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Artificial intelligence to detect unknown stimulants from scientific literature and media reports

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ABSTRACT

The world market for food supplements is large and is driven by the claims of these products to, for example, treat obesity, increase focus and alertness, decrease appetite, decrease the need for sleep or reduce impulsivity. The use of illegal compounds in food supplements is a continuous threat, certainly because these compounds and products have not been tested for safety by competent authorities. It is therefore of the utmost importance for the competent authorities to know when new products are being marketed and to warn users against potential health risks. In this study, an approach is presented to detect new and unknown stimulants in food supplements using machine learning. Twenty new stimulants were identified from two different data sources, namely scientific literature applying word embedding on > 2 million abstracts and articles from formal and social media on the world wide web using text mining. The results show that the developed approach may be suitable to detect "unknowns" in the emerging risk identification activities performed by the competent authorities, which is currently a major hurdle.

1. Introduction

The global dietary supplements market size was estimated at USD 140.3 billion in 2020 and is expected to expand at an annual growth rate of 8.6% from 2021 to 2028.[1] Factors, such as rising health concerns and the changing lifestyle and dietary habits have been driving this growth in demand.[1] Consumers find supplements attractive to compensate for imbalances of nutrients in their diet or unhealthy lifestyle, and to prevent chronic diseases, among others (Biesterbos et al., 2019). Claims about the benefits of food supplements, and the marketing thereof, are regulated in Europe through directives such as (Ref-2002/46/EC, 2002).

1.1. Overview of supplements market

Food supplements include products such as vitamins, energy drinks, protein drinks, weight loss supplements and exotic or novel foods. A subgroup of food supplements are stimulants, which are agents (e.g., drugs) that produce a temporary increase of the functional activity or efficiency of an organism. Often in the consumer market they are used to treat obesity, increase focus and alertness, decrease appetite or decrease need for sleep (Carroll et al., 2006). Although these compounds are legally regulated, illegal compounds are also sold as food stimulants, such as the banned substance 1,3-DMAA in sport supplements being marketed as an extract of *Aconitum kusnezoffii* (Cohen et al., 2018) . While its consumption may have the intended effect of increasing the muscle mass of an unaware user, serious adverse effects are common (Martin et al., 2018). Not only well-known enhancers are illegally added to supplements, but experimental or even prohibited substances may be used (Cohen et al., 2018).

Because of its market potential and difficulty to control, an increase in adulteration (e.g., adding synthetic compounds or illicit herbal materials) has been observed (Končić, 2018) and a further increase is expected. To obtain an overview of adulteration of food supplements on the Dutch market, the Netherlands Food and Consumer Product Safety Authority (NVWA) analysed samples collected from 2013 to 2018 and observed that 64% of the samples contained one or more unauthorized pharmacological active compounds or plant toxins (Biesterbos et al., 2019). This result demonstrates that regular monitoring of market samples is important to protect public health, but the wealth of potential compounds that can be used and the criminal aspects related to these

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[1] https://www.grandviewresearch.com/industry-analysis/dietary-supplements-market.

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illegal practices, makes this a growing challenge. The database used for screening the samples in the study of Biesterbos et al. contained >1500 compounds (i.e. pharmaceutical substances, adulterants and plant toxins) and is continuously being expanded based on new information and reported adulterations (Biesterbos et al., 2019).

1.2. Proposed approach

In this study, a novel approach is presented to find new compounds that can be used illegally in food supplements and which should be added to the database used for the screening. The focus was on the subcategory "stimulants" of which 428 compounds were present in the reference database.

The first data source explored was scientific literature, where the focus was on compounds that can be used in supplements and have been described in literature. For an expert, it would be unfeasible to read the overwhelming amount of scientific literature available in this topic to find new stimulants that should be added to the monitoring list. However, machine learning has made it possible to gather information automatically from text through natural language processing (NLP) techniques (Chowdhary, 2020). A word embedding model was developed to find unknown stimulants automatically from the scientific literature in this study. A word embedding model captures words in high-dimensional vectors, called embeddings, while preserving syntactic and semantic relationships to other words (Bengio et al., 2003; Mikolov, Corrado, et al., 2013; Pennington et al., 2014, pp. 1532–1543). This results in a model in which related words are closer together in vector space. It is trained in an unsupervised way, meaning that a labelled dataset is not required. The embeddings are learned by looking at what words appear in the same context or co-occur together often. A very good example of how a word embedding model works can be found in the famous example of the embeddings of "King" - "Man" + "Woman" which results in the embedding for "Queen" (Mikolov, Yih, & Zweig, 2013), showing that semantic information is captured by the model in a systematic way. Using such a word embedding model, words that co-occur together with the word "stimulant" can be found, which will be the case for compounds that are described as stimulants in the scientific literature.

The second data source, which is aimed to find new compounds that are already on the market and of which its usage is described on the internet, is the European Media Monitor (EMM). EMM is a news aggregation service operated by the European Commission which is based on text mining, searching the world wide web (official websites, blogs etc.) for news reports 24/7 in 60 languages (Bouzembrak et al., 2018). It consists of 3 platforms being NewsExplorer, NewsBrief, and MedISys, of which the latter displays articles with interest to public health (e.g., diseases, plant pests, psychoactive substances). In this study, MedISys was used to collect publications on new stimulants used or discussed somewhere in the world.

The approach developed in this study yielded new stimulants that potentially can or are illegally used as stimulants in food supplements and which can pose a health risk for the user. The approach was developed for stimulants in food supplements, but the methodology may be applied to any other topic. In emerging risk identification (ERI) as employed by authorities to identify food safety risks at an early stage (Marvin et al., 2009; Meijer et al., 2020), this approach may be suitable to be wider implemented to find "unknowns", which is the major hurdle in ERI.

2. Materials and methods

In this study the list of stimulants present in the reference list of Wageningen Food Safety Research (WFSR), which is used to screen samples from the Dutch Food Safety authority (NVWA), was taken as a starting point. This list was developed over several years and consists of 428 different compounds varying from prescription medicine to prohibited recreational drugs. "Unknown" stimulants are defined as those stimulants that are not included in this reference list.

The approach developed for the identification of unknown stimulant compounds in food supplements consisted of i) "word embedding" of the relevant scientific literature complemented with ii) text mining the world wide web using the MedISys infrastructure.

2.1. Word embedding to detect unknown stimulants from scientific literature

2.1.1. Data collection

The list of 428 stimulants present in the reference database, complemented with their synonyms as found in PubChem,[2] was used to collect scientific publications from Europe PMC[3] for the period 1990–2019. Europe PMC was used as a data source because it is an open-access literature database containing over 38 million abstracts from specifically biomedical and life sciences research articles. Titles and abstracts that contained one or more of the search terms were collected, yielding a total of 2.1 million scientific articles.

2.1.2. Word embedding model

The word embedding model used in this study is the Word2Vec neural network variation created by Tshitoyan et al. (Tshitoyan et al., 2019). They used the word embedding model to predict new thermoelectric materials automatically from abstracts of scientific literature. A Word2Vec model contains three layers (an input, hidden and output layer) and is trained by predicting the probability for each word in the vocabulary that it appears in the context of a specific target word. After training, the word embeddings are set to the learned weights of the hidden layer, where the word embedding of the i'th word in the vocabulary corresponds to the i'th row of the weights. The weights of the output layer are called the output embeddings, where the i'th column embeds the context words of the i'th word in the vocabulary. The code created by Tshitoyan et al. to build and train the Word2Vec model is openly available[4] and was written using Python 3.6. Their code was used to train our own word embedding model.

The 2.1 million titles and abstracts were used as training data for the word embedding model to find related stimulants in the scientific literature that were not present in the list of 428 stimulants. Each title and its respective abstract were concatenated as one data point. These texts were pre-processed by removing uninformative words, like the copyright information or section information (e.g., words like introduction, conclusion) to only retain the words containing the information on the actual research. More pre-processing was done in the framework by Tsitoyan et al. in which words were deaccented and lowercased, unless the word was a chemical formula or abbreviation, and all numbers were converted to a special number token. The model was trained with the hyperparameters as set in the available framework. This meant training a skip-gram neural network with a hidden layer of size 200 with a negative sampling loss, using 15 negative samples, for 30 epochs. Training was done with an initial learning rate of 0.01 which decreased to 0.0001 over time, a context window of 8 and subsampling with a 0.0001 threshold. The Word2vec phrases were created with a phrase count of 10, a score threshold of 15 and a phrase depth of 2. From the trained word embedding model, the words of which the output embedding was closest to the word embedding of the word "stimulant" in the learned vector space were collected. This results in the collection of words that are contextually the most similar to "stimulant" based on their co-occurrence in the training data, including those compounds described as stimulant or mentioned together with words related to stimulants. As in the research by Tsitoyan et al. only words that occur

[2] https://pubchem.ncbi.nlm.nih.gov/.

[3] https://europepmc.org/.

[4] https://github.com/materialsintelligence/mat2vec.

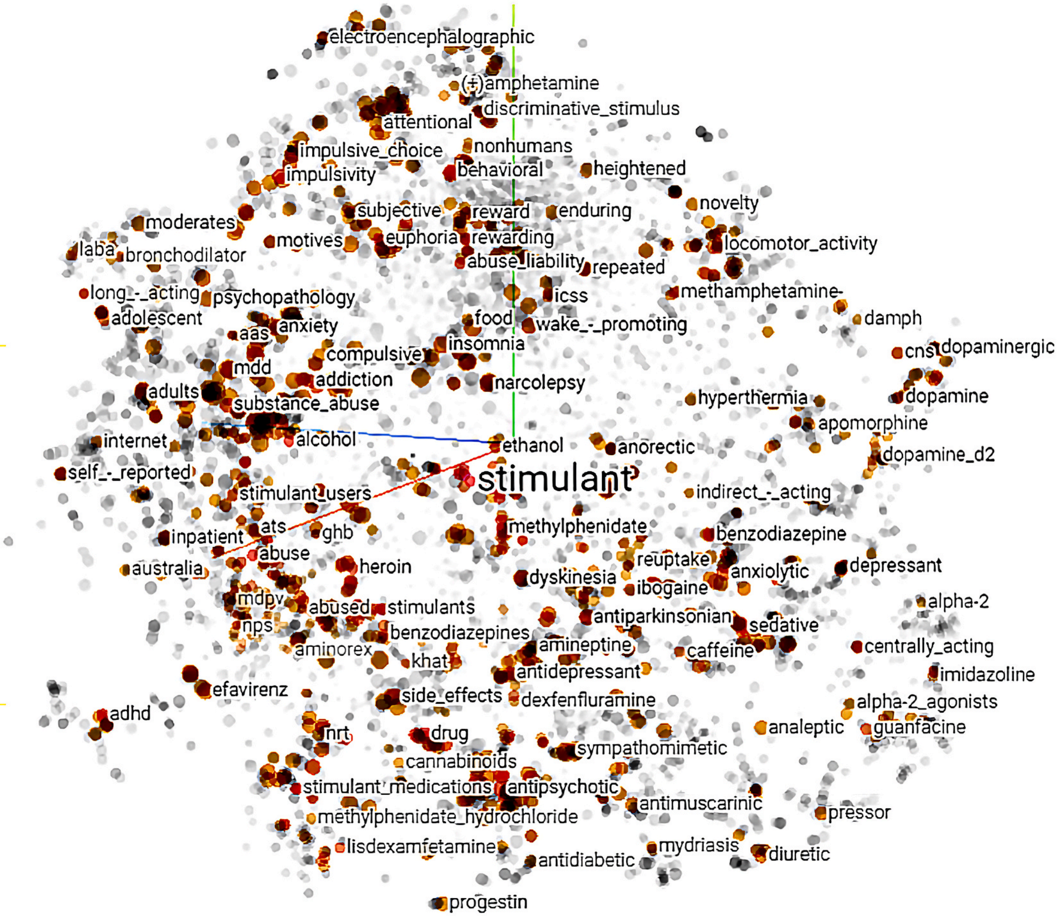


Fig. 1. The word embeddings from the trained model projected in three-dimensional space centralizing the word embedding for "stimulant". A darker colour represents a denser cluster of neighbours. Examples of the neighbouring words are plotted next to their corresponding points in space. The projection was created with t-distributed stochastic neighbour embedding (t-SNE) using cosine distance, a perplexity of 30, a learning rate of 10 and 1000 iterations with the Tensorflow embedding projector (Smilkov et al., 2016). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

more than three times in the training data were considered in order to have a more accurate representation of the data. Furthermore, since this study focused on finding stimulants, all words that were not chemical compounds were removed from the collected set by checking the words against the PubChem database. As a last step, the stimulants from the existing reference database together with their synonyms were also removed from the set, leaving only possible new stimulants. The top 50 compounds from this set were evaluated by an expert for their validity.

2.2. A MedISys text mining model to detect unknown stimulants on the world wide web

The MedISys infrastructure does not collect publications on the world wide web on stimulants in food supplements specifically and therefore must be trained for this purpose. This includes the development of a dedicated filter to find publications of interest followed by a validation step to reduce the extent of "noise" (irrelevant publications). WFSR has special permission from the owner (Joint Research Centre) to develop filters on the MedISys infrastructure.

2.2.1. Developing a filter for stimulants in food supplements on the MedISys infrastructure

The construction of a filter in MedISys for stimulants was done according to the steps defined in (Bouzembrak et al., 2018) and consists of the following 3 steps: (i) development of a set of keywords, (ii) creating a new filter in MedISys for stimulants based on the defined set of keywords, and (iii) evaluation and improvement of the performance of the newly developed filter.

Step 1. All stimulants present in the WFSR database (i.e. 428 chemical names) were combined with and without the words "similar", "replace", "stimulants", "supplements", "food supplements", and "new stimulants". These keywords were added to increase the chance to find articles that describe new unknown compounds other than those present in the reference database and used as keywords. Only English terms were used.

Step 2. A new filter was created in MedISys in which the developed set of keywords were integrated (Bouzembrak et al., 2018).

Step 3. The filter was tested over a period of 6 months in which the performance (i.e., % of relevant articles collected) was examined by an expert and keywords were adjusted to improve its performance. For example, by identifying keywords that should be excluded or if a keyword should appear together and in the same order. These keywords were combined in the article with "+" as a symbol used (e.g., "food supplements" was converted to "food + supplements"). After two iterations, the filter reached a relevance level of 78%, which is considered optimal. This optimized filter was run for one year (July 2018 to end of June 2019) and the collected publications (i.e., 806 articles) were evaluated by an expert. Stimulants other than those in the reference set were recorded.

Since the reports collected and presented on the MedISys system are only visible as long as these reports are available on the original location, an automatic retrieval system was created that retrieves the collected reports from the MedISys website and stores them on a data

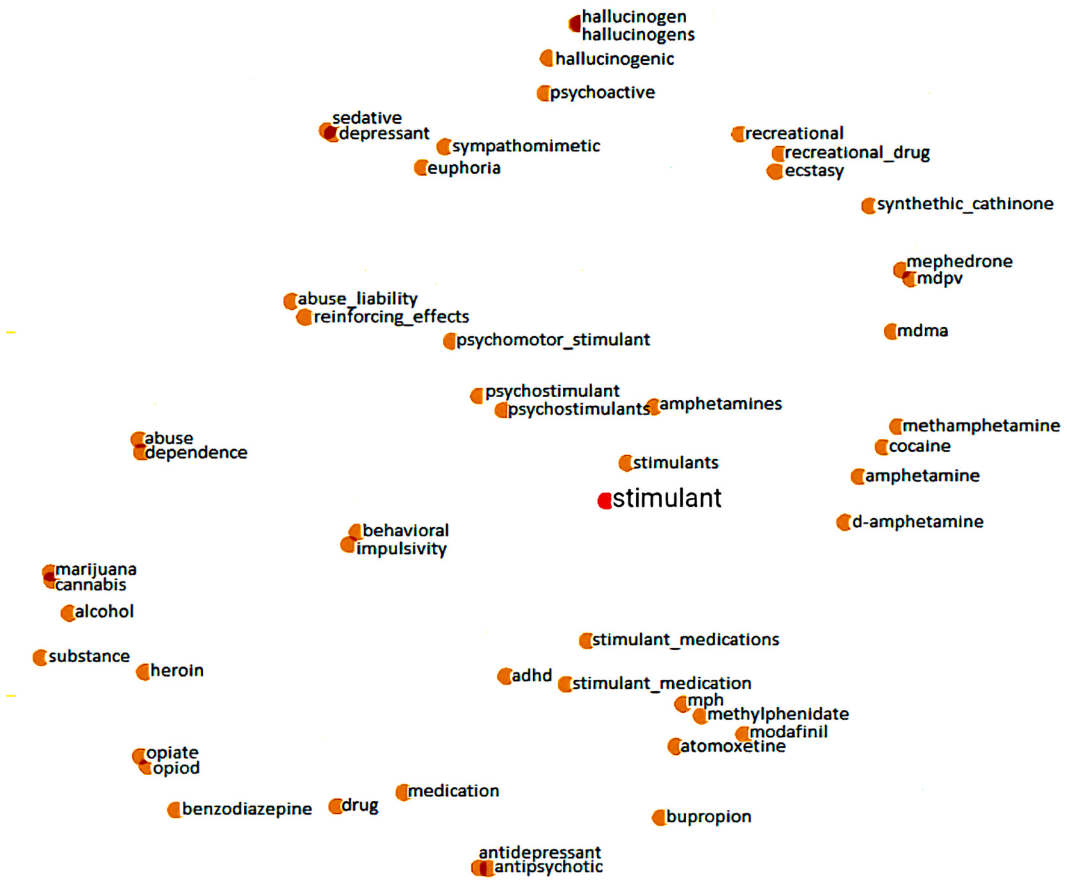


Fig. 2. The word embeddings of the word “stimulant” and its closest 50 neighbours taken from the trained word embedding model projected in two-dimensional space. The projection was created with t-distributed stochastic neighbour embedding (t-SNE) using cosine distance, a perplexity of 5, a learning rate of 10 and 5000 iterations with the Tensorflow embedding projector (Smilkov et al., 2016).

infrastructure at WFSR for further analysis. To this end, a script was developed in Python 3.6, which is run on the WFSR infrastructure inside a Docker container on an OpenShift cluster. This system collects new articles from the MedISys website once every 6 h. The data is stored in an Elasticsearch 7.1 database hosted on a cloud infrastructure at WFSR and visualised in a dashboard using Kibana software.

The data available for each report on MedISys includes the country of origin, the date, the time of collection by MedISys, the keywords present in the article, the source of the article, a link to the original website, and an automatically generated summary. If the original article was not written in English, a translation of the article title and of the automatically generated summary was produced using the Google Translate API and stored alongside the original text.

3. Results & discussion

3.1. Detection of unknown stimulants from the scientific literature using word embedding

From the trained word embedding model, the collection of words that in vector space were closest to the vector of the word “stimulant” were collected. In Fig. 1, a three-dimensional representation of the trained word embedding space is shown. The projection presented centralizes the word embedding for “stimulant” and shows the top 1000 nearest neighbours in colour. Examples of the neighbouring words are plotted next to their corresponding points in space. In Fig. 2, a two-dimensional projection of the word embeddings for “stimulant” and its closest 50 neighbours are presented. Analysing these figures reveals that the word embedding model has been successful in learning which words appear in a similar context to the word “stimulant”. From Fig. 2 it can also be seen more clearly that semantically related words get placed closer together in vector space, resulting in small clusters of similar words.

From the collections of words closest to the word “stimulant”, only the words that were chemical compounds were saved. The known stimulants from the reference database were removed and the remaining 50 highest ranking compounds (see supplement 1) were analysed for possible new stimulants by an expert in food supplement safety. Many of the top 50 compounds were upon inspection discarded as a possible new stimulant for several reasons. The first being that some of the found compounds were not meant as a compound in this context. Examples of this are “Hallucinogen” or “CNS”, both have an entry in PubChem as a synonym of a compound, but it is obvious that in this case the words have a different meaning. Hallucinogens are next to stimulants a different class of drugs, while CNS stands for central nervous system. For both it is very logical that the words co-occur together with the word stimulant. Other reasons for exclusion are that the compounds are not registered synonyms in PubChem for stimulants already in the known list of stimulants (e.g., Lisdexamfetamin or Cath), that they are salts or known metabolites of the existing stimulant list (e.g., N-Cyanomethylmethamphetamine or Dl-Threo-Methylphenidate) or that the compounds are not considered stimulants (Fursultiamine or 2,2,2-Trichloroethyl Chloroformate). For the latter case, the found compounds are often used together with stimulants or their structures are similar to a specific stimulant which makes them a suitable treatment for addiction of that stimulant, which explains their co-occurrence with the word stimulant.

After removing the excluded compounds, a list of fourteen new

Table 1
List of newly identified unknown stimulants from scientific literature.

Stimulant name	Description
2-Benzhydrylpiperidine	2-Benzhydrylpiperidine, also known as desoxypipradrol or 2-DPMP, is a drug which acts as a norepinephrine-dopamine reuptake inhibitor. It is used as a recreational drug, but because of its toxicity and adverse health-effects it is already being controlled in some countries (Corkery et al., 2012).
RTI-98	RTI-98, also known as nor-beta-CIT, is a drug closely related to cocaine. It acts as an uptake inhibitor of dopamine, norepinephrine and serotonin. RTI-98 is mainly used in scientific research as it can be used to assess the density of serotonin transporters in the brain well (Joensuu et al., 2007; Tolliver & Carney, 1995).
N-methyl-2-AI	N-methyl-2-AI, also known as N-methyl-2-aminoindane or NM-2-AI, is an analogue of amphetamine, and works as a dopamine and norepinephrine releasing agent. It is being sold as a designer drug, but little is known about its toxicity (Manier et al., 2020; Mestria et al., 2020).
5-(2-Aminopropyl)Indole	5-(2-Aminopropyl)Indole, also known as 5-IT or 5-API, is a designer drug working as a dopamine, norepinephrine and serotonin releasing agent. The compound is an indole derivative and isomer of alpha-methyltryptamine. Because of the high risk for abuse and possible adverse health effects it has been banned in most western countries (Katselou et al., 2015; Marusich et al., 2016).
Ethylphenidate	Ethylphenidate is a psychoactive substance that is an analogue of methylphenidate (Ritalin). It works similarly to methylphenidate and is a dopamine and norepinephrine releasing agent. It is used as a recreational stimulant. Because of severe adverse health effects, it has been banned in several countries (Maskell et al., 2016; Parks et al., 2015).
D2PM	D2PM, also known as diphenylprolinol, is a psychoactive designer drug that is a norepinephrine-dopamine reuptake inhibitor. D2PM is a pyrrolidine analogue and acts similarly to cocaine. It has been established that it produces toxic effects in humans, but is still available as a 'legal high' (Wood & Dargan, 2012).
(+)-UH232	(+)-UH232 is an aminotetralin derivative. It is considered a weak stimulant and acts as a mixed agonist-antagonist for dopamine receptors. (+)-UH232 has been mainly used in scientific research as it can be used to assess the role of dopamine receptors in the brain well (Kling-Petersen et al., 1994).
7-(beta-Chloroethyl) Theophylline	7-(Beta-Chloroethyl)Theophyllin, also known as 7-(2-chloroethyl)Theophylline or 7-CET, is a derivative of the natural compound theophylline and is an adenosine receptor antagonist. The effect is similar to caffeine, but more potent (Coffin & Spealman, 1989).
N-Methyl-3-Phenyl-Norbornan-2-Amine	N-Methyl-3-Phenyl-Norbornan-2-Amine, also known as Camfetamine, is closely related to fencamfamine, but it has a stronger stimulating effect. The compound works as an indirect dopaminergic agonist. It is sold as a designer drug and is mostly unregulated. Little is known about the potential health risks related to its use (Cinosi et al., 2014).
Paraxanthine	Paraxanthine, also known as 1,7-Dimethylxanthine, is a derivative of xanthine and metabolite of caffeine, with similar stimulating properties. It acts as an antagonist for adenosine receptors (Benowitz et al., 1995).

stimulants is left. Of this list two stimulants were merged with other stimulants in the list, because they were synonyms of each other (2-Benzhydrylpiperidine = Desoxypipradrol and 5-(2-Aminopropyl)Indole = 5-IT). The remaining twelve stimulants were judged for the possibility of being added to food supplements. Two of the stimulants, 6-Hydroxytrypargine and Oxolinic Acid, were considered not relevant for food supplements as the former is a spider toxin and the latter is in use as an antibiotic. The other ten stimulants were considered relevant to include in the stimulant database and are shown in Table 1, including a short description.

3.2. Detection of unknown stimulants from formal and social media using MedISys

Within MedISys, a filter was created to collect publications worldwide on unknown stimulants in food supplements. This filter was applied in the period July 2018 to June 2019. The collected articles were transferred from the MedISys to a cloud infrastructure, where it is stored for further analysis. Information on the collected articles is shown in a dashboard with interconnected panels (Fig. 3). As shown in Panel 1 of Fig. 3, in this period, 806 articles were collected and a considerable variation was observed in the number of articles per week in the period analysed (Panel 2 of Fig. 3).

The articles originated from many countries (i.e. 49, see Panel 5 of Fig. 3), but the majority came from United States (68%) followed by United Kingdom (7%), India (2.6%), the Netherlands (2.6%) and Australia (1.6%). Most of the articles (i.e. 67%) were associate with keyword "similar" followed by keyword "MDMA" (47%), "stimulant" (30%) and "supplement" (12%) (Panel 3 of Fig. 3). To visualise the content of the collected articles (i.e., titles and abstracts) a co-occurrence network visualisation was prepared (Fig. 4).

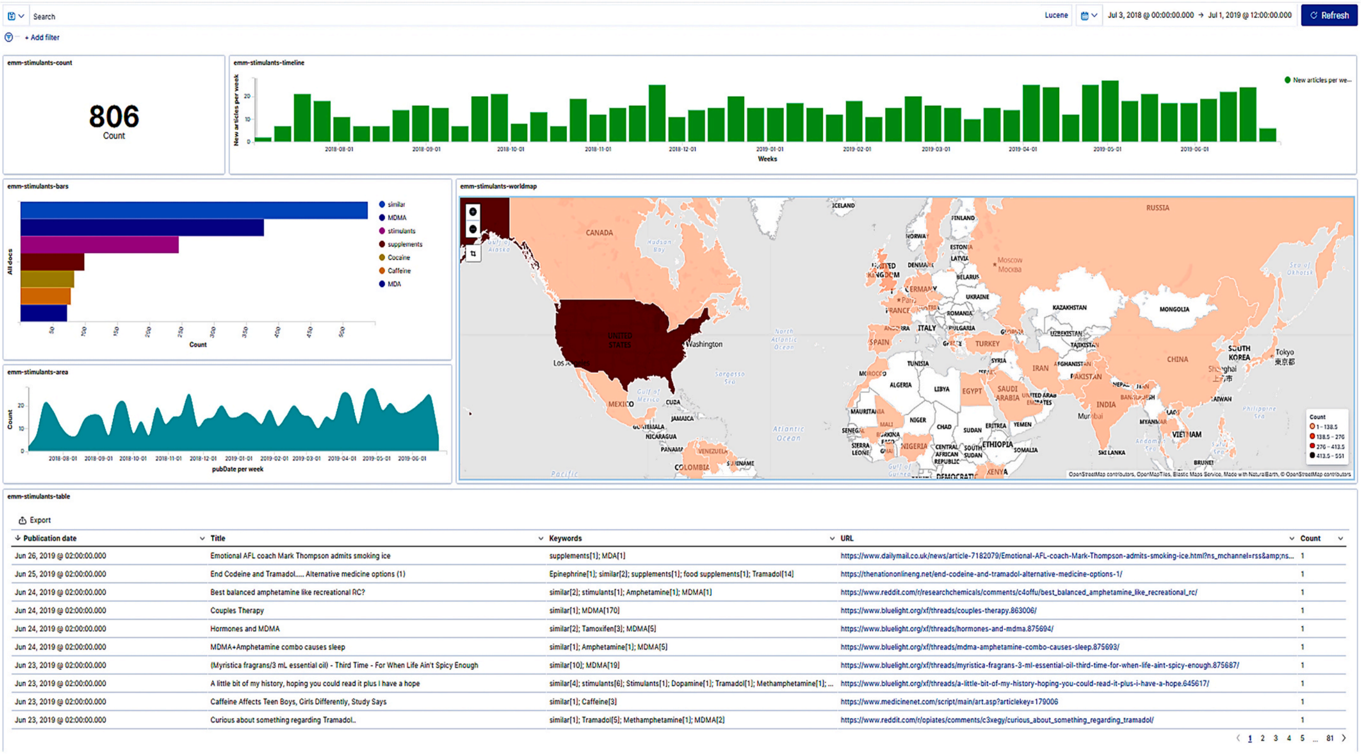
In the network, each circle represents a word and the size indicates the number of times it was mentioned in the title and abstracts. The words that co-occur often are located closer to each other in the network. Five groups can be distinguished, which are indicated in different colours in Fig. 4. The groups are centred around the words: (i) use, (ii) report, (iii) week/hour, (iv) supplement and (v) ecstasy.

All articles collected were analysed by an expert on food supplements with the focus to find other stimulants than those included in the reference database. Articles that were associated with the keyword "similar" (i.e. 538) are of special interest because these may mention new, unknown stimulants. This evaluation yielded in total 27 possible unknown stimulants (see Supplement 2). Upon closer inspection some of the compounds were identified as synonyms of each other and were therefore merged together. Further assessment revealed that eleven of the remaining compounds found could not be classified as stimulants, but rather were drugs with different properties (e.g., hallucinogenic or dissociative). These compounds were consequently removed from the list of possible stimulants. Ultimately, this resulted in a final list of ten unknown stimulants and are shown in Table 2, including a short description.

3.3. Comparison of the methodologies to detect unknown stimulants

It is remarkable that both methodologies yielded completely different new stimulants, indicating that these methods are complementary. One could expect that compounds being developed and discussed in the scientific literature would proceed the application in products that are on the market. To verify this, the stimulants found online in media were first checked against the top 250 possible stimulants from the word embedding to see if they had been ranked lower than the top 50 that was checked by the expert, but were still relatively contextually close to the word "stimulant". Only one of the stimulants appeared in the top 250: 3-Fluorophenmetrazine (3-Fpm) which was number 123. Next, the remaining stimulants found in online media were searched in the corpus that the word embedding model was trained on. All stimulants except methamnetamine were present in the corpus, which is a logical consequence of the fact that there is very little

[5] www.vosviewer.com.



Publication date	Title	Keywords	URL	Count
Jun 26, 2019 @ 02:00:00.000	Emotional AFL coach Mark Thompson admits smoking ice	supplements[1]; MDA[1]	https://www.dailymail.co.uk/news/article-7182079/Emotional-AFL-coach-Mark-Thompson-admits-smoking-ice.html?ns_mchannel=rss&amp;ns...	1
Jun 25, 2019 @ 02:00:00.000	End Codeine and Tramadol..... Alternative medicine options (1)	Epinephrine[1]; similar[2]; supplements[1]; food supplements[1]; Tramadol[14]	https://thenationonlineng.net/end-codeine-and-tramadol-alternative-medicine-options-1/	1
Jun 24, 2019 @ 02:00:00.000	Best balanced amphetamine like recreational RC?	similar[2]; stimulants[1]; Amphetamine[1]; MDMA[1]	https://www.reddit.com/r/researchchemicals/comments/c4offu/best_balanced_amphetamine_like_recreational_rc/	1
Jun 24, 2019 @ 02:00:00.000	Couples Therapy	similar[1]; MDMA[170]	https://www.bluelight.org/xf/threads/couples-therapy.863006/	1
Jun 24, 2019 @ 02:00:00.000	Hormones and MDMA	similar[2]; Tamoxifen[3]; MDMA[5]	https://www.bluelight.org/xf/threads/hormones-and-mdma.875694/	1
Jun 24, 2019 @ 02:00:00.000	MDMA+Amphetamine combo causes sleep	similar[1]; Amphetamine[1]; MDMA[5]	https://www.bluelight.org/xf/threads/mdma-amphetamine-combo-causes-sleep.875693/	1
Jun 23, 2019 @ 02:00:00.000	(Myristica fragrans/3 mL essential oil) - Third Time - For When Life Ain't Spicy Enough	similar[10]; MDMA[19]	https://www.bluelight.org/xf/threads/myristica-fragrans-3-ml-essential-oil-third-time-for-when-life-aint-spicy-enough.875687/	1
Jun 23, 2019 @ 02:00:00.000	A little bit of my history, hoping you could read it plus I have a hope	similar[4]; stimulants[6]; Stimulants[1]; Dopamine[1]; Tramadol[1]; Methamphetamine[1]; ...	https://www.bluelight.org/xf/threads/a-little-bit-of-my-history-hoping-you-could-read-it-plus-i-have-a-hope.645617/	1
Jun 23, 2019 @ 02:00:00.000	Caffeine Affects Teen Boys, Girls Differently, Study Says	similar[1]; Caffeine[3]	https://www.medicinenet.com/script/main/art.asp?articlekey=179006	1
Jun 23, 2019 @ 02:00:00.000	Curious about something regarding Tramadol..	similar[1]; Tramadol[5]; Methamphetamine[1]; MDMA[2]	https://www.reddit.com/r/opiates/comments/c3xegy/curious_about_something_regarding_tramadol/	1

Fig. 3. Dashboard showing, in various panels, information of the collected articles. Panel are numbered from left to right, top to bottom. Panel 1: Total number of articles collected. Panel 2: Number of articles per week. Panel 3: Number of articles collected with a defined keyword. Panel 4: World map showing the number of articles per country. Panel 5: Table with the hyper link to the original location of the articles.

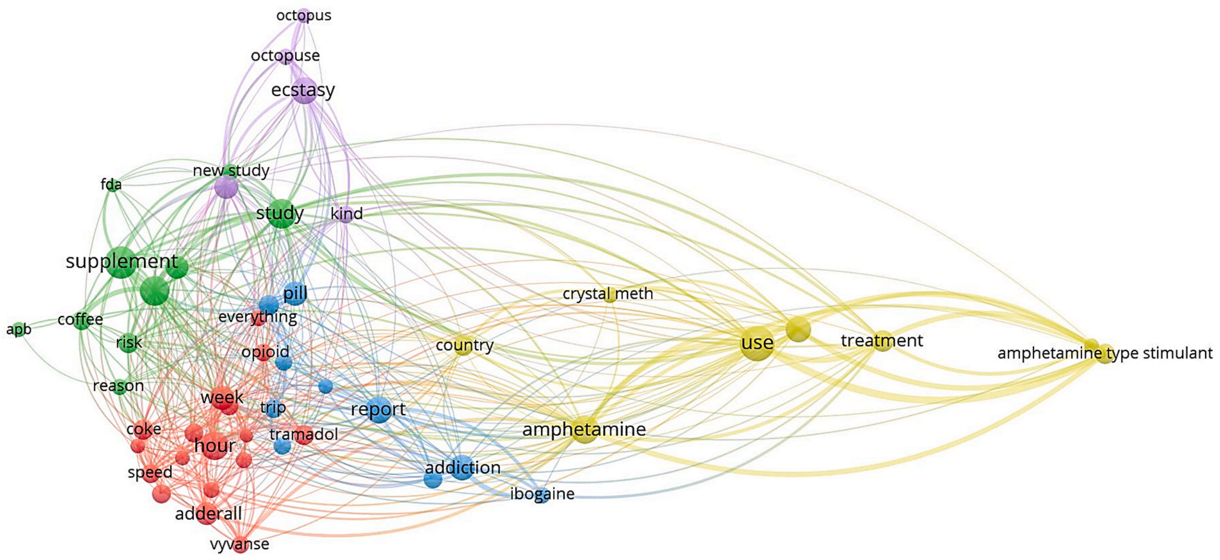


Fig. 4. Network visualisation of the titles and abstracts. The network was created with VOSviewer,[5] only the top 50 terms that were mentioned at least 13 times are shown.

scientific literature to find about methamnetamine. The frequency of being present in an abstract varied across the rest of the stimulants, but for almost all the occurrence ranged between 1 and 30 times. Dextromethorphan was an exception to this, the compound was present in 1293 abstracts. Dextromethorphan has been researched extensively as a treatment for a variety of health conditions or in the context of drug metabolism, but only around 20 abstracts discussed its psychoactive properties. Upon inspection of the scientific abstracts containing the stimulants found in media, it became apparent that they were not described as stimulants, but rather as new psychoactive substances (NPS). NPS are a group of compounds often known as designer drugs or "legal highs" that can be categorised as cannabinoids, stimulants, depressants and hallucinogens (Shafi et al., 2020). It appeared that, when scientific literature discusses new drugs that are being recreationally used or abused, which currently is where these stimulants occur most in literature, the distinction between the different categories of NPS is seldom made and their individual properties are not described in the abstract. Unless the corpus contains literature stating (indirectly) the

Table 2
List of unknown stimulants collected from media on the world wide web by MedISys.

Stimulant name	Description
25C-NBOMe	25C-NBOMe, also known as N-(2-methoxybenzyl)-2-(4-chloro-2,5-dimethoxyphenyl)ethanamine, is a derivative of the phenethylamine 2C-C. Next to the hallucinogenic effects the NBOMe drugs are known for, 25C-NBOMe also has a stimulating effect comparable to MDMA. It is a partial agonist of 5-HT2A receptors. It has a high risk of acute toxicity, and fatalities by 25C-NBOMe have been reported. 25C-NBOMe has been a worldwide controlled substance since 2015 (Bersani et al., 2014; Wohlfarth et al., 2017).
25I-NBOMe	25I-NBOMe, also known as 2-(4-Iodo-2,5-dimethoxyphenyl)-N-((2-methoxyphenyl)methyl)ethanamine, is a derivative of the phenethylamine 2C-I. Similar to 25C-NBOMe, although known for its hallucinogenic effects, 25I-NBOMe has been shown to have stimulating properties. It is a full agonist for the 5-HT2A receptor. Usage may lead to severe clinical toxicity in its users. 25I-NBOMe has been a worldwide controlled substance since 2015 (Hill et al., 2013; Wohlfarth et al., 2017)..
6-APB	6-APB, also known as 6-(2-aminopropyl)benzofuran, is a designer drug with both hallucinogenic and stimulant properties. It is both an uptake inhibitor and releasing agent of dopamine, norepinephrine and serotonin and acts as an agonist of 5-HT2A and 5-HT2B receptors. Because of the interaction with 5-HT2B receptors, 6-APB is cardiotoxic with long-term use, but also has the potential for acute toxicity. It is a controlled substance in several countries, but remains one of the most sold new psychoactive substances in Europe (Brandt et al., 2020; Chan et al., 2013; Roque Bravo et al., 2020).
5-APB	5-APB, also known as 5-(2-aminopropyl)benzofuran, is similarly to 6-APB a designer drug with hallucinogenic and stimulant properties. It is both an uptake inhibitor and releasing agent of dopamine, norepinephrine and serotonin and acts as an agonist of 5-HT2A and 5-HT2B receptors. Because of the interaction with 5-HT2B receptors, 5-APB is cardiotoxic with long-term use, but also has the potential for acute toxicity and seems to be more toxic than 6-APB. It is only controlled in a few countries. (Brandt et al., 2020;Roque Bravo et al., 2020; Welter et al., 2015).
5-MeO-DALT	5-MeO-DALT, also known as N,N-Diallyl-5-methoxytryptamine, is mostly used as a hallucinogenic drug, but drug users also report more energy, euphoria and arousal when taking it. Little information can be found in scientific literature about its exact stimulant mechanisms in humans. Research has shown, however, increased locomotor activity in rodents when administrating 5-MeO-DALT. It is a controlled substance in several countries (Corkery, Durkin, et al., 2012; Gatch et al., 2017).
Dextromethorphan	Dextromethorphan, also called DXM, is a cough medicine which has been used since the 1950's. Abuse of dextromethorphan has been frequent, because of its stimulating and psychoactive properties. It acts as a serotonin reuptake inhibitor and is a NMDA receptor antagonist. Dextromethorphan has minimal adverse reactions at low doses, but when taken frequently and in higher doses can lead to severe intoxication (Logan et al., 2009; Reissig et al., 2012; Schwartz et al., 2008).
5-MeO-MiPT	5-MeO-MiPT, also called moxy, is a psychedelic with stimulant properties. It inhibits the re-uptake of 5-HT, dopamine and norepinephrine. The toxicity is still relatively unknown, but recent research showed evidence of acute toxicity in mice when given a high dose. 5-MeO-MiPT is still uncontrolled in large parts of the world (Altuncı et al., 2021; Repke et al., 1985).
3-Fpm	3-Fpm, also known as 3-Fluorophenmetrazine, is a designer drug. It is a derivative of phenmetrazine. 3-Fpm is a norepinephrine-dopamine releasing agent. The toxicity of 3-Fpm has not been studied well at the moment of writing, although reports of severe adverse effects in human users have already been reported. It has been made a controlled substance in a few countries (Bäckberg et al., 2016; Fawzy et al., 2017; Mayer et al., 2018).
N-Ethylhexedrone	N-Ethylhexedrone, also known as Hexen, is a designer drug with stimulant properties similar to amphetamine. It is a synthetic cathinone and acts as a norepinephrine-dopamine reuptake inhibitor. There is limited data available in the scientific literature about the toxicity of N-ethylhexedrone in humans, but fatal N-ethylhexedrone intoxications have already been reported and recent research has shown toxicity in vitro. N-Ethylhexedrone is an internationally controlled substance since 2020 (de Mello-Sampayo et al., 2021; Domagalska et al., 2021; ECD, 2020; Majchrzak et al., 2018).
Methamnetamine	Methamnetamine, also known as MNA or PAL-1046, is an analog of methampethamine and has similar stimulant properties. It is being sold as a designer drug and acts as a releasing agent of serotonin, norepeniphrine and dopamine. There is very little scientific literature available about methamnetamine and its toxicity, but it is currently being detected in drug screenings across Europe. Methamnetamine is an uncontrolled substance in most countries (Lajtai et al., 2020; Richeval et al., 2019; Rothman et al., 2012).

stimulant properties of a compound or by comparing the compound to a known stimulant, the word embedding model will not associate the compound strongly with the word 'stimulant'. In media, however, these designer drugs are often described together with their effects, which makes it easier to extract the stimulating ones. Media can thus best be used to identify stimulants that are new and up-and-coming among recreational drug users, and scientific literature can identify the stimulants that through research have been discovered to have those properties or stimulants that are established enough in the recreational drug world to have been the specific target or research.

3.4. *Limitations of the approach*

In the approach developed here, the reference list of the stimulant database was taken as a starting point, and therefore determines the outcome of the analysis. A word embedding model that is purely machine driven may also be too narrow to understand why and how markets tend to adapt which is generally influenced by parameters such as costs, availability of resources and the law and order situation of a country. Compounds found that are not on the reference list were considered as "unknown" in this study. It is clear that for other controlling organisations that have a different reference list, "unknown" compounds may be labeled differently. Another limitation is that in the scientific literature approach, only English literature was considered. English was also the dominant language in the online media dataset, but articles written in other languages, including Spanish, Chinese and Arabic, were also collected, translated and analysed. Many of the keywords, being chemical names or acronyms, were universally found across multiple languages, whereas other keyword such as "similar" require the addition of a suitable translation to the filter. An additional technical challenge in this field is the transliteration of characters between English and Arabic and Chinese character sets. To be able to search in these languages natively, the keywords need to be translated into the right characters. It is evident that especially for the methodology to search in online media, more unknown stimulants may be found when more languages are included. For example in China and Latin America where many new developments around stimulants have appeared in the last few years (INCB, 2020). In addition, other websites and databases that are more dedicated to publications on stimulants could be queried in addition to the MedISys search engine. A last limitation is that, currently, in both methodologies an expert must assess the results delivered by the systems. This is a time-consuming activity and preferably should be automated in the future.

4. Conclusions

In this study, it was shown that word embedding using scientific literature and text mining of the online media may both be used to detect new compounds that were unknown as stimulant in food supplements. In total 20 new compounds were found and many of these may cause adverse health effects when consumed. Remarkably, both data sources and associated methodologies yielded different compounds, hence showing the complementary nature of the two sets of data and the necessity to analyse both the scientific literature and the online media. It is suggested that the developed approach can be used in other topics to find highly relevant but hitherto unknown for their (potential) use. This approach may in particularly be relevant for food safety authorities in their emerging risk identification activities to detect new compounds that may pose a health risk to consumers.

CRediT authorship contribution statement

Anand K. Gavai: Conceptualization, Methodology, Writing – review & editing, Writing – original draft. **Yamine Bouzembrak:** Conceptualization, Methodology, Writing – review & editing, Writing – original draft. **Leonieke M. van den Bulk:** Methodology, Writing – review & editing, Visualisation, Validation, Writing – original draft. **Ningjing Liu:** Data curation, Writing – review & editing. **Lennert F.D. van Overbeeke:** Data curation, Writing – review & editing. **Lukas J. van den Heuvel:** Writing – review & editing. **Hans Mol:** expert domain knowledge, Validation, Writing – review & editing. **Hans J.P. Marvin:** Conceptualization, Methodology, Writing – review & editing, Writing – original draft.

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Appendix A. Supplementary data

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