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Trends in drug substances detected in illegal weight-loss medicines and dietary supplements

A 2002-2007 survey and health risk analysis

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A 2002-2007 survey and health risk analysis

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Abstract

Trends in drug substances detected in illegal weight-loss medicines and dietary supplements

A 2002-2007 survey and health risk analysis

Illegal weight-loss products identified in the Netherlands have become increasingly dangerous from 2002-2007. Analyses showed increasing numbers of counterfeit medicines and of dietary supplements adulterated with drug substances. In addition, herbal ingredients that were banned for safety concerns are being replaced by pharmaceutical drugs. Unknowing use of these products may lead to psychosis, cardiovascular problems and even to death. This is shown by a trend analysis on 256 suspect samples gathered by four national laboratories in the Netherlands, including the RIVM.

Internationally, the use of illegal weight-loss medicines and dietary supplements has led to many cases of serious health damage and occasionally even to death. Because the active ingredients detected in the Netherlands are largely the same as those found in other countries, similar events may occur in this country. It is therefore recommended to register such health complaints in order to gain insight into the scale and severity of the problem.

Adulterated dietary supplements pose the highest health risks. Because the medicines used in the product are not mentioned on the labels, consumers are kept unaware of the risks. Consumers assume they are taking a natural product but are unwittingly exposed to dangerous medicines. If adverse effects cannot be readily attributed to an adulterated dietary supplement, adequate medical treatment may be delayed. Health risks are also high for counterfeit medicines because their composition and quality are unreliable and they are taken without prescription.

Key words:

slimming, weight-loss, dietary supplements, health risk, illegal, counterfeit

Rapport in het kort

Trends in werkzame stoffen aangetroffen in illegale afslankmiddelen

Een overzicht van 2002-2007 en van gezondheidsrisico's

In Nederland aangetroffen illegale afslankmiddelen zijn tussen 2002 en 2007 gevaarlijker geworden. Steeds vaker betreft het vervalsingen van echte medicijnen en voedingssupplementen waaraan illegaal geneesmiddelen zijn toegevoegd. Ook blijken de na 2004 verboden afslankkruiden (efedrines) te worden vervangen door geneesmiddelen (bv. sibutramine). Onkundig gebruik kan leiden tot psychoses, hart- en vaatproblemen en zelfs tot de dood. Dit blijkt uit een trendanalyse op 256 verdachte monsters bijeengebracht door vier nationale laboratoria in Nederland, waaronder het RIVM.

Internationaal heeft het gebruik van illegale afslankmiddelen veel gevallen van ernstige gezondheidsschade veroorzaakt en soms zelfs tot de dood geleid. Omdat de in Nederland aangetroffen werkzame bestanddelen overwegend dezelfde zijn als in andere landen, kunnen soortgelijke effecten ook hier optreden. Een goede registratie van deze gezondheidsklachten wordt aanbevolen om oog te krijgen voor de ernst en de omvang van het probleem.

Gezondheidsrisico's zijn het hoogst bij vervalste voedingssupplementen. Doordat de aanwezige geneesmiddelen doelbewust niet op de etiketten staan vermeld, is de consument zich niet bewust van de risico's. Consumenten denken voor een natuurlijk product te kiezen, maar worden onbewust blootgesteld aan gevaarlijke geneesmiddelen. Als bijwerkingen niet snel worden toegeschreven aan een vervalst voedingssupplement, kan dat adequate medische behandeling vertragen.

Gezondheidsrisico's zijn ook hoog voor namaak medicijnen omdat de samenstelling en kwaliteit onbetrouwbaar zijn en ze zonder een recept van een arts worden gebruikt.

Trefwoorden:

afslanken, afvallen, voedingssupplementen, gezondheidsrisico, illegaal, vervalsing

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Summary

In order to survey the drug substances used in illegal weight-loss medicines and dietary supplements from 2002-2007, a database of suspect products was constructed based on the analyses of four Dutch laboratories. Each laboratory contributed suspect weight-loss products that had been brought in for analysis by the Dutch inspectorates, customs, police or local pharmacists.

A total of 256 suspect weight-loss products were included in the collective database, 83% of which were dietary supplements and 17% were medicines confiscated outside the official distribution chain. In 90% of the weight-loss products one or more drug substances were identified. A total of 20 different drug substances were identified, mostly ephedrine and sibutramine in moderate to high dosages (Table 2). The weight-loss drugs identified are associated with serious adverse effects and have also been frequently identified in weight-loss products in other countries. In an attempt to assess adverse effects in the Netherlands, a national database was accessed for information on potential intoxications after exposure to weight-loss products.

Over the period 2002-2004, the database consisted mainly of suspect dietary supplements and a few suspect medicines. The majority of the dietary supplements contained ephedrine, which was legal at that time despite concerns over health risks. After the ban on ephedrine in the Netherlands in 2004, ephedrine remained the predominant drug substance identified in the database of suspect weight-loss products. Although ephedrine was identified less frequently, this was compensated for by an increase in dietary supplements secretly containing sibutramine or designer analogues. Such adulterated dietary supplements are deliberately mislabelled products that claim to be 'all natural' yet contain pharmaceutical drug substances.

Another trend observed is the increase in counterfeit weight-loss medicines after 2004. Counterfeit medicines generally either contained the wrong drug substance or the correct substance in a lower dose. In addition to a weight-loss drug, counterfeit medicines occasionally also contain the laxative phenolphthalein, which was withdrawn following concerns over its carcinogenicity.

Information on potential intoxication after exposure to weight-loss products showed that most cases were related to products claiming to contain ephedrine. After the ban on ephedrine, the number of potential intoxications with ephedrine decreased. However, the number of potential intoxications with alleged ephedrine-free weight-loss products and 'unknown' weight-loss products increased. Although none of these products were actually analysed, it is assumed that these products contained ephedrine or sibutramine. Trends in potential ephedrine intoxication for all ages proved to be similar to trends in young children (<13 years old), suggesting that these children have easy access to these products.

The overall health risks of illegal weight-loss medicines and dietary supplements have increased with the rise in counterfeit medicines and adulterated dietary supplements. Consumers of these products are unaware of which drug substance they are taking and how much of it, as are their physicians. In the case of adulterated dietary supplements, consumers are not even aware they are taking a drug substance. In some countries, the provision of adequate medical assistance has been hampered by the inability of consumers and physicians to recognize the adverse health effects associated with adulterated dietary supplements.

1 Introduction

Weight-loss medicines are among the most prominently marketed health products outside the official medicines distribution chain. This market is fed by the growing discord between an overweight Western society, the contemporary ideal figure and the restrictive prescribing of weight-loss medicines. Because weight-loss drugs have reputedly high health risks, their presence in counterfeit medicines and dietary supplements is worrying.¹ This report presents a health risk analysis, based on a database of suspect weight-loss medicines and dietary supplements analysed from 2002-2007. Further information was gathered by searching scientific literature and databases for reports on weight-loss medicines and dietary supplements regarding chemical analysis and exposures / adverse events.

This report intends to provide an overview of the drug substances identified in suspect weight-loss products, to discuss the consequences for public health and to make recommendations. This report does not investigate the quality or efficacy of suspect samples, nor were all declared ingredients verified for their presence.

In the Netherlands, all medicines are subject to the Medicines Act. The Medicines Act is based on European Law defining a medicine to be a formulated product that either contains a drug substance or is presented as a medicine by appearance or claim. A medicine may cure or prevent disease or may act as a prophylactic. However, a formulated product containing a drug substance is only subject to the Medicines Act after a court of justice has decided it is a medicine.

Dietary supplements are subject to the Commodities Act. The Commodities Act is based on European Law and has specific legislation regarding dietary supplements. Dietary supplements (e.g. vitamins, minerals, herbal preparations) may be presented in a pharmaceutical form (e.g. tablets, capsules) though may not claim to be medicines and require no pre-marketing evaluation for safety or efficacy. The Commodities Act requires adequate labelling and prohibits the sale of unsafe foods. A section in the Commodities Act covers certain herbals that are banned for human consumption for reasons of safety and toxicity. Such herbals may also be subject to the Medicines Act because the Medicines Act does not discriminate between the synthetic or natural origin of active substances. In this report these herbals will consistently be referred to as dietary supplements.

A notorious problem is that new designer analogues of registered medicines are neither automatically subject to the Medicines Act nor to the Commodities Act. Firstly, because designer analogues are unknown to the health authorities they cannot be considered as medicines. Secondly, because designer analogues are unknown to science they cannot be considered unsafe or toxic. Thirdly, with respect to adequate labelling, manufacturers may claim that a designer analogue is believed to originate from one of the declared natural ingredients.

Suspect weight-loss products were brought in by the Netherlands Health Care Inspectorate (IGZ), enforcing the Dutch Medicines Act and the Food and Consumer Product Safety Authority (VWA) enforcing the Commodities Act. Suspect weight-loss medicines were confiscated outside the official medicines distribution chain. Complementing the RIVM data over this period are the chemical analysis results of three sister institutes in the Netherlands. The Netherlands Forensic Institute (NFI), the Customs Laboratory (DL) and the Laboratory of Dutch Pharmacists (LNA) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) have kindly shared their data enabling us to analyze trends on illegal weight-loss medicines creating a more representative overview of the illegal market. Samples were taken non-systematically and case by case in the course of enforcement activities and therefore do not necessarily present a representative picture.

A list of inquiries after exposures (possible intoxications) to weight-loss products by physicians from 2000-2007 was kindly provided by the National Poisons Information Centre (NVIC).

2 Materials and methods

2.1 Database construction

2.1.1 Sample sources and selection

Samples analysed by the four laboratories were brought in by the Netherlands Health Care Inspectorate (IGZ), the Food and Consumer Product Safety Authority (VWA), Dutch Customs, the police or public pharmacists (Figure 1). Suspect weight-loss medicines and dietary supplements were sampled case by case without the objective of random sampling. Suspect medicines were brought in for analysis following confiscation outside the official distribution chain. The motives for analyzing suspect products are given in Figure 1.

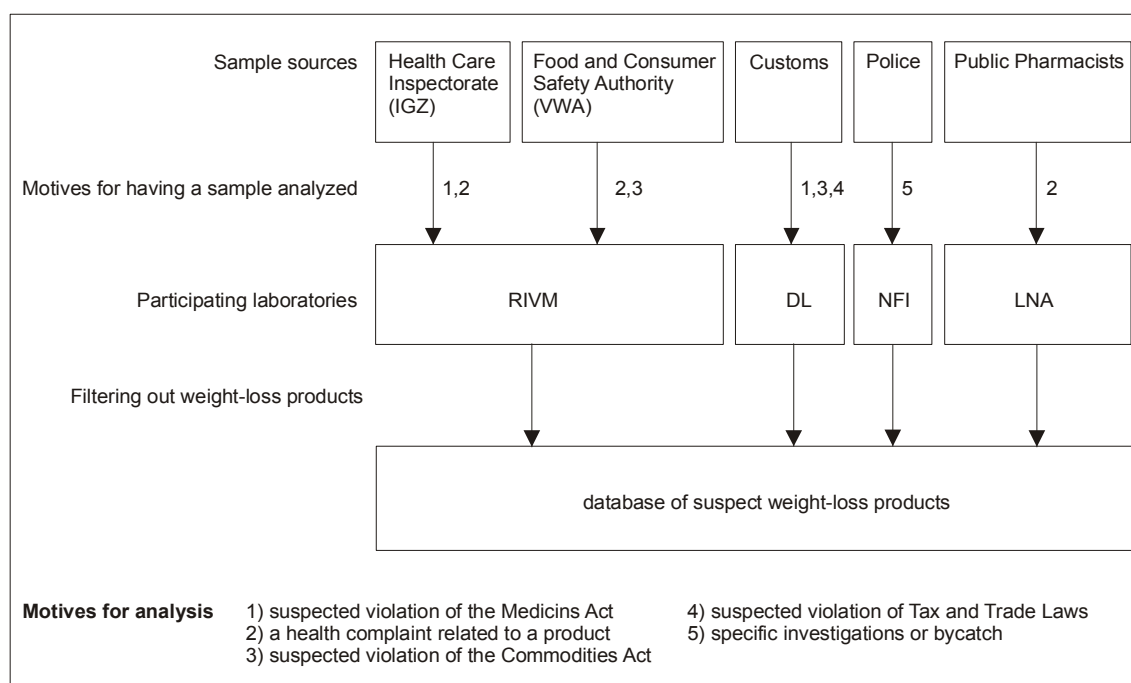


Figure 1 Sources, background and flow of the samples

The samples were analysed using HPLC-DAD, HPLC-DAD-MS, ESI-(IT)-MS, and TLC techniques, depending on the laboratory. No attempts were made to perform a complete chemical or botanical analysis, to verify the accuracy of the entire declared composition or to verify any potential weight-loss efficacy. Each laboratory entered the analysis data into their own laboratory database. The laboratory databases and the (searchable) parameters entered were not necessarily the same. In general, the datasets contained information on the product name, appearance and the drug substance(s) identified. Dosage and product claim (indication) had generally not been investigated or had not been entered into the laboratory database.

Illegal weight-loss products were filtered out of the laboratory databases by searching on: 1) product names of weight-loss medicines (e.g. Reductil, Orlistat), 2) product claims (e.g. slimming, weight-loss) and 3) known drug substances used in weight-loss products (e.g. amphetamine, ephedrine).

Search terms 1 and 2 would retrieve weight-loss products containing any drug substance or no drug substance. Search term 3 was used to retrieve products for which the active weight-loss ingredient was entered into the laboratory database and had no searchable name or claim. Search term 3 would not return weight-loss products in which drug substances were absent or had no known use in weight-loss.

2.1.2 Classification into categories

The samples entered into the database of suspect weight-loss products in this survey were classified as shown in Figure 2. The samples were first classified as a medicine or a dietary supplement based on the product claim. If no claim had been recorded, the classification was made based on the recorded visual presentation of the packaging, the tablets or capsules. Tablets and capsules brought in for analysis without any packaging were generally classified as medicines unless the content was described as natural or herbal.

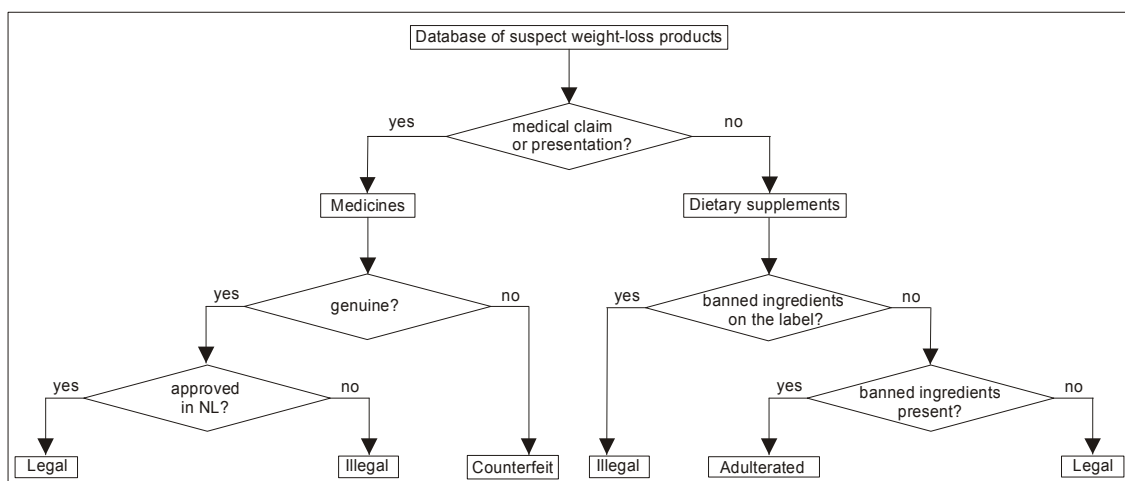


Figure 2 Decision tree for the classification of suspect weight-loss products in the database

The medicines were classified as ‘genuine’ or ‘counterfeit’, based on appearance and chemical analysis. Genuine medicines were further classified as ‘approved’ or ‘unapproved’ for the Dutch market: legal medicines or illegal medicines. The distinction between ‘approved’ and ‘unapproved’ was made to enable categorizing authentic foreign medicines that are not available on the official Dutch market. Legal medicines may be included in the database of suspect weight-loss products if they were considered suspicious at the time of sampling. Counterfeit medicines are considered an illegal copy or imitation of any authentic medicine. The product categories and examples are given in Table 1.

Dietary supplements were classified into three categories. If banned ingredients were declared on the label, then the products were classified as illegal dietary supplements, regardless of the results of the chemical analysis. For products with no banned ingredients declared on the label further classification depended on the results of the chemical analysis.*

* Because of health risk concerns over dietary supplements with ephedrines prior to their ban, these contemporary legal dietary supplements were considered suspect weight-loss products at the time of sampling.

When no banned ingredients were detected, products were classified as legal dietary supplements, based on the few parameters investigated.[†] When undeclared drug substances were identified, products were classified as adulterated dietary supplements. The possibility of products being accidentally contaminated with weight-loss drug substances is not considered. Any dietary supplement containing undeclared drug substances is considered adulterated, implying the intentional act of tampering with the product. The nature of the adulterant – a natural or pharmaceutical drug substance – was not considered in this classification, only the fact that it was secretly present.

It was not verified whether the declared natural drug substances actually had natural origins. Unapproved ingredients with a molecular structure related to that of known pharmaceutical drug substances are regarded as designer analogues[‡] and treated as medicines in this report, regardless of the product in which they were found.

Table 1 Product categories for the Netherlands and examples

Product categories	Examples
Legal medicines	Authentic Reductil (sibutramine)
Illegal medicines	Authentic Meridia (sibutramine)
Counterfeit medicines	A copy or imitation of Reductil
Legal dietary supplements	A product marketed as a dietary supplement in which no banned drug substances were identified nor were they declared on the label.
Illegal dietary supplements	A product marketed as a dietary supplement claiming to contain ephedrine.
Adulterated dietary supplements	A product marketed as a dietary supplement yet containing drug substance (e.g. sibutramine).

2.1.3 Interpretation

Ephedrine[§] was banned from dietary supplements in 2004 and thus their product category changed from legal dietary supplements to illegal dietary supplements. Because ephedrine is frequently used in weight-loss products, it was decided to analyze trends in the period before the ban (2002-2004) and after the ban (2005-2007).

The regulatory status of synephrine (*Citrus aurantium*) is unclear. However, as synephrine was patented in 1931 (DE566,578) as an adrenergic drug substance, was used as a medicine, and health risks have been described², it is regarded a medicine in this survey.

The database of suspect weight-loss products was initially considered to analyze trends in the main categories of medicines and dietary supplements. Trends were then considered for the six product categories. Finally, all identified drug substances were considered together, to assess trends and health risks.

[†] It should be noted that in the time span this report covers some herbal preparations have become banned substances. *Ephedra* species (ephedrine alkaloids) were banned from foodstuffs in 2004 and yohimbine in 2007. *Hoodia gordonii* (P57, a steroid) is considered an endangered species since 2005 and is therefore illegal to import.

[‡] Currently known designer analogues are nitroso-fenfluramine, homosibutramine, desmethyl- and bis-desmethyl-sibutramine.

[§] *Ephedra* species contain a number of structurally related alkaloids with the highest levels for ephedrine. For convenience, this report will refer to ephedra alkaloids as 'ephedrine'. In this report no distinction is made between ephedrine used as an energizer or an appetite suppressant.

2.2 Database survey at the NVIC

All products containing pharmacological drug substances may cause adverse effects. Attributing these adverse effects to illegal weight-loss medicines and dietary supplements is only possible if the actual product is investigated following a health complaint to IGZ, VWA or a pharmacist. Since these cases are rare it was attempted to link the laboratory cases to incidences of poisoning. Therefore, our collaboration was extended to include the National Poisons Information Centre (NVIC).

If a consumer or a patient reports a health complaint to a physician and poisoning is suspected, the physician may voluntarily contact the NVIC for information. The NVIC records information on the exposure (name of the substance/product, time, amount, route of exposure) and on the subject (age, bodyweight). Based on these data and additional factors, such as duration of (chronic) exposure, underlying diseases and use of medication, the NVIC informs physicians about the potential severity of the poisoning, possible symptoms and treatment options. The NVIC receives around 37,000 inquiries each year about some 50,000 exposures.** These data reflect the trends and epidemiology of poisonings in the Netherlands. The NVIC relies solely on label information provided by the physician and does not perform any chemical analysis on the products involved.

To search the NVIC database the NVIC was provided with all the names of weight-loss products analysed by the four laboratories from 2002-2007, chemical names and general search terms (e.g. slimming, weight-loss). The products were classified as a medicine or as a dietary supplement, based on the information recorded by the NVIC.

2.3 Literature survey

Relevant scientific literature was gathered through bibliographic search engines on the internet (Pubmed, Winspurs) using the following search terms or combinations thereof; slimming, weight-loss, safety, adulterated, counterfeit, herbal, dietary supplement, pulmonary hypertension, death, kidney failure and liver damage. RIVM reports on ephedra³ and so-called smartshops⁴ were used for background information.

** The number of exposures is higher than the number of inquiries because of multiple exposures in the same patient.

3 Results

3.1 Database of suspect weight-loss products

Of all the suspect samples brought in for analysis from 2002-2007, a total of 256 products were included in the database of suspect weight-loss products. The RIVM contributed 89 suspect samples, the LNA 18 samples, the NFI 128 samples and the DL 21 samples. In Appendix 1 the analysis results are listed for the samples analysed by each of the four laboratories from 2002-2007. The following data are listed: the year of analysis, product name, appearance, dosage form, API identified and content. The entry was left blank when no data were available.

The main classification of the samples into medicines and dietary supplements is shown in Figure 3a. Suspect dietary supplements make up an average of 83% of the samples and suspect medicines 17%. Trends in the database of suspect weight-loss products show the number of medicines increasing since the ban on ephedrines in 2004 (Figure 3b). The share in suspect medicines has risen from 10% in 2002-2004 to 25% in 2005-2007.

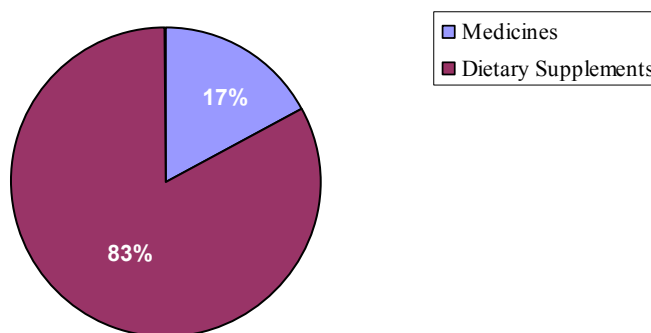


Figure 3a Main categories in the database of suspect weight-loss products 2002-2007

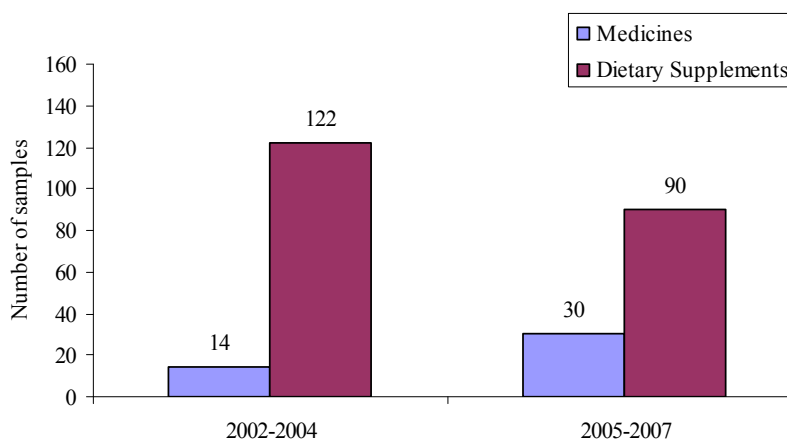


Figure 3b Trends in number of medicines and dietary supplements in the database of suspect weight-loss products before the ban on ephedrines (2002-2004) and after (2005-2007)

3.1.1 Suspect weight-loss medicines

Over the period 2002-2007 the database of suspect weight-loss products contained a total of 44 suspect weight-loss medicines (Figure 4). Until 2005 mostly legal medicines (diuretics) and counterfeit medicines (caffeine instead of phentermine) were identified. Illegal medicines were identified on two occasions and concerned diuretics only.

From 2005, the proportion of counterfeit medicine increased sharply comprising products such as counterfeit Meridia, Reductil, Adipex, Xenical and Ionamin. Among the medicines, the proportion of counterfeits doubled to almost 90%. Table 2 shows counterfeits of brand medicines identified, their composition and the number of cases detected. Eight counterfeits of unknown brands were not included in this table. Counterfeit Xenical was the only counterfeit medicine that did not contain a drug substance. Other counterfeit medicines mostly either contained the wrong drug substance or the correct substance usually in a lower amount. The only legal medicines analysed were the weight-loss medicines Reductil and Xenical and some diuretics.

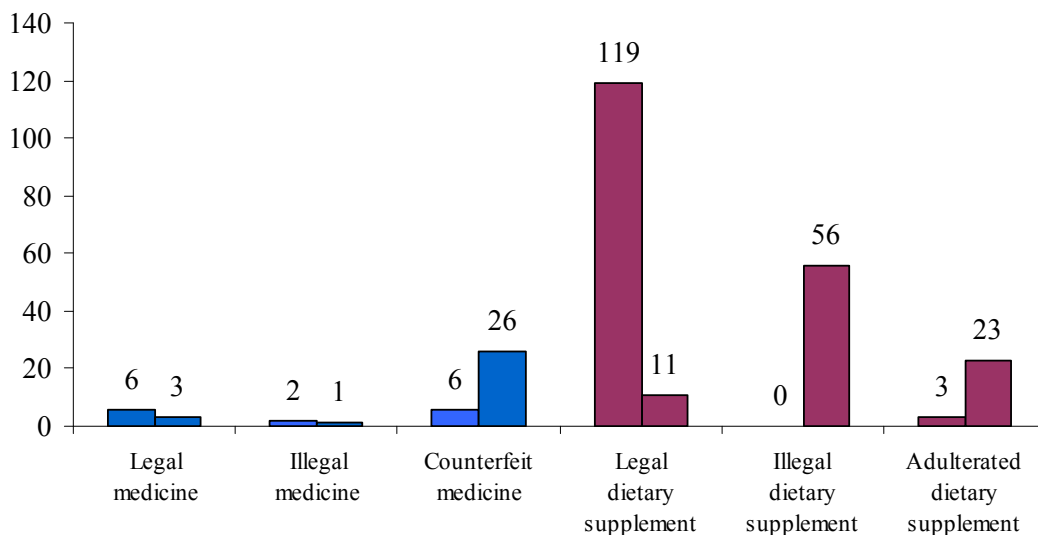


Figure 4 Trends in product categories in the database of suspect weight-loss products over 2002-2004 (left bars) and 2005-2007 (right bars). Number of samples indicated

Table 2 Counterfeits of brand medicines identified, their supposed and actual compositions and the number of separate cases they were identified

Name	Genuine	Counterfeit	# Cases
Meridia	15 mg sibutramine	5.5 mg sibutramine	4
A-167	37 mg phentermine	6 mg sibutramine	8
Xenical	120 mg orlistat	placebo	3
Ionamin	15 mg phentermine	24 mg caffeine + 5.6 mg amphetamine	1
Reductil	10 mg sibutramine	6 - 30 mg caffeine	3
		10 mg sibutramine	3
		0.7 mg phenolphthalein	1

3.1.2 Suspect dietary supplements for weight-loss

Over the period 2002-2004 the database of suspect weight-loss products contained a total of 122 suspect dietary supplements (Figure 4). Few adulterated dietary supplements were identified, and no dietary supplements with banned ingredients declared on the label were identified. About 98% (n = 119) of the suspect samples were legal dietary supplements but were not without health risks. The vast majority (n = 105) contained ephedrines, usually accompanied by high levels of caffeine and synephrine.

Over the period 2005-2007 the database of suspect weight-loss products contained a total of 90 suspect dietary supplements for weight-loss, 62% (n = 56) containing ephedrines, now being categorised as dietary supplements containing banned drug substances. The share in legal dietary supplements decreased to 13% (n = 11) usually involving products containing caffeine, vitamins and amino-acids. The decrease in products with ephedrines is compensated for by a drastic increase (8x) in adulterated dietary supplements (mainly sibutramine).

3.1.3 Drug substances identified

Out of the 256 weight-loss products in the database of suspect weight-loss products, 8 did not contain a drug substance (Table 3). In the remaining 248 weight-loss products a total of 20 different drug substances were identified; 16 pharmaceutical drug substances and 4 naturally occurring drug substances. One ingredient was detected that could not be identified. Table 4 shows the combinations of ingredients found in the period 2002-2007. Figure 5a shows the trends in the therapeutic class of the drugs substances in the database of suspect weight-loss product. Figure 5b shows the trends in the stimulants identified in the database of suspect weight-loss products.

Table 3 Drug substances identified (in alphabetical order)

Frequently identified	Incidentally identified
ephedrines	althiazide
caffeine	amphetamine
sibutramine	desmethyilsibutramine
synephrine	dexamethazone-21-acetate
	fenfluramine
	furosemide
	Human Growth Hormone
	hydrochlorothiazide
	phenobarbital
	phenolphthalein
	phentermine
	phentoin
	salicylic acid
	spironolacton
	triamterene
	yohimbine

Table 4 Combinations of ingredients detected in single products

Combinations
caffeine, ephedrines, synephrine
caffeine, ephedrines
phenylalanine, arginine, pyridoxine, nicotinamide
pyridoxine, nicotinamide
sibutramine, phenolphthalein
phentoin, phenobarbital, ephedrine
caffeine, acetylsalicylic acid
spironolacton, althiazide

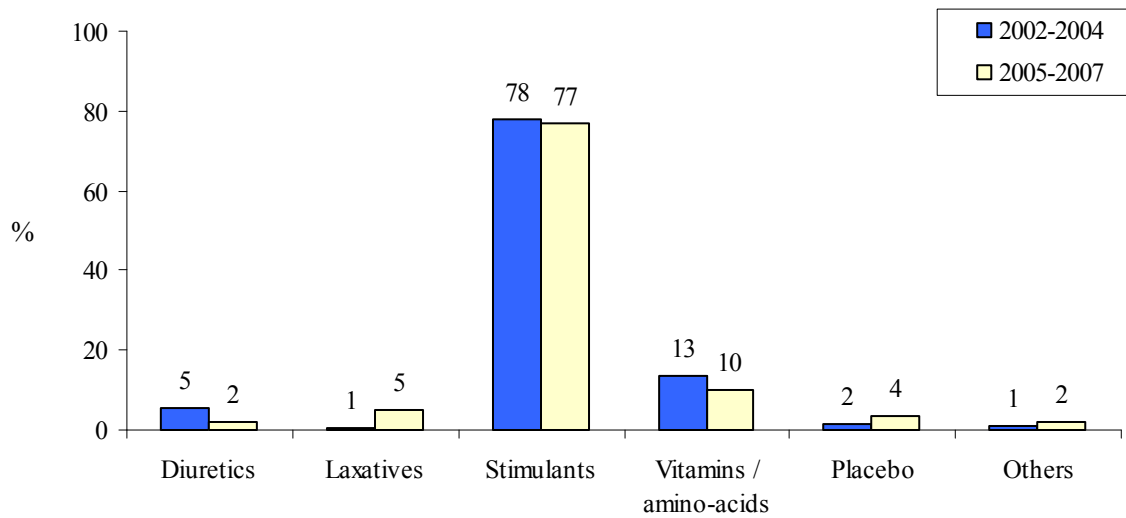


Figure 5a Trends in therapeutic class of drug substances in the database of suspect weight-loss products (2002-2004 and 2005-2007, n = 324). Stimulants include ephedrines, sibutramine and its designer analogues, synephrine, caffeine, amphetamine, and phentermine

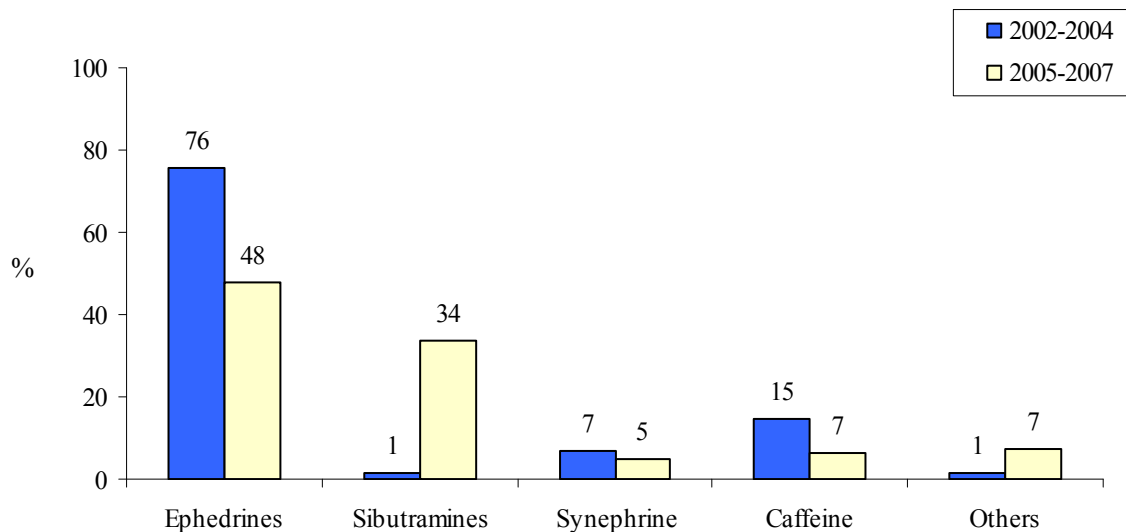


Figure 5b Trends in the stimulants identified in the database of suspect weight-loss products over 2002-2004 (n = 144) and over 2005-2007 (n = 107)

3.1.4 Inquiries at the NVIC after exposures to weight-loss products

Most of the inquiries following exposures to weight-loss products in which the NVIC was consulted involved dietary supplements (Appendix 2). The vast majority of these dietary supplements were products claiming to contain ephedrines. However, as none of these samples were analysed in a laboratory the actual ingredients remain unknown. Even though the NVIC database and the laboratory database have several ephedrine related product names in common, this does not mean that these are of the same composition.

The number of exposures to ephedrines increased 10-fold from 2000-2004. This may be attributed to increasing dosages observed in that period but also to the public awareness of the risks (and benefits) that ephedrines received from 1999-2001.³⁻⁶ In that period health concerns over ephedrines prompted large scale sampling and chemical analysis by the inspectorates providing the fundamentals for the 2004 ban. After being banned in 2004 the number of inquiries gradually subsided to the 2000-2001 level (Figure 6). In 2004 the first exposures were reported for dietary supplements marketed as ‘ephedrine free’ and this number has since remained rather constant.

Figure 6 shows the total number of exposures to ephedrines in young children (<13 years old), for all ages, and the total number of samples in which ephedrines were identified. In this figure trends in exposures are clearly not matched by trends in the identification of ephedrines.

Exposure to weight-loss medicines regularly results in consultations with the NVIC. In general it was not possible to discriminate legal from counterfeit medicine or prescribed medicine from unprescribed medicine. The majority of exposures are recorded for the diuretics furosemide and spironolacton, although these are few (respectively 0.002% and 0.003% in 2007) in relation to the number of prescriptions.^{††} The number of inquiries after exposures to Reductil and Xenical in relation to the number of prescriptions are somewhat higher (respectively 0.009% and 0.02% in 2007).

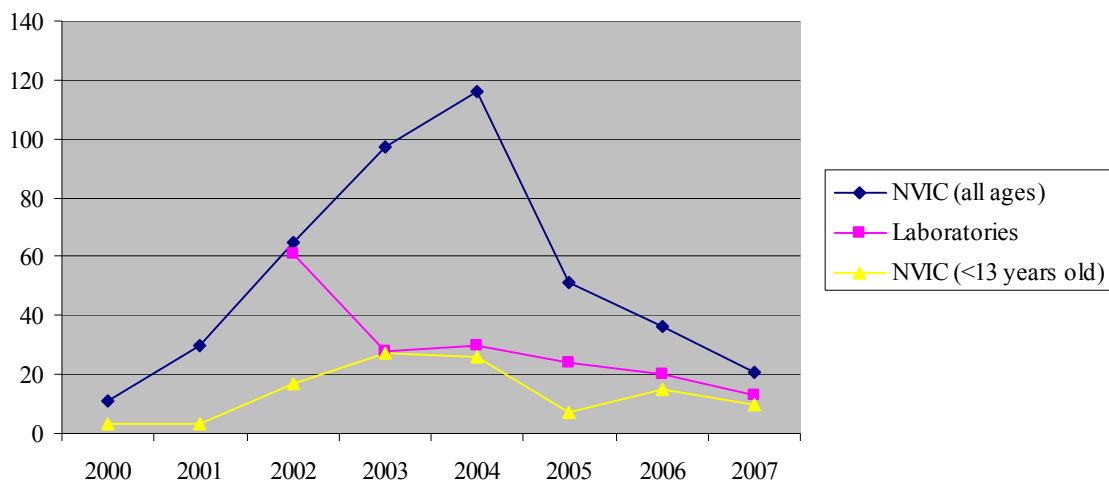


Figure 6 Total number of exposures reported for ephedrines in young children (<13 years old), all ages, and the number of samples in which ephedrines were identified by the laboratories

Retrospectively, it is not possible to distinguish the intention of the overdose from the NVIC inquiries. Some people may have taken diuretics for weight-loss purposes; however other causes, such as suicide attempts (with multiple drug intake, including a diuretic) and accidental overdosing, are included in these figures. Surprising is the sudden increase in the number of reported exposures to unknown weight-loss tablets and capsules to the NVIC in 2006-2007 (Appendix 2). Although, the actual content of both types of products is unknown, the presence of sibutramine or ephedrines is suspected.

When considering the age of the exposed persons it becomes apparent that young children (< 13 years old) significantly contribute to the total number of exposures. In the case of exposures to medicines this contribution is probably accidental and unrelated to weight-loss. Therefore, this number was excluded

^{††} Number of prescriptions derived from the Drug Information System of the Health Care Insurance Board (www.GIPdatabank.nl).

from the dataset. However, this may be different in the case of dietary supplements. The trend observed for exposures to ephedrines in young children matches the trend observed for all ages (Figure 6). This indicates that adults do not recognize the risk of dietary supplements, or do not keep them securely out of reach, and may even give these supplements to (obese) children. Young children contributed to almost 50% of the exposures to 'unknown weight-loss products' in 2006-2007 (n = 23).

3.2 Literature survey

The bibliographic search engines predominantly returned scientific reports on the use and effectiveness of weight-loss drug substances and on their detection in dietary supplements. Casualties caused by genuine medicines, adulterated dietary supplements and unsafe natural products were reported regularly.

Literature describes that fighting overweight is but one reason to seek pharmaceutical or herbal assistance in losing weight. Other reasons include the desire to minimize body fat among bodybuilders and slimming for pathological reasons (e.g. anorexia). The drug substances used to promote weight loss include stimulants that suppress appetite, metabolism altering agents and substances being abused for weight-loss purposes like laxatives and diuretics (Figure 5a).

Laxatives and diuretics are predominantly abused by subjects with eating disorders, but also by bodybuilders and athletes.⁷⁻⁹ As several laxatives are currently available in the Netherlands without prescription, there seems to be no reason for consumers to buy suspect weight-loss products. However, diuretics cannot be obtained without a prescription and are also traded for weight-loss purposes outside the official medicines distribution chain. Although neither laxatives nor diuretics are considered to be real weight-loss drugs, the rapid results caused by dehydration may cause consumers to perceive otherwise.

Efficacious weight-loss drugs have been associated with unacceptable morbidity and mortality for over a century. Despite the risks the prospect of losing weight fast and effortless is still tempting many. The booming trade in shady weight-loss products is therefore a worrying development.¹⁰

Modern pharmaceutical management of bodyweight reduction probably started in 1893 with the introduction of weight-loss medicines based on thyroid hormones.¹ About half a century later the introduction of dinitrophenol (DNP) and amphetamine followed. Since then, the world has seen the regular introduction of new weight-loss drug substances, mostly stimulants acting as an appetite suppressant. However, by the time the weight-loss drugs orlistat (Xenical) and sibutramine (Reductil, Meridia) were introduced in 1997-1998, almost all of their predecessors had been banned for causing unacceptable health risks.¹

Thyroid hormones were withdrawn in the 1980s after being associated with cardiac problems and sudden death. Many stimulants (e.g. amphetamine, aminorex) were withdrawn after being associated with dependency, palpitations, pulmonary hypertension and valvular heart disease. DNP was withdrawn for causing a variety of adverse events but is still available on the internet¹¹ and regularly causes fatalities by starting an uncontrollable cycle resulting in dehydration, exhaustion and (potentially lethal) high body temperatures.¹²⁻¹⁷ The internet suggests that DNP is mostly used in bodybuilding circles and the dangers are generally well described.¹¹

For sibutramine there were safety concerns relating to the potential cardiovascular risks. A large scale study focusing on these cardiovascular risks demonstrated sibutramine to be safe even in high-risk subjects.¹⁸ However, other serious side effects (e.g. psychosis) are reported for sibutramine in legal medicines¹⁹⁻²³ and adulterated dietary supplements alike.^{10,24,25} Acute psychosis in patients with a latent

morbidity is described in the patient information leaflet (PIL). Therefore, the non-prescriptive or unwitting use of sibutramine or its analogues is explicitly dangerous.

Using dietary supplements as a weight-loss aid is described to be mostly ineffective and, despite public perception, not necessarily safe.²⁶⁻³³ Effective dietary supplements usually contain stimulants (e.g. ephedrine, norephedrine) which were banned from dietary supplements in the Netherlands in 2004 for health risk concerns.^{1,34}

4 Discussion

4.1 Ingredients and risks

Before market authorisation is granted for a medicine in the Netherlands, the Dutch Medicines Evaluation Board (CBG) thoroughly reviews different aspects of the product. Medicines can be authorised when a positive risk/benefit ratio is ascertained. The benefit is the expected improvement of one's condition, and the risk is the possible adverse effects caused by the medication or its formulation. Medicines are strictly regulated in order to minimize the health risks of the adverse effects. Therefore, pharmacology, toxicology, indication for use, and also technical quality are among the aspects judged by the Medicines Evaluation Board.

For prescribed medicines it is important that a physician assesses whether an individual patient should receive a certain medicine. Factors like physical condition, medical history, and/or the use of other medicines could prevent a physician from prescribing a medicine. A person using prescription medication without consulting a physician is deliberately taking a risk which may cost the individuals health and the health care system (e.g. hospital admissions, days not a work). Literature clearly states that weight-loss medicines pose a high health risk in certain people, especially after long-term use. Therefore, weight-loss medicines are prescribed restrictively and usually in combination with a programme to change a patient's lifestyle. In order to limit the health risks for weight-loss drugs, the risk/benefit ratio needs to be assessed and monitored by a physician. This necessity is emphasised by the market withdrawals of many unsafe weight-loss medicines in the past and the present withdrawal of the promising weight-loss drug Acomplia (rimonabant)³⁵.

Medicines analysed by the laboratories in this report were prescribed-only medicines, confiscated outside the official medicines distribution chain. Consumers using these products do so without consulting a physician and are therefore endangering themselves. In addition, the uncertainty about the drug substance actually present, its dose, the formulation and contaminants increases the health risk.

As dietary supplements are more loosely regulated than medicines, the risk/benefit ratio does not need to be evaluated before market introduction. Thus, for dietary supplements there is an inherent uncertainty about presence of the drug substance, its dose, the formulation and contaminants. This survey has also shown that in many cases product labels cannot be trusted, thus increasing the health risks. Furthermore, consumers of dietary supplements are not likely to consult their physician on such matters, therefore increasing the health risks even further.

A notorious problem is that dietary supplements containing new designer analogues of registered medicines are not automatically subject to the Medicines Act or to the Commodities Act. Firstly, because designer analogues are unknown to the health authorities cannot be considered as medicines. Secondly, because designer analogues are unknown to science they cannot be considered unsafe or toxic. Thirdly, with respect to adequate labeling, manufacturers may claim a designer analogue is believed to originate from one of the declared natural ingredients.

The most important factors contributing to the total health risk are (i) the pharmacological risk caused by the drug substance and its dose, (ii) whether or not the drug substance is declared on the label, and (iii) whether or not the drug substance was prescribed and in what dose regimen. The collective database of the four laboratories mostly contains information on the drug substance alone. Dosage is estimated infrequently and label information is rarely present. The database of suspect weight-loss

products does not contain any information about the consumers. The health risks are therefore assessed by taking into account the drug substances used.

4.1.1 Laxatives

Phenolphthalein is a laxative that was withdrawn as a medicine several years ago after concerns about carcinogenicity. It was the only laxative found by the laboratories and was not reported to the NVIC. Phenolphthalein was identified as the single drug substance in counterfeit Reductil and in combination with sibutramine in several dietary supplements in 2006-2007.

It is unclear why phenolphthalein has recently surfaced in several weight-loss products, because laxatives are not very effective as weight-loss drugs.⁸ Phenolphthalein by itself does not present an acute health risk in the dosages found, but as it is cheap and widely available it is expected to be identified more frequently in the future. Long-term exposure to phenolphthalein should be prevented because of cancer risks. Also, the abuse of laxatives in general, always carries a risk of organ damage resulting from dehydration.⁸

Exposures to phenolphthalein were not reported to the NVIC, which is not surprising considering it seems to primarily be used secretly in counterfeit medicine or adulterated dietary supplements.

4.1.2 Diuretics

Diuretics were mainly detected in genuine medicines, but not all were registered for use in the Netherlands. Diuretics, like laxatives, are not very effective as weight-loss drugs but have similar health risks.⁸

Genuine approved diuretics, even when traded illegally, do not present a large health risk. Because the majority of the diuretics concerned legal medicine it may be assumed consumers are informed about the properties of the medicine and the risks associated. Risks are higher for the unwitting users of adulterated dietary supplements with diuretics, although so far no casualties have been reported in literature.^{36,37} The identification of some anti-epileptic drugs with diuretic properties in counterfeit medicines together with ephedrine is raising concerns over the potential effects. Although such a product seems to pose a health risk, it was only identified on one occasion.

4.1.3 Stimulants

The main stimulants identified in the period 2002-2004 were ephedrine, synephrine and caffeine. Products frequently contain combinations of these ingredients in efficacious dosages (Appendix 1). Since the ban on ephedrine in 2004 they are still regularly detected by DL, and the NFI. Their illegal use elsewhere in Europe is illustrated by a recent series of adverse events including one death in Denmark attributed to the use of such products purchased over the internet.³⁸

After the ban on ephedrine, manufacturers changed to using the weaker stimulant synephrine, although it was not identified by the laboratories more frequently. Although several Dutch web stores claim synephrine to be legal it is actually subject to the Medicines Act. Web stores also claim to offer other legal alternatives in dietary supplements with herbs known to contain stimulant drug substances (e.g. phenylethylamines). It is unclear whether these drug substances are actually present, whether they are legal, and what their effect would be.

As of 2005, moderate levels of sibutramine were frequently identified in counterfeit medicines and dietary supplements. It seems that in the industrialised countries sibutramine is becoming the most popular drug substance in illegal weight-loss products. One of the three designer drugs of sibutramine known today has been identified by the RIVM and DL in an adulterated dietary supplement.²⁴

The increased use of sibutramine in illegal weight-loss products is not reflected in the exposures recorded by the NVIC. This may largely be attributed to sibutramine not being declared on the label of

these dietary supplements and thus not being recognised as a causative agent in intoxications. Such adulterated dietary supplements may be listed under the increasing number of ‘unknown weight-loss products’ (Appendix 2), and these products were not analysed.

4.1.4 Vitamins / amino-acids

The vitamins and amino-acids found in this survey are frequently used in weight-loss products in high dosages but their efficacy is doubtful. The ingredients are allowed when in compliance with the Commodities Act.

4.1.5 Others

The lipase inhibitor orlistat (Xenical) was the only other weight-loss drug identified in the database of suspect weight-loss products. It was present in the database only once, as a legal medicine. None of the counterfeit Xenical capsules contained a drug substance. Though some exposures were reported to the NVIC, Xenical is not considered a potential health risk and is available over-the-counter in some countries. Surprisingly, the number of exposures recorded by the NVIC for Xenical and Reductil are similar even though Reductil is prescribed more often.

Four pharmaceutical drug substances were detected that have no specific bearing on losing weight but may have an auxiliary function.^{**} Noticeably absent in the database of suspect weight-loss products and the NVIC database were (counterfeit) Acomplia (rimonabant), DNP and thyroid hormone preparations. Suspect Acomplia is widely available outside the official distribution chain and Dutch web-forums suggest that DNP and thyroid hormones are still used. Because Acomplia was recently withdrawn from the official market it is an interesting case for monitoring the impact on the illegal trade.

4.1.6 Combinations of ingredients

The combinations of ingredients identified are listed in table 4. The potentially hazardous combinations are combinations involving ephedrine, caffeine and synephrine or salicylic acid. Interaction profiles are unknown for the combinations of sibutramine / phenolphthalein and phentoin / phenobarbital / ephedrine.

4.2 Trends

Literature increasingly reports on dietary supplements adulterated with thyroid preparations, weight-loss drug substances and designer analogues.^{24,25,39-49} Adulterated dietary weight-loss products are responsible for most hospital admissions reported, involving symptoms of psychosis, poisoning and liver damage.¹⁰ A case of mass poisoning was reported in Japan in 2002 where a designer analogue of fenfluramine in a herbal tea was linked to over 800 cases of serious health damage and some deaths.^{39,45} Similar clinical cases are reported on a smaller scale in Singapore and the United Kingdom.^{50,51} Since this survey has shown that adulterated dietary supplements were also found in the Netherlands, it is expected that clinical cases will surface in the future.

The availability of counterfeit Xenical, Reductil and Meridia (outside of the official distribution chain) and illegal dietary supplements has increased enormously since 2002. The majority of the pharmaceutical drug substances identified in these products changed from diuretics to sibutramine. At the same time the products in which they were predominantly identified changed from legal to counterfeit medicines and adulterated dietary supplements.

^{**} E.g. two anti-epileptic drugs, phentoin and phenobarbital, were identified in a dietary supplement together with ephedrine.

The naturally occurring drug substances identified were predominantly ephedrines, synephrine and caffeine, frequently in combination with each other. The share of weight-loss dietary supplements in which ephedrines were detected decreased from 88% in 2002-2004 to 62% in 2005-2007. In our set of data this decrease in ephedrines is compensated for by the increase in the identification of sibutramine and its analogues in adulterated dietary supplements and counterfeit medicines.

As with the illegal erectogenics, suspect weight-loss medicines and adulterated dietary supplements are likely to contain one or more of any drug substance in dosages high enough to produce a noticeable effect. By doing so, manufacturers seem to be increasingly interested in creating a loyal customer base and a stable market.

A stable market for finished products is unlikely to be achieved through sustained infiltration of counterfeits into the well-protected official medicines distribution chain. In the long-term there is more to gain and less to risk in creating a stable market parallel to the official market. Besides, Xenical and Reductil are prescribed restrictively, resulting in a small official market in the Netherlands.

Manufacturers of suspect weight-loss dietary supplements seem to become aware of the pharmacological, analytical and legal aspects of their trade. Firstly, their use of designer drugs and of herbs with naturally occurring analogues of ephedrine shows that they keep up with scientific media and patent literature. Secondly, by using dietary supplements as a matrix to hide drug substances the identification process is slowed down and confusion created over their legal status. Thirdly, manufacturers and retailers know that it is hard to prove criminal intent when trading adulterated dietary supplements. Once caught, one can credibly claim of being unaware of a pharmaceutical 'contamination' because testing commodities for pharmaceutical adulterants is not a prerequisite before marketing.

In the present study, there are safety concerns with 21 of the 26 of the ingredients detected. Sibutramine and its designer analogues, ephedrines, and synephrine are considered to pose the highest risk. One of the main concerns is that subjects usually take weight-loss medicines or dietary supplements on a daily basis over a prolonged time. Initial results or lack of initial result may prompt consumers to increase their dosage to a dangerous level.¹⁶ Adverse events may be treated properly if a connection can be made between the symptoms and the product. For adulterated dietary supplements and counterfeit medicine this connection is often hard to make because one is unaware of the product not being what it seems. In addition, a subject experiencing a psychotic episode caused by sibutramine is unlikely to be of any help in relating medical or dietary history during anamneses.

The explosive growth in Ritalin (methylphenidate) prescriptions may result in the medicine being abused as a weight-loss drug. Though this behaviour on a limited scale has been reported abroad, there are no indications of such a trend in the Netherlands at present.⁵²

4.3 Conclusions

The health risks of illegal weight-loss medicines and dietary supplements have increased from 2002-2007. The increase can mainly be attributed to consumers being misled by deliberately mislabelled dietary supplements and by the availability of counterfeit medicines of unreliable composition outside the official distribution chain. The use of moderate but efficacious dosages of drug substances is creating a false sense of reliability of the unofficial system.

The drug substances detected in this survey were also detected in suspect weight-loss products analysed by other countries. The ingredients that reportedly caused the most serious casualties in the UK, Germany and throughout South-East Asia (DNP, usnic acid, nitroso-fenfluramine) were not observed in this survey with the exception of sibutramine and its analogues. However, the use of DNP in the Netherlands is suspected after monitoring Dutch web forums on bodybuilding. Dangerous drug

substances not yet identified in the Netherlands have turned up within the European Union and may surface in the future.

Provided no large scale accidents are reported in the media, consumers' trust in illegal weight-loss products will grow to a level that may undermine trust in the official system. To a certain extent this has already happened as prices for illegal weight-loss medicines and dietary supplements often are comparable to prices of the legal medicines. It seems that outside of the official distribution chain consumers expect a positive correlation between price and efficacy. Once their expectation has been confirmed, the satisfied customer returns for more of the same.

The inquiries at the NVIC following exposures to weight-loss products are an opportunity to link suspect medicines and dietary supplements to drug substances and adverse events. A more vigorous follow-up by the NVIC may help uncover more cases of health damage.

4.4 Limitations of the study

This survey is not the result of coherent sampling as samples were brought in for analysis case by case. With the participation of multiple laboratories, the authors aim to draw the best representative picture available. However, as each laboratory serves its own specific (legal) task, different parameters may be investigated to meet their own objectives. Therefore, important data for assessing health risks (e.g. dosage) was infrequently available. In addition, samples were not consistently entered into a database as a weight-loss product. In such cases database searches on drug substances only generated samples that had tested positive for weight-loss drug substances, while samples with no or other drug substances were missed.

The authors realize that adverse events are bound to be underreported by the unwitting users of dangerous dietary supplements as well as those knowingly using illegal products. Even when complaints are reported and recognised very few will make it into a scientific publication. Therefore, the cases reported in literature probably only represent a small proportion of the actual cases.

Although the NVIC data gives a good indication of the occurrence of actual exposures, the data is limited by not knowing the actual ingredients, dosage or intended use.

4.5 Recommendations

1. Harmonize and expand the analysis parameters recorded by laboratories, as this would greatly improve the coherence of the dataset and facilitate the health risk assessment. Ingredients, dose, label information and intended use are the most valuable analysis parameters.
2. Designer analogues of registered medicines should automatically be made subject to the Medicines Act.
3. Dieticians and physicians should warn their clients against the risks of buying weight-loss medicines outside of the official medicine distribution chain and advise caution when buying dietary supplements to aid weight loss.
4. The use of dietary supplements should be asked for at hospital admissions. In the case of a suspected intoxication the product should be retrieved and analysed. Follow-up of inquiries at the NVIC could be helpful in identifying such cases and in linking actual symptoms in patients to ingredients identified by analysis.

5. Measures should be taken to prevent the further formation of a stable and highly accessible market in illegal weight-loss medicines and dietary supplements parallel to the official market.
6. Undertake international action against notorious manufacturers of adulterated dietary supplements.
7. Initiate a public warning campaign against suspect dietary weight-loss products.
8. Investigate the background of inquires at the NVIC after exposures to weight-loss products with a special focus on intoxications in (young) children.
9. Investigate the consequences of the market withdrawal of Acomplia (rimonabant) with respect to the trade in (counterfeit) Acomplia outside of the official distribution chain.
10. Investigate the impact on the health of consumers of illegal weight-loss products and the evolving costs (e.g. first aid, hospital admissions, non-productive days).

Appendix 1 Analysis results

LM = Legal medicine approved for the Dutch market
 IM = Illegal medicine unapproved for the Dutch market
 CM = Counterfeit medicine
 LDS = Legal dietary supplement
 IDS = Illegal dietary supplements
 ADS = Adulterated dietary supplements

Analyzing Lab	Product name	Ingredients	Dose (mg)	Product category
2002				
RIVM	Stack 5	Ephedrines Synephrine Caffeine	6 - -	LDS
	Stack II	Ephedrines Caffeine	35 -	LDS
	Stack II	Ephedrines Caffeine	36 -	LDS
	Stacker 3	Ephedrines Caffeine	28 -	LDS
	Xenadrine RFA-1	Ephedrines Synephrine Caffeine	10 2.5 -	LDS
	Ionamin forte	Caffeine	-	CM
	Furosemid Ratiopharm 20	Furosemide	10 mg/mL	LM
	Ionamin Forte	Caffeine	32	CM
	Stacker 3	Ephedrines Caffeine	25 -	LDS
	Stacker 4	Ephedrines Caffeine	21 -	LDS
	Stack Booster 1	Ephedrines Caffeine Synephrine	14 - -	LDS
	Capsule	Ephedrines	10	LDS
	Capsule	Ephedrines	49	LDS
	Capsule	Ephedrines	46	LDS
	Tablets	Ephedrines	33	LDS
	Capsule	Ephedrines	17	LDS
	Ephedra kruid	None found		ADS
	JAG	Ephedrines	22	LDS
	Stacker 4	Ephedrines Synephrine Caffeine	19 - -	LDS
	Stacker 4	Ephedrines Synephrine Caffeine	19 - -	LDS

	JAG	Ephedrines Caffeine	20 -	LDS
	Stacker tabs			LDS
	Stacker 4	Ephedrines Synephrine Caffeine	19 - -	LDS
	Ionamin Forte	Caffeine	24	CM
NFI	34 separate cases	Ephedrine		LDS
LNA	Light brown capsule	Ephedrine HCl		LDS
	Yellow capsule	Ephedrine Caffeine		LDS
DL	none reported			
	2003			
RIVM	Phentermine	Amphetamine Caffeine	5.6 6.2	CM
	Capsule	Phenylalanine Arginine Pyridoxine Nicotinamide		LDS
	Capsule	Phenylalanine Arginine Pyridoxine Nicotinamide		LDS
	Capsule	Phenylalanine Arginine Pyridoxine Nicotinamide		LDS
	Capsule	Phenylalanine Arginine Pyridoxine Nicotinamide		LDS
	Capsule	Phenylalanine Arginine Pyridoxine Nicotinamide		LDS
	Capsule	Phenylalanine Arginine Pyridoxine Nicotinamide		LDS
NFI	25 cases	Ephedrines		LDS
	Unknown	Phenfluramine		CM
	Fur 40	Furosemide		LM
	Dumex 80P	Furosemide		LM
	Dumex 40 mg	Furosemide		LM
LNA	White capsules	-		LDS
	Yellow Tablet	Nicotinamide Riboflavine		LDS
	White/blue capsule	Pyridoxine		LDS
DL	Ephedrine 25 adipose destructo	Ephedrines		LDS
	Stacker 3 with chitosan	Ephedrines		LDS
	Ephedra 850 capsule	Ephedrines		LDS

2004				
RIVM	Super cap	Ephedrines		LDS
	Maxadrine	Ephedrines Synephrine Caffeine		LDS
	White jar	Ephedrines Caffeine		LDS
	White jar	Ephedrines Synephrine Caffeine		LDS
	Dyma-Burn Extreme	Ephedrines Synephrine	11	LDS
	Stack force	Ephedrines Synephrine	17 -	LDS
LNA	Yellow/white capsule	Nicotinamide Pyridoxine		LDS
	Orange capsule	-		LDS
	Green capsule	-		LDS
NFI	16 cases	Ephedrines		LDS
	Unknown	Furosemide		LM
	Unknown	Furosemide		LM
DL	White tablets	Ephedrine Phentoin Phenobarbital		CM
	White tablets "MB"	Ephedrines		LDS
	White round tablets	Ephedrines		LDS
	White tablets "MB"	Ephedrines		LDS
	Buffered Vitamine C	Sibutramine	50	ADS
	Blue capsules	Sibutramine Phenolphthalein Caffeine	8 - -	ADS
	Aldactone 100	Spironolacton		IM
	Aldactazine	Spironolacton Althiazide		IM
2005				
RIVM	Stacker 2	Ephedrines		IDS
	D&E	Ephedrines		IDS
	Explore X	Ephedrines		IDS
	D&E	Ephedrines		IDS
	Stacker 4	Ephedrines		IDS
	Purple passion	Ephedrines		IDS
	Jag	Ephedrines		IDS
	Li Da	Sibutramine	25	ADS
	Meizitang	Sibutramine	28	ADS
	Jian fei jiao nang	Desmethylsibutramine	9	ADS
	Li Da	Sibutramine	20	ADS
	Capsules	Ephedrines	42	IDS
	Capsules	Ephedrines	42	IDS

	Keep fit reduce fat caps.	Ephedrines		IDS
	Reductil 10	Sibutramine	10	LM
	Yellow Stack	Synephrine		IDS
	Stacker 2	Synephrine		IDS
	3 Capsules	Pyridoxine Nicotinamide Arginine Phenylalanine		LDS
	Plastic tube	Caffeine	0.1 mg/mL	LDS
	Super stacker +	Synephrine Yohimbine Caffeine	0.25 3 0.25	IDS
	Super stacker +	Synephrine Yohimbine Caffeine	0.25 3 0.25	IDS
LNA	White capsule	Nicotinamide Pyridoxine		LDS
	Red capsule	-		LDS
	Brown/white capsule	Ephedrines Caffeine		IDS
	White capsule	-		LDS
NFI	Unknown	Phentermine		CM
	9 cases	Ephedrines		IDS
DL	Darling	Sibutramine		ADS
	Jian Fei Jiao Nang	Sibutramine, Desmethylsbutramine		ADS
	Darling	Sibutramine	18	ADS
	Qianzimei Weight Reducing Caps	Sibutramine	2	ADS
2006				
RIVM	A-167	Sibutramine	4	CM
	A-167	Sibutramine	5	CM
	Reductil	Sibutramine	10	CM
	Reductil	Sibutramine	10	CM
	Furosemide	Furosemide	40	LM
	Xenical	Orlistat	120	LM
	Meridia	Sibutramine	6	CM
	A-167	Sibutramine	5	CM
	A-167	Sibutramine	6	CM
	A-167	Sibutramine	5	CM
	A-167	Sibutramine	6	CM
	Merida 15	Sibutramine	5	CM
	A-167	Sibutramine	6	CM
	Meridia 15	Sibutramine	6	CM
	Xenical 120	-	-	CM
	A-167	Sibutramine	5.5	CM
	Xenical	-	-	CM
	A-167	Sibutramine	6	CM

	Meridia	Sibutramine	6	CM
	Beauty Platinum Slimming	Sibutramine Phenolphthalein	1 9	ADS
	Beauty Platinum Slimming	Sibutramine Phenolphthalein	1 8	ADS
	GoGoEnergy 4-HER	-		IDS
	GoGoEnergy 4-HER	-		IDS
	Stacker 3 XPLC	Caffeine		LDS
	NuSlank X-trine	Caffeine		LDS
	NuSlank X-trine	Caffeine		LDS
LNA	Capsules with cream	Dexamethason acetate		CM
NFI		Sibutramine		CM
	20 cases	Ephedrines		IDS
DL	Herbal capsules	Sibutramine, Phenolphthalein		ADS
	HCA Believe	Sibutramine		ADS
2007				
RIVM	Reductil 15	Phenolphthalein	0.7	CM
	Xenical	-	-	CM
	Miazoi	Sibutramine	10	ADS
	Miazoi	Sibutramine	10	ADS
	Capsule 1	Phenylalanine Arginine Pyridoxine Nicotinamide		ALDS
	Capsule 2	Phenylalanine Arginine Pyridoxine Nicotinamide		ALDS
LNA	Capsule, brown content	Phenolphthalein		UDS
	Capsule, yellow content	Phenolphthalein		UDS
	White round tablets	Unknown alkaloid		ALDS
	Yellow round tablets	Triamtereen Hydrochloorthiazide		CM
	White capsules	Caffeine Salicylic acid		ADS
NFI	Unknown	Sibutramine		CM
	TRK P15	Phentermine		CM
	TRK P30	Phentermine		CM
	Powder	Phentermine Pseudo-ephedrine		ADS
	11 cases	Ephedrines		UDS
	Unknown	Synephrine		UDS
	Xin Li Da	Sibutramine		ADS
	Relizine tabletten	Pseudo-ephedrine Triprolidine		IM
	Cosmetics capsules	Sibutramine, Phenolphthalein		ADS

Appendix 2 Number of cases reported to the NVIC

		2000	2001	2002	2003	2004	2005	2006	2007
MEDICINS (>13 years of age)									
Laxatives	phenolphthalein	not reported							
Diuretics	furosemide	4	7	9	8	15	23	23	28
	spironolacton	2	1	3	6	2	7	11	13
Stimulants	phentermine	7	4		1				
	dexfenfluramine					1			
	fenfluramine					1			
	sibutramine			1			1	2	4
Others	orlistat	3		3	1	2		1	1
DIETARY SUPPLEMENTS (all ages)									
Stimulants	citrus aurantium (with synephrine)	1							
	betalean (slimmingtablet (with synephrine))			1					
	jag fat assimilator (energizer)					1			
	ephedra		8	24	31	27	20	16	17
	ephedra supercap		1			1			
	fatburner (25 mg ephedra)					2		1	
	final e (energizer with ephedra)				1				
	power cuts (with ephedra, guarana)		1						
	purple passion (ephedra)		1						
	sexplor (sida cordifolia / ephedra-alkaloids)			1					

DIETARY SUPPLEMENTS (all ages) continued	2000	2001	2002	2003	2004	2005	2006	2007
sida acuta (ephedra-alkaloids)				1				
sida cordifolia (ephedra-alkaloids)				1				
sida rhombifolia (ephedra-alkaloids)				1				
sinephedrine (synephrine, ephedra alkaloid)	1		1					
sinephrine (=synephrine, ephedra-alkaloid)	1							
smart caps (ephedra)	1							
stack		1						
stack 5 weight-loss capsules (m double you)				4	2			
stack booster 1 weight-loss caps. (vitalife)				5	7	4		
stack ii weight-loss capsules (m double you)			1	10	6	8	1	
stacker	1	5	4	1				
stacker 2 weight-loss capsules (nve stacker)	3	4	16	11	30	7	8	
stacker 3 weight-loss capsules (nve stacker)	1	5	10	6	16	4	6	
stacker 4 weight-loss capsules (nve stacker)			6	10	22	6	2	
stacker with ephedrine and caffeine								2
stacker supercap extreme (ephedrine)							2	2
stargate capsules (ephedra preparation)	1					1		
xenadrine (caffeine, ephedrine)	1			1				
yellow jacket (energizer with ephedra)					1			
yellow jacket		2						
yellow stack					1	1		
yellow sub (with ephedra)				1				
seacitrus (with ephedra-alkaloids)				12				
zhishi (citrus aurantium / ephedra-alkaloids)				1				
eph850 (ephedra)		1						
exenical			1					
fatlose xenadrine		1						

Vitamins /aa's

not investigated because exposures can not be attributed to use of weight-loss products

DIETARY SUPPLEMENTS (all ages) continued		2000	2001	2002	2003	2004	2005	2006	2007
Others	appelazijn (weight-loss product)		1	2	2	3		1	1
	bional kilolite (weight-loss product)								1
	chitosan weight-loss product				1				
	fat and burn (weight-loss product)				1	1	1		
	herbalife slimming preparation				2	3	1		
	kruidvat slimming tablet								1
	leader slim (weight-loss pr. with guarana)					1			
	reduce fat fast (weight-loss product)		1						
	reduslim (weight-loss product)		1						
	removyl (weight-loss product, etheric oils)						1		4
	sundown weight-loss capsules			1					
	x-trine 3 (nuslank)							3	1
Others marked as ephedra free	ephedra free stacker						3	7	5
	super cap - herbal energizer					3	3		
	super cap extreme with jaborandi, caffeine					1			
Unknown	Unknown weight-loss products		2	9	3			12	11

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