INTRODUCTION

A range of diseases have been treated by psychoactive substances. According to a recent European survey for 2010, brain disorders, including drug addiction, are major health problems: the €798 billion total cost related to their treatment is comparable to the combined cost spent on cancer, cardiovascular diseases, and diabetes.1 Psychoactive medicines are also indispensable for the treatment of pain and obesity. However, due to their mode of action, all such drugs are liable to misuse or abuse, which could be prevented by prescription requirements or even stringent control (prohibition). To minimize use-related harm, international regulations have been developed. The majority of substances under international control by UN conventions of 1961 and 1971 had been scrutinized pharmacologically before scheduling; many of them are still being used in human therapy. By contrast, less is known about the so-called new psychoactive substances (NPSs), i.e., drugs not covered by UN conventions. Since 2008, NPSs have been emerging in unprecedented number globally (Figs. 1 and 2).2,3

Most of these chemicals have not been studied in animals or allowed for human consumption; they are usually picked from scientific publications and patents describing data of in vivo assays usually confined to a single pharmacological target. While UN-controlled drugs are usually produced clandestinely and sold on the black market, the active ingredients of NPSs are freely manufactured and marketed in bulk (multi-kilo) quantities along with as industrial chemicals, paints, pesticides, pharmaceuticals and their intermediates. They are offered in high purity as “research chemicals” with the label “solely for non human consumption”, thus there seem to be no justified reasons and currently there are no legal tools to curb their production and trade. There is no shortage of data on the estimated local or global market of illicit drugs, but virtually no relevant figures are available for NPSs. Clearly, a broader scientific and economic scrutiny, with special regard to the supply side, of the NPS phenomenon is justified. This may help us to understand the phenomenon and to formulate adequate policies to solve problems already existing and prevent those that can realistically be expected.

Why synthetics?

Before the discovery of the anesthetic properties of simple synthetic chemicals (e.g., nitrous oxide, ether, chloroform) in the mid-19th century, all medicines were of natural origin. In subsequent decades, important synthetic psychoactive medicines (barbiturates, amphetamines, benzodiazepines, synthetic opioids, etc.) were devised by the pharmaceutical industry and introduced into the clinic. Developments in synthetic techniques and manufacturing technologies now allow the production of even structurally complex drugs. During the drug discovery process, tinkering with the chemical structure of a lead compound results in hundreds of structural analogs most of which, however, are discarded due to their undesirable biological properties but the research results are usually disclosed in papers or patents. Once published, this information could, however, ‘spill over’: the scientific literature can provide both recipes and ideas for ingenious yet unscrupulous chemists who capitalize on earlier discoveries. Unsurprisingly, most NPSs are such synthetic chemicals although there are a few notable natural-product exceptions.4 Based on already existing multi-purpose industrial equipment common in chemical industry and on trained personnel, manufacturing these chemicals has several advantages over cultivating drug-producing plants: 1) economic scale; 2) large amounts can be prepared within weeks; 3) production is independent of climate or weather conditions and not affected by plant diseases; 4) the pure active ingredient is highly concentrated facilitating transport; 5) production process for structural analogs is similar and easily adaptable.

Why now?

Although known earlier, a broad range of synthetic drugs for non-medical use were popularized in the 1990s.5 Yet - with the notable exception of MDMA - few of them were widely available during the 1972–2007 period. Potent synthetic cannabinoids, the prototypes of many current analogs, have been known since the early-1980s (but see Fig. 3), though the quest for therapeutically useful, non-psychotropic cannabinoids6 accelerated after the discovery of cannabinoid receptors in the early 1990s. Such scientific progress have provided impetus for the developers of NPSs.7 The entry of well trained new players on the supply side is indicated by the unprecedented structural diversity (and novelty!) of NPSs: clearly, the producers are familiar with medicinal and organic chemistry literature. Also, over the past two decades synthetic organic chemistry progressed in leaps and bounds; many processes that were once laboratory curiosities can now be carried out on an industrial scale. Finally, all such professional information has now become accessible on the Internet virtually to anyone.

Why global?

The profit-driven chemical industry behind NPSs, which are produced and traded without any legal restriction, enjoys the same benefits of globalization as any other legitimate industry: global customer base, reliance on the economies of scale and on low labor costs, fast shipping services and Internet communication.

The role of prohibition, if any

Prohibition has curtailed, but not eliminated the demand for and supply of a wide range of drugs. Yet, “the international drug control system is floundering, for the first time, under the speed and creativity of the phenomenon known as new psychoactive substances.”8 Conventional thinking suggests that NPSs are emerging to replace prohibited drugs. I am proposing that the phenomenon be analyzed in a broader context considering factors other than criminalization or the lack of it. Conceivably, it is the unique psychoactivity of these that creates ‘demand’. Marketing anything that promises ‘artificial paradise’ would sell. While legal restrictions may certainly shape (strain?) market operations, the emergence of companies churning out affordable, high quality, though pharmacologically poorly characterized, ‘recreational’ chemicals as commodities with unique effects, has induced a paradigm shift. Medicinal chemistry research, the ever-enlarging source of NPS prototypes, by itself is a challenge to the present regulatory system, which appears to be irrelevant in the decisions of NPS-suppliers.
While the NPS phenomenon is a global one, customs seizures and searches on Internet market places indicate that most of these chemicals are sourced from Asian chemical companies. Individual shipments of pure active ingredients may amount to 100 kg. In emerging countries, like China and India, industrial export and innovation are major engines of economic growth. In addition to science & technology centers established there by multinational companies during the past two decades, local chemical companies of NPSs, are mainly due to the prioritization by the Chinese government of the development of science and technology economy to produce products for export during the 10th and the 11th Five-Year Plans (2001–2005; 2006–2010); R&D projects in biotechnology, which includes chemical substances, continue to be especially supported. For example, between 2007–2012 biomedical R&D expenditures increased from $2.0 billion to $8.4 billion. Competitive R&D obviously requires skilled labor. In the China, science and technology workforce increased from 0.9 million in 2000 to over 3.5 million in 2013; over supply of highly trained chemists has even been suggested. Overseas returnees (who trained in chemistry and business have played a pivotal role in opening up and globalization the country. China has become the second leading country in high-quality science output, especially in chemistry and the number of scientific publications doubled between 2005 and 2011 (Fig. 4). The investments in education and academic research are reflected by similar dynamic changes that have occurred in the fine chemicals & pharmaceutical area (R&D and production capacity). During the past decade, overall growth of the pharmaceutical industry (R&D and production capacity) has been impressive while other industrial countries essentially showed stagnation (Fig. 5). China has become the largest exporter of active pharmaceutical ingredients. This trend might not continue, however: now there appears to be an over-capacity of pharmaceuticals and related chemicals without high technical innovation leading to decreasing profits; a new driving force is thus required to push the pharmaceuticals and fine chemicals industry. In such an economic environment the production of any chemical with potential demand, including custom-manufacture of drugs with purported psychoactive properties similar to an established drug, regardless its regulatory status, is a natural choice for a profit-oriented industrialist. This is what history teaches us.

While epidemiological data on use and estimates on production of NPSs are lacking, the serious adverse health effects, including fatalities, due to their use are real and should not be shrugged off. The complex and variable (but not unpredictable) nature of the NPS phenomenon urgently calls for adequate responses. The phenomenon is a product of the technological – and partly social – changes of the 21st. It is an international challenge which calls for regulatory innovation preferably on an international level.

Then and now...

There are those who smuggling opium to seduce the Chinese people and so cause the spread of the poison to all provinces. Such persons who only care to profit themselves, and disregard their harm to others, are not tolerated by the laws of heaven and are unanimously hated by human beings... The wealth of China is used to profit the barbarians... Of all that China exports to foreign countries, there is not a single thing which is not beneficial to people: they are of benefit when eaten, or of benefit when used, or of benefit when result... Is there a single article from China which has done any harm to foreign countries?... How can it be that the living souls that dwell within these seas, should be left wild and untamed; to be the crucible of artificers, and depraved people of various tribes under the dominion of your honourable nation. And we have heard that in your honourable nation too, the people are not permitted to inhale the drug, and that offenders in this particular expose themselves to sure punishment. It is clearly from a knowledge of its injurious effects on man, that they have directed severe prohibitions against it. But what is the prohibition of its use, in comparison with the prohibition of its being sold—it of its being manufactured,—as a means of thoroughly purifying the source?... Though not making use of it oneself, to venture necessarily upon the manufacture and sale of it, and with it to seduce the simple folk of this land, is to seek one’s own livelihood by the exposure of others to death, to seek one’s own advantage by other men’s injury. (From Commission Lin Zexu’s letter to the British Crown, 1839).

An unanticipated thing happened while I was in prison: The market changed dramatically, and my job was effectively outsourced to China. I have mixed feelings about the increased availability of these chemicals. In today’s climate I might never have become a chemist. Half the chemicals that motivated me to sit down with a chemistry textbook can be purchased online with a debit card. Strangely enough, the research-chemical market put scores of hardworking American clandestine chemists out of business. I can’t compete with China, so I’m yet another victim of globalization! (by a clandestine chemist; for a recent symbolic example, see Fig. 6.)

Conclusions

Academic and industrial laboratories synthesize tens of thousands of new bioactive substances annually during medicinal chemistry research. Most NPSs or their prototypes were made only on a small scale and tested in the laboratory but not developed further. Their large scale production and appearance on the drug market dates back to only 10 years and coincides with the emergence of the Chinese chemical industry with skilled and cheap human resources. These scientific and economic factors, combined with globalization, are the reasons for the unprecedented global spread of legal, as well as illegal, manufactured and traded commodities. Existing international regulations of narcotics & psychotropic substances not only have little importance but appear to be inadequate and unable to deal with the problem and to prevent the health consequences related to the consumption of these clinically untested chemicals. It is desirable to restrict the use of NPSs but doing this without impeding legitimate chemical and neuroscience research and R&D of new chemicals is a daunting task.

REFERENCES

17. Xia Y et al (2014) China’s rise as a major contributor to science and technology, Proc Natl Acad Sci USA 111, 9437

Figure 4. Scientific output trends of leading countries as reflected by publications

Figure 5. Global chemical trade and shipments by the three major producer countries billion US$