products as the legit vendors, but either never shipped them, shipped wrong substances or products of low quality (impure and/or containing other active substances). This led to the emergence of online platforms for rating vendors (Reddit groups, the website SafeorScam and later Scamlogs), which increased the pressure on vendors to provide good service and quality control for their products.[71,72] Another important source of information for NPS users were drug forums (e.g. Bluelight and Drugsforum) and websites with encyclopedia-like libraries (e.g. Erowid), where experiences, dosages, drug interactions and side-effects were discussed.[71,73] This exchange of information alleviated the dangers of ingesting unknown chemicals to some extent.

About 10 to 15 years after the first appearance of online NPS trade the market had grown to an extent as to come into the focus of public awareness. Since the worldwide ban of mephedrone and the first seizures of synthetic cannabinoids in 2010, law makers and law enforcement agencies NPS had started reacting to the new situation, mostly unilaterally.[74,75] Many countries added the most widespread NPS and those of greatest concern to their drug laws on a yearly basis, which led to the development of new, still legal NPS with effect profiles comparable to those that have been banned.[69,74,75] The ineffectiveness of such an approach became soon apparent: the use of NPS and the numbers of hospitalizations kept increasing, but the drug users were forced to try more and more new substances with unknown biological and toxicological properties.[76] Therefore, the legislators of many countries passed laws commonly called “blanket bans” aiming to cover most or all already available or emerging NPS. The USA already had the Federal Analogue Act, which stated that any chemical "substantially

similar" to scheduled substances were automatically also scheduled, if intended for human consumption.[77] While covering a wide range of NPS, this law has an obvious flaw of not properly defining what constitutes a substantial similarity. The UK, which had the largest numbers of NPS users and NPS related hospitalizations in Europe, passed the Psychoactive Substances Act 2016, making all non-whitelisted psychoactive substances illegal.[78] This law is flawed much in the same way as the US version because it is not completely clear when a substance can be called psychoactive and because it must be proved in each case separately.[79] Other countries like Germany have passed laws controlling whole classes of compounds, based on their chemical structure.[80,81] This approach was also employed by Dutch legislators for the intended update of the Opium Act. While scheduling well-defined classes of compounds is better than loose definitions from a legal point of view, there are still considerable drawbacks to such an approach and to blanket bans in general. An important argument against all blanket bans and especially the use of psychoactivity as the criterion is its being in contradiction to the rationale behind drug prohibition, which is to minimize harm caused by drug use.[79] Therefore, a risk assessment must be undertaken before banning a drug.[79,82] In an open letter to the British prime minister signed by more than 40 academics, Prof. David Nutt argued that the Psychoactive Substances Act 2016 would not only increase the total harm caused by drug use in UK for reasons discussed later, but would also be downright unethical.[83] This essay focuses on the expected consequences of scheduling substance categories and the practical effects of such prohibitive measures on the social harm caused by drug and NPS use, without an in-depth analysis of the ethical side. The main three issues discussed extensively in this work are as follows:

1. Difficulties in understanding and enforcing the new law caused by the complexity of definition
2. Inhibitive effect on the work of scientific institutions and the chemical industry
3. General ineffectiveness of prohibition as a public health tool

This work will also address some of the arguments made by the Dutch government in favor of passing the update to the Opium Act and demonstrate their weakness.

2. Consequences of the proposed update to the Opium Act

2.1 Difficulties in understanding the definition

The proposed update to the Opium Act defines categories by their chemical structure. More precisely, the law breaks down the relevant core structures into their structural elements and then defines which substituents in which positions are within the scope of a category. The categories are defined in a very broad manner so as to include every even remotely plausible chemical of the respective type. This approach is meant to leave no ambiguity about the legal status of a substance if its chemical structure is known. However, this would require a high degree of organic-chemical understanding from anyone trying to determine the legal status of a compound. The intended law in its current state places the

responsibility for understanding it on the owners of chemicals and does not distinguish in any form between big corporations, small businesses or organizations and private persons. The latter two groups are likely to be strongly affected by the lack of expertise necessary to understand the categories, which would create some legal ambiguity from their point of view, despite the intent of the law. It's not unlikely that substances studied or used for something completely unrelated to biology or pharmacology will fall under one of the categories, which might go unnoticed in a small company or a scientific research group. For example, it is conceivable that substances which would fall under the synthetic cannabinoid category, would be studied by physicists for uses in organic electronics due to the coupled π-electron systems. In such a case, even if the researcher performing the study thinks of verifying the legal status of the chemicals, it's possible that he/she will not be able to understand the scope of the categories sufficiently, because this level of organic chemistry knowledge is not typically obtained when studying physics.

Since the new law also targets possession, many users of NPS will likely be uncertain about their legal situation, even if they put in efforts not to buy illegal chemicals. The category definition will also be beyond the knowledge scope of most law enforcement agents. The enforcement of the law will require every seized drug sample to be fully identified and reviewed by an expert, rather than just compared against a list of scheduled substances. Until now, the case could be dropped if the analyzed substance did not correspond to any scheduled substance. The analysis was comparatively easy and mostly done with chromatographic methods, often coupled to a mass spectrometric detector (e.g. GC-MS or HPLC-MS). Under the updated law, the substance will need to be analyzed with additional methods like 2D NMR techniques. The identification of new structures will require the work of highly trained experts rather than lab technicians who can perform forensic routing analytics. In consequence, forensic laboratories will suffer from additional workload and will either have longer waiting times or they will have to increase capacities (requiring more funding). Most likely, drug offense cases will therefore have longer processing times. Since most drug offense cases deal with possession of small to medium amounts and are consequently of minor public interest, having them drag on would constitute a waste of public funds.

It can be summarized that few people without chemistry background will be able to fully understand the scope covered by the three categories. This will lead to some degree of uncertainty for end-users, manufacturers and distributors of chemicals and require additional efforts both from them and forensic laboratories.

2.2 Inhibitive effect on research

As discussed in the introduction, two of the three categories contain a multitude of already used pharmaceuticals and many other psychoactive substances with potential therapeutic applications. It seems likely that more compounds with useful biological activities will be discovered in the future, especially among the diverse class of PEA. It is, in fact, likely that even among the NPS that have been

sold for recreational purposes some will find medical applications in the future, since most NPS have been synthesized to mimic the effects of psychoactive pharmaceutic drugs. There are already examples for therapeutic uses of well-known NPS, such as the use of methoxetamine (MXE) to treat phantom pain and depression while avoiding ketamine bladder syndrome[84,85] or 3-methylmethcathinone assisted psychotherapy.[86] Additionally, it's possible that substances fitting into one of the categories could have non-medical uses or be intermediates in the syntheses of useful compounds.

The lawmakers tried to avoid disrupting the work of the chemical industry and research institutions by building in possibilities of exemptions and licenses to produce and work with NPS and other scheduled drugs. Other countries like the USA, UK and Germany have similar policies. However, in the past there have been various cases of prohibition impeding research, despite the possibilities of obtaining the right to legally work with controlled substances.[87] One example is the studying of MDMA-assisted psychotherapy, which has been poorly documented but widely and successfully used in the 1970s and 1980s.[1,88–90] Recent, placebo-controlled clinical studies have shown a lot of promise for MDMA-assisted psychotherapy to treat post-traumatic stress disorder (PTSD)[36] and social anxiety in autistic patients.[91] The need for such studies was discussed years before 2018 when those studies were published.[92] One of the reasons for the delay was caused by major obstacles caused by prohibition.[92,93] For phase III trials, GMP grade MDMA is required by law. While MDMA of high purity is cheap and widely available on the black market, there are hardly any sources for non-analytic amounts of legal MDMA, due to the regulations and costs associated with obtaining a license and storage facilities for controlled substances.[87,94] This necessitates custom production by licensed sources, thus adding high amounts to the already considerable extra costs caused by licensing, storage and safety demands.[87,94] The need for all institutions (like hospitals and research labs) and everyone involved (doctors, researchers, lab technicians) to be licensed and certified drives the costs and delays even further up.[95] In the UK studying a Schedule 1 drug takes many years of bureaucratic preparation and is estimated to cost about 10-fold the than similar studies with a "legal" drug.[87,93] Financing such expensive studies poses another challenge. Because of the stigma attached to illegal drugs, it can be difficult to obtain funding for the research, especially from public budgets.[96] A common way to fund studies with scheduled drugs is through the Multidisciplinary Association for Psychedelic Studies (MAPS), a donation-funded non-profit organization.[93,96]

Understandably, most pharmaceutical companies avoid developing new psychoactive medicines with similar pharmacological properties to illegal drugs. There is concern that the new drugs will be scheduled before getting final approval, thus creating new bureaucratic hurdles, increasing the development costs and creating a negative image for the new drug.[87] There are many examples of research and development of new drugs being terminated because of their appearance in NPS shops and subsequent ban.[97] One of them, the dissociative anesthetic MXE, has been mentioned before in this chapter as a treatment option for phantom pain and depression.[84,85] The only legal pharmaceutical with a similar mode of action (primarily as a NMDA receptor antagonist) is ketamine. It has also shown promise as a treatment option for both conditions,[98–100] but it has some serious side effects, including the so-called "ketamine bladder syndrome".[101,102] Ketamine was developed as a dissociative anesthetic

to replace phencyclidine (PCP), so its duration of action was optimized for this application and is relatively short.[103] This is an obvious drawback of the drug when used to treat chronic pain, because of the large quantities patients would require on a regular basis and associated side effects. Unfortunately, blanket bans and the fear of further prohibition inhibit any research into NMDA receptor antagonist, especially arylcyclohexylamines, some of which could be better tailored for some of the various uses of ketamine and are likely to be have fewer side effects and better oral bioavailability than ketamine. Another example of research halted by an NPS ban was the development of previously legal MDMA analogues as treatments for dyskinesias in Parkinson's disease.[97] Again, one of these substances would likely have been better suited to treat the condition than MDMA, which has considerable side effects. In a different case, a clinical trial of psilocybin to treat patients with OCD showed promising result.[104] Disappointingly, a follow-up study could not be conducted due to the disproportionate costs of obtaining the (licensed and legal) psilocybin.[105]

Another obstacle caused by prohibition is the bureaucracy involved in shipping controlled substances, primarily due to import-export regulations. These regulations differ from country to country and do not consider the amount, meaning that even miniscule quantities required for analytics and many areas of research are subject to the same harsh rules.[87] This complicates interinstitutional cooperation and unnecessarily limits research that requires amounts below the threshold for biological activity (most preclinical in-vitro studies, imaging studies).

For science the consequences of prohibition extend far beyond the medical applications of drugs and directly affect such research areas as neuroscience and the study of the harm potential of different drugs, which after all is crucial to make informed policy decisions. For neuroscientists studying consciousness, understanding the role and function of the $5HT_{2A}$ receptor activated by psychedelics is of profound interest.[105] Because consciousness is a human trait, the information available from animal studies is of limited applicability. Human studies, on the other hand, are limited by the mentioned earlier difficulties of conducting research with scheduled substances and lack of safety data about the psychedelics that are not yet scheduled.[105] Scheduling all psychedelics or indeed even all PEA would include all N-(2-methoxybenzyl) PEA (NBOMe compounds), which were designed as highly potent and selective $5HT_{2A}$ agonists to map and otherwise study the receptor system.[106] Furthermore, quick or even proactive scheduling of emerging NPS reduces the opportunities to study their toxicological properties and harm potential.[105]

Finally, it can be concluded that the provisions made to reduce the impact of scheduling psychoactive drugs on science are mostly insufficient.[105] The regulations differ from state to state but are generally so harsh that they inhibit scientific research and industrial commitment to an overwhelming degree.

2.3 Ineffectiveness and harm of prohibition

The general ineffectiveness of prohibition as a preventive public health measure is perhaps the most important argument against the planned substantial widening of the scope targeted by the Opium Act.

Intuitively, making the production, trade and possession of anything dangerous illegal while threatening perpetrators with serious penalties seems like a logical action. It aims towards limiting or ideally eliminating availability of the dangerous good, while sending a message about the dangers associated with it. Unfortunately, the actual consequences of such an approach differ dramatically from the intuitively expected, as will be elaborated throughout this chapter.

The main reason why the results of prohibition fail to meet the expectations is that it does not eliminate demand.[107] While the demand for some kinds of dangerous goods (e.g. weapons or toxic fuel additives) can be eliminated or substantially decreased, the same is impossible to achieve for psychoactive drugs. People have been using psychoactive drugs throughout all human history.[108–111] They were used by priests or shamans in religious ceremonies, medicinally by sick people and recreationally by large parts of the population, usually in a socially accepted way.[108,110] The drugs used in rituals, religious ceremonies, spiritual healing and other religious settings were mostly cannabis,[112,113] psychedelics and other hallucinogens[114–116] and were therefore not or only mildly addictive. In contrast, there were addictive substances among the medicinally used drugs (opium and other poppy formulations, coca leaves), as well as among the culturally accepted intoxicants (alcohol, tobacco, coca leaves, cath leaves). Different groups of drugs (stimulants, depressants, psychedelics, dissociatives etc.) are useful in different situations and appeal to different people, which is why the universally legal alcohol, nicotine and caffeine are insufficient to eliminate the demand for other psychoactive substances. Furthermore, the choice of drugs as well as the ways of using them, are highly dependent on the cultural background of their users.[82,117] The most obvious examples are the use of LSD and other psychedelics by the pacifist counterculture (hippies) of the 1960s[118] and the use of MDMA and stimulants in the electronic music scene.[119]

Isolated cases of regulations and bans of addictive drugs have started as early as the 19th century but their effect was not properly documented and studied at the time.[67] The first well documented experiment on a sufficiently large scale was the US alcohol prohibition from 1920 till 1933. While there was a steep decline of per capita alcohol consumption shortly after the ban, there was scarcely any long-term effect.[120–122] Since the demand was practically unchanged, the alcohol production was picked up by criminal organizations, creating a huge black market.[123] Besides failing to significantly reduce long-term alcohol consumption, the prohibition reform led to a number of undesired and harmful effects. It created or strengthened organized crime.[123,124] Many people got poisoned by drinking low quality bootleg alcohol or denatured industrial alcohol containing methanol, pyridine and benzene.[125,126] Additionally, the social cost of law enforcement and incarceration, as well as lacking tax revenues are worth mentioning, especially since the economic collapse of the Great Depression was a major reason why the alcohol prohibition was repealed.[122,127]

The next milestone in the history of prohibition was the begin of US president Richard Nixon's so-called "War on Drugs", which he declared in 1971 after passing the Controlled Substances Act (CSA) a year earlier.[128,129] The practical steps taken by his government included an increase in federal funding for drug-control agencies, the founding of the Drug Enforcement Administration (DEA) and intruding harsh

penalties for drug crimes (even for possession of small quantities).[128] Critics have repeatedly noted that the US drug laws of that era were and their mode of enforcement were dictated by political and racist agendas rather than aiming to reduce harm and social cost of drug abuse.[105,128,130] Under Nixon's rule the USA strongly influenced the content of the United Nations (UN) Convention on Psychotropic Substances of 1971,[131] an update to the Single Convention on Narcotic Drugs passed in 1961.[132] In the following decades, the US continued exerting economic, political and even military pressure on other nations to adopt hardline policies and strongly enforce prohibition.[131,133,134] The results of the War on Drugs on the levels of drug use are hard to judge quantitatively, due to the absence of any drug use data for a hypothetical scenario without strict worldwide prohibition. However, it seems obvious from US and worldwide drug abuse statistics of the last five decades that the War on Drugs has not reached its goals.[135–137] In fact, the ongoing opioid crisis in the US is a convincing example of the policy's failure.[138] Despite all efforts, the USA are continually the nation with the highest level of illegal drug use.[139] Counterintuitively, the use of severe punishments such as long prison sentences or even the death penalty does not function as a deterrent and hardly had any effect on the levels of drug use.[140,141] At the same time, waging the War on Drugs came at a staggering cost. Since its commencement, the US spent more than a trillion USD in futile efforts to get drug production, trafficking and abuse under control by treating it as a criminal matter.[142–144] Almost half of that cost went into imprisoning drug offenders, most of whom were arrested for possession of small quantities.[143,145] The War on Drugs contributed to the USA having by far the biggest prison population worldwide, with 2.3 million people serving jailtime (2008), amounting to about 1% of the country's adult population and 24.7% of the total number of judicial prisoner worldwide.[146] While this situation is damaging to society, incarceration of drug users has no objective benefits. It has little effect on drug abuse levels,[138] leads to a dramatical increase in overdose mortality among freshly released prisoners[147] and has a negligible effect on public safety.[148] The consequences of being convicted on drug charges are often more harmful to people's lives than the drug use itself.[149] To illustrate the veracity of this statement, it is important to know the following facts. A drug felony conviction in the US and many other countries can cost a person most opportunities in life, even after a mild sentence. It is almost impossible to find proper housing and get a good, well-paid job for someone with a criminal record.[95,150,151] The diminished chances of achieving any ambitious goals in life and legally earning money tend to push people back into drug use and trade, as well as to other criminal activities, thus creating a vicious cycle.[151] According to the United Nations Office on Drugs and Crime (UNODC), there are about 230 million users of illegal drugs in the world, 90% of whom are not viewed as problematic.[135,142] It seems obvious that this majority of drug users would suffer more from the consequences of breaking the drug laws than of their unproblematic drug use. To support this, it is important to mention that neither the legal status of a drug nor even its schedule placement are good criteria for the harm potential of a drug. A study published in the renowned medical journal "The Lancet" in 2010 applied scientific criteria to quantitatively assess the harm to users and other people done by various legal and illegal drugs. Among the 20 drugs discussed in the paper, alcohol was ranked the most dangerous and tobacco was placed on rank 6, while the Schedule 1 drugs MDMA, LSD and psilocybin mushrooms ended up at the end of the ranking.[152] Worldwide, an estimated 3 million people die every year from conditions caused by extensive alcohol

use[153] and more than 8 million people from smoking-related diseases, with 1.2 million of those victims being non-smokers exposed to second-hand smoke.[154] This corresponds to about 5% and >14% of the total number of deaths and clearly illustrates the extend of harm caused by legal drugs. Additionally, both legal drugs are known to be highly addictive, causing both psychological and physical dependence.[155–157] The addictive potential of nicotine is considered to be on par with the most addictive illegal drugs,[158] while alcohol withdrawal can even be fatal.[159] In contrast, illegal psychedelics like LSD and psilocybin are neither addictive nor toxic,[160,161] causing less harm among their users than alcohol and tobacco.[152]

Another consequence of the War on Drugs and prohibition-based policies in general is the formation of a black market, putting most of the manufacturing and distribution in the hands of organized crime, as was the case during the alcohol prohibition. The social problems associated with this development are numerous, with violence committed by criminal organizations (e.g. drug cartels or gangs) perhaps being the gravest of them. Especially Latin America, where all of the world's cocaine production takes place, has seen its share of cartel wars and brutal violent crimes committed by the drug cartels.[134,162] In recent years Mexico was hit especially hard, after trying to dismantle the cartels by force in 2006. Between 2007 and 2018 a total of 115000 murders in Mexico have been attributed to organized crime.[163] Another adverse effect of having wealthy and influential criminal organizations is increased corruption.[164,165] Keeping influential people in various institution on the payroll is an obvious and easy way for criminal organizations to widen their influence and avoid interference in their schemes.

The need to buy on the black market is also detrimental for the safety and wellbeing of drug users, primarily due to the lack of quality control. Street drugs often contain cutting agents or synthetic byproducts, some of which are harmful or even dangerous.[166–169] Drug users cannot be certain about the identity and quality of the drugs they purchase, which often leads to potentially dangerous accidents and overdoses.[170,171] Opioids with varying potencies of supposedly the same drug (mostly heroin) are especially dangerous and have caused a great number of overdose fatalities.[172,173]

Prohibition, especially combined with anti-drug propaganda, stigmatizes drug users and makes it difficult for people suffering from substance addictions to get help. Substance addiction and addiction in general have been recognized to be diseases rather than the results of poor choices.[174,175] Accordingly addiction and problematic substance use should be viewed as a public health rather than criminal justice issue when developing or revising drug policies. In the last two decades some states including Portugal, the Czech Republic and several Latin American countries have recognized the failure of a purely prohibitive approach and have adopted evidence-based strategies, decriminalizing possession of small quantities among other measures.[176] The term decriminalization means removing criminal prosecution of low-level drug offenses (use, possession and trade of small quantities) or replacing it with administrative punishments (e.g. fines). It's distinct from a full legalization, which also includes legal and taxed manufacturing and distribution, and has recently been applied to cannabis in several states in the US, Canada and Uruguay. Besides the well-known semi-legalization of cannabis, the Netherlands have also adopted a form of decriminalization for other drugs, which is not part of the

Opium Act but rather a long-standing policy to instruct prosecutors not to prosecute possession of minor amounts.[176]

Decriminalization policies have been successful wherever applied.[145,177] They had no significant influence on the numbers of drug users but led to considerable reduction of harm associated with drug use.[145,176,177] Besides the already mentioned advantages in refraining from incarceration, other positive trends arising from harm reduction measures were identified. People with substance abuse problems were encouraged to seek help, resulting in an increased uptake into therapy.[176] Deaths by overdose could be significantly reduced where prescription maintenance programs were implemented and supervision was offered.[177] Making naloxone available to opioid users and lay helpers also contributed towards this goal.[178,179] Handing out free syringes and other drug paraphernalia have reduced infection rate with HIV and other diseases.[180] The earlier described dangers of lacking quality control have been addressed by allowing drug checking.[181] Another cheap and important harm reduction measure that is often combined with drug checking services consists of providing and spreading scientifically accurate and unbiased information about drugs, their interactions and safer use techniques. This approach is in stark contrast to most formerly employed drug information campaigns such as “just say no!”, which only mentioned the dangers addressed potential users by on an emotional level without distinguishing between different kinds of drugs and providing little real information.

The evidence presented in this chapter clearly shows that prohibition is ineffective in preventing substance use/abuse, while being costly and harmful for drug users. The persistent demand creates a black market and strengthens organized crime, creating a multitude of serious problems. On the other hand, more liberal evidence-based policies aimed at harm reduction have been widely successful.

3. Counterarguments

This chapter deals with the Dutch legislators’ stated reasons for the proposed changes to the Opium Act and brings up counterarguments. The first stated reason is that scheduling those substances would serve as a warning about their potential dangers, which should in combination with the threat of punishment discourage the use of those drugs.[6] As has been extensively discussed in the former chapter, there is little chance of such an effect, at least in the long term. The users of NPS will either continue using them, or switch (back) to their already illegal analogues from black market sources. This is what happened in the UK where the Home Office admitted its failure to achieve any of the harm reduction goals.[78]

The second argument made in favor of passing the Opium Act update was that it would enable law enforcement agencies to fight organized drug crime more effectively and close a legal loophole used by criminals.[6] However, the effect that should be expected would be quite the opposite. As detailed before, prohibition only creates a black market from which criminal organizations profit. From a simple

economic point of view, it is obvious that the largest profits are to be generated where the demand exceeds the supply. Therefore, most criminal organizations focus on illegal drugs with the highest demand to supply ratio and preferably with addictive properties to ensure future demand. It's estimated the heroin (100-110 billion USD) and cocaine (110-130 billion USD) trade alone make up between half and two third of the global illicit drug market (roughly 360 billion USD).[182] The market share of synthetic drugs (60 billion USD) is only around 17%, with NPS being a minor fraction of that amount. As detailed in the introduction, the greater part of the NPS trade was not in the hands of typical organized crime. On the contrary, most NPS online vendors and wholesale distributors took care to operate as closely resembling legit chemical suppliers as possible, all the while paying taxes and trying to minimize the chances of legal persecution. Most NPS were legally produced in China and underwent some form of quality control, especially in recent years.[69] Most online NPS vendors also took care not to sell substances like potent opioids that had a high risk of fatal accidents and even quickly stopped selling drugs (e.g. 5-IT and 4,4'-DMAR) that were reported to have been involved in fatal accidents.[70] The NPS market was and still is partially self-regulated and arguably poses less danger to users than the alternative black market or darknet sales, while contributing to the economy. This invalidates the argument made by the legislators in favor of passing the blanket ban. Instead, the law makers should consider regulating the already existing market by imposing some form of control, comparable to the rules applying to the alcohol and tobacco industry. A rough proposal what such regulations could look like will be discussed in the following chapter.

The last and most solid argument in favor of passing the Opium Act update was that it would enable the Dutch law enforcement agencies to effectively cooperate with other countries where NPS that are still legal in the Netherlands are scheduled.[6] While this would undeniably be the case, it remains doubtful whether this cooperation would benefit anyone. As explained before, it is very unlikely to reduce drug use, since the NPS distribution would simply shift to a different EU country. Therefore, the Dutch state would only lose tax income without achieving any beneficial public health effect, domestic or global. Moreover, there are various example of prohibition leading to an increased use of more harmful drugs , such as cannabis to synthetic cannabinoids, smoked opium to injected heroin or MDMA to the highly dangerous amphetamines PMA and PMMA.[76] Furthermore, the banning NPS is not the only possible way to prevent the shipping of NPS to countries where they are scheduled. Instead, a law could be passed to explicitly prohibit shipping to countries where the product is banned or its legal status is ambiguous. An even better solution would be a system where NPS production and sales remain legal but are regulated. In this scenario, such shipping restrictions could be included in the licensing conditions for manufacturers and vendors. This would facilitate the enforcement of the shipping rule and give the authorities some control over the NPS trade, as will be elaborated in the following chapter.

4. Legalization and regulation of the NPS market

As mentioned in chapter 2.3, a growing number of governments worldwide are coming to realize that the War on Drugs is lost, since prohibition failed to solve the problem of drug abuse and even exacerbated the harm.[149,183] There is a general global tendency towards liberalization of drug policies in the shape of decriminalization, evidence-based harm reduction and a growing number of countries legalizing the medical and recreational use of cannabis.[176,184] At the same time, the most common reaction to address the growing market share and number of NPS was to impose blanket bans.[69,82,185] This seemingly paradox actions can be explained in the same way that addiction expert Mark Haden used to explain why no drugs other than cannabis have been legalized so far: in a 2017 interview he called it "being scared of leadership", meaning that politicians avoid introducing controversial policies that don't have majority support in polls even if they are confident that the policies would be beneficial for society.[186] It's understandable that after decades of anti-drug propaganda consisting of scaremongering and war-rhetoric,[187] a full reversal or any kind of radical reform is difficult to "sell" to the voters. Nevertheless, there are many objective arguments in favor of a full (re)legalization, even compared to the relatively successful decriminalization policies. Legalization would shrink or eliminate the black market thus taking away a major source of income from organized crime. It would allow quality control of the drugs sold, thus reducing the harm to users. Also, legalization would strongly facilitate and accelerate scientific research (s. chapter 2.2), while generating considerable additional tax income, parts of which could be spent on expanding treatment options for people with problematic substance use who seek help.

As mentioned above, legislators everywhere are anxious to go against the public opinion and are especially reluctant to be the first country to legalize drugs that have formerly been considered hard, disregarding any evidence. Additionally, the international drug treaties create obligations that are difficult to ignore and that can be used as excuses not to try any radical policy changes. However, since the emerging NPS are not included in the schedules of either treaty,[129,188] they offer a great opportunity to experiment with evidence-based policies by regulating the market.[70,189] The Netherlands are known for their pioneering role in adopting sensible, progressive policies that have strong opposition around the world. The most famous examples were euthanasia,[190] cannabis decriminalization[191] and gay marriages.[192] The Netherlands thus paved the way for similar developments in other countries. A regulated legalization of NPS would, if it's well drafted and executed, likely be equally successful and should gain international acceptance in time.

As of this day there has been only one attempt to create a legal, regulated NPS selling system. The Psychoactive Substances Act 2013 (PSA13) in New Zealand prohibits selling psychoactive substances, unless they can be proved to be of low risk in humans.[193,194] After approval is granted, additional regulations regarding advertising, minimal age, sale environment and reporting of adverse effects apply. The application costs for each substance are 180,000 NZD (approximately 97,500 €), in addition to the cost of the required experiments, which were estimated to be over 1 million NZD (542,000 €).[185]

The difficulty and high cost of obtaining a license combined with the relatively small market size in New Zealand precluded applications for manufacturing licenses, making NPS effectively illegal.[185]

A system to regulate the sales of NPS to end users in the Netherlands could be realized by first restricting the sale of organic chemicals with known biological activity or insufficient toxicological data to private persons. At the same time vendors would be allowed to apply for a distributor license. The licensing should provide a framework of rules for the distributor, such as the following:

- Clear labeling of products, including available information and relevant warnings
- Quality control of each batch by a neutral third-party laboratory or a public institution
- Keeping a complete order and shipping history, including batch numbers and dates of manufacturing
- No shipping to countries where the product is banned or can be presumed illegal
- No sales to customers below a certain age (18 or higher), require proof of identity

The set of regulations presented here can be changed or extended according to the goals of the policy makers. It may for example be combined with a public health and prevention-oriented policies. This could be accomplished by creating a record of domestic customers and their purchases, which could be used to identify problematic substance use patterns. Once identified, those people could be invited for a consultation with an addiction and drug use expert and be offered help. Another way of harm reduction in such a system could be to create a licensing procedure for customer, who would have to pass a short course on basic pharmacology of psychoactive substances, drug-drug interactions and safety measures for reducing the risks drug use. This would be comparable to obtaining a driving license. Such a framework would not only educate potential NPS users and reduce the risks associated with the drugs but would also allow close monitoring of use patterns and motivations, as well as of mid- and long-term health effects of the drugs used. The data collected in this way would be highly beneficial for future harm reduction efforts, since toxicological data on most NPS is extremely scarce. This regulatory system would be the first of its kind and would provide new insight into the advantages and pitfalls of NPS legalization. This knowledge could be used by other countries to implement similar policies and might ultimately lead to a harmonization of the European response to the challenges created by NPS.

Legalization and regulation of NPS sales for human consumption would also make additional taxation of those drugs possible, comparable to alcohol and tobacco taxes. The tax rate could be variable and depend upon the pharmacological class of the drug, its potency, addictive properties and other known dangers. This way the use of large quantities of addictive and dangerous NPS could be discouraged. The income generated by this tax could be used to finance the monitoring of the market and NPS vendors and to create more treatment options for people suffering from substance abuse disorders.

5. Conclusion

The data and arguments presented in this essay show that conclusively blanket bans in general and the proposed change of legislation in particular are ineffective in minimizing the harm associated with drug use. The continually existing and even growing demand for NPS and legal alternatives of scheduled drugs precludes the long-term success of any measures aiming to restrict supply. Proactive scheduling of a wide array of chemicals is ethically dubious and creates various new problems in a similar way that drug prohibition is known to cause. The most serious of these problems are an increase of organized crime and associated violence, harm from adulterated or misidentified drugs and the impediment of research, including the assessment of risks and damage caused by NPS. With this in mind, a liberal, evidence-based approach to NPS market regulation with the focus on harm reduction and human rights was recommended. Implementing such a policy would mean adopting a more courageous stance on handling the challenges and opportunities presented by the rapidly growing NPS market, instead of bowing to international pressure and passing a blanket ban as an act of desperation. The Netherlands would lead by example thus reasserting their image as an ethically progressive and pragmatic country, while profiting economically and avoiding the pitfalls of outdated drug policies.

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