General European OMCL Network
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
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Official Medicines Control Laboratories (OMCL)

Market Surveillance of Suspected Illegal Products (MSSIP)

MSSIP007: Nootropics

Scope of the study:	The scope of the study was defined as any product (medicine, herbal medicine, dietary supplement, raw material, etc.) labelled as nootropic and/or containing illicit (nootropic) substances, or unauthorised novel food with purported nootropic activity.
Time frame:	January 2020 - September 2024
Countries involved:	10
Number of participating laboratories:	12
Number of samples in scope:	159 samples, containing in total 166 molecules
Number of unique molecules:	34
Scientific advisors:	Céline Vanhee and Eric Deconinck (Sciensano, Belgium)

Summary Report

Part of this study has been published as a peer-reviewed article in Journal of Xenobiotics (https://doi.org/10.3390/jox15030088).

1. Introduction

Based on the outcome of the 5th Market Surveillance Study on Suspected Illegal Products (MSSIP005) focusing on non-INN active pharmaceutical ingredients (APIs), health products containing selective androgen receptor modulators (SARMs), nootropics and biological products were identified as possible subjects of interest for future MSSIP studies. MSSIP006 focused on SARMs, metabolic modulators and small-molecule growth hormone secretagogues used as performance-enhancing substances. The present study, **MSSIP007**, focuses on nootropic substances, as decided by the Falsified Medicines Working Group (Bilthoven, November 2022).

Nootropics are natural, semi-synthetic or synthetic compounds that improve cognitive function, attention, memory and creativity, reduce stress and promote better sleep quality and overall brain health. Therefore, they are also called smart drugs, brain boosters or cognitive enhancers. In recent years, several reports emerged, demonstrating the adulteration of purported nootropic

health products, often presented as dietary supplements. These items were either adulterated with nootropic pharmaceuticals, contained unauthorised food with purported nootropic effects, contained unapproved or banned pharmaceuticals, or even research chemicals for which limited to no pharmacological and/or toxicological data is available. Furthermore, substandard and falsified (SF) medicines are also used, including prescription-only medicines such as methylphenidate, high doses of melatonin or modafinil, often purchased over the internet.

The objective of this study was to map the different types of illicit nootropics that circulate in the various member states of the General European OMCL Network (GEON) and to raise awareness of this phenomenon among the public and the European Commission.

2. Scope of study

The participating OMCLs were asked to provide data on products containing natural, semi-synthetic or synthetic nootropics tested in their laboratory between January 2020 and September 2024, and to report the presence and the identity of the API to the EDQM. If quantitative data were available, they were also asked to report them.

It was agreed that any product (medicines, herbal medicines, food supplements, cosmetics, medical devices, etc.) containing semi-synthetic or synthetic nootropics would be in the scope of this study, as well as products containing purified natural nootropic molecules (levodopa, 5-hydroxytryptophan (5-HTP), *N*-acetyl cysteine, etc.).

Products containing well-known naturally occurring substances with a nootropic effect (e.g. astaxanthin, berberine, caffeine, carnosine, choline, creatine, fisetin, glutathione, glycine, omega-3 fatty acids, piperine, resveratrol, taurine, theanine, theobromine and quercetin) or naturally occurring authorised herbal molecules with nootropic effects originating from *Ginko biloba*, *Melissa officinalis*, *Magnolia officinalis*, *Panax ginseng*, *Passiflora incarnata*, *Piper methysticum*, *Polygala Tenuifolia*, *Rosmarinus officinalis,* Sage, *Theobroma cacao*, and *Valeriana officinalis*, for example*,* were considered out of scope of the present study.

Products containing cocaine, amphetamine and analogues sold or purchased as party drugs were also considered out of scope of the study, although products containing these molecules sold for their nootropic effects were included.

3. Selection of samples

Results were reported for 199 samples, of which 40 were excluded. Twenty-two samples containing (pseudo)ephedrine, synephrine or phenethylamine were not reported to be sold as nootropic, but as weight loss-enhancing products. Next, dietary supplements containing nootropics that are authorised up to a certain concentration were excluded if quantification data were absent or if they were compliant with the legislation of the reporting country. Five samples that claimed to contain nootropics but did not were also excluded.
In total, 159 samples were taken into account for further analysis. A product containing one molecule within the scope was taken into account, but the additionally reported molecules that were out of scope were excluded from the analysis of detected molecules.

4. Origin of tested samples

The majority of the samples were obtained from the illegal supply chain (69%), while 13% came from the legal supply chain (pharmacies and retail shops), as shown in Table 1 and Figure 1. This 13% originating from the legal supply chain can mainly be attributed to the presence of unauthorised novel food ingredients (e.g. huperzine A from *Huperzia serrata* or 5-HTP) or exceeding the maximum tolerated level of melatonin in dietary supplements. For the remaining 18% of the sample set, the reporting OMCLs were not able to determine whether the sample originated from the legal or illegal supply chain.

Illegal market	109
Unknown	29
Legal market/pharmacy/retail	21

Table 1

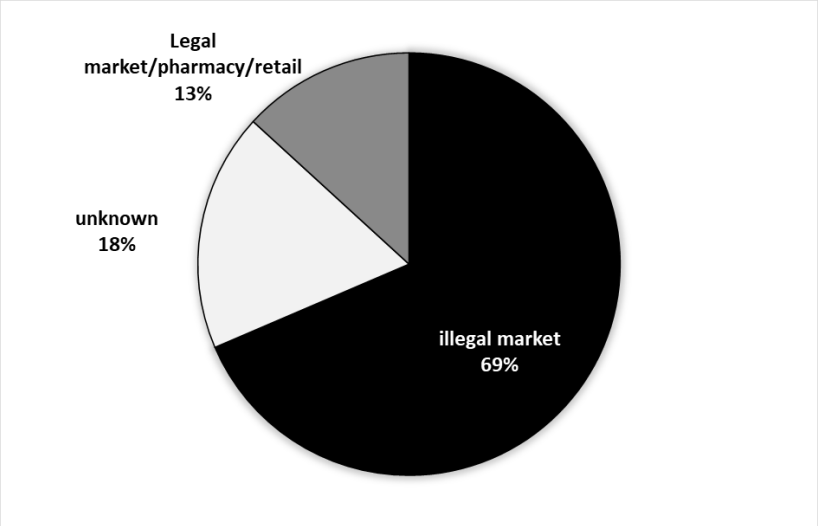

Figure 1

More than 74% of the samples came from customs or law enforcement agencies, while only 8% came from routine inspections. Of the remaining samples, 7% were reported to originate from the internet and 5% from doping authorities (see Table 2 and Figure 2).

Customs and/or police	118
Pharmacy or retail shop	13
Internet	11
Doping authority	8
Other	9

Table 2

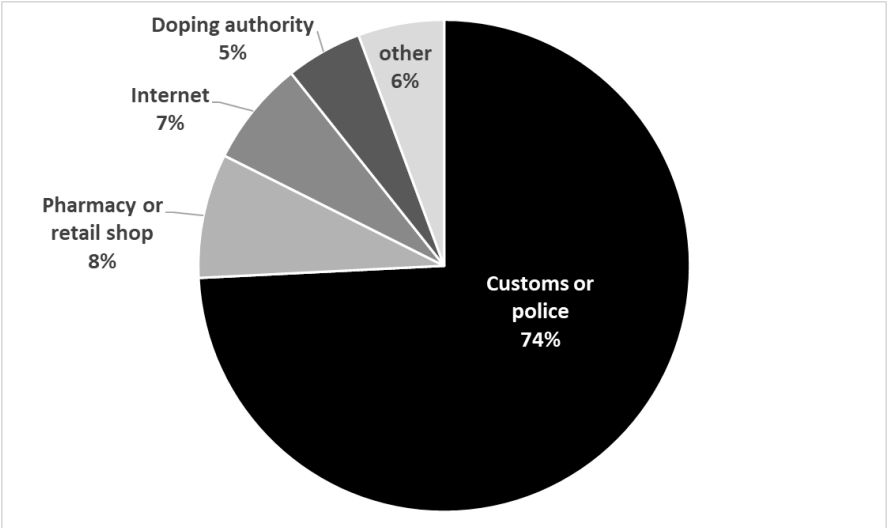

Figure 2

The majority of the samples providers were law enforcement agencies or customs (45%), and inspectorate or medicines agency (34%). The latter is not so surprising, as these inspectors are the main contact point for laboratory analysis in some countries. In addition, 15% of the samples had no reported sample provider and 6% came from doping authorities.

Law enforcement agency/customs	71
Inspector	55
Not reported	24
Doping authority	9

Table 3

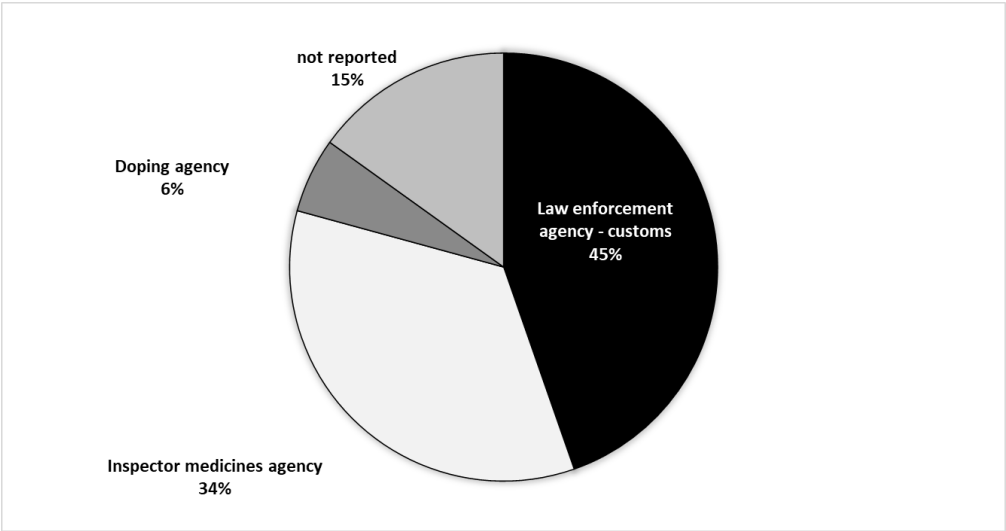

Figure 3

5. Product types of tested samples

The majority of the samples were either sold or presented as a dietary supplement (49%) or as a medicine (32%), as illustrated by Table 4 and Figure 4. The remaining samples were sold or presented as large bags of raw material (8%) or the OMCL in question was not able to determine how the material was presented to the patient or consumer (12%).

Dietary supplement	78
SF medicine	50
Unknown	19
Raw material	12

Table 4

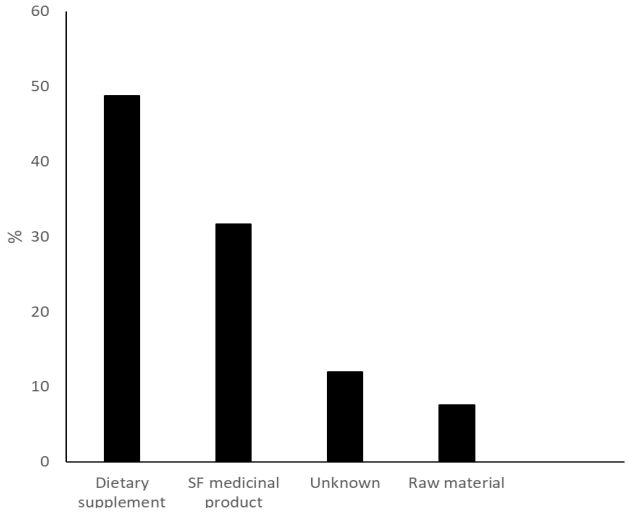

Figure 4

The different reported dosage forms of the samples are given in Table 5 and Figure 5. It can be noted that the majority of the samples were either capsules or tablets (≈ 71%), followed by powders (24%), liquids for either oral or nasal use (4%) and gummies (1%). This finding is not necessarily surprising, as these nootropic molecules are often taken orally.

Capsule/tablet	113
Powder	37
Liquid	7
Gummy	2

Table 5

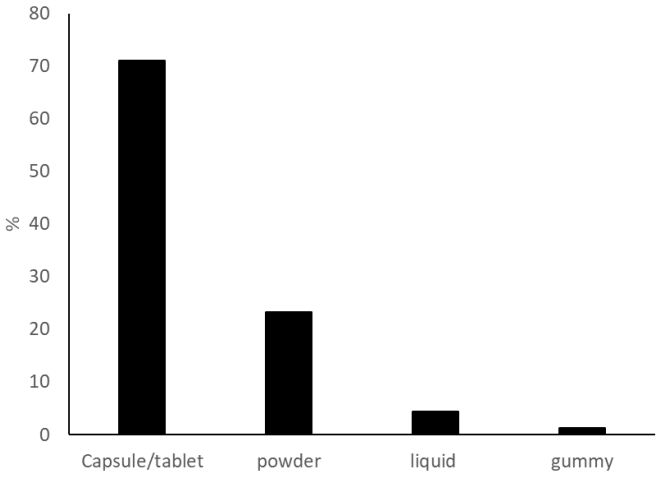

Figure 5

6. Detected molecules

In total, 34 unique and distinct nootropic molecules were identified (see Table 6). The top three reported molecules, **melatonin, modafinil** and **levodopa (L-Dopa)**, accounted for more than half of the total entries. These are well-known nootropics that are used either as sleep medicines or dietary supplements (depending on the amount of melatonin and the country), as central nervous system (CNS) stimulants used to treat certain cases of narcolepsy, and in medication for Alzheimer's disease (in combination with other molecules).

Molecule found		Detection frequency	# laboratories where encountered	Mainly presented as
Name	CAS number			
Melatonin	73-31-4	33	7	Dietary supplement
Modafinil	68693-11-8	25	6	SF medicine and dietary supplement
L-Dopa	59-92-7	21	4	Dietary supplement
Noopept	157115-85-0	9	4	SF medicine and dietary supplement
5-HTP	56-69-9	8	4	Dietary supplement
Adrafinil	63547-13-7	6	2	SF medicine and dietary supplement
Piracetam	7491-74-9	6	3	SF medicine and dietary supplement
Phenibut	1078-21-3	5	4	Dietary supplement
Aniracetam	72432-10-1	4	3	SF medicine
Huperzine A	102518-79-6	4	2	Dietary supplement
Methylphenidate	113-45-1	4	1	SF medicine
Mitragynine	4098-40-2	4	4	SF medicine and dietary supplement
Pregabalin	148553-50-8	4	4	SF medicine
Emoxypine	2364-75-2	4	2	SF medicine and dietary supplement
DMAA	105-41-9	3	3	Dietary supplement
DMPA	28292-43-5	3	2	Dietary supplement

Evodiamine	518-17-2	3	1	Dietary supplement
Bromantane	87913-26-6	2	2	n.d.
Mazindol	22232-71-9	2	2	Dietary supplement
Nefiracetam	77191-36-7	2	1	SF medicine
Pramiracetam	68497-62-1	2	1	SF medicine
Vinpocetine	42971-09-5	2	2	SF medicine
9-MBC	2521-07-5	1	1	unknown
Meclofenoxate	51-68-3	1	1	No information
Dihexa	1401708-83-5	1	1	Dietary supplement
Gabapentin	60142-96-3	1	1	SF medicine
Galantamine	357-70-0	1	1	No information
IDRA-21	22503-72-6	1	1	No information
J-147	1146963-51-0	1	1	No information
N-acetyl tyrosine	537-55-3	1	1	Dietary supplement
Neboglamine	163000-63-3	1	1	SF medicine
NSI-189	1270138-40-3	1	1	No information
Oxiracetam	62613-82-5	1	1	No information
Phenylpiracetam	77472-70-9	1	1	SF medicine
Picamilon	34562-97-5	1	1	Dietary supplement

Table 6: List of molecules (and corresponding CAS number) encountered by the different laboratories sorted according to their prevalence and their current legal status. Abbreviations: DMAA = dimethylamylamine; DMPA = 1,4-dimethylpentylamine; 5-HTP = 5-hydroxytryptophan; L-Dopa = levodopa; 9-MBC = 9-methyl-β-carboline; n.d. = not determined

In 50.5% of cases, the detected molecule was listed on the packaging, although some samples claimed to contain other nootropic molecules, which were not detected during the analyses performed.

In addition to proper identification, the amount present is of paramount importance, especially in the case of melatonin, as the regulation of melatonin and the amount allowed in dietary supplements varies from country to country. In Australia and some EU countries, it is a prescription drug and thus not allowed in dietary supplements. The limit for over-the-counter (OTC) melatonin products in Germany, Luxembourg and Belgium is set at 0.3 mg, up to 1 mg in Italy, Spain and Poland, and 2 mg in France. The minimum dosage that was encountered corresponded to 0.5 mg per capsule or tablet. Of the 35 samples containing melatonin, 21 exceeded the lowest therapeutic dosage, corresponding to 1 mg, while five samples exceeded the recommended maximum dosage of 10 mg a day by at least 20%. The maximum amount of melatonin in one dietary supplement corresponded to 20.3 mg per unit (capsule or tablet), which is double the recommended maximum daily dose (see Figure 6).

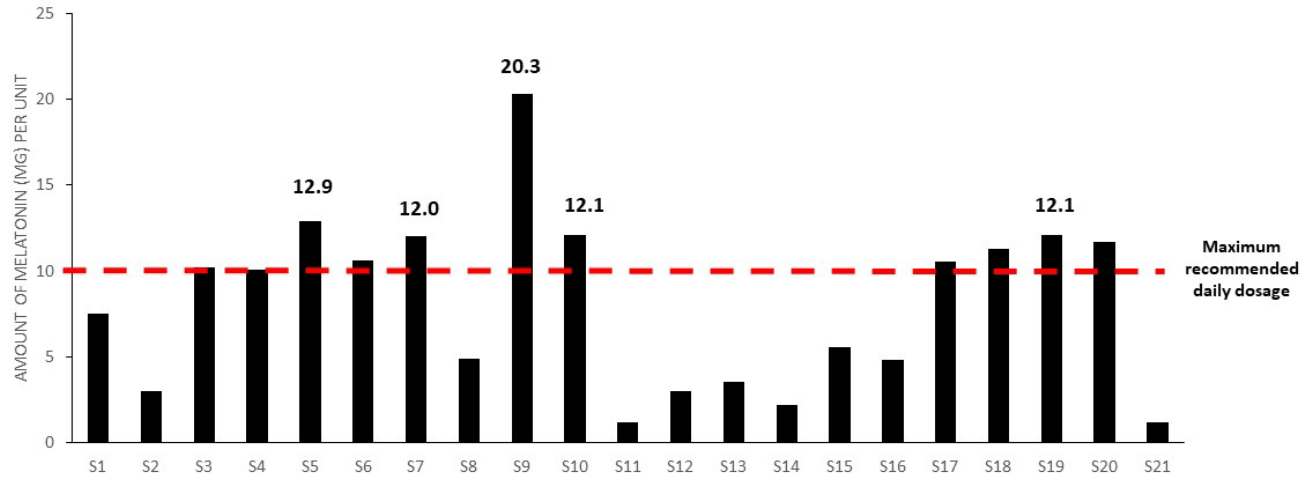

Figure 6

The amount of modafinil found varied from 88 to 197.3 mg per unit, which represents a therapeutic dosage as often quantities of 100-400 mg per day are given. The third most common molecule L-Dopa, often encountered in dietary supplements containing the unauthorised novel food *Mucuna pruriens*, was present in quantities ranging from 1.2 to 40 mg per capsule or tablet. These amounts are lower than the pharmacological quantities often used in medicinal products. These products also contain concomitant drugs to inhibit the peripheral metabolism of L-Dopa to dopamine and concurrent undesired side-effects such as nausea due to the peripheral dopamine production. Other acetylcholinesterase (AChE) inhibitors were also found, such as the prescription drugs galantamine, huperzine A, as well as the potential AChE inhibitor evodiamine and the psychoactive compound mitragynine. The amount of galantamine found was about 4 mg per capsule or tablet which, if taken twice a day, would correspond to a pharmacological dosage. Molecules belonging to the AChE inhibitors account for 20% of the samples and CNS stimulants for 22% (see Figure 7).

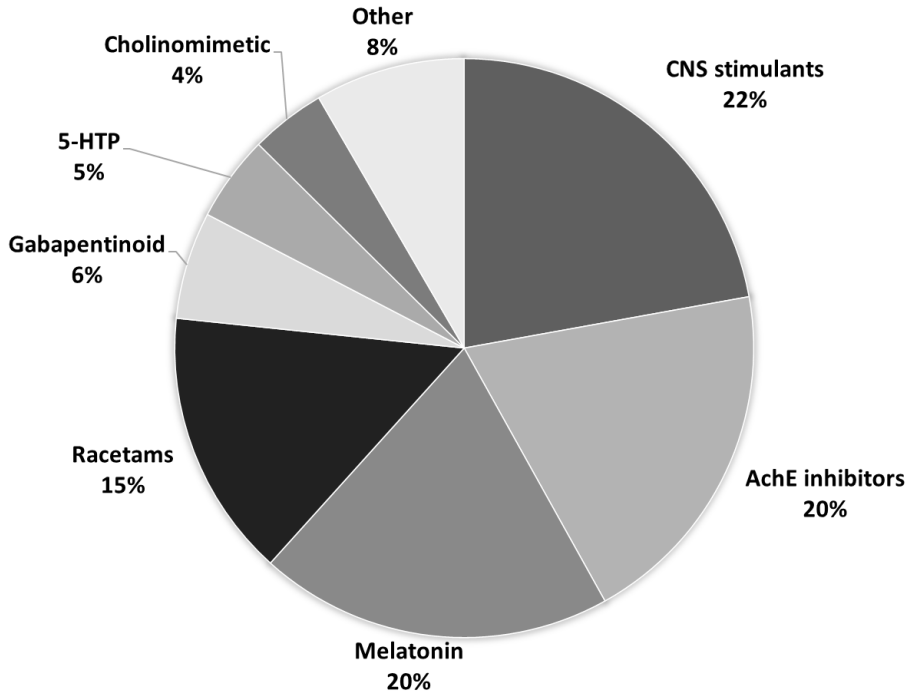

Figure 7

In addition to AChE inhibitors, CNS stimulants and melatonin, members of the racetam family were found several times and represented 15% of the reported samples. Noopept was the most commonly encountered and is currently used as a prescription medicine in Russia; however, its use has not been authorised in the EU or Australia. Often noopept was presented or sold as raw material in bulk with a purity of up to 100%. Piracetam and aniracetam were also detected and, in the case of aniracetam, up to pharmacologically relevant doses (the maximum dosage of aniracetam corresponds to 750 mg a day). Several other piracetam homologues were also found, but less frequently. It should be noted that in the case of the homologue phenylpiracetam, bulk quantities of raw material were intercepted with purities close to 100%.

Other drug classes such as the gabapentinoids, represented here by the prescription drugs gabapentin, phenibut and pregabalin, and cholinomimetics, including dimethylamylamine (DMAA), 1,4-dimethylpentylamine (DMPA) and meclofenoxate or centrophenoxine, account for 6% and 4% of the samples, respectively. Phenibut is another Russian prescription drug that is not authorised in the EU or Australia. As for noopept and phenylpiracetam, bulk quantities of raw material were intercepted. Several research molecules, many for which only *in vitro* and animal data are available, were reported by several OMCLs and they accounted for 8% of the samples. Obviously, it is impossible to determine whether the amount found in these samples reflects a pharmacological dosage. Lastly, 5% of the samples were positive for the unauthorised novel food commodity 5-HTP. 5-HTP may boost serotonin levels and have a positive effect on mood, depression, anxiety, sleep, appetite and pain, although high-quality clinical studies are lacking. There have been reports associating eosinophilia-myalgia syndrome with 5-HTP supplements that may have been contaminated.

7. Conclusions and perspectives

From the results of this study, it is evident that illegal nootropics – in the form of SF medicines, unauthorised raw materials, dietary supplements adulterated with prescription drugs, unapproved drugs, banned substances, unauthorised novel foods and even research chemicals that have not yet initiated clinical trials – are circulating in parts of Europe and Australia. The 13 participating OMCLs reported 159 different samples, 166 molecule identification entries and 34 unique molecules. Given that only a limited number of OMCLs participated in this study, and that the majority of samples originated from customs or law enforcement agencies, which also have their own laboratories, it is likely that this study only highlights a very small fraction of this booming market, and that many more illicit nootropics are in circulation, including in the form of illicit dietary supplements.

In the case of melatonin, five of the 21 samples exceeded the recommended maximum daily amount of 10 mg by at least 20%. One sample contained 20 mg of melatonin. Although a life-threatening melatonin overdose is very rare in adults, high dosages could result in unwanted side-effects such as drowsiness, dizziness, fatigue, headache, confusion, nightmares, hypotension, tachycardia and hypothermia. Nevertheless, lethal melatonin overdoses have been reported in children in the past and care should be taken with these types of products. There is also the question of whether this is part of a more global problem, as melatonin supplements have recently come under scrutiny in the USA.

Unauthorised drugs, such as the Russian prescription drugs noopept, phenylpiracetam and phenibut were also encountered, often in large bulk quantities of raw material. These findings are quite worrying as they reflect not only the personal usage of a single individual, but also suggest more widespread sales and trafficking activity, with products potentially being compounded with malicious intent in the countries participating in the study. Furthermore, research chemicals with limited or no clinical or toxicological data are being used in Europe and Australia and promoted online.

In conclusion, the results of this study illustrate the need for continuous efforts to control not only suspected SF and suspicious raw materials, but also suspicious dietary supplements for their composition. In the latter case, the consumer is likely not aware that they are taking a prescription medicine, an unapproved drug, an unauthorised novel food or even a research molecule for which little to no toxicological data are available. This certainly carries some risk, as the occurrence of any potential adverse effects will not immediately be linked to the supplement by the patient or healthcare professional. In addition, these illegally added substances may interfere with other medicines, with consequences for the development or treatment of existing diseases.