DRUG ADULTERANTS AND THEIR EFFECTS ON THE HEALTH OF USERS: A CRITICAL REVIEW

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The authors of this paper hereby state that they have no conflict of interest.

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KEY POINTS:

- The purity of drugs is highly variable and depends on the region or epidemiological context. Evidence shows that there is a broad spectrum of adulterants in the drugs that are most prevalent worldwide.
- Drug adulteration is constantly changing, with an overall trend toward a decline in the purity of most drugs over the past 10 years. Some adulterants enhance the psychoactive effects of a drug and may contribute to its addictive potential.
- Some adulterants are associated with a significant increase in the risk of overdose and death due to acute poisoning (e.g., fentanyl in cocaine or heroin, adulterants in MDMA and LSD, adulterations of new psychoactive substances or NPS); others are related to complications that appear following chronic use in subjects who may be genetically predisposed (e.g., levamisole in cocaine).
- Deaths in the studies examined appear to be related to the drugs involved, to poly-drug use, and to the dose consumed.
- Considering the gaps in knowledge, it would seem necessary to conduct a standardized analysis of chemical composition and expand it to include a broader spectrum of substances, using similar protocols with more representative samples in the various countries and regions, to obtain a complete chemical characterization of the drugs analyzed.
- The quality of the information and evidence available on the harms to health caused by some adulterants varies widely. While the most common adulterations of some substances are well known, the emergence of NPS has led to gaps in knowledge about the drugs being used and their composition.
- Coordination among supply control agencies and those organizations that have access to samples obtained directly from users appears to be needed to achieve common objectives. Early warning systems in the different countries are fundamental to such coordination.
- In the current context of legalization or regularization of the marijuana market in a number of countries, more rigorous research must be conducted on possible

contamination by pesticides used on crops, and their possible effects on cannabis use -- particularly smoked cannabis, given current evidence linking adulterations of marijuana with respiratory disease.

- Studies of the toxic health effects of adulterants and their association with the drug that is used are based on experimental studies, and essentially on case reports and case series. Epidemiological context, clinical presentation, complications (as seen clinically and in histopathology), and analytical confirmation are the basic pillars in analyzing the toxicity of an adulterant or an adulterant/drug combination.
- Health professionals, the community, and most importantly drug users should be aware of the risks inherent in the adulterations of the drugs they are using, as well as the potential chronic, long-term toxic effects that may be attributable to the presence of one or more adulterants.
- Hospitals need to have trained personnel, the necessary material resources, and the means to communicate immediately with local laboratories to identify the adulterants. Early diagnosis makes for better treatment and reduces morbidity and mortality.
- To address this public health problem, it is necessary to develop research and action protocols and to strengthen networks involving government agencies (e.g., early warning systems), clinical and forensic laboratories, and nongovernmental organizations with access to users, as well as universities and toxicology centers.

Contents

1. INTRODUCTION

The threats and emerging problems related to drug use and trafficking include the adulteration of classic drugs and a variety of chemical substances covered by the term new psychoactive substances (NPS) (Busardò et al., 2016). Some countries have made strides in the chemical characterization of drugs and have been able to identify a large number of adulterants. The creation of early warning systems in various regions since the beginning of this century and the development of new laboratory techniques have enabled analysis to be conducted of NPS and their chemical composition (Van der Biest & Walckiers, 2004); however, it is necessary to learn more about the effects of adulterants on the health of drug users and the involvement of adulterants in drug-related morbidity and mortality.

For drug users, purity is synonymous with quality; however, people use drugs that on the whole are not composed exclusively of the active principle(s) for which they are consumed. The degree of purity and therefore the composition of an illicit drug will vary depending on where it is obtained, and may change from one week to the next, or even from one day to the next.

Many substances that are different from the psychoactive drug itself can be found, using different mechanisms (Cole et al., 2010). These substances are commonly called **adulterants (Figure 1)**.

Strictly speaking, the word adulterant refers to pharmacologically active substances with properties similar to the drug itself, which are added to offset the potency lost in dilution; however, this paper looks at a broader range of substances found in prevalently used drugs, including:

Chemical contaminants -- These are normally part of the process of synthesizing, manufacturing, and processing the drug. They are generally solvents, acids or bases, plant-derived alkaloids, or synthesized compounds.

Microbiological contaminants -- In this case, bacterial or fungal contamination can occur during the synthesis, storage, or handling of the drug (Cole et al., 2010).

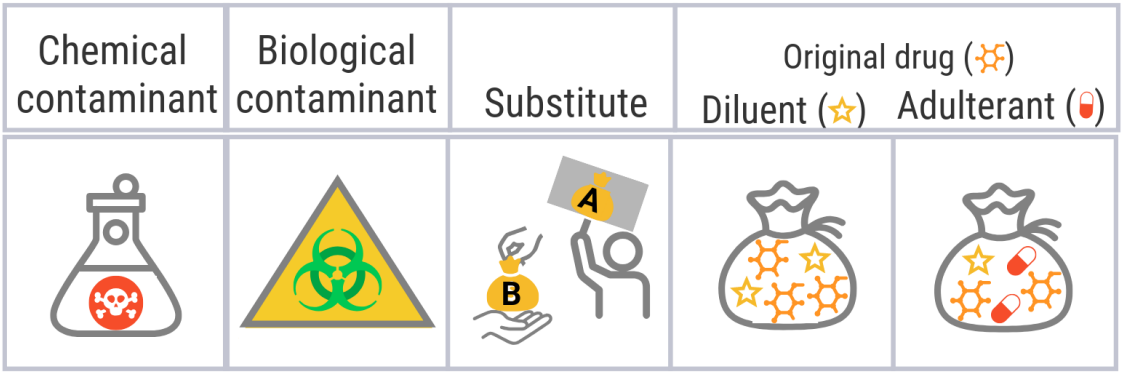
Diluents -- These are inert or structurally different compounds that are added to the drug to increase its bulk and reduce its active principle. In general, they share certain

characteristics with the drug itself, such as color, consistency, and taste (e.g., sugars, talc, mannitol).

Substitutes -- As the name implies, these substances are present instead of the drug intended for use. They are pharmacologically active and tend to share some of the effects of the drug they are substituting.

In some cases, an adulterant helps the drug to be administered; this is the case with caffeine or procaine, which can vaporize heroin at lower temperatures and thus make it easier to smoke (Cole et al., 2011).

Figure 1: Substances that can be found in drugs



Some authors classify adulterants as inactive to refer to diluents, and active to refer to the adulterants themselves. Most diluents are not highly toxic, even though they may be involved in the pathogenesis of some diseases related to chronic use (Wurcel et al., 2015). One example: Granulomas caused by a foreign body in the lung as a consequence of the local toxic effect of "inactive" adulterants have been reported as a complication of injected drugs (Dettmeyer et al., 2010).

Various authors include both dilution and substitution under the term adulteration, even though these are different concepts, as discussed above (Neves & Nunes, 2008).

The past 10 years have seen the emergence, particularly in countries of Eastern Europe, of new, homemade substances that are produced using industrial products, under conditions of extreme microbiological and toxicological risk, due to the products and doses used (Chintalova-Dallas et al., 2009; Hearne et al., 2016).

The effects of drugs depend on the substances that are used and on the routes of administration, as well as on the individual and his or her environment. From a

toxicological standpoint, the complexity lies in the fact that the effects sought and the undesired effects do not depend solely on one active principle but rather on a mix or variety of substances that may impact the addictive disorder and aggravate the acute and chronic toxicity of the original compound.

2. OBJECTIVES OF THIS STUDY

2.1. Overall objective:

- To describe the principal adulterants found in the drugs of highest prevalence and greatest toxicological impact.
- Provide up-to-date information on the studies conducted on the neurobiological and toxic effects of adulterants, and on the physical and psychic harm they cause.

2.2. Specific objectives:

- Differentiate in the existing literature between the harm associated with the consumption of adulterants and the consumption of adulterants in combination with the main drugs of use.
- Conduct a review of the data on deaths associated with the use of adulterants.
- Identify knowledge gaps in this area.

3. METHODOLOGY

The authors of this paper conducted a systematic review of scientific articles published in peer-reviewed scientific journals between January 1, 2000, and June 1, 2018, following the guidelines set out in the PRISMA Statement of 2009 (Moher et al., 2009), in accordance with the overall objectives proposed for this study. This review included an analysis of databases such as PubMed-Medline, Cochrane Library, VHL Virtual Health Library (which includes LILACS, SciELO, IBECS), Science Direct, Springer, and Scopus. Combinations of English and Spanish terms were used, following the Medical Subject Headings (MeSH):

- “adulterants + drugs of abuse,” “cutting agents + drugs of abuse,” “alcohol + adulterations,” and combinations of “overdose,” “acute poisoning,” “toxicity,” “death,” “cocaine,” “opioids,” “opiates,” “heroin,” “fentanyl,” “marijuana,”

"cannabis," "cannabinoids," "amphetamines," "MDMA," "ecstasy," "LSD," "phenylethylamines," "new psychoactive substances," "levamisole," "phenacetin," and "methanol."

Inclusion criteria:

- analytical and review studies that confirm the presence of adulterants in the samples analyzed.
- preclinical studies and clinical case reports that show an association between the presence of an adulterant or adulterants and a toxic effect and/or harm to health. The presence of adulterants must have been confirmed analytically in the substance(s) used and/or in biological fluids/tissues in the cases examined, or the reported toxic effect is strongly associated, from a clinical and epidemiological standpoint, with the adulterant(s) involved.

A descriptive review was also conducted of electronic and printed sources of information, using the same terms and combinations and the same criteria for inclusion, in order to include studies that were considered to be important but were not included in the systematic review of the databases noted above:

- articles in peer-reviewed journals that were not recognized by the search strategy used in the systematic review but that might be relevant for this study (e.g., case reports).
- articles in books, supplements, monographs, articles in non-peer-reviewed journals, technical reports, or other databases in the following areas: preclinical, analytical, clinical, and forensic.
- information from courses, seminars, and congresses related to the topic (abstracts, reports, presentations).
- information from academic institutes and societies, and governmental and nongovernmental agencies.

3.1. Systematic review

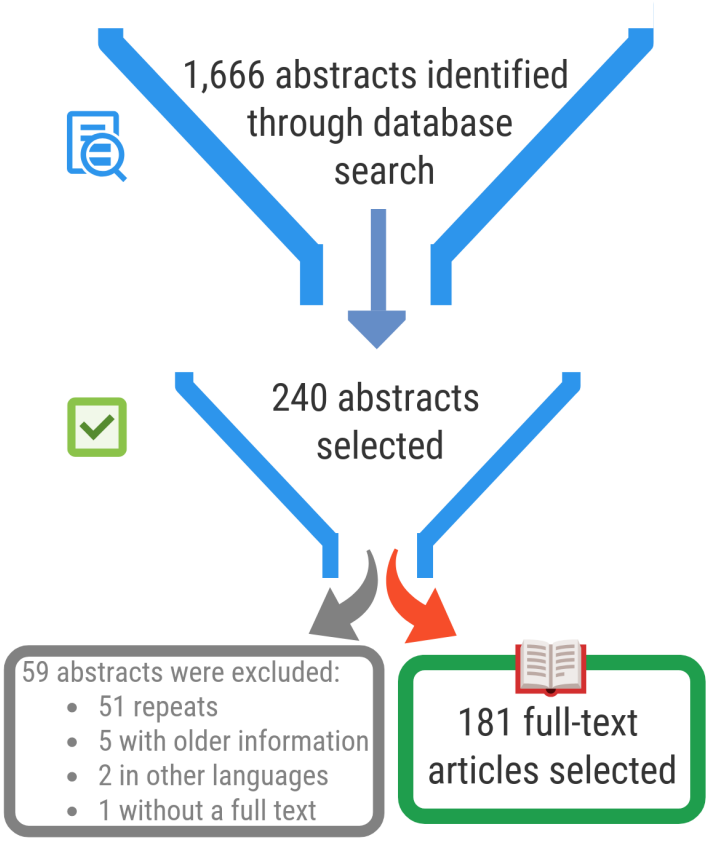
The systematic review identified 1,666 abstracts or summaries in the databases listed above, 240 of which were selected.

Of these, the following were excluded:

- 51 abstracts that were repeats.
- 5 abstracts that included information prior to the year 2000.
- 2 abstracts whose full text was published in a language other than English or Spanish.
- 1 abstract published without a full text.

Therefore, 181 abstracts that were published with a full text were selected for review **(Figure 2)**.

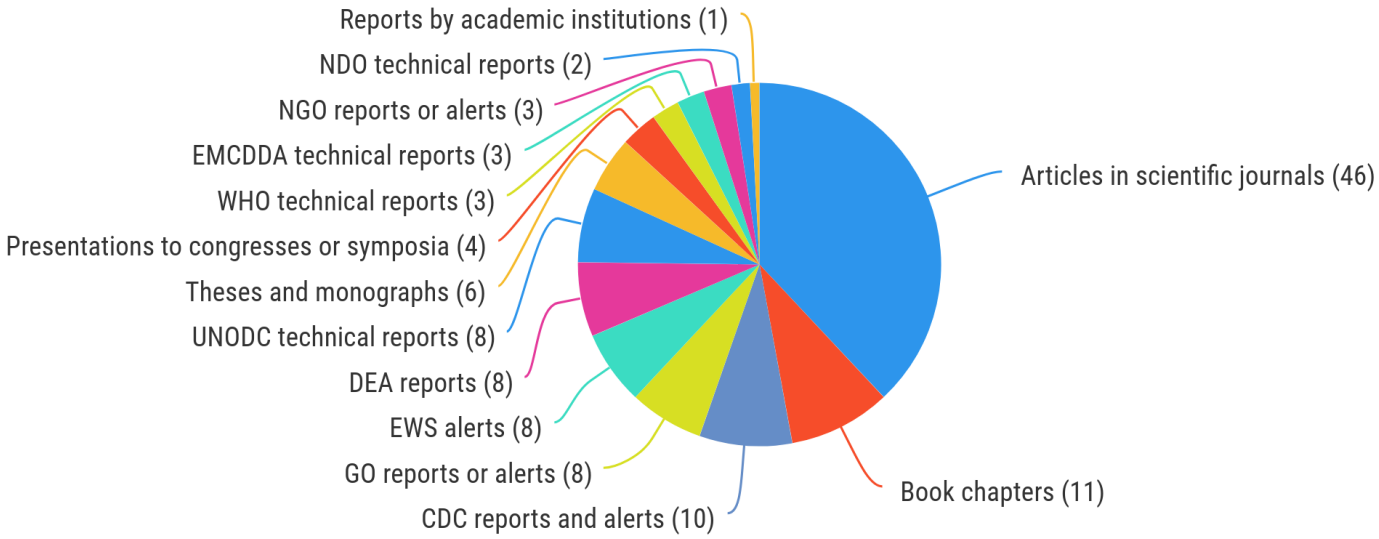
Figure 2: Algorithm for selection of published works for the systematic review



3.2. Descriptive review

In line with the above objectives, **Figure 3** gives the sources of information resulting from the descriptive review.

Figure 3: Sources of information in the descriptive review



Note: absolut numbers for each source are shown.

GO=Governmental organizations; NGO=Nongovernmental organizations; EWS=Early warning systems; NDO=National drug observatories; CDC=U.S. Centers for Disease Control and Prevention; DEA=U.S. Drug Enforcement Administration; EMCDDA= European Monitoring Centre for Drugs and Drug Addiction; UNODC=United Nations Office on Drugs and Crime; WHO=World Health Organization.

The following sources of information on adulterations of cocaine in Brazil were also used for the case reports or clinical and/or forensic case series:

- *Capes* Periodicals Portal (www.periodicos.capes.gov.br/) using the key words: "caffeine, Brazil," "levamisole, Brazil," "phenacetin, Brazil," "lidocaine, Brazil," "hydroxyzine, Brazil," and "procaine, Brazil" as descriptors.
- Thesis portal of the University of São Paulo (www.teses.usp.br/) with key words "cocaine, sample (*amostra*)."

4. ADULTERANTS FOUND IN THE DRUGS TESTED

4.1. Cocaine and its derivatives (cocaine hydrochloride, smokable cocaines)

The alkaloid "cocaine" comes from the leaves of a plant in the *Erythroxylaceae* family. A multistage production process yields derivatives with different physical/chemical properties and levels of purity, conditions that determine the route of administration and the onset of the effects.

Cocaine base paste (CBP) is an intermediate product in the production of cocaine hydrochloride. It is a yellowish-white or brownish powder of pasty consistency. CBP is alkaline and liposoluble. Its low volatility point and its properties as a base allow it to be smoked. It contains varying percentages of cocaine alkaloid, other coca leaf alkaloids, contaminants and impurities resulting from the manufacturing process, and adulterants. In Argentina, it is called *pasta base* or *paco*, and *pasta base* also in Chile and Uruguay. In Paraguay, it is called *chespi* or *crack*. In Brazil, depending on the degree of adulteration of the CBP, it is termed *merla* (with a high percentage of solvents and battery acids) or *oxi* (residue of the *pasta base* with gasoline, kerosene, and lime). A "refined" cocaine base has also been found (Zacca et al., 2014; Raverta et al., 2016).

Cocaine hydrochloride is obtained from cocaine base paste which is treated with hydrochloric acid; the cocaine hydrochloride is subsequently extracted with acetone and ethanol. It is a white, crystalline powder, bitter in taste, which may be inhaled or snorted. The percentage of cocaine ranges from 15% to 75%. It is an acid form of cocaine, which makes it water-soluble and therefore also able to be used intravenously.

Cocaine base or crack is obtained by adding ammonia to an aqueous solution of cocaine hydrochloride with sodium bicarbonate to alkalize it. It is heated to 98°C, which causes the free base to precipitate in the form of paste, which when dried looks like porcelain and forms large flakes.

Both CBP and crack are smokable cocaines, the composition of which varies according to the local, regional, and worldwide epidemiological context.

Free base is produced when the cocaine hydrochloride alkaloid is released using a base such as bicarbonate, together with solvents such as ammonia and ether, heated to high temperatures (800°C), which means that it is rarely consumed.

Adulterations have been reported in samples of all of the coca leaf derivatives discussed above (Castaño, 2003; Pascale, 2005; Pascale, Negrin, & Laborde, 2010; UNODC, 2012).

4.1.1. Presence of adulterants in South America

4.1.1.1. Analyses of samples seized in Brazil

According to information already reported in the study coordinated by the Inter-American Drug Abuse Control Commission (Raverta et al., 2016), smokable cocaines in Brazil -- even though they may be called *crack* or, less often, *merla* or *oxy* -- show characteristics of cocaine base paste. Whatever their composition or form in which they were obtained, in Brazil it is generally agreed (by, for example, academics, health services, the media) to use the word *crack* for smokable cocaine. Tests to distinguish the various forms of smokable cocaine are conducted only in the laboratories of the Federal Police. When such analyses are conducted in the states, they are for academic purposes and not as part of routine laboratory work.

The criteria used by the Brazilian Federal Police are the same as those used by the U.S. Drug Enforcement Administration (DEA). Samples containing less than 2% of cinnamoylcocaine content relative to cocaine are classified as "highly oxidized"; those with 2% to 6% are classified as "moderately oxidized"; and those with more than 6% are classified as "not oxidized." The “not oxidized” samples are considered to be “coca paste” or “base paste,” while the highly oxidized and moderately oxidized samples are classified as “cocaine base.” The molten, non-crumbly rocks of coca that contain significant quantities of carbonates are classified as crack. *Merla* is also found in central Brazil; it is cocaine in freebase form mixed with water (up to 70%) and sodium salts (such as sulfate, carbonate, and bicarbonate.)

Table 2 shows the studies that analyzed samples of cocaine seized in Brazil during the period under study.

Table 1: Adulterants founds in seizures of crack/cocaine[1] *in natura*[†]

Studies	Country/ countries	Year	State(s) (City/cities)*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
Mídio et al., 2000	Brazil	1996	SP (São Paulo)	Cocaine hydrochloride	233	HPTLC and TLC GC/FID and GC/MS	1–96.42	Lid, Pro
Bernardo et al., 2003	Brazil	2001	MG (Alfenas & Varginha)	Cocaine (form not determined)	209	Scott Test and TLC GC/FID	4.3–87.1	Caf, Lid, Pri
Carvalho & Mídio, 2003	Brazil	1997	SP (São Paulo)	Cocaine hydrochloride	389	TLC GC/FID GC/MS	0–72.5	Caf, Lid, Pro

[1] For the purposes of this survey, the term *crack* refers to the various forms of smokable cocaine, and is the term normally used in Brazil. In articles where a distinction is made, that will be noted. The phrase "not determined" was used when it was not possible to determine the form, and appears here as "Cocaine (form not determined)."

Studies	Country/ countries	Year	State(s) (City/cities)*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
Chasin et al., 2003	Brazil	2000	SP (São Paulo)	Crack, cocaine hydrochloride	121	GC/FID	50	Caf, Lid
da Silva Junior et al., 2012	Brazil	2009–2011	AC	Crack, cocaine, *oxi*[2] cocaine	43	IR GC/FID HS/GC/MS	50–85 (average 73)	Phen
Costa et al., 2013	Brazil	2011–2012	SP (São Paulo)	Crack, *pasta base*, cocaine base, cocaine hydrochloride	221	GC/FID	–	Ami, Ben, Caf, Lid, Phen, Pro
Magalhães, 2013	Brazil	July 2008–May 2010	AM MG	Cocaine (form not determined)	31	GC/MS	AM: 15.4–97.8	N/C (AM) Ben, Caf, Lid

[2] The term *Oxi* refers to the presence of calcium oxide and kerosene (or gasoline) instead of carbonate or bicarbonate, normally present in the form called *crack*.

Studies	Country/ countries	Year	State(s) (City/cities)*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
							MG: 6.4–75.3	
Neves, 2013	Brazil	2011–2012	RO (Porto Velho)	Crack, *pasta base*, cocaine hydrochloride, *merla*	116	GC/MS	41–80	Ami, Lid
Botelho et al., 2014	Brazil	2009–2012	AC, AM, DF, MT, MS, PR, RO, SP	Crack, *pasta base*, cocaine hydrochloride	210	GC/FID	71	Ben, Caf, Dil, Hyd, Lev, Lid, Phen
Fukushima et al., 2014	Brazil	2008–2009	SP (São Paulo)	Crack	404	TLC GC/FID	71.3	Ben, Caf, Lid, Pro
Fiorani, 2014	Brazil	2007–2012	PR	Crack (or undifferentiated paste), cocaine	115	HPLC/DAD	0–90	Caf, Dil, Phen

Studies	Country/ countries	Year	State(s) (City/cities)*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
				hydrochloride				
Zacca et al., 2014	Brazil		AC, AM, MS, RO, SP (São Paulo)	Crack, cocaine	267	GC/FID	69–74	Ben, Caf, Dil, Lid, Phen
Grobério et al., 2015	Brazil	2009–-2013	AC, AM, DF, PR, MT, MS, SP	Crack, cocaine hydrochloride	1085	ATR/FT/IR GC/FID	24.2–99.9	Ace, Ami, Ben, Caf, Dil, Hyd, Phen, Lid, Lev, Pro
Lapachinske, 2015	Brazil	2011	SP (São Paulo)	Cocaine (form not determined)	54	Scott test GC/MS GC/NPD	16.5–91.4	Caf, Phen, Lev, Lid, 4-dimethylaminoantipyrine
Marcelo et al., 2015	Brazil	2011–2012	RS	Crack, cocaine hydrochloride	513	FT/IR	–	Caf, Lid, Phen
Penido et al., 2015	Brazil	N/C	AM	Crack, cocaine	N/C	Raman FT/IR/ATR	–	Lid, Caf, Ben

Studies	Country/ countries	Year	State(s) (City/cities)*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
				hydrochloride, and paste				
De Souza et. al., 2016	Brazil	2008–2012	ES	Cocaine (form not determined)	512	GC/MS	–	Caf, Phen, Caf
Maldaner et al., 2015	Brazil	2010–2013	DF	Crack, cocaine hydrochloride	159	GC/FID	5.5–99.9	Ami, Caf, Ben, Dil, Lev, Lid, Phen
Maldaner et al., 2016	Brazil	2011–2014	BA (Salvador), DF, GO (Goiânia), MT (Primavera do Leste), SP (São Paulo)	Crack, cocaine hydrochloride, cocaine base, and form not determined	642	GC/FID	44–66 (mean: 49.8)	Ami, Ben, Caf, Lev, Lid, Phen, Pro
Ferreira, 2018	Brazil	2014–2015	SP (Araçatuba and region)	Cocaine (form not determined)	92	GC/MS	–	Ami, Ben, Caf, Car, Ket, Lev, Lid, Meth, Phen, Ben

* AC=Acre, AM=Amazonas, BA=Bahia, DF=Distrito Federal, ES=Espírito Santo, GO=Goiás, MG=Minas Gerais, MS=Mato Grosso do Sul, MT=Mato Grosso, PR=Paraná, RO=Rondônia, RS=Rio Grande do Sul, SP=São Paulo.

** TLC=thin-layer chromatography; HPTLC=high-performance thin-layer chromatography; TLC=thin-layer chromatography; GC/FID=gas chromatography with flame ionization detector; GC/MS=gas chromatography/mass spectrometry; HPLC/DAD=high-performance liquid chromatography with diode-array detection; IR=infrared spectroscopy; HS=Headspace GC/MS technique; ATR/FT/IR=attenuated total reflectance Fourier transform infrared spectroscopy; GC/NPD=gas chromatography with nitrogen phosphorus detector.

*** Average concentration or limit of the findings.

**** Ace=acetaminophen (paracetamol), Ami=aminopyrine, Ben=benzocaine, Caf=caffeine, Car=carisoprodol, Dil=diltiazem, Ket=ketamine, Hyd=hydroxyzine, Lid=lidocaine, Lev=levamisole, MDMA=3,4-methylenedioxymethamphetamine or 1-(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine, Meth=methotrimeprazine, Phen=phenacetin, Pri=prilocaine, Pro=procaine.

† One or more adulterants may be present in each sample.

Mídio et al. (2000) analyzed samples positive for cocaine or adulterants by performing TLC or HPTLC screening, using GC/FID, and the samples that contained adulterants were confirmed by GC/MS. The adulterants found were lidocaine in 3.41% of the samples and procaine with a frequency of 0.9%. The levels of cocaine varied: 3.44% of the samples had a content of cocaine that ranged from 0% to 1%; 76.82% of the samples had cocaine content of over 1% and less than 30%; 9.01% of the samples contained between 30% and 50% cocaine; 6.87% of the samples had a cocaine content of 50% to 80%; and 3.86% of the samples had a cocaine content of 80% to 96.42%.

In the study by Bernardo et al. (2003), no initial tests were done to distinguish between cocaine hydrochloride and cocaine base, and thus the table considers the samples as "cocaine." Cocaine was found in 80.9% of the samples analyzed; however, there were samples sold as cocaine that do not contain the cocaine compound. Caffeine was found in 50.2% of the samples, with a content ranging from 2.8% to 63.3%, and lidocaine was found in 65%, with a variable content of 0.5% to 92%. Prilocaine was the adulterant found most infrequently, in 11% of the samples, with a content of 1.2% to 20.7%. In addition to the analyses of the adulterants, qualitative and TLC testing was conducted to verify the presence of diluents. The tests showed that carbonates and bicarbonates were found in 41.2% of the samples, talc in 51.2%, and sugars in 9.6%.

Carvalho et al. found the adulterants lidocaine and procaine in 19 samples in concentrations ranging from 1% to 60.2% of the total. Caffeine was found in only two samples. In addition to the search for adulterants, the research also found the presence of diluents using spot tests and TLC analysis, which showed the following compounds: carbonates and bicarbonates, in 19.3%, silicates in 13.9%, sugars (glucose, lactose, and saccharose) in 9.6%, starch in 5.6%, borates in 3.1%, and sulfates in 2.8% of the samples (Carvalho & Mídio, 2003).

In the study by Chasin et al., lidocaine appeared as an adulterant of cocaine in 91% of the cases analyzed, and caffeine in 64%. The average content of lidocaine in the samples was 27.2%, but the caffeine content was not determined. This study was designed to use the data from analysis of the seized materials to establish a parallel with the findings in the biological matrices that were also analyzed (Chasin et al., 2003).

Da Silva Junior et al. (2012) reported phenacetin as the only adulterant, at levels ranging from 0.4% to 10% in five samples seized by the Federal Police of Acre and in seven samples seized by the State Police of Acre.

In the study by Costa et al. (2013), the principal drug measured was phenacetin, found in 126 of the samples with an average content of 8.3%. Other adulterants identified were as follows (number/average content): lidocaine (15/2.3%), caffeine (9/3.4%), benzocaine (5/3.3%), and procaine (2/0.5%). No samples containing levamisole, hydroxyzine, or diltiazem were found. Qualitative analyses showed that in 51 samples, aminopyrine was found in addition to phenacetin.

Magalhães et al. (2013) conducted GC/MS analysis of samples seized in the state of Amazonas. The adulterants sought were not detected, although the cocaine content in these samples varied from 15.4% to 97.8%. In the samples seized in Minas Gerais, caffeine was the most common adulterant, found in 76% of the samples, with content ranging from 0.55% to 64.53%; this was followed by lidocaine, present in 66.7% of the samples, with content of 1.63% to 57.67%, and benzocaine, which was found in only one sample from Minas Gerais, with a content of 8.48%. The purity of the cocaine in the samples from that state ranged from 6.4% to 75.3%.

Neves (2013) reported that of 116 samples analyzed, 13.8% contained aminopyrine while only 0.86% contained lidocaine. The diluents most frequently found were sodium (97.5%), bicarbonate/carbonate (53.3%), sulphate (21.6%), magnesium (10%), and borate (11.7%).

In the study by Botelho et al. (2014), phenacetin was the adulterant that was found most frequently (30% of the total number of samples), and it was identified in seizures in all the states. Levamisole (18%), caffeine (6%), and lidocaine (4%) were also identified. Benzocaine, diltiazem, and hydroxyzine were identified in only two of the samples of the total number analyzed.

Fukushima et al. (2014) observed that the adulterants identified in São Paulo were as follows (number/average content): lidocaine (25/0.7%), benzocaine (19/0.6%), caffeine (22/0.4%), and procaine (9/0.02%). The absolute number of the samples that contained adulterants were, respectively, 9.16% lidocaine, benzocaine, and caffeine and 14.57% other adulterants, totaling 23.73%.

The study by Fiorani et al. (2014) showed that caffeine was the adulterant most often detected in 37.4% of the samples, diltiazem was found in only one sample, and phenacetin in five samples. The study also investigated degradation products, and found benzoylecgonine in 81 samples and benzoic acid in four. It found differences in the cocaine content: 13% of the samples had no detectable level of cocaine, while 45.2% had a cocaine content of between 80% and 97%.

Zacca et al. (2014) reported that phenacetin was the adulterant most frequently found, ranging from 2% to 14% in samples from Amazonas. Two samples, from Amazonas and Mato Grosso do Sul, had a caffeine content of 2% and 12%, respectively. One of the samples from the state of Amazonas contained 3% diltiazem.

In the study by Grobério et al. (2014), the authors differentiated between the adulterants found in crack and those found in cocaine hydrochloride. The following were found in crack: benzocaine in 6.3% of the samples, and also acetaminophen or paracetamol (1.2%), phenacetin (41.1%), caffeine (1.7%), lidocaine (3.4%), aminopyrine (13.6%), levamisole (1%), hydroxyzine (3.2%), and diltiazem (0.3%). In the samples of cocaine hydrochloride, phenacetin was found in 2.4% of the samples, and also caffeine (2.4%), lidocaine (3.3%), aminopyrine (1.8%), levamisole (7.9%), procaine (0.5%), and diltiazem (8%).

The study by Lapachinske et al. (2015) analyzed samples seized in the International Airport of São Paulo. It was significant in demonstrating that unlike what had been expected and reported in the literature, the cocaine destined for international trafficking did not have a high level of purity, and most of it was adulterated (70.4%). The adulterants detected were: levamisole in 55.6% of the samples, with content ranging from 0.7% to 23%; lidocaine in 14.8%, with content of 0.6%–30.6%; caffeine in 9.2%, with content of 2.4%–16.1%; phenacetin in 9.2%, with content of 5.6%–12.1%; and 4-dimethylaminoantipyrine in 1.8%, with content of 1.2%.

Marcelo et al. (2015) analyzed 313 seizures of cocaine (277 of cocaine hydrochloride and 36 of crack) in the state of Rio Grande do Sul using Fourier transform infrared spectroscopy (FT/IR) in the “fingerprint region” (1800 - 650 cm-1) to detect possible adulterants. Chemometrics was used to identify similarities among standards of cocaine-adulterant mixtures and distinguish between the presence of cocaine, salt, or base. Fifteen combinations of standard solid mixtures of cocaine (salt and base),

phenacetin, lidocaine, and caffeine, in different preset concentrations, and the qualitative standard spectra of these mixes were obtained. Qualitatively, the samples of cocaine hydrochloride were mostly adulterated with caffeine and lidocaine, while the crack was adulterated only with phenacetin.

The study by Penido et al. (2015) proposed comparing the use of Raman and FT/IR techniques as methods to identify cocaine and the possible adulterants added, as well as degradation products, in samples seized by the police. Raman spectra and FT/IR/ATR spectra were obtained of all the samples and also of some substances commonly used as adulterants (caffeine, lidocaine, benzocaine, as well as diluents, aluminum sulfate, sodium carbonate, sodium bicarbonate, magnesium trisilicate, and starch). It was found that powder cocaine base, powdered cocaine hydrochloride, and rocks of crack showed differences in their chemical structures, which were differentiated by the two methodologies, Raman spectroscopy and FT/IR spectroscopy. The majority of the samples showed characteristic peaks of degradation products, such as benzoylecgonine and benzoic acid, while some showed evidence of adulteration with aluminum sulfate and sodium carbonate. Raman spectroscopy proved to be better than FT/IR for identifying benzoic acid and inorganic adulterants in cocaine.

Maldaner conducted two studies with different collaborators in 2015 and 2016. In the first one, the samples of cocaine hydrochloride showed the following adulterants, with the following frequencies and content: 5% of the samples contained benzocaine, with a mean content of 0.6%; 26% showed phenacetin, with an average content of 24%; 11% showed lidocaine, with an average content of 9.7%; 12% showed aminopyrine, with an average content of 3.1%; 19% showed levamisole, with an average content of 6.3%; and 5% showed diltiazem, with an average content of 2.5%. For the samples of crack, the distribution was as follows: 11% of the samples contained benzocaine, with an average content of 0.6%; 53% contained phenacetin, with an average content of 24.6%; 11% showed caffeine, with an average content of 0.6%; 4% showed lidocaine, with an average content of 3.3%; and 25% of the samples showed aminopyrine, with an average content of 3.1% (Maldaner et al., 2015).

In the second study, the smokable forms of cocaine had an average level of purity of 66%, while the purity was 44.5% in the form of hydrochloride salts. In the samples where adulteration was identified, phenacetin was the most frequent substance, present in 53% of the samples. Caffeine and lidocaine were the adulterants found most often in

the samples of cocaine hydrochloride. In some samples (referenced as "n.d." for not determined), it was not possible to determine the form of presentation because of low purity and high adulteration. In these samples, phenacetin, caffeine, and lidocaine were the adulterants found most often. The findings show the predominance of phenacetin as the principal adulterant of street cocaine, found in 47% of the samples. The adulterants caffeine and lidocaine (19% and 13%, respectively) were more prevalent than aminopyrine (8%), benzocaine (7%), and levamisole (3%), while procaine was identified in one sample (Maldaner et al., 2016).

The samples analyzed by De Souza et al. (2016) were collected in 15 cities in the state of Espírito Santo: Cariacica, Guarapari, Vitória, Serra, Vila Velha, Alegre, Cachoeiro de Itapemirim, Anchieta, Linhares, Colatina, Aracruz, São Mateus, Pinheiros, Conceição da Barra, and Barra de São Francisco. Cocaine and its adulterants were found as follows, by the year in which the samples were seized: for samples seized in 2008, the results were: cocaine (75%), caffeine (18%), and lidocaine (25%). In the samples seized in 2009, the frequency was: cocaine (83%), caffeine (23%), and lidocaine (25%). The frequency was identical in 2010 and 2011: cocaine (98%), caffeine (15%), and lidocaine (6%). Finally, in 2012 cocaine and its adulterants were obtained as follows: cocaine (99%), phenacetin (13%), caffeine (12%), and lidocaine (4%). In addition to investigating possible adulterants present in samples of cocaine seized in the state of Espírito Santo, this research was also designed to propose a method for making quantitative estimates of the substances found, using chemometric tools (De Souza et al., 2016).

A recent master's research paper studied samples that were collected at random from the Crime Institute in Araçatuba. These samples came from seizures made in the cities of Araçatuba (65.34% of the samples), Birigui (4.95%), Penápolis (4.95%), Andradina (0.99%), Guararapes (2.97%), Valparaíso (2.97%), Buritama (1.98%), Coroados (0.99%), General Salgado (0.99%), Nova Luzitânia (0.99%), and Pereira Barreto (0.99%). The research found adulterants in the following frequencies: caffeine, 68.48%; lidocaine, 47.83%; phenacetin, 45.65%; levamisole, 30.43%; carisoprodol, 2.17%; benzocaine, 1.09%; methotrimeprazine, 1.09%; aminopyrine, 2.17%; and ketamine hydrochloride, 1.09%. In addition to these adulterants, other alkaloids were identified as the product of thermal degradation, such as methyl ecgonine ester in

78.26% of the samples, isoforms of natural cinnamoylcocaine alkaloid in 9.78%, and the oxidation product norcocaine in 6.53% of the samples (Ferreira, 2018).

This review during the period under study shows variable percentages of adulterants in samples of cocaine hydrochloride and smokable cocaines in Brazil. Caffeine and lidocaine were the adulterants found most frequently throughout the period, while a significant increase has been seen in recent years in phenacetin, both qualitatively and quantitatively, and levamisole to a lesser extent. Although the level of purity of cocaine is highly variable, more recent studies also show that the level of purity in smokable cocaines is greater than in cocaine hydrochloride. Other adulterants found were benzocaine, procaine, prilocaine, acetaminophen, aminopyrine, hydroxyzine, and diltiazem.

4.1.1.2. Analysis conducted through the PRADICAN project

In 2012, the European Union's Programme against Illicit Drugs in the Andean Community (know by its Spanish language acronym, PRADICAN) quantified and described the chemical composition of 608 samples of cocaine (393 of cocaine base and 215 of cocaine hydrochloride) seized in 27 cities of the Andean subregion in Bolivia, Colombia, and Peru, using gas chromatography/mass spectroscopy **(Table 2)**. Three adulterants were found in Bolivia (phenacetin, lidocaine, and mannitol). Mass spectroscopy could not be used in Bolivia, which meant that no findings could be obtained for a larger number of adulterants. No detailed information was obtained from the analysis in that country (Secretaría General de la Comunidad Andina, 2013a). Seven adulterants were found in the samples studied in Colombia (caffeine, phenacetin, lidocaine, aminopyrine, levamisole, diltiazem, and hydroxyzine). Of these, the adulterants found most often were: caffeine (76.7%), phenacetin (52.8%), levamisole (21.7%), and lidocaine (15.5%) (Secretaría General de la Comunidad Andina, 2013b). In Peru, caffeine was reported in three samples, phenacetin in one sample, lidocaine in three samples, and orphenadrine in one sample. The latter drug, used as a muscle relaxant, was described as rarely found as a cocaine adulterant (Secretaría General de la Comunidad Andina, 2012).

4.1.1.3. Analysis conducted as part of the project on smokable cocaine in Argentina, Brazil, Chile, Paraguay, and Uruguay (OID-CICAD-SMS-OAS)

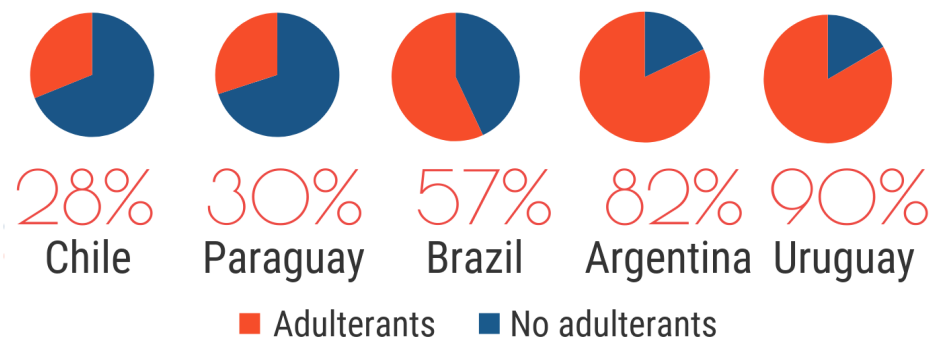
The project on smokable cocaine in Argentina, Brazil, Chile, Paraguay, and Uruguay provided detailed information on the presence of adulterants in samples of smokable cocaine substances in the countries involved. The study was coordinated by the Inter-American Observatory on Drugs of the Inter-American Drug Abuse Control Commission, part of the Secretariat for Multidimensional Security of the Organization of American States (OID-CICAD-SMS-OAS).

In Argentina, analyses were included of 4,590 samples from 28 judicial cases in the cities of La Matanza, Lomas de Zamora, and La Plata seized between October 2014 and February 2015 (SEDRONAR, 2015). In Brazil, 642 samples seized between 2011 and 2014 in five Brazilian states were included (Maldaner et al., 2016). In Chile, 25,175 samples of smokable cocaines seized nationwide over the 2009–2014 period were analyzed. In Paraguay, the project included 3,175 samples of cocaine taken from seizures throughout the country during the period 2009-2014. Fifty-six percent (1,766 samples) were forms of smokable cocaine, and 44% (1,409 samples) were cocaine hydrochloride. In Uruguay, an analysis was done of 306 samples of smokable cocaine selected at random from seizures in 2014 and 2015 (62 and 244 samples, respectively) (Scorza, 2015).

The principal findings of the project are detailed in **Table 2.**

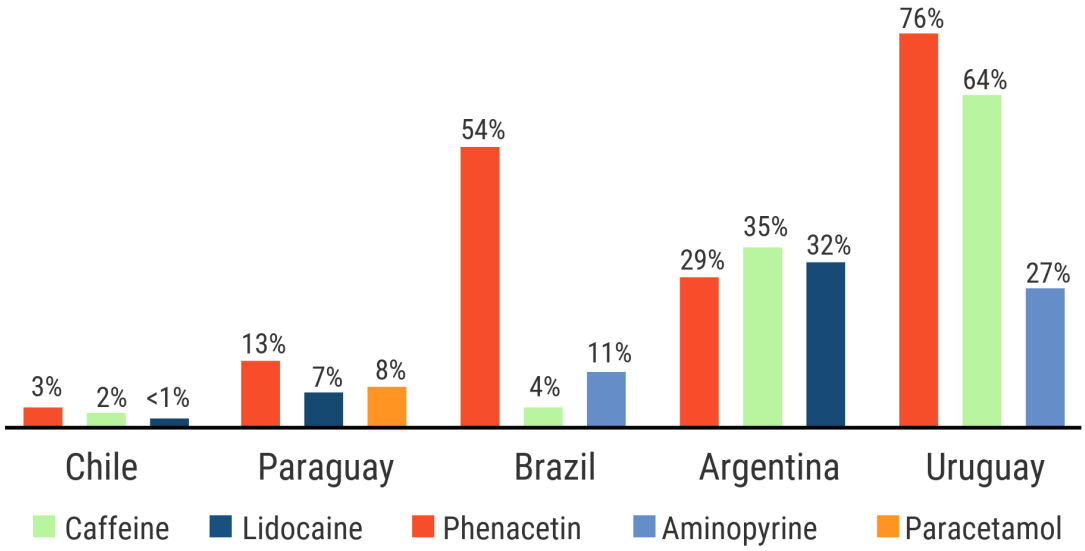
The percentage of adulterated samples is shown in **Figure 4**. The percent of samples adulterated was higher in Argentina, Brazil, and Uruguay than in Chile and Paraguay.

Figure 4: **Percentage of adultered samples by country**



The percentages of adulterants in samples of smokable cocaines available on the street varied by country, and is shown in **Figure 5**.

Figure 5: **The three most common adulterants in smokable cocaine per country**



Note: Percents refer to the % of samples that tested positive for each substance. Some samples could contain more than one adulterant.

Phenacetin was found in all the adulterated samples, with high prevalence in Brazil and Uruguay. In Chile, the presence of adulterants declined during the period under study. Paracetamol, caffeine, lidocaine, and aminopyrine were among the three most important adulterants found in the countries examined. Levamisole was also present in percentages that varied by country, but with an overall upward trend (Duffau et al., 2015; Raverta et al., 2016).

4.1.1.4. Other analyses conducted in South America

A study in Colombia described the analysis of 65 samples of cocaine hydrochloride seized in different areas of the country. Adulterants such as caffeine (30.77%) and hydroxyzine (24.62%) were most frequently found. Alkaloids such as norcocaine (93.85%), tropacocaine (92.31%), and benzoylecgonine (92.31%) were also found, as well as 136 residual solvents (ethanol, methanol, ether, ketones, and other hydrocarbons) in the samples analyzed (Garzón, Parada, & Florián, 2009).

Another study analyzed 109 samples of cocaine base paste seized in Colombia in the first half of 2010, and found an average purity of 37%. Caffeine was identified as an

adulterant in 57% of the samples and phenacetin in 2.8%. Other coca alkaloids (tropacocaine, trans cinnamoylcocaine, norcocaine, and ecgonine methyl ester) were also reported in this study (Sabogal Carmona & Urrego Novoa, 2012).

Both studies are detailed in **Table 2**.

Table 2: Adulterants found in seizures of smokable cocaine and cocaine hydrochloride in South America†

Studies	Country/ Countries	Year	State(s) City/cities Places*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
Garzón et al., 2009	Colombia	N/R	Throughout the country	Cocaine hydrochloride	65	GC/MS/FID HS/GC/FID	64.58–95.83	Caf, Lid, Lev, Phen
Sabogal Carmona et al., 2012	Colombia	January–June 2010	Throughout the country	*Basuco* or cocaine base paste	103	GC/MS	4–70 (mean: 37)	Caf, Phen
PRADICAN project, 2013	Bolivia Colombia Peru	2012	3 cities (Bolivia)	Cocaine hydrochloride and cocaine base	172	FID	Mean: 67.1	Phen, Lid, Man
			13 cities (Colombia)	Cocaine hydrochloride and cocaine base	373	GC/MS/FID	Mean: 50.9	Caf, Phen, Lid, Lev, Ami, Hyd, Dil
			9 cities (Peru)	Cocaine hydrochloride and cocaine base	63	GC/MS	Mean: 51.0	Caf, Phen, Lid, Orph

Studies	Country/ Countries	Year	State(s) City/cities Places*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
OID-CICAD-SMS-OAS project, 2016	Argentina	October 2014–February 2015	La Matanza, Lomas de Zamora, and La Plata	Samples of cocaine sold as *paco*	4,590 (179 batches)	GC/MS/FID	0.16–73.23	Caf, Lid, Phen, Dil, Ben, Ace
	Brazil	2011–2014	BA (Salvador), DF, GO (Goiânia), MT (Primavera do Leste), SP (São Paulo)	Crack, cocaine hydrochloride, cocaine base, and form not determined	642	GC/FID	44–66 (mean: 49.8)	Ben, Phen, Caf, Lid, Ami, Lev, Pro
	Chile	2009–2014	Throughout the country, in regions	Smokable cocaines	25,175	GC/FID GC/MS	2–99 (mean: 35.2)	Caf, Phen, Lid, Ami, Lev, Pro, Carb
	Paraguay	2009–2014	Throughout the country	Cocaine hydrochloride, cocaine base	3,175	GC/FID GC/MS	1–100 (mean: 56.72)	Caf, Lid, Ben, Phen, Lev, Ace
	Uruguay	2014–	17 departments	Cocaine base	306	Modified	Mean: 40	Caf, Phen,

Studies	Country/ Countries	Year	State(s) City/cities Places*	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) ***	Adulterants found****
		2015				Scott test, GC/MS, HPLC/DAD		Ami, Lid, Ben, Lev, Pro

* BA=Bahia, DF=Distrito Federal, GO=Goiás, MG=Minas Gerais, MT=Mato Grosso, SP=São Paulo.

** GC/FID=gas chromatography with flame ionization detector; GC/MS=gas chromatography with mass spectrometry; HPLC/DAD=high-performance liquid chromatography with diode-array detection; GC/MS/FID=gas chromatography/mass spectrometry and flame ionization detector; HS/GC/FID=Headspace/gas chromatography with flame ionization detector.

*** Average concentration or limit of the findings.

**** Ace=acetaminophen, Ami=aminopyrine, Ben=benzocaine, Caf=caffeine, Carb=carbonates, Dil=diltiazem, Hyd=hydroxycine, Lid=lidocaine, Lev=levamisole, Man=mannitol, Phen=phenacetin, Pro=procaine.

N/R=not reported.

† One or more adulterants may be present in each sample.

4.1.2. Studies and analyses reported in Europe

In their analysis of samples of cocaine seized in the city of Aarhus, Denmark, over a two-year period (2002-2003), Andreasen, Lindholst, & Kaa (2009) found adulterants in 87% of the total of 147 samples. Lidocaine was the adulterant found most often (65%), followed by phenacetin (42%), caffeine (24%), and creatine (22%).

A study by Brunt et al. (2009) analyzed 2,824 samples of cocaine in users between 1999 and 2007, and linked the presence of adulterants to harm to health. Phenacetin, lidocaine, procaine, benzocaine, caffeine, hydroxyzine, and diltiazem were the adulterants found most frequently.

Evrard, Legleye, & Cadet-Taïrou (2010) analyzed 343 samples of cocaine in France, 75% of which contained at least one adulterant. Phenacetin (54%), caffeine (17%), acetaminophen (14%), and diltiazem and lidocaine (11%) were the ones most frequently reported.

Schneider & Meys (2011) analyzed 471 samples of cocaine seized in Luxembourg over the 2005-2010 period. The lowest level of purity of cocaine was reported in 2009 (43.2%) and the highest in 2005 (54.7%). Fourteen adulterants were identified in different samples, with phenacetin as the predominant substance (24% on average), followed by acetaminophen and ibuprofen, averaging 16.5% and 10.3% respectively. The authors reported fluctuations in the presence of adulterants during the period under study. Levamisole showed an upward trend over this period.

In the study by Broséus et al. (2015), 6,586 samples of cocaine were seized in the western region of Switzerland between 2006 and 2014. The average level of purity fell from 40% to 30%. The most prevalent adulterants were phenacetin (80%), levamisole (65%), lidocaine (47%), caffeine (39%), diltiazem (26%), and hydroxyzine (25%) .

The Trans European Drug Information (TEDI) project analyzed the presence and composition of illicit substances obtained from drug users (cocaine, ecstasy, amphetamines, NPS) in six European countries over the 2008-2013 period. A total of 45,859 samples were included in the study. The lowest mean purity of cocaine was found in Austria (42% between 2008 and 2013), rising to an average of 60% in Spain, the Netherlands, and Switzerland in 2013. In that year, levamisole was the adulterant most often found, followed by phenacetin and caffeine. Other adulterants reported

throughout the period were lidocaine, procaine, tetracaine, hydroxyzine, and diltiazem (Brunt et al., 2017a).

A recent study showed the presence of levamisole (31.8%) in 88 samples of cocaine seized in the Rome metropolitan area during one year, as well as caffeine (6.8%), lidocaine (2.3%), acetaminophen (2.3%), and phenacetin (1.1%) (Martello et al., 2017).

Bertol et al. (2018) analyzed the chemical composition of drugs seized in Florence, Italy, between 2006 and 2016. Some 10.4% of these samples were cocaine. Lidocaine, phenacetin, and levamisole were the adulterants found most often.

Table 3 describes relevant studies on the analysis of cocaine samples seized in Europe during the period under study.

Phenacetin, levamisole, caffeine, diltiazem, and hydroxyzine are considered to be the adulterants of cocaine currently found most often in Europe. During the period under study, the most notable diluents were: glucose, saccharose, lactose, mannitol, inositol, starch, and carbonates. The authors suggest that some are added in the country where cocaine is produced (diltiazem, hydroxyzine, levamisole), while others such as phenacetin and lidocaine are added after being imported into Europe. Regardless, seizures have been reported of these two adulterants where the intention was to adulterate the cocaine *in situ*. Caffeine appears to be added before and after the cocaine arrives in these European countries (Broséus, Gentile, & Esseiva, 2016).

Table 3: Studies analyzed on adulterants found in samples of cocaine in Europe[†]

Studies	Country/ countries	Year	State(s) City Region	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) **	Adulterants found ***
Brunt et al., 2009	Netherlands	1999–2007	N/R	Powder cocaine not determined	2,824	TLC GC/NPD GC/MS	Mean: 39–82	Phen, Lid, Pro, Ben, Caf, Hyd, Dil, Lev, Atro
Andreasen et al., 2009	Denmark	2002–2003	Aarhus	Cocaine hydrochloride	147	GC/MS HPLC/DAD	0.3–78 (mean: 35)	Lid, Phen, Caf, Crea, Pro, Ace, Ben, Phz, Ephe, Mir, Ket.
Evrard et al., 2010	France	May 2006 – Dec 2006	N/R	Cocaine hydrochloride	343	GC/MS	Mean: 22	Phen, Caf, Ace, Dil, Lid Lev, Hyd, ASA, Prop
Schneider et al., 2011	Luxembourg	2005–2010	N/R	Cocaine hydrochloride	471	GC/MS HPLC/UV/DAD	0.2–100 (mean: 50.6)	Caf, Dil, Lid, Lev, Hyd, Pro, Ace, Ibu, Methylephe, Dic, Ben, Ephe, Atro
Broséus et	Switzerland	2006–	Western	Cocaine not	6,586	GC/MS	1–99	Phen, Lev, Lid, Caf, Dil,

Studies	Country/ countries	Year	State(s) City Region	Drug(s)	Number of samples analyzed	Technique used**	Degree of purity (%) **	Adulterants found ***
al., 2015		2014	Switzerland	determined			(mean: 30–40)	Hyd, Pro, Tetra, Ace, Crea, Ben
TEDI project, 2016	Spain, Switzerland, Belgium, Austria, Portugal, Netherlands	2008–2013	N/R	Powder cocaine not determined	N/R	LC/DAD GC/MS TLC HPLC	N/R overall	Lev, Phen, Caf, Lid, Prop, Tetra, Hyd, Dil
Martello et al., 2017	Italy	1 year N/R	Rome	Powder cocaine not determined	88	GC/FID GC/MS	40–73 (mean: 55%)	Lev, Caf, Lid, Ace, Phen
Bertol et al., 2018	Italy	2006–2016	Florence	Cocaine hydrochloride	1,087	GC/MS LC/MS/MS GC/FID	26.7–98	Lid, Phen, Lev

* ASA=acetylsalicylic acid, Ace=acetaminophen, Atro=atropine, Ben=benzocaine, Caf=caffeine, Crea=creatina, Dic=diclofenac, Ket=ketamine, Dil=diltiazem, Eph=ephedrine, Hyd=hydroxyzin, Ibu=ibuprofen, Lid=lidocaine, Lev=levamisole, Methylephe=methylephedrine; Mir=mirtazapine, Phen=phenacetin, Phz=phenazone, Pro=procaine, Prop=propoxyphene, Tetra=tetracaine.

** TLC=thin-layer chromatography; GC/NPD=gas chromatography with nitrogen phosphorus detector; GC/MS=gas chromatography/mass spectrometry; HPLC/DAD=high-performance liquid chromatography with diode-array detection; HPLC/UV/DAD=high-performance liquid chromatography with ultraviolet detector and diode-array detection; LC/DAD=liquid chromatography with diode-array detection; HPLC=high-performance liquid chromatography; LC/MS/MS=liquid chromatography with tandem mass spectrometry; GC/FID=gas chromatography with flame ionization detector.

*** Average concentration (which may be a range depending on the period under study) or limit of the findings.

N/R=not reported.

† One or more adulterants may be present in each sample.

4.1.3. Analysis of seizures in Africa

A retrospective observational study published in 2017 analyzed the chemical composition of 154 samples of powder cocaine seized in Morocco over the 2007-2016 period. Purity ranged from 17% to 90%. More than 80% of the samples were found to be adulterated, 60% of them with one substance and 25% with two. The adulterants most frequently reported were levamisole (63.4%), phenacetin (29.1%), diltiazem (14.2%), caffeine (8.2%), lidocaine (5.2%), and acetaminophen (3%). The authors report that some substances that were highly prevalent over the 2007-2008 period, such as diltiazem, were largely replaced by levamisole and phenacetin starting in 2009, coinciding with the worldwide trend referred to earlier (Stambouli & El Bouri, 2017).

4.1.4. Alerts to presence of fentanyl and derivatives in seizures of cocaine

Fentanyl is an opioid analgesic 50 times more potent than heroin and 100 times more than morphine. Doses of 2 mg may be fatal. In 2016 and 2017, the DEA reported the presence of cocaine adulterated with fentanyl and its derivatives (acetyl fentanyl, carfentanil, furanyl fentanyl, and p-fluoroisobutyrfentanyl) in 180 samples in the state of Florida, United States. Carfentanil, which is 10,000 times more potent than morphine, was found most often (DEA, 2018a).

The DEA also reported an increase in adulterations of cocaine with fentanyl and derivatives in the U.S. state of Pennsylvania. Between 2015 and 2017, 214 samples of cocaine seized in Pennsylvania contained fentanyl; more than half (n=134) were reported in 2017. Around 59% of the total number of seizures of cocaine/fentanyl also contained heroin. The DEA report states that heroin, which is sometimes mixed with cocaine for street sales, has in large part been replaced by fentanyl and its analogues (DEA, 2018b).

4.2. Amphetamine-type stimulants (ATS) and NPS

Synthetic drugs are substances prepared in clandestine laboratories using changes in the chemical structure to produce effects similar to or more potent than those of the "classic" drugs, resulting in synthetic stimulants (such as substituted amphetamines), narcotics (synthetic opioids), and psychodysleptics/dissociatives (arylcyclohexylamines such as ketamine). Some of these substances were synthesized by the pharmaceutical industry at the beginning of the twentieth century and then abandoned because they did

not produce the desired effects or because they were considered to be harmful to human health. Continual molecular changes made to these substances (to sidestep the controls and prohibitions of international agencies) have led to the development of thousands of synthetic drugs (Ministerio de Sanidad, Política Social e Igualdad de España, 2011). This increase in the supply of synthetic drugs has led to a new name for them: "new psychoactive substances" (NPS) **(Table 4)**. Known in the market by such names as "designer drugs," "emerging drugs," "legal highs," "euphoric herbals," and "bath salts," NPS are being incorporated into international conventions so that they can be prohibited and recognized as illegal drugs (Weaver, Hopper, & Gunderson, 2015; Head, 2016; UNODC, 2018). These substances contain impurities or adulterants that are sometimes used to lower their cost and/or to enhance their psychoactive effects, such as dextromethorphan, 2-aminoindane, lidocaine, and caffeine (Assi et al., 2015).

Table 4: New psychoactive substances

Types of NPS	Examples
Phenylethylamines and amphetamine derivatives	Methamphetamine Methylenedioxyamphetamines (MDMA - ecstasy) Methoxyamphetamines (PMA, PMMA) Synthetic cathinones (mephedrone, methylone, MDVP, butylone) 2C-X (2C-I, 2C-B, 2C-C) DOX (DOI, DOB, DOC) 25X-NBOMe (25I-NBOMe, 25B-NBOMe, 25C-NBOMe)
Arylcyclohexylamines	Ketamine, phencyclidine
Piperazines	Benzylpiperazine (BZP) and mCPP (meta-Chlorophenylpiperazine)
Synthetic cannabinoids	JWH-018, CP 47497, JWH-073, HU-210 *(Spice drugs)*

MDMA=methylenodioxy-methamphetamine; PMA=paramethoxyamphetamine; PMMA=paramethoxymethylamphetamine; MDVP=methylenodioxypyrovalerone.

- Ecstasy is a derivative of the amphetamine molecule, 3,4-methylenedioxymethamphetamine (MDMA). It is taken orally, generally in the form of tablets or "pills," less frequently in the form of powder or "crystals." The tablets vary in color, form, size, and concentration of the substance. They are classically sold as pills imprinted with different logos. The use of ecstasy increased in parallel to the underground culture and rave parties in Europe during the 1980s. The adulterants used in MDMA pills or crystals may vary to include: other amphetamines such as MDA (methylenodioxyamphetamine), MDEA (2,3 methylenodioxy-ethylamphetamine), PMA (paramethoxyamphetamine) and PMMA (paramethoxymethylamphetamine), synthetic cathinones, piperazines, paracetamol, caffeine, ephedrine, cocaine, dextromethorphan, and ketamine, with reports of fatalities resulting from the use of adulterated pills or crystals (Galicia, Alonso, & Nogué, 2014). In an indication of market response to adulteration, some studies show high concentrations of MDMA in pills and crystals and an absence of adulterants (UNODC, 2017a). In some studies, these drugs were obtained by users on the dark web or illicit Internet market (Caudevilla et al., 2016). The term "molly" has been adopted at rave parties and other places where ecstasy is used to refer to high-purity MDMA; however, studies conducted at raves have shown great variations in the concentration of MDMA in these supposedly "purer" presentations. In a study conducted in the United States over the 2010-2015 period, colorimetric assay analyses showed the presence of MDMA in only 60% of the 529 samples collected, with no significant differences between ecstasy and molly (Saleemi et al., 2017).

- Synthetic cathinones are phenylethylamines (beta-ceti amphetamines), known as "bath salts" or "legal highs," in the form of a whitish powder that is inhaled (nasally) or swallowed, with predominantly sympathetic stimulation and in some cases, serotonin stimulation. Acute toxic effects most frequently reported are agitation, confusion, mydriasis, tachycardia, arterial hypertension, hyperthermia, trembling, seizures, rhabdomyolysis, and acute renal injury (Prosser & Nelson, 2012; Nelson, Bryant, & Aks, 2014).

- Piperazines act as a stimulant of the central nervous system. At higher doses, they have hallucinogenic effects. Benzylpiperazine (BZP) stimulates the release and inhibits the reuptake of serotonin, dopamine, and noradrenalin, while phenylpiperazines (m-Chlorophenylpiperazine or mCPP); 1-3-trifluoromethylphenylpiperazine or TFMPP) have predominantly serotonin agonist action (Ministerio de Sanidad, Política Social e Igualdad de España, 2011; Arbo, Bastos, & Carmo, 2012). A mix of BZP and TMFPP produces effects similar to those of MDMA (Rosenbaum, Carreiro, & Babu, 2012).

- Derivatives of 2 C phenylethylamines (25C-NBOMe, 25I-NBOMe, 25B-NBOMe) are either swallowed or absorbed orally by means of stamps, or in powder or liquid form. They are occasionally sold as LSD (on stamps, cards, or blotters) or as adulterants of MDMA. They have hallucinogenic effects (even in doses of micrograms) and stimulant effects via sympathetic serotonin stimulation. Acute poisoning may cause confusion, agitation, hallucinations, mydriasis, tachycardia and arterial hypertension, hyperthermia, seizures, rhabdomyolysis, and acute renal injury (Zuba, Sekuła, & Buczek, 2012; Nikolaou, Papoutsis, & Dona, 2014).

- Synthetic cannabinoids, known as "K2" or "Spice," are synthetic drugs that contain compounds similar to tetrahydrocannabinol. They act on the cannabinoid receptors with a potent agonist effect, and may cause acute poisoning characterized by anxiety, agitation, nausea and vomiting, tachycardia and arterial hypertension, chest pain, and hallucinations (Nelson, Bryant, & Aks, 2014; Pourmand et al., 2018).

4.2.1. The situation in Europe

A number of studies over the past decade have shown the purity and presence of adulterants in samples of ecstasy in European countries.

Wood et al. (2011) showed a concentration of MDMA distributed bimodally in 101 samples of ecstasy tablets seized in the United Kingdom: 20-40 mg and 60-80 mg of MDMA per tablet, respectively. All of the samples contained less than 100 mg of MDMA, raising warnings about adulterations and possible health effects for users.

Vidal Giné et al. (2016) studied the composition of 6,200 samples of ecstasy in Spain over the period 2000–2014; the predominant form of presentation was powder or crystals (60.6%) rather than pills (38.8%). MDMA as the single substance was more frequent in crystals. Also reported in the case of crystals were a larger number of adulterants in a single sample. Adulterants such as mCPP, caffeine, metoclopramide, 2,5-dimethoxy-4-bromophenethylamine (2C-B), amphetamine, paracetamol, buflomedil, TFMPP, MDEA, and phenacetin were found in tablets. Caffeine, phenacetin, lidocaine, paracetamol, dextromethorphan, buflomedil, procaine, methamphetamine, mCPP, and methylone were found in crystals. Caffeine was found to be the most frequent adulterant in both presentations. Other adulterants such as phenacetin, lidocaine, dextromethorphan, and methamphetamine were detected almost exclusively in crystals. This study also showed higher purity levels of MDMA tablets starting in 2010; however, adulterants continued to increase in both presentations throughout the period (Vidal Giné et al., 2016).

A study by some of the same authors, published in 2014, analyzed the presence of NPS in illicit drugs under international control in 2009-2012. Samples of MDMA tested by Energy Control showed the presence of: 1-phenylethan-1-amine, 2C-B (2,5-dimethoxy-4-bromophenethylamine), 2C-I (2,5-dimethoxy-4-iodo phenethylamine), 2-FA (1-(2-fluorophenyl)propan-2-amine), 2-MMC (2-(methylamine)-1-(2-methylphenyl)propan-1-one, 3-FA (1-(3-fluorophenyl)propan-2-amine, 4-FMA 1-(4-fluorophenyl)-N-methylpropan-2-amina, 4-MEC (2-ethylamine-1-(4-methylphenyl)propan-1-one), buphedrone, dimethylcathinone, mephedrone, methylone, and methoxetamine. The adulterant most frequently reported in MDMA tablets was 2C-B. Synthetic cathinones such as mephedrone and methylone were also prevalent, particularly in crystals (Vidal Giné, Espinosa, & Vilamala, 2014).

In 2014, the Belgian Early Warning System reported the presence on the market of ecstasy tablets with high MDMA content or with the presence of 4-fluoro-amphetamine (4-FA/4-FMP) as an adulterant (BEWSD, 2014).

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) warned of the presence of a new NPS, called 4,4′-DMAR or 4-methyl-5-(4-methylphenyl)-4,5-dihydro-oxazol-2-amine, with seizures of tablets and powder containing the substance reported in countries such as Finland, Hungary, Netherlands, and Romania. The tablets

bore several different logos, which suggested the possibility that they were being sold as ecstasy (EMCDDA, 2014).

Adulterants have been found in recent years in a number of European cities in ecstasy tablets of high toxicity, both intrinsically and in combination with MDMA, such as 2CB, ketamine, piperazines (TMFPP, mCPP, BZP), PMA, and PMMA (EMCDDA, 2016). Case reports on the acute toxic effects of these adulterations will be analyzed later.

4.2.2. United States

In the United States, a study by Tanner-Smith (2006) analyzing 1,214 ecstasy tablets from 1999 to 2005 showed that 39% contained only MDMA, and 46% contained only substances other than MDMA (MDA, methylenedioxy-ethylamphetamine or MDE, caffeine, ketamine, and dextromethorphan). In 15% of cases, the tests found combinations of MDMA with other substances, with MDA, methamphetamine, caffeine, dextromethorphan, and pseudo-ephedrine being the most frequent. The level of purity declined during the period of the study.

Adulterations of NPS were reported in various parts of the United States in 2015 (Head, 2016), with the following findings:

- nicotine, lidocaine, methyl sulfone, and caffeine in samples of synthetic cannabinoids.
- MDMA, ketamine, 4-methoxy-methamphetamine or 4-MeO-MA, 2C-B, dimethyltryptamine or DMT, caffeine, dimethyl sulfone, cocaine, heroin, fentanyl, acetyl-fentanyl, quinine, diphenhydramine, and ibuprofen in samples of synthetic cathinones.
- combinations of synthetic cannabinoids and cathinones (e.g., alpha-PVP, AB PINACA).

4.2.3. South America

In Brazil, a number of authors have stated that approximately 45% of ecstasy tablets seized in São Paulo contained MDMA; however, a study by Moreira et al. (2016) did not find MDMA in the samples analyzed by means of Raman spectroscopy, but did find caffeine, dextromethorphan, a bk-MDMA analogue, and clobenzorex.

In Colombia, a study conducted by the Drug Observatory of the National Narcotics Department, in coordination with the Intelligence Group – Anti-Narcotics Division of the National Police, described synthetic drugs being sold in Bogotá. The study collected 330 samples of synthetic drugs and analyzed them by means of gas chromatography/mass spectrometry (GC/MS). A total of 250 different chemical substances were identified. They included over-the-counter and controlled drugs, veterinary drugs, illicit drugs, and industrial chemical substances. MDMA was found in 58 samples, 53 of which also contained caffeine; methamphetamine was detected in 28 samples, in low concentrations (3% to 28%). MDEA and MDA were also found. Caffeine was the predominant adulterant, found in 41% of the total number of samples (Bernal, 2010).

Synthetic cathinones have been detected in Colombia in recent years (methylone, ethylone, and alpha-PVP), in tablets or capsules of ecstasy as well as in crystals sold as pure MDMA (Ministerio de Justicia y del Derecho de Colombia, 2017a). In August 2017, the Colombian Early Warning System issued an alert about the presence in Colombia of butylone in tablets sold as ecstasy (Ministerio de Justicia y del Derecho de Colombia, 2017b).

Other adulterants of substances sold as MDMA or ecstasy were also found, based on the study *Characterization of market aspects and chemical composition of synthetic drugs and emerging substances* (Ministerio de Justicia y del Derecho de Colombia, 2017a):

- ketamine (in 2008).
- phenylethylamines: PMA and 2,5 dimethoxy-4-chloroamphetamine or DOC (both in 2013), 4 methylamphetamine (in 2014).
- 2-(4-ethyl-2,5 dimethoxyphenyl) ethylamine or 2C-E (in 2014), a 2C drug with stimulant and hallucinogenic effect.
- 5-methoxy–N-methyl–N-isopropyltryptamine or 5-MeO-MIPT, commonly known as “moxy” (hallucinogenic tryptamine) in 2015.

In the first half of 2018, the Early Warning System of the Uruguayan Observatory on Drugs put together a database of the information obtained from analyzing samples, most of which had been seized or else provided by users (Sistema de Alerta Temprana en

Drogas en Uruguay – Uruguayan Early Warning System on Drugs, 2018), noting the following:

- tablets of ecstasy with varying MDMA content associated with other substances such as ASA (acetylsalicylic acid), caffeine, amphetamine, ephedrine, MDA, MDEA.
- some tablets contained more than 150 mg of MDMA, in notably high concentrations.
- crystals with high MDMA content in powder.

4.2.4. Asia and Oceania

Adulterations of MDMA with PMA or PMMA have been reported in countries such as Australia, and have caused fatalities (Caldicott, 2003).

In Hong Kong, ecstasy tablets usually contain MDMA, MDA, methamphetamine, and/or ketamine. Cheng et al. (2006) studied impurities in 89 samples of ecstasy seized in Hong Kong, most of which were found to be precursors of MDMA. Caffeine is the adulterant of MDMA found most frequently in that region, according to the authors.

In both Asia and Oceania, studies in 2012-2013 showed that most of the countries detected piperazines (BZP and TFMPP), synthetic cannabinoids (JWH-018117), and synthetic cathinones (mephedrone, methylone) in seizures of ecstasy tablets (UNODC, 2015).

Methamphetamine is the synthetic drug prevalent in East and Southeast Asia (in the form of tablets and crystals), while ecstasy has spread from Oceania to countries in Asia (UNODC, 2015).

A number of studies have analyzed impurities and adulterants of methamphetamine seized in Asian countries. The study by Zhang et al. (2008) examined 48 samples of methamphetamine from eight seizures in China, and found precursors such as ephedrine and pseudoephedrine, as well as impurities resulting from synthesis, such as 1,2-dimethyl-3-phenylaziridine, 1,3-dimethyl-2-phenylnaphthalene, and 1-benzyl-3-methylnaphthalene. A similar study had earlier described impurities with similar characteristics in Thailand (Puthaviriyakorn et al., 2002).

Choe et al. (2013) found impurities and adulterants in methamphetamine crystals from 609 seizures in Korea over the period 2006-2011, using GC/FID/MS. The adulterants included acetaminophen (paracetamol), caffeine, phenacetin, ambroxol, chlorpheniramine, desloratadine, barbital, ketamine, and dimethyl sulfone.

4.3. Derivatives of opium, heroin, synthetic opioids (fentanyl and derivatives)

4.3.1. Opium

Opium is a natural alkaloid derived from the *Papaver Somniferum* plant or poppy.

In its purest form, opium has a soft and sticky consistency like tar, and hardens over time. It may be consumed orally, generally chewed, or less frequently smoked. Prepared opium, which generally has a harder consistency, goes through a process of water extraction and is smoked. The term opiate refers to substances derived from opium, including morphine as a natural opiate and some derivatives (codeine, papaverine, noscapine). Heroin (diamorphine or diacetylmorphine) is a semi-synthetic opiate derived from morphine. Opioids are synthetic substances with an effect that is analogous to morphine, usually used as analgesics (fentanyl, methadone). A wide variety of synthetic opioids are currently sold on the illicit market, some of which are extremely potent and may produce overdose with a high fatality rate (UNODC, 2016).

Opium may be contaminated or adulterated with metals such as lead, thallium, or arsenic (Alinejad et al., 2018).

Several studies in Asia, particularly Iran, refer to the possible causes of the presence of lead: Contamination may occur during production, particularly during the process of refining raw opium into a brownish substance of firm, pasty consistency, which is pressed into bricks and left to dry in the open air. Adulterations with lead (lead oxide, lead nitrate, or lead acetate) to increase volume have also been described. Another source of contamination is during the cultivation phase. Most of the opium consumed in Iran and neighboring countries comes from central and southern Afghanistan, where the soil in growing areas is contaminated with lead, in some cases as the result of mining activity. The presence of lead in opium has been confirmed by analytical studies (Hayatbakhsh et al., 2017; Alinejad et al., 2018; Soltaninejad & Shahina, 2018).

Adulterations of opium with thallium to increase bulk have also been reported (Ghaderi et al., 2015).

4.3.2. Analysis of samples of heroin

Klemenc (2000) analyzed 110 samples of heroin seized by the Slovenian Police during the 1997–1999 period. These samples were characterized by the presence of noscapine, an opium alkaloid. The percentages ranged from 2.38% to 61.27%, with high concentrations in some samples (Klemenc, 2000).

The study by Zhang et al. (2004) analyzed 500 samples of heroin seized in China. The adulterants most commonly found were caffeine, acetaminophen, theophylline, and phenacetin. The most frequent combination was acetaminophen, theophylline, and phenacetin (29%). Procaine, niacinamide, rimifon, and phenobarbital were also found, in smaller percentages.

The Anti-Narcotics Police of Afghanistan (2008) seized a total of almost 1.3 tons of heroin between August and December 2008. The adulterants found were chiefly phenolphthalein, acetaminophen, and chloroquine, and caffeine to a lesser extent (UNODC, 2008).

In their analysis of samples of heroin seized in the city of Aarhus, Denmark, over a two-year period (2002-2003), Andreasen et al. (2009) found adulterants in 132 samples. Caffeine and acetaminophen were the adulterants most frequently found (22% and 27% respectively), followed by griseofulvin (2%).

Schneider & Meys (2011) analyzed 962 samples of heroin seized in Luxembourg between 2005 and 2010. Eight adulterants were found in different samples, with acetaminophen (average of 46.9%) and caffeine (average of 24.2%) being the main substances. Piracetam, phenacetin, morphine, codeine (21.7% in one sample), cocaine, and diltiazem were found, but less frequently.

The study by Broséus et al. (2015) reported that 3,054 samples of heroin were seized in the western part of Switzerland between 2006 and 2014. The average level of purity rose from 10% to 15%. The main adulterants were caffeine (97%) and acetaminophen (96%), and much less frequently griseofulvin (12%), phenacetin (5%), dextromethorphan (2%), lidocaine (2%), and levamisole (2%).

The analysis of samples of heroin seized by the Anti-Narcotics Division of the Colombian National Police in 2016 included six state capital cities and one municipality. The analysis covers the period April 2014 to October 2015. A total of 127 samples were seized. Caffeine (69%) and diltiazem (50%) were the adulterants most frequently found; others were lidocaine (6%), levamisole (4%), and acetaminophen (not quantified) (Ministerio de Justicia y del Derecho de Colombia, 2016).

Bertol et al. (2018) analyzed the chemical composition of drugs seized in Florence, Italy, between 2006 and 2016. Around 6.5% of these samples were heroin. The levels of purity were higher than the average estimated values for the Italian and European markets. The study did not report on adulterants found in samples of heroin.

Caudevilla et al. (2018) analyzed 108 samples of heroin coming from the European Union, the United States, and Canada between 2014 and 2018. The principal adulterants found were caffeine, acetaminophen, and phenacetin. The report notes the increase in fentanyl-type adulterants and its derivatives, with potential serious exposure of users. It also examines the significance of the notable increase in the sales of psychoactive substances via the dark web or illicit Internet markets.

Table 5 describes the studies analyzing samples of heroin.

Substances such as caffeine and acetaminophen (paracetamol) are the adulterants reported most frequently. Caffeine can vaporize heroin at lower temperatures, making it easier to smoke (Cole et al., 2010). Its psychoactive effect as a stimulant and positive reinforcer may also explain its high prevalence in these samples.

In comparison with the adulterants of cocaine, common adulterants of heroin are local anesthetics (procaine also aids in smoking, in the same way as caffeine), diltiazem, and phenacetin. The presence of phenacetin may be explained as a way to increase the volume and improve the organoleptic characteristics of the product, and probably because of its reinforcing effects on the reward system -- something that is not yet fully established.

Other adulterants, such as barbiturates and opiates, contribute to the psychoactive effect and act as a central nervous system depressant.

The next chapter refers to occurrences of clinical cases of adulterations of heroin due to overdose with compounds that are analyzed in detail, as is the case of clenbuterol and synthetic opioids -- particularly fentanyl and its derivatives, which are not specified in **Table 5**.

Table 5: Adulterants found in seizures of heroin†

Studies	Country/ Countries	Year	State(s) City/cities Place(s)	Drug(s)	Number of samples analyzed	Technique used*	Degree of purity (%) **	Adulterants found***
Klemenc, 2000	Slovenia	1997–1999	N/R	Heroin	110	GC/MS	N/R	Noscapine
Zhang et al., 2004	China	N/R	Yunnan, Guangdong, Jilin, Xinjiang, Gansu, Nei Mongol, Northeast region	Heroin	500	GC/MS	20–more than 70	Ace, Caf, Theo, Phen, Pro, Nia, Rim, Phbt
UNODC, 2008	Afghanistan	2008	Nimroz, Zarang Ghor, Kandahar, Herat, Hilmand, Grashk, Kunduz, Kabul	Heroin	1.3 tons	TLC UV/VIS spectroscopy	N/R	Phenolphthalein, Caf, Ace, Chlo
Andreasen et al., 2009	Denmark	2002 –2003	Aarhus	Heroin	132	GC/MS HPLC/DAD	3–51 (mean: 23)	Caf, Ace, Gri, Dzp, Fbt, Piracetam, Met, Pro, Barb, AA, SA

Studies	Country/ Countries	Year	State(s) City/cities Place(s)	Drug(s)	Number of samples analyzed	Technique used*	Degree of purity (%) **	Adulterants found***
Schneider et al., 2011	Luxembourg	2005 –2010	N/R	Heroin	962	GC/MS HPLC/UV/DAD	0.1–86.7 (mean: 17.6)	Ace, Caf, Piracetam, Phen, Mor, Cod, Coc, Dil
Broséus et al., 2015	Switzerland	2006 –2014	Western region of Switzerland	Heroin	3,054	GC/MS	1–80 (mean: 10-15)	Caf, Ace, Gris, Phen, Dmx, Lid, Lev
Ministerio de Justicia y del Derecho de Colombia, 2016	Colombia	2014 –2015	Armenia, Bogotá, Cali, Cúcuta, Medellín, Pereira, Santander de Quilichao	Heroin	127	GC/MS HPLC	27–98 (mean: 62.7)	Caf, Dil, Lid, Lev, Ace
Bertol et al., 2018	Italy	2006 –2016	Florence	Heroin	679	GC/MS LC/MS/MS	0.5–63 (mean: 14%)	N/R
Caudevilla et al., 2018	Spain	2014 –2018	European Union United States Canada	Heroin	108	GC/MS	2–89	Caf, Ace, Phen, Fentanyl & derivatives, Dxm,

Studies	Country/ Countries	Year	State(s) City/cities Place(s)	Drug(s)	Number of samples analyzed	Technique used*	Degree of purity (%) **	Adulterants found***
								Coc, Lid, Dil

* GC/MS=gas chromatography/mass spectrometry; TLC=thin-layer chromatography; HPLC/DAD=high-performance liquid chromatography with diode-array detection; HPLC/UV/DAD=high-performance liquid chromatography with ultraviolet detection and diode-array detection; LC/MS/MS=liquid chromatography with tandem mass spectrometry; UV/VIS=ultraviolet-visible spectrometry.

** Average concentration or limit of the findings. N/R=not reported.

*** AA=ascorbic acid; Ace=acetaminophen, SA=salicylic acid, Barb=barbital, Caf=caffeine, Coc=cocaine, Cod=codeine, Chlo=chloroquine, Dil=diltiazem, Dxm=dextrometorphan, Dzp=diazepam, Phen=phenacetin, Phbt=phenobarbital, Gri=griseofulvin, Lev=levamisole, Lid=lidocaine, Nia=niacinamide, Pro=procaine, Rim=rimifon, Theo=theophylline.

† One or more adulterants may be present in each sample.

4.3.3. Fentanyl and its derivatives

Fentanyl is a synthetic opioid used as an analgesic or anesthetic drug. Its euphoriant effect has led to its nonmedical use by drug users, particularly users of heroin or other opiates, and the development of an illicit market for fentanyl and its derivatives. The heroin available on the streets is frequently adulterated with fentanyl or its derivatives (Carroll, Marshall, Rich, & Green, 2017). Fentanyl adulterations of pharmaceutical products sold on the illicit market as oxycodone, hydrocodone, or alprazolam have also been reported (Canadian Centre on Substance Abuse and Addiction, 2016; DEA, 2016a; Health and Human Services Department, 2016).

Although the first reports of illicitly manufactured fentanyl in the United States were published in the 1980s, a type of heroin called "Tango and Cash" was described in 1991. It contained 12% fentanyl, causing approximately 126 overdose deaths (DEA, 2017a). Fatal overdoses have been reported more frequently over the past 10 years in various parts of the United States, particularly in the East (Algren et al., 2013; Gladden, Martinez, & Seth, 2016; Tomassoni et al., 2017).

Many fentanyl derivatives are currently available on the illicit market, such as 4-fluoroisobutyril fentanyl, furanyl-fentanyl, acryl-fentanyl, acetyl-fentanyl, carfentanil, and 3-methylfentanyl, among others. Other synthetic opioids such as U-47700 and AH-7921 have also been found. Some opioid users seek out fentanyl, but more frequently in combination with heroin (*speedballing*) or the use of heroin adulterated with fentanyl or its derivatives (DEA 2017a; Prekupec, Mansky, & Baumann, 2017; Drummer et al., 2018).

In terms of its acute toxicity, fentanyl is 50 to 100 times more potent than morphine and 30 to 50 times more potent than heroin. Carfentanil is 10,000 times more potent than morphine (Misailidi et al., 2018). Fentanyl and its analogues may be presented in powder form or in tablets, capsules, liquids, or blotter papers (DEA, 2017a).

According to a recent report by the DEA, 877 samples containing fentanyl were identified in 2016, representing 68% of seizures of synthetic opioids. Around 46.5% of those samples contained fentanyl alone, and around 42% also contained heroin. Other derivatives of fentanyl identified were furanylfentanyl (n=142) and acetyl-fentanyl (n=112) (DEA, 2018c).

Compounds containing illicitly manufactured fentanyl and its analogues have spread from the United States to Europe, Japan, China, Canada, and Australia (Pichini, Solimini, Berretta, Pacifici, & Busardò, 2017; UNODC, 2017b; UNODC, 2018). And the sale of products adulterated with fentanyl or its derivatives has spread outside the United States. One of the illicit markets chosen by users in Europe is the Internet. Quintana et al. (2017) showed the presence of ocfentanil in four samples of a product sold as heroin on the illicit Internet market or dark web. Caffeine and acetaminophen were found in all of the samples and heroin in half of them. The caffeine was measured in two of the samples (26% and 27% caffeine, 29% and 33% acetaminophen). The percentage of heroin was 3%–16%. Users described an effect that was less euphoriant than the effect expected with heroin, with more intense withdrawal symptoms, which is related to its short duration of action (Misailidi et al., 2018).

4.4. Cannabis – marijuana derivatives

The word cannabis refers to the *Cannabis sativa L.* plant, which is grown worldwide and has been cultivated for thousands of years to produce fiber (hemp) and for recreational, medicinal, and religious purposes. According to the World Health Organization, cannabis is the generic term that covers psychoactive preparations derived from the *Cannabis sativa* plant (WHO, 2012). From the standpoint of pharmacognosy, the term covers not only the plant but also its different forms of presentation for consumption, components, and derivatives of natural or synthetic origin (Fernández Ruiz, Lorenzo Fernández, & Leza Cerro, 2009).

The chemical composition of *Cannabis sativa L.* is very complex in that it contains more than 400 chemical products (monoterpenes and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenated compounds, and amino acids) and 70 cannabinoids isolated up to the year 2005, with delta 9-THC producing the greatest psychoactive effect (Rodríguez Carranza, 2012).

During cultivation, it may be contaminated by fertilizers (such as nitrogen and potassium), or by pesticides sprayed on the plant. Some studies have shown traces of pesticides on the plants that would not involve a risk of poisoning (National Cannabis Prevention and Information Centre, 2011); however, the safety conditions in which pesticides are applied are not well managed in most of the growing areas where marijuana is illegal, which represents a risk (McLaren et al., 2008).

Heavy metals (such as lead) that contaminate the soil where the crops are grown are potential contaminants of the plants and their derivatives (National Cannabis Prevention and Information Centre, 2011).

There is evidence that during storage, cannabis may undergo microbiological contamination with mold (*Penicillium* genus) and *Aspergillus flavus* and *Aspergillus fumigatus* fungi. Fungal contamination in samples of plants, marijuana, and products sold in coffee shops in Holland has been reported (McLaren et al., 2008).

Substances are often added during the illicit sales of cannabis derivatives, to increase their volume or to create the appearance of greater potency. The presence has been reported of small glass "beads" or particles added to the marijuana to increase its volume and to mimic the translucent crystalline appearance of the resin glands, which contain large quantities of THC. The United Kingdom Department of Health reported that between January and March 2007, 5% to 10% of the marijuana analyzed was contaminated with glass beads (Department of Health, 2007).

Cannabis may be adulterated with psychoactive substances to increase the effect of the THC and thus mask the lower potency of some products, and also to reduce undesired effects such as changes in memory, tachycardia, dry mouth, and changes in motor coordination. There is also evidence of adulterations with tobacco, anticholinergic agents such as *Datura* plants, and cholinergics such as calamus root, *Acorus calamus* (McPartland, 2008; McPartland, Blanchon, & Musty, 2008; Solimini et al., 2017).

4.5. LSD

LSD (lysergic acid diethylamide) was discovered in 1938 by Albert Hofmann, a researcher at Sandoz Laboratories. It is the prototype of a hallucinogenic drug. It is known by users as "acid" or "trip" (referring to the hallucinogenic effect that is sought). It is usually consumed by mouth on small pieces of blotter paper or on sugar cubes held under the tongue (sublingually). It may also be taken in the form of small pills or microdots. The dose ranges from 50 to 200 ug. It is easily absorbed by all routes, and its effects appear in 30 to 90 minutes, lasting from five to eight hours (Snook, 2017).

In recent years, with the growth of NPS on the illicit market, cases of LSD stamps being adulterated with stimulant drugs and synthetic opioids have increased, both in Europe and in the Americas.

In their study of NPS in illegal drugs in 2009-2012, Vidal Giné, Espinosa, & Vilamala (2014) showed that 20 NPS were present in nine samples of LSD tested by Energy Control, with more than one substance found on each stamp: 25C-NBOMe (n=1), 25I-NBOMe (n=3), 2C-B (n=3), 2C-E (n=1), 2C-I (n=1), 4-ACO-DIPT or 2-[bis(1-methylethyl)amino]ethyl]-1H-Indol-4-ol acetate (n=1), DMA or 2-(3,4-Dimethoxyphenyl)propylamine (n=1), DOC or 1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine (n=1). Eight NPS were not identified.

The European Union-supported project I-TREND, the report of which was published in 2015, was conducted in several European countries (France, Netherlands, Poland, United Kingdom) to analyze NPS bought from online shops (n=184). The study found stamps or blotters containing 25I-NBOMe sold as LSD (The Trimbos Institut, 2015).

At the 2014 Boom Festival in Portugal, Martins et al. (2017) analyzed 245 samples that, as far as users were concerned, were LSD. Only 67.3% of the samples contained LSD alone; 0.8% contained LSD with adulterants, and 24.1% of the samples did not contain LSD but rather an NPS, including DOx (11.4%) and 25x-NBOMe (9.8%).

In Colombia, the study *Characterization of market aspects and chemical composition of synthetic drugs and emerging substances* showed the presence of NPS as adulterants on blotters sold as LSD (Ministry of Justice and Law of Colombia, 2017a):

- derivatives of 2 C phenelethylamines: 25C-NBOMe, 25I-NBOMe, 25B-NBOMe, 25D-NBOMe, 25E-NBOMe, 25G-NBOMe, and 25H-NBOMe, over the period 2013-2014.
- DOC (2013) and DOI (2014).
- 5-methoxy–N-methyl–N-isopropyltryptamine or 5-MeO-MIPT, commonly known as “moxy” (hallucinogenic tryptamine) in 2015.

In the first half of 2018, the Early Warning System of the Uruguayan Observatory on Drugs reported in its database the presence of blotters usually sold as LSD, replaced with derivatives of the 2 C phenelethylamines (25C-NBOMe, 25I-NBOMe, 25B-NBOMe) on eight blotters, hallucinogenic phenelethylamines (DOB, DOC, DOI) on six blotters, 2 C-B on one blotter, and fentanyl on one blotter with the logo “Bicycle day” (Uruguayan Early Warning System on Drugs, 2018).

5. HEALTH EFFECTS OF ADULTERANTS

This chapter will examine:

- the addictive potential or reinforcing mechanism of the effect of the adulterated substance.
- the acute toxic effects and potential synergic effect with the adulterated drug.
- evidence of repercussions or complications of chronic use.

This analysis will be done by adulterant, citing the scientific evidence based on case reviews or reports.

5.1. ADULTERANTS OF COCAINE

5.1.1. LEVAMISOLE

5.1.1.1. General concepts

Levamisole is an anthelmintic (de-worming) drug for human and veterinary use. Studies have also shown its properties as an immunomodulator of lymphocytes B and T, monocytes, and macrophages (Dubé P, 2010). It was used in the 1970s in inflammation pathologies and as an adjuvant in oncology; these treatments were lengthy, and adverse effects were described, notably agranulocytosis and vasculitis (Williams et al., 1978). Levamisole continued to be used as a coadjuvant to 5-fluorouracil (5-FU) in chemotherapy treatment of advanced colon cancer until the first decade of this century. The adverse effects reported and the subsequent discovery of levamisole as an adulterant of cocaine caused it to be withdrawn from the pharmaceutical market in humans, and it was restricted exclusively to veterinary use as an anthelmintic (DEA, 2013).

Levamisole was detected in 2002 in the United States as an adulterant of cocaine; the first series of cases of agranulocytosis linked to levamisole was reported in 2006 (Lee, Ladizinski, & Federman, 2012). Levamisole in samples of cocaine rose from 1% to 70% over a period of 10 years, accompanied by a significant increase in reports of cases of neutropenia and severe infections in New Mexico, Washington, Colorado, and

Arizona (United States), as well as in Alberta, British Columbia, and Ontario, in Canada (Brackney et al., 2009; Knowles et al., 2009; Dubé, 2010; Wiegand, 2010).

5.1.1.2. Significant toxicokinetic aspects

Information on the pharmacokinetics of levamisole when it is inhaled (snorted, smoked) or taken intravenously is limited. Its absorption is well documented in experimental studies and *in vivo.* A study conducted in a hospital in the U.S. city of Denver, Colorado, analyzed urine samples from 249 patients who had tested positive for cocaine, and 194 of them tested positive for levamisole (Buchanan et al., 2011); however, studies concluded that absorption may be greater in women, which might explain in part their greater biological vulnerability to the toxic effects of levamisole (Brunt et al., 2017b). The drug has a significant hepatic metabolism, which results in the formation of two active metabolites: p-hydroxy-levamisole and aminorex (Bertol et al., 2011). Only 3% is eliminated unchanged through the kidneys. Levamisole has a short elimination half-life of five hours (Dubé, 2010); however, studies have reported that following an oral dose of 100 mg, levamisole and aminorex can be detected up to 39 and 54 hours, respectively, after intake (Hess et al., 2013). Levamisole in urine cannot be detected by conventional immunological tests or screening but requires techniques such as gas chromatography/mass spectrometry, which are not available in every hospital laboratory. Its short half-life is a limitation on detection in urine (Magliocca, Coker, & Parker, 2013).

5.1.1.3. Mechanism of action

Levamisole has multiple pharmacological actions that may be related to its use as an adulterant of cocaine and the harmful side effects on health. The substance:

- is an agonist of the cholinergic receptor of acetylcholine.
- interacts with the opioid system and increases levels of morphine and codeine in experimental models.
- changes the metabolism of neurotransmitters such as dopamine, noradrenaline, and serotonin.
- increases the release of dopamine in some areas of the brain, a mechanism mediated by its cholinergic agonist action via its metabolite aminorex.

5.1.1.4. Role as adulterant of cocaine

One of the reasons levamisole has become a principal adulterant of cocaine is that it possesses similar physical characteristics. It is also widely available at low cost in veterinary medicine and does not interfere with the colorimetric tests generally used to detect the presence of cocaine. The melting point of levamisole is below that reported for smokable cocaines, and it is unnoticeable when smoked (Brunt et al., 2017b).

The neurobiological effects of levamisole combined with cocaine have been the subject of a number of studies over the last decade, and various hypotheses have been suggested. Levamisole may enhance the euphoria and the psychostimulant effect of cocaine by a number of different mechanisms (Larocque & Hoffman, 2012; Lee, Ladizinski, & Federman, 2012; Auffenberg, Rosenthal, & Dresner, 2013; Tallarida, Tallarida, & Rawls, 2015; Brunt et al., 2017b; Kudlacek et al., 2017a).

- It has an agonist effect on nicotine receptors, which seems to translate into greater dopaminergic action (due to an increase in glutamatergic activity) and stimulant effects on the sympathetic nervous system.
- It is a selective inhibitor of the monoamine oxidase enzyme (MAO) A and inhibitor of noradrenaline reuptake.
- One of its principal metabolites, aminorex, has an amphetamine-like structure, with a dopaminergic, noradrenergic, and serotoninergic agonist effect.

Aminorex (2-amino-5-phenyl-2-oxazoline) is an amphetamine derivative developed in the 1960s by the pharmaceutical industry as an appetite suppressant in some European countries. It was withdrawn from the market and sales were banned in 1972. It was also detected as a doping agent in racehorses, to whom levamisole was administered as an anthelmintic (Kudlacek et al., 2017b). Both aminorex and 4-methylaminorex were substances that were used illicitly, having a psychostimulant effect significantly greater than cocaine in animals and sharing its indirect sympathomimetic effects (Chang, Osterloh, & Thomas, 2010).

It has been suggested that the modulating effects of aminorex on dopamine, noradrenaline, and serotonin transporters are independent of those produced by levamisole. Both effects are longer-lasting than those induced by cocaine, and therefore both levamisole and aminorex may prolong the psychostimulant effect (Hofmaier et al., 2014).

From a neurobiological standpoint, levamisole has a psychostimulant effect that is synergic with that of cocaine, which means greater addictive potential and greater risk of dependence (Raymon & Isenschmid, 2009; Dubé , 2010; Tallarida et al., 2014).

5.1.1.5. Toxic effects of levamisole as an adulterant of cocaine

Table 6 shows the clinical manifestations, complications, and findings in complementary studies related to the toxic effect of levamisole as an adulterant of cocaine.

Table 6: Toxic effects induced by levamisole as an adulterant of cocaine

Toxic effects
General malaise, weakness, fatigue, arthralgia, fever
Necrosis of the skin, hemorrhagic bullae, retiform purpura, vasculitis
Pyoderma gangrenosum
Pauci-immune glomerulonephritis, membranous nephropathy, acute renal injury
Alveolar hemorrhage, pulmonary arterial hypertension, pulmonary edema
Leukoencephalopathy
Leukopenia, neutropenia, agranulocytosis, anemia, plaquetopenia
Hyponatremia
Positive for ANCAs, ANA, anti-PR3, anti-dsDNA, lupus anticoagulant, anti-HLE*

* ANCAs=antineutrophil cytoplasmic antibodies; ANA: antinuclear antibodies; anti-PR3=antiproteinase 3 antibodies; anti-dsDNA=anti-double stranded DNA antibodies; anti-HLE=anti-elastase antibodies.

Table 7 shows case reviews or case reports (including series of up to six patients) related to the toxic effects and complications from the use of levamisole as an adulterant of cocaine. The drug used in most cases was cocaine hydrochloride, with fewer reports of crack or smokable cocaines. The association of levamisole with these complications is seen in clinical manifestations and complications that are similar or common to the different reports (some of which were fatal) based on immunologic and serologic findings and histopathology studies. In the great majority of cases, there was analytical confirmation of the presence of cocaine and/or metabolites and levamisole in body fluids (most frequently urine). The drug used (cocaine hydrochloride) was analyzed in

only one case, in which 23% levamisole was found through mass spectrometry (Farmer et al., 2012).

The complications and their physiopathological mechanisms will now be examined. The two main complications reported were hematological (agranulocytosis and neutropenia) and dermatological (vasculopathy).

A) Hematological manifestations

Agranulocytosis and neutropenia

Agranulocytosis is a rare clinical-hematological syndrome, characterized by a neutrophil count of less than 500/mm^3, associated with severe infectious manifestations. Its most frequent etiology is pharmacological. This may be initially accompanied by malaise, muscle weakness, feverish sensation, and a flu-like syndrome (Maciel & Duranona, 2016).

A rare serious adverse effect has been described in patients treated with levamisole, probably because of immune-mediated reactions. An association was found between this complication due to levamisole and the HLA B27 genotype, whose presence would suggest a genetic predisposition (Brunt et al., 2017b).

Numerous clinical cases have been published over the last 10 years on the presence of agranulocytosis and neutropenia associated with the use of cocaine adulterated with levamisole **(Table 7)**. This complication is not generally associated with rheumatological disorder induced by cocaine, or with drug-induced vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA), which in these cases would reflect the pathogenic role of levamisole (Nolan & Jen, 2015).

The first cases reported in the United States and Canada concerned adult users of cocaine hydrochloride and, less frequently, smokable cocaines (specified as crack in those reports). They presented with fever as the predominant symptom, along with a variety of respiratory and skin infections. Cocaine or its metabolites, as well as levamisole, were found in the urine of the patients (Knowles et al., 2009; Zhu, Legatt, & Turner, 2009; Buchanan et al., 2010; Wiens et al., 2010). Pellegrini et al. (2013) report a case with similar characteristics in Argentina but without analytical confirmation of levamisole in the patient's urine.

Numerous cases have been reported of necrotic skin lesions or purpuric lesions, with associated leukopenia and/or neutropenia (Muirhead & Eide, 2010; Han, Sreenivasan, & Dutz, 2011; Arora et al., 2012; Belfonte et al., 2013; Garcés Montoya, Berrouet Mejía, & Velásquez Escobar, 2015; O'Neal, 2015; Lopera, 2016; Sirvent et al., 2016; Veronese et al., 2016; Salehi, Morgan, & Gabriel, 2017; Khan et al., 2018).

In the reported cases of agranulocytosis in cocaine users, various hematological changes were found, such as myeloid hypoplasia, a larger number of plasmocytoid lymphocytes, bone marrow plasmocytosis, and megakaryocytic hyperplasia (Nolan & Jen, 2015).

The mechanism suggested for agranulocytosis and neutropenia induced by levamisole-adulterated cocaine is the activation of the immune system producing ANCA autoantibodies. The presence of these autoantibodies has also been related to a genetic predisposition related to the HLA B27 genotype (Buxton et al., 2015; Wolford et al., 2016; Juanena et al., 2017).

Other hematological complications related to the use of levamisole-adulterated cocaine have been described, including plaquetopenia and normocytic normochromic anemia, as seen in chronic inflammation processes in these immune-mediated cases (Carrara et al., 2016; Lopera, 2016; Veronese et al., 2016; Juanena et al., 2017).

In general, the hematological changes do not require specific treatment, and there is spontaneous recovery in five to ten days after stopping use (Buchanan & Lavonas, 2012; Pellegrini et al., 2013). A granulocyte colony-stimulating factor is indicated in cases of febrile neutropenia with a count of less than 100/mm^3 (Juanena et al., 2017).

B) Immunological and serological changes

The reported cases of agranulocytosis and vasculitis related to the use of levamisole-adulterated cocaine show the presence of elevated autoantibody titers, essentially pANCA (perinuclear antineutrophil cytoplasmic antibodies) with no significant increase in myeloperoxidase antibodies, which may be related to the presence of atypical pANCA antigens. This finding is characteristic but not pathognomonic of levamisole-induced vasculopathy (Larocque & Hoffman, 2012; Nolan & Jen, 2015). Elevated titers have also been reported of antinuclear antibodies (ANA), antiproteinase 3 (anti-Pr3), antiphospholypids (anticardiolipin and lupus anticoagulant), anti-double stranded DNA

(anti-dsDNA), and anti-elastase (anti-HLE), as will be seen in the cases described in **Table 7** (Lee, Ladizinski, & Federman, 2012; Schmoeller, da Silva, & Staub, 2015).

Cocaine-induced vasculitis (without presence of levamisole) is generally characterized by high titers of c-ANCA (cytoplasmatic). The finding of high titers of multiple antibodies differentiates the levamisole immuno-mediated changes from idiopathic ANCA vasculitis, in which in general there are lower titers of a specific antibody (Nolan & Jen, 2015).

C) Cutaneous vasculopathy – vasculitis

Numerous studies since 2009 have reported the presence of a cutaneous vasculopathy syndrome associated with cocaine adulterated with levamisole (Muirhead & Eide, 2010; Han, Sreenivasan, & Dutz, 2011; Arora, Jain, Bhanot, & Natesan, 2012; Belfonte et al., 2013; Garcés Montoya, Berrouet Mejía, & Velásquez Escobar, 2015; O'Neal, 2015; Lopera, 2016; Sirvent et al., 2016; Veronese et al., 2016; Salehi, Morgan, & Gabriel, 2017; Khan et al., 2018). This syndrome is predominant among women, by mechanisms that are not yet established (Buchanan & Lavonas, 2012; Brunt et al., 2017b).

Purpuric plaque lesions have been described as having a retiform or angulated pattern, and/or bullous lesions that are occasionally hemorrhagic, necrotic areas and ulcers. The skin lesions are found mostly on the auricle and extremities, and are more frequent on the cheeks, nose, and palate (Buchanan & Lavonas, 2012; Larocque & Hoffman, 2012; Magliocca, Coker, & Parker, 2013; Lawrence et al., 2014; Formeister, Falcone, & Mair, 2015; Jadhav et al., 2015).

This syndrome is associated with the hematological changes described (agranulocytosis, neutropenia) in more than half of the cases and high titers of autoantibodies, particularly ANCA, in 95% to 100% of the cases (Arora, 2013; Marquez et al., 2017). **Table 7** describes a case of vasculopathy with negative ANCA (Salehi et al., 2017).

Histopathologic analysis shows small vessel vasculitis (leukocytoclastic vasculitis), thrombotic vasculopathy, or mixed. Even though leukocytoclastic vasculitis due to cocaine and other causes is associated with high titers of ANCA, the topography of the lesions on earlobes and cheeks is characteristic of vasculopathy due to levamisole-

adulterated cocaine (Arora, 2013; Souied et al., 2014; Nolan & Jen, 2015; Roberts & Chévez-Barrios, 2015).

The differential diagnoses of vasculopathic syndrome due to levamisole-adulterated cocaine include bacterial and viral infections, adverse reactions to medications, paraneoplastic syndromes, connectivopathy, cryoglobulinemia, and Wegener's granulomatosis, among others (Chung et al., 2011).

The physiopathological mechanisms suggested are a synergy between the immune-mediated effects of cocaine and levamisole, as well as cross-sensitization between the two substances. Chronic users of levamisole-adulterated cocaine may be subject to a process of sensitization to levamisole (Brunt et al., 2017b).

The evolution and outcome of the skin lesions depends on their severity and size, and range from conservative treatment to resectioning of necrotic lesions, sacrectomy and autografts, and amputations. In all cases, cessation of cocaine use is essential to avoiding recurrences (Formeister, Falcone, & Mair, 2015; Juanena et al., 2017).

D) Kidney disease

There are reports of cases that associate the use of levamisole-adulterated cocaine with kidney disease, with the presence of rapidly progressing pauci-immune necrotizing glomerulonephritis (Carlson et al., 2014; Sirvent et al., 2016; Veronese et al., 2016). Membranous nephropathy associated with exposure to levamisole as an adulterant of cocaine has also been described (Carrara et al., 2015; Roca Argente et al., 2015), and a finding of focal segmental glomerulosclerosis in one fatal case (Indorato, Romano, & Barbera, 2016). The presentation is acute renal injury, with findings of hematuria and varying degrees of proteinuria in urine sediment in patient studies, as well as vasculitis (Collister et al., 2017) and associated hematological and cutaneous alterations (Baptiste et al., 2015; Nolan & Jen, 2015; Veronese et al., 2016).

Reactive thiols in the structure of levamisole cause the substance to behave like a hapten, entering the immune system and promoting the maturation of dendritic cells, release of proinflammatory cytokines, and production of antibodies that cause cytotoxicity, leading to vasculitis, necrosis, and intravascular thrombosis in various organs such as the kidneys. Kidney damage is also the result of nephrotoxicity caused

by cocaine, which includes hemodynamic alterations, oxidative stress, synthesis and degradation of extracellular matrix, and renal atherogenesis (Veronese et al., 2016).

E) Pulmonary complications

Case studies have been published of pulmonary hypertension in users of levamisole-adulterated cocaine (Hess et al., 2014; Karch et al., 2014). It is suggested that the metabolite aminorex may contribute to this toxic effect via its serotonergic agonist effect and the action of serotonin on pulmonary arterial microcirculation (Karch et al., 2012; Hofmaier et al., 2014). Some of these cases were fatal; the autopsies found pulmonary arterial enlargement and perivascular infiltrate (Karch et al., 2016).

Pulmonary edema in the context of a cardiac complication has also been reported in forensic cases (Michaud et al., 2014; Indorato et al., 2016; Karch et al., 2016). The synergy between cocaine and levamisole/aminorex may lead to greater risk of myocardial ischemia, arterial hypertension, arrhythmia, and cardiogenic pulmonary edema (Raymon & Isenschmid, 2009; Michaud et al., 2014; Indorato et al., 2016).

Vasculopathy as a side effect of the consumption of levamisole-adulterated cocaine may also manifest in the lungs with alveolar hemorrhage (Juanena et al., 2017).

F) Leukoencephalopathy

Multifocal inflammatory leukoencephalopathy is an adverse reaction described for levamisole, with damage to the white matter, which manifests as muscle weakness, hemiparesis, aphasia, and cognitive changes (Brunt et al., 2017b).

There are reports of cases of cocaine-induced leukoencephalopathy, suggesting immuno-mediated mechanisms. Although the association with levamisole could not be demonstrated in the majority of these cases, the fact that it is a known adverse reaction to the use of levamisole, and the finding of lesions in topographies different from those reported with cocaine use, suggest the hypothesis that levamisole may play a pathenogenic role in these cases (Gonzalez-Duarte & Williams, 2013; Hantson et al., 2015; Vosoughi & Schmidt, 2015).

G) Other complications

Pyoderma gangrenosum has been reported as a complication of the use of levamisole-adulterated cocaine, with a cutaneous clinical presentation different from the vasculopathetic syndrome, but with ANCA antibodies and positive antiphospholipids.

It is characterized by a variety of ulcerated lesions, bullae, and/or pustules on the lower limbs (Jeong et al., 2016).

Three cases have been described of patients with hyponatremia -- a rare complication in the case of cocaine use -- who presented with metabolites of cocaine and levamisole testing positive in urine, suggesting a possible causality between the complication and the adulteration of cocaine with levamisole (Friend, Milone, & Perrone, 2012).

Although there is no consensus as to the risk of developing these complications when using levamisole-adulterated cocaine, the hypothesis in the majority of the cases published since 2009, and ever larger in number, is that it may be associated with the higher percentage of levamisole in the samples of cocaine consumed over the years and with greater exposure to levamisole. In addition, due to the physiopathological mechanisms discussed above, chronic use of at least one gram of cocaine per day would lead to exposure to more than 100 mg of levamisole per day, a dose associated with the appearance of complications such as vasculopathy and agranulocytosis (Nolan & Jen, 2015; Brunt et al., 2017b).

Currently, the clinical presentation of a patient with a vasculopathic syndrome of characteristic topography, accompanied by agranulocytosis and/or neutropenia and with elevated titers of antibodies, particularly pANCA, strongly suggests the suspicion of the use of levamisole-adulterated cocaine.

Table 7: Case reports or case series involving levamisole-adulterated cocaine

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology*** **	Analysis of the substance used (if pertinent)
Zhu et al., 2009	Canada	Cocaine HCl inh.	Female 38 yrs	Fever, cellulitis, pneumonia, bacteremia (*E. coli*), cystitis (*Klebsiella pneumoniae*)	Agranulocytosis Lupus anticoagulant +	N/R	LEV urine + COC urine +	N/R
		Cocaine HCl inh.	Female 41 yrs	Fever	Agranulocytosis Lupus anticoagulant +	N/R	LEV urine + COC urine +	N/R
		Cocaine HCl inh.	Female 18 yrs	Fever, aphthae, peritonsillar abscess, cellulitis	Agranulocytosis Lupus anticoagulant +	N/R	LEV urine + COC urine +	N/R
		Cocaine HCl inh.	Female 44 yrs	Fever	Agranulocytosis Lupus anticoagulant +	N/R	LEV urine + COC urine +	N/R
		Cocaine HCl inh.	Male 48 yrs	Fever, mumps, cellulitis of the face and neck that required OI	Agranulocytosis Lupus anticoagulant +	N/R	LEV urine + COC urine +	N/R
Wiens et al., 2010	Canada	Cocaine HCl inh.	Female 28 yrs	Fever, pneumonia	Severe neutropenia	N/R	LEV urine +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology*** **	Analysis of the substance used (if pertinent)
		Cocaine HCl inh.	Male 60 yrs	Fever, odynophagia, malaise	Severe neutropenia	N/R	LEV urine + COC urine +	N/R
Buchanan et al., 2010	United States	Crack	Adult male	Fever, pharyngeal erythema, night sweats, headache, dark urine, intermittent tinnitus	Leukopenia with severe neutropenia ANCA+	Moderate myeloid hypoplasia with lowered mature neutrophils and megakaryocytic hyperplasia in biopsy of bone marrow	BZE urine +	N/R
Muirhead et al., 2011	United States	Cocaine HCl inh.	Female 54 yrs	Painful necrotic skin lesions on face, ears, breasts, and limbs	Neutropenia and lymphopenia ANCA+ pANCA+ Anti-PR3+	Vasculopathy with intravascular fibrin deposition in skin biopsy	LEV urine + COC urine +	N/R
Han et al., 2011	Canada	Cocaine HCl inh.	Female 52 yrs	Retiform purpura, intermittent painful ecchymosis on limbs, with ulceration of nose, ears, and	Leukopenia with neutropenia pANCA+ Anti-PR3+	Extensive thrombotic vasculopathy without	N/R	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
				cheeks	Anticardiolipin Ac IgM+	vasculitis in skin biopsy		
Arora et al., 2012	United States	Crack	Female 44 yrs	Purpuric lesions, painful maculopapular skin rash on limbs, cheeks, and earlobes. Poor outcome: superinfection, necrosis, and spontaneous amputation of nose and surgical above-the-knee amputation of lower limbs	Leukopenia with neutropenia Lupus anticoagulant + ANCA MPO+	Leukocytoclastic vasculitis and small vessel thrombosis in skin biopsy	LEV urine + COC urine +	N/R
Belfonte et al., 2012	United States	Cocaine HCl inh.	Female 45 yrs	Ulcerated necrotic lesions on the four limbs, face, and ears	Neutropenia pANCA+ Anti-PR3+ ANCA MPO+	N/R	LEV urine + COC urine +	N/R
		Crack	Female 40 yrs	Chest pain, maculopapular necrotic cutaneous lesions on the four limbs and breasts	Leukopenia with neutropenia ANA+ pANCA+	Leukocytoclastic vasculitis in skin biopsy	LEV urine (not determined) COC urine +	N/R
		Crack	Female 43 yrs	Purpuric macular cutaneous lesions in plaques on the four limbs, lips, nose, and ears	Neutropenia ANA+ pANCA+	Vasculitis with small vessel fibrin thrombi in	COC urine +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology***	Analysis of the substance used (if pertinent)
						skin biopsy		
Farmer et al., 2012	United States	Cocaine HCl inh.	Male 52 yrs	Fatigue, arthralgia, fever, painful purpuric lesions on limbs, trunk, and right ear	pANCA+	Thrombotic vasculopathy with secondary neutrophilic inflammation in skin biopsy	N/R	LEV 23%
Friend et al., 2012	United States	Cocaine HCl inh.	Male 26 yrs	Chest pain, arterial hypertension, tachycardia	Hyponatremia Rhabdomyolysis	N/R	LEV urine + BZE urine +	N/R
		Cocaine HCl inh.	Male 39 yrs	Chest pain, dyspnea, sweating and psychomotor agitation, tachycardia	Hyponatremia attributed to inadequate secretion of ADH Elevated creatininemia levels	N/R	LEV urine + BZE urine +	N/R
		Cocaine HCl inh.	Male 57 yrs	Weakness, vomiting, polyuria, and polydipsia, slight dehydration, tachycardia	Hyponatremia Elevated creatininemia levels	N/R	LEV urine + BZE urine +	N/R
González et al.,	Mexico	Cocaine HCl	Female 40 yrs	Confusion, recurring motor aphasia, fever	Recurring PML (3 consecutive	N/R	N/R	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
2013		inh.			episodes of lesions on white matter by MRI)			
Pellegrini et al., 2013	Argentina	Cocaine HCl inh.	Male 36 yrs	Fever, aphthous ulcers on buccal mucosa, erythema and amygdala hypertrophy, painful submaxillary adenomegalia	Leukopenia with neutropenia (agranulocytosis)	N/R	COC urine +	N/R
Auffenberg et al., 2013	United States	Cocaine HCl inh.	Female 48 yrs	Fever, cough, rhinorrhea, dyspnea, hypotension, pneumonia, intubation, purpuric lesions on forearms developing into phlyctenae and necrotic plaques	Leukopenia with neutropenia pANCA+	Vaso-oclusive vasculitis in skin autopsy	COC urine +	N/R
Karch et al., 2014 (Forensic case)	Tunis	Cocaine HCl inh.	Male 51 yrs	Severe dyspnea, cardiac arrest, death	N/R	Cyanosis of face and fingers. Reddened, poorly expanded lungs (autopsy histopathology)	LEV blood + (0.01 mg/L) LEV urine + (0.07 mg/L) BZE blood + (2.79 mg/L) BZE urine + (288.7 mg/L)	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
							COC blood + (0.15 mg/L) COC urine + (36.19 mg/L) Detected also in: brain, liver, lung, hair	
Michaud et al., 2014 (Forensic case)	Switzer-land	Cocaine HCl inh.	Male 25 yrs	MI one year previously, no subsequent treatment; currently, chest pain, ventricular fibrillation, death	Elevated levels of troponin I in post-mortem analysis	Pulmonary and pleural edema. Myocardial hypertrophy with atheromatous in coronary artery plaque erosion (autopsy histopathology)	LEV urine + LEV pericardial fluid + BZE blood + (0.61 mg/L) COC blood + (0.34 mg/L) COC hair +	N/R
Souied et	United	Crack	Male 39	Painful purpuric lesions on	Hyperleukocytosis	Acute	COC urine +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
al., 2014	States		yrs	right hand, left foot, ears (necrotic), and nose	ANA+ pANCA+ Anticardiolipin Ac IgM+	inflammation of the epidermis with perivascular inflammation with foci and associated thrombus in biopsy of upper sector of pavilion of the left ear		
Formeister et al., 2014	United States	Cocaine HCl inh.	Female 29 yrs	Painful purpuric lesions on ears, hard palate, nose, cheeks, lips, upper limbs, right and left foot, ears, and nose	Anemia Anti-PR3+ Anticardiolipin IgM + aFL phosphatydyl-glycerol, and phosphatidyl serine IgG +	Leukocytoclastic vasculitis in skin biopsy	COC urine –	N/R
Lawrence et al., 2014	United States	Crack	Female 33 yrs	Fever, nausea, anorexia, cough, painful purpuric lesions on cheeks, nose,	Thrombocytopenia ANCA+ Ac. Anti-PR3+		LEV urine + COC urine +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
				back, and the four limbs. Evolution to necrosis of the lesions. Hypotension and lactic acidosis				
Hantson et al., 2015	Belgium	Cocaine HCl inh.	Male 22 yrs	Cephalea, ataxia, and paresthesia of the right half of the body	Hyperproteino-rrhaquia in CSF, PML (NMR), developing to necrotic-cystic lesions. Suspected Susac syndrome	N/R	LEV hair + BZE hair + COC hair +	N/R
Jadhav et al., 2015	United States	Cocaine HCl inh.	Female 35 yrs	Necrotic purpuric lesions on arms, auricular pavilions, buttocks, and fingers	Anti-PR3+ Elevated PCR	Thrombotic vasculopathy probably secondary to levamisole	LEV urine - COC urine -	N/R
Baptiste et al., 2015	United States	Crack	Male 43 yrs	Cachexia, fever, weakness, reduced superficial sensitivity on lower limbs	Elevated creatininemia and BUN levels Slight proteinuria & hematuria ANCA+	ANCA vasculitis induced by levamisole in renal biopsy	BZE urine +	N/R
Roca Argente	Spain	Cocaine HCl	Male 49 yrs	Oligo-anuric renal failure, hematuria,	Elevated creatininemia and	Thrombotic vasculitis in	N/R	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
et al., 2015		IV		necrotic skin lesions on nose, trunk, and limbs	azotemia levels. Hemoccult positive for MRSA Anemia Thrombocytopenia ANCA+ Anti-PR3+ ANCA MPO+	peritoneal biopsy Membranous glomerulonephritis with cellular crescents in renal biopsy		
Vosoughi et al., 2015	Canada	Cocaine HCl inh.	Male 25 yrs	Hemiparesis of left side of body with compromised facial nerve	Slight to moderate elevation of liver transaminases PML (NMR)	N/R	COC urine +	N/R
		Cocaine HCl inh.	Female 41 yrs	Confusion, changes in balance and behavior, aphasia, urinary incontinence, cognitive decline, and multifocal neurological deficits	Elevation of creatininemia and BUN levels Elevated CRP PML (NMR)	N/R	COC urine +	N/R
Carrara et al., 2015	Italy	Crack	Female 34 yrs	Large, painful ulcerated necrotic lesions on both lower limbs	Elevation of creatininemia levels. Anemia	Necroticizing glomerulonephritis in renal biopsy	LEV urine - COC urine +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
					Thrombocytopenia Hematuria ANA+ pANCA+ ANCA MPO+			
Garcés-Montoya et al., 2015	Colombia	Cocaine HCl inh.	Male 30 yrs	Feverish sensation, asthenia, adynamia, painful ulcerated lesion with necrotic center on lower left limb	Leukopenia with neutropenia pANCA+ Lupus anticoagulant +	Acute vasculitis in skin biopsy	N/R	N/R
		Cocaine HCl inh.	Male 27 yrs	Arthralgia, malaise, purpuric lesions with blisters on lower limbs, necrotic lesions on auricular pavilions	pANCA+	Pseudovasculi-tis with venous thrombosis in skin biopsy	N/R	N/R
		Cocaine HCl inh.	Female 31 yrs	Painful ulcerated purpuric lesion on right buttock, purpuric lesion on right thigh	Anemia Leukopenia Thrombocytosis pANCA+	Leukocytoclastic vasculitis in skin biopsy	N/R	N/R
O'Neal, 2015	United States	Crack.	Female 43 yrs	Painful purpuric lesions on the four limbs, nose, and ears; necrosis; subsequently, spontaneous amputation of nose	Leukopenia with neutropenia Thrombocytosis	N/R	N/R	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration*	Case report(s)**	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology****	Analysis of the substance used (if pertinent)
Schmoeller et al., 2015	Brazil	Cocaine HCl inh.	Male 50 yrs	Necrotic lesions on ears, tongue, scrotum, and lower limbs	Neutropenia, pANCA + ANCA MPO + ANA + Anticardiolipin Ig G & IgM +	Intravascular thrombosis	COC urine +	N/R
Indorato et al., 2016 (Forensic cases)	Italy	Cocaine HCl IV	Male 38 yrs	Chest pain and nausea, puncture site on forearm, death in emergency room. Severe purpuric eruptions on arms and back	N/R	Slight coronary atherosclerosis Pulmonary edema, focal segmental glomerulosclero-sis (autopsy histopathology)	LEV blood + (5 mg/L) LEV urine + (97.2 mg/L) BZE blood + (3.6 mg/L) BZE urine + (82.6 mg/L) COC blood+ (3 mg/L) COC urine + (49.3 mg/L) Also detected in: brain, liver, lung, kidney, hair	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
		Cocaine HCl inh.	Male 31 yrs	Found dead in his car, no lesions	N/R	Localized myocardial fibrosis with extension to anterior wall. Slight coronary atherosclerosis (autopsy histopathology)	LEV blood + (1.6 mg/L) LEV urine + (23.1 mg/L) BZE blood + (0.9 mg/L) BZE urine + (40.9 mg/L) COC blood+ (0.5 mg/L) COC urine + (39 mg/L) Also detected in: brain, liver, lung, kidney, hair	N/R
Karch et al., 2016 (Forensic cases)	United States	Cocaine HCl inh.	Male 51 yrs	Sudden death	N/R	Severe pulmonary edema. Cardiomegaly: remodeling and interstitial	LEV blood + (13.5 mg/L) LEV urine + (61.3 mg/L) BZE blood +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology****	Analysis of the substance used (if pertinent)
						myocardial fibrosis (autopsy histopathology)	(1.8 mg/L) BZE urine + (93.6 mg/L) COC blood+ (0.74 mg/L) COC urine + (26.3 mg/L)	
		Cocaine HCl inh.	Male 35 yrs	Death one hour following use of cocaine hydrochloride	N/R	Severe pulmonary and cerebral edema. Myocardial necrosis in patches. Pulmonary arterial enlargement and perivascular infiltrates (autopsy histopathology)	LEV blood + (17.9 mg/L) LEV urine + (70.2 mg/L) BZE blood + (4.6 mg/L) BZE urine + (248.3 mg/L) COC blood+ (0.95 mg/L) COC urine + (34.7 mg/L)	N/R
Lopera et	Colombia	Cocaine HCl	Male 31	Lesions on auricular	Anemia	Thrombotic	N/R	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
al., 2016		inh.	yrs	pavilions, vasculitic lesions on both thighs, necrotic appearance	Leukopenia with neutropenia ANCA+ ANCA MPO+	vasculopathy and acute vasculitis in skin biopsy Hypocellularity in bone marrow biopsy		
Sirvent et al., 2016	Spain	Cocaine HCl inh.	Male 47 yrs	Two years previous, skin lesions and lesions on ear lobes (neutropenia with ANA and ANCA+); currently, arthralgia, nephrotic syndrome	Anemia Leukopenia Elevated creatininemia levels. Proteinuria ANA+ ANCA+ ANCA MPO+ Anti-PR3 +	Necroticizing glomerulonephri-tis in renal biopsy	COC urine +	N/R
Veronese et al., 2016	Brazil	Cocaine HCl inh.	Male 49 yrs	Erythematous skin lesions, with foci of edema and bilateral necrosis on ears, thighs, and sides	Anemia Leukopenia ANCA + ANCA MPO + Anti-PR3 + Elevated	Small vessel neutrophilic leukocytoclastic vasculitis in skin biopsy Tubulointerstitial infiltrate,	LEV urine + COC urine +	COC 62,8 % LEV 32,2%

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
					creatininemia levels	multifocal rupture of glomerular basal membrane and intraglomerular necrosis in renal biopsy		
Collister et al., 2017	Canada	Crack	Male 53 yrs	Purpuric bilateral skin lesions on abdomen, thighs and legs bilaterally, necrotic lesions on both ears, renal injury	Anemia Acute renal injury Anti-dsDNA + ANCA+ ANCA MPO+	Diffuse capillary enlargement in renal biopsy ANCA-related vasculitis	BZE urine not obtained	N/R
		Cocaine HCl inh. Crack	Male 35 yrs	Arthromyalgia, hemoptysis, renal pulmonary syndrome, mouth ulcers, Raynaud's phenomenon	Anemia Thrombocytosis Acute renal injury ANCA+ ANCA MPO+	Segmentary fibrinoid necrosis in renal biopsy ANCA-associated vasculitis	LEV urine + (liquid chromatogra-phy) BZE urine +	N/R
		Cocaine HCl inh.	Male 34 yrs	Arterial hypertension, hyperpigmented lesions on limbs	Anemia ANCA+ ANCA MPO+	ANCA-related vasculitis	LEV urine + (liquid chromatograp hy)	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology** **	Analysis of the substance used (if pertinent)
							BZE urine +	
Juanena et al., 2017	Uruguay	Cocaine HCl inh.	Male 40 yrs	Macular-equimotic lesions on limbs, trunk, and buttocks, distal ischemia of fingers and toes, fever	Anemia Leukopenia with neutropenia, plaquetopenia ANCA MPO +	Leukocytoclastic vasculitis in skin biopsy	BZE urine +	N/R
		Cocaine HCl inh.	Male 40 yrs	Necrotic lesions on backs of arms, front of thighs, and auricular pavilion	Anemia Leukocytosis with neutrophilia Acute renal injury ANCA +	Leukocytoclastic vasculitis in skin biopsy	N/R	N/R
		Cocaine HCl inh.	Male 36 yrs	Extensive necrosis of the auricular pavilions, cheeks, nose, and left upper arm	Anemia Leukopenia without neutropenia Acute renal injury ANCA MPO, ANA & AP +	Necrosis of skin associated with vasculitis with fibrin thrombi in skin biopsy	BZE urine +	N/R
Salehi et al., 2017	United States	Cocaine HCl inh.	Male 58 yrs	Painful pruriginous skin rash on limbs; polyarthralgia; articular edema in left 5th proximal interphalangeal articulation, knees, and	Leukopenia Increased CRP	Acute and chronic inflammation of dermis, perivascular	LEV urine + COC urine +	N/R

Studies	Country/ countries	Cocaine type or derivative and route of administration *	Case report(s) **	Clinical manifestations and complications**	Laboratory***	Histopathology	Analytical toxicology***	Analysis of the substance used (if pertinent)
				ankles; bilateral purpuric skin lesions on arms and legs		inflammation, and vasculitis in dermis and subcutaneous cells in skin autopsy		
Khan et al., 2018	United States	Cocaine HCl I/R	Male 59 yrs	Fever, pharyngeal erythema, abdominal pain and distension, bloody diarrhea	Neutropenia Lactic acidosis	Ulceration and mucus and transmural necrosis: ischemic changes in biopsy of large intestine (cecum, sigmoids, and rectum)	COC urine +	N/R

*Cocaine HCl=cocaine hydrochloride; inh=inhaled; IV=intravenous; I/R=intrarrectal; N/R=not reported.

** yrs=years of age; OI=orotraqueal intubation; MI=myocardial infarction; NMR=nuclear magnetic resonance; CSF=cerebrospinal fluid; ADH=antidiuretic hormone; PML=multifocal leukoencephalopathy; BUN=blood urea nitrogen; CRP=C-reactive protein; MRSA=methicillin -resistant Staphylococcus aureus.

***ANCA=antineutrophil cytoplasmic antibodies; pANCA=perinuclear anti-neutrophil cytoplasmic antibodies; ANCA MPO=anti-neutrophil cytoplasmic myeloperoxidase antibodies; ANA=antinuclear antibodies; AP=antiphospholipid antibodies; Anti-dsDNA=anti-double stranded DNA antibodies; Anti-PR3=antiproteinase 3 antibodies; APS=antiphospholipid antibodies.

****BZE=benzoylecgonine; COC=cocaine; LEV=levamisole.

5.1.2. LOCAL ANESTHETICS

Local anesthetics such as lidocaine, benzocaine, and procaine have been described as adulterants of cocaine, particularly of cocaine hydrochloride. The adulteration generally is done to counteract the loss of potency secondary to the presence of other adulterants that have no pharmacological action (talc, sugar, among others). The adulterants mimic the numbing effect on mucous membranes (nose, mouth) that cocaine may produce as a result of vasoconstriction. Such local anesthetics tend to make it possible to use larger doses of cocaine (Saraghi & Hersh, 2014).

The study by Chasin et al. (2003) analyzed 172 samples of blood and urine in 48 live individuals and 124 deceased persons, all involving a medical/legal event. The intention of this study was to use the information from the analysis of the material seized (cocaine) to establish a parallel with the findings in the biological matrices that were also analyzed. In the analysis of the biological matrices (blood and urine), the incidence of lidocaine was 43% of the samples, with values of between 0.3 and 28.0 µg/ml in whole blood, and 2.7 and 131.0 µg/ml in urine. The clinical histories and medical records of the cases analyzed do not refer to the use of lidocaine during the hospital stay, thereby showing lidocaine as an adulterant of cocaine.

Another study in Brazil applied the methodology used in samples of vitreous humor in victims of violent deaths such as traffic accidents, homicides, suicides, and assaults. In one sample, related to homicide, lidocaine was found along with cocaine and its metabolites, which could be due to the use of adulterated cocaine (Costa, 2008).

Local anesthetics can potentiate toxic effects of cocaine such as cardiac arrhythmia or seizures (Schwartz & Kaufman, 2015). In the case of one fatality, a cardiotoxic effect following the intravenous use of lidocaine-adulterated cocaine was suggested (Barbera et al., 2013). A side effect of exposure to local anesthetics in adulterations of cocaine is methemoglobinemia, a clinical syndrome produced by an aberrant form of hemoglobin (methemoglobinemia), as a result of the oxidation of the iron in the heme group from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. This change in its structure led to a reduction in the capacity to transport oxygen to the tissue (anoxia transport). Methemoglobinemia may be a severe, potentially fatal clinical picture. Cyanosis may be the initial or predominant clinical manifestation. It is accompanied by a greyish tint to the skin; the blood is brown in color; and, depending on the severity, it may cause headache,

dizziness, dyspnea, depressed consciousness, coma, and seizures. The antidote treatment is based on the administration of methylene blue (Price, 2015; Curry & Kang, 2017).

Methemoglobinemia due to drug use has been described in cases of adulteration of cocaine and use of volatile nitrites (poppers) (Hunter et al., 2011).

Other adulterants of cocaine, such as phenacetin, may cause methemoglobinemia (Price, 2015; Curry & Kang, 2017).

Some authors suggest that in some cases in which the existence of an adulterant causing this clinical syndrome has been confirmed, the other adulterants that might cause it have not been looked for. The association of more than one adulterant of this type may increase the risk of methemoglobinemia (Hunter et al., 2011).

Methemoglobinemia due to the use of cocaine adulterated with local anesthetics has been reported in the international scientific literature (Chakladar et al., 2010). In one fatal case, more than one agent was identified, namely lidocaine, benzocaine, and phenacetin (Matthews, Oladapo, & Morgan, 2009).

5.1.3. PHENACETIN

Phenacetin is a nonsteroidal anti-inflammatory drug (NSAID), prohibited for commercial use in 1980 because of its carcinogenic and kidney-damaging effect (Cosby, 2014; Grosser, Smyth, & Fitzgerald, 2018). Self-medication of high doses of phenacetin as an analgesic has been associated with tubulointerstitial nephritis and cancer of the kidney and bladder (Cole et al., 2010).

This adulterant is used to enhance the bitter taste of cocaine hydrochloride and to improve its appearance. Phenacetin makes the mixture shiny (Raverta et al., 2016). Along these lines, there have been reports in Argentina since 2015 of a form of cocaine called *alita de mosca* (“little fly wing”), a white crystalline powder containing 80% cocaine hydrochloride and 20% phenacetin (Jones, Suarez Ordoñez, & Browne, 2015).

With regard to phenacetin as an adulterant of smokable cocaines, there is experimental evidence that phenacetin smoked together with cocaine base paste is absorbed into the circulatory system through the lungs, and is found in plasma and urine of users of smokable cocaine (Sena et al., 2017; Abin-Carriquiry et al., 2018).

Unlike the situation with other adulterants (levamisole, local anesthetics), it is not yet known why phenacetin is used as an adulterant of cocaine. Although it was reported that phenacetin might activate mechanisms related to the reinforcing effect of stimulant drugs (Abbott & Hellemans, 2000), no studies were found that showed evidence of its effect on the central nervous system and its interaction with cocaine (Abin-Carriquiry et al., 2018).

An experimental study in Brazil, based on a predictive model with smokable cocaines, showed that the melatonin receptor, which intervenes in the regulation of the circadian rhythm of the sleep-wake cycle, might be the target of both substances (crack and phenacetin), which may enhance sleeplessness during a period of uninterrupted use of smokable cocaines (Castro et al., 2017).

Phenacetin may cause hematological changes, such as hemolytic anemia, methemoglobinemia, and sulfohemoglobinemia (Curry & Kang, 2017). A fatal case of methemoglobinemia associated with local anesthetics and phenacetin was described in 2009. The limitation of that report was that there is more than one substance capable of inducing this complication, and it cannot therefore be attributed exclusively to phenacetin (Matthews, Oladapo, & Morgan, 2009).

There was an anecdotal report of fatality of a body packer in whom cocaine adulterated with phenacetin was identified (Fucci, 2004).

Although phenacetin is an adulterant of recognized acute, chronic, and long-term toxicity, present in a significant percentage of samples of cocaine hydrochloride and smokable cocaines worldwide, there are very few reports that can document its toxic effects on cocaine users. One hypothesis may be related to the dosage and time of exposure, since the reports of nephrotoxicity and its carcinogenic effect are associated with high doses for a prolonged period of time.

5.1.4. CAFFEINE

Caffeine is a recognized adulterant of cocaine (chloride and smokable cocaines). Many countries do not control sales of caffeine, which makes it an adulterant that is used because of its low cost.

Experimental studies have shown that caffeine enhances cocaine-induced motor stimulation. Studies conducted in Uruguay showed that caffeine may increase the

psychostimulant action of cocaine base paste and its positive reinforcing effect, which would have implications for its addictive potential (Meikle et al., 2009; López-Hill et al., 2011; Prieto et al., 2012; Prieto et al., 2016; Muñiz et al., 2017). Other studies have shown it to be stable when used as a smokable substance, establishing a synergy with cocaine (Abin-Carriquiry et al., 2018).

There are reports that link caffeine-adulterated cocaine with a greater risk of mood changes, anxiety, and sleep disorders (Cole et al., 2011). At high doses, caffeine may, through sympathetic stimulation, potentiate the toxic effects of cocaine being absorbed by any route (Hoffman, 2015).

Sena et al. (2017) demonstrated the presence of caffeine in urine in four out of five crack users studied in Brazil, by means of the use of liquid-liquid microextraction based on solidification of a floating organic drop (DLLME/SFO), followed by analysis in high-performance liquid chromatography equipped with photodiode-array detector (HPLC/PDA). Concentrations ranged from 415.70 to 735.25 ng/ml.

5.1.5. OTHER ADULTERANTS OF COCAINE

Toxic effects of other adulterants of cocaine have also been reported.

In 2005, the EMCDDA and the REITOX (*Réseau Européen d'Information sur les Drogues et les Toxicomanies*, for its French language acronym) Early Warning System in Europe reported the appearance of serious acute poisonings related to the adulteration of cocaine with **atropine**. Reports from Italy, Holland, France, and the United Kingdom showed numerous cases of acute poisoning characterized by clinical manifestations resulting from the cocaine/atropine combination: mydriasis, tachycardia, arterial hypertension, agitation, seizures, confusion, hallucinations, and acute psychosis.

Diltiazem is a drug with an antiarrhythmic, anti-ischemic, and antihypertensive effect. Authors suggest that its use may be related to "mitigating" the toxic cardiovascular effects of cocaine; however, there are experimental studies done at the end of the 1980s that show greater toxicity (Derlet & Albertson, 1989), as well as clinical studies that show a greater prevalence of toxic cardiac effects and hallucinations (possibly due to hypoxemia) when cocaine is adulterated with diltiazem (Brunt et al., 2009).

Hydroxyzine is an antihistamine used as an antiallergic drug, reported as an adulterant of cocaine for more than a decade (Fucci, 2007). It has an anticholinergic effect, which

may potentiate the side effects of the sympathetic stimulation of cocaine (Kudlacek et al., 2017a). As an adulterant, hydroxyzine has been associated with cardiac arrhythmias and hallucinations (Brunt et al., 2009; Knuth et al., 2018).

There are a few reports of adulterations of cocaine with **superwarfarin rodenticide (brodifacoum, bromadiolone)**, whose prolonged anticoagulant effect caused bleeding that manifested as epistaxis, otorrhagia, and hematuria (Waien, Hayes, & Leonardo, 2001; Otero et al., 2012).

Phenytoin, an anti-seizure drug, has been reported as an adulterant of cocaine. There is a case report of acute cocaine poisoning accompanied by some clinical manifestations characteristic of acute phenytoin poisoning (ataxia, dysarthria, confusion, nystagmus) and elevated plasma levels (Roldan, 2014).

Dipyrone was banned in some countries as an analgesic and antipyretic because of the risk of adverse effects (agranulocytosis, neutropenia) that this drug and another derivative of pyrazolone, **aminopyrine**, may cause in the blood (Browne Jr., 2015; Isaacs, Harper, & Miller, 2017). There is evidence of both dipyrone and aminopyrine as adulterants of cocaine. Although no reports were found of cases from the period under review that showed that these substances could be attributed to toxic effects in cocaine users, this adulteration may increase the risk of the hematological complications described.

The use of **paracetamol** as a cocaine adulterant would increase the risk of hepatotoxicity due to cocaine (Browne Jr., 2015; Grosser, Smyth, & Fitzgerald, 2018).

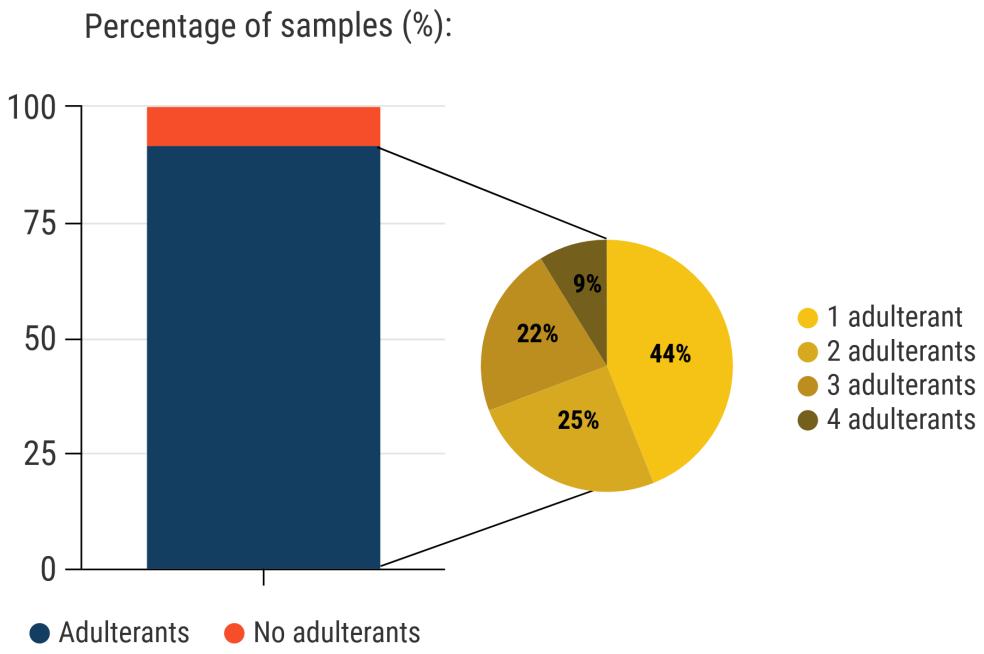
Cases have been reported of combinations of cocaine with **fentanyl** in a single substance, which may represent an adulteration or substitution of heroin with fentanyl and its analogues. Regarding the first case, between July 15 and 18, 2016, an increase of 170% was reported in the number of cases of opioid overdose in a hospital emergency department in British Columbia, Canada, (n=43 over four days), where more than half of the patients had a recent history of using crack that had been adulterated with **furanylfentanyl** (Klar et al., 2016). In the United States, the DEA reported in some states such as Pennsylvania an increase in fatal cases related to the use of cocaine with fentanyl (from 17% in 2016 to 33% in 2017), seen in samples seized with both substances. Among the different hypotheses suggested: users may have received

fentanyl or fentanyl/cocaine instead of heroin without knowing it, or some were in fact were seeking to use fentanyl (DEA, 2018b).

Amphetamine-type stimulants (ATS) like MDMA (methylenedioxy-methamphetamine), synthetic cathinones, and 2 C-B have been found in recent years. Their toxic effects will be described below. The adulteration of cocaine with this type of substance increases the risk of overdose with a greater sympathomimetic effect (Kudlacek et al., 2017b).

A study conducted as part of a project of the Inter-American Drug Abuse Control Commission (know by its Spanish language acronym, CICAD) examined the hair of users of smokable cocaines for adulterants found in samples obtained on the street in different Brazilian states and by the Brazilian Federal Police; these included the substances aminopyrine, benzocaine, phenacetin, hydroxyzine, levamisole, lidocaine, and procaine. The findings were characterized using the biomarker for smokable cocaine, anhydroecgonine-methyl-ester, considered the metabolite necessary for inclusion of the sample in the experiment. The analytical findings of the hair samples to verify the use of smokable cocaine, as well as the characterization of the adulterants, showed that of a total of 50 samples, adulterants were detected in 91.7%. The levels and frequency of detection of each of the adulterants were: hydroxyzine (0.4 ng/mg, 3.3%), benzocaine (1.1 ng/mg, 6.7%), procaine (1.2 ng/mg, 8.3%), aminopyrine (2.6 ng/mg, 15.0%), lidocaine (7.7 ng/mg, 21.7%), levamisole (2.1 ng/mg, 46.7%), and phenacetin (6.7 ng/mg, 78,3%). Phenacetin alone was detected in 36.7% of the samples analyzed, and in combination with levamisole in 35.0%. A single adulterant was found in 40% of the samples, and simultaneous combinations of two, three, and four adulterants were detected in 23.3%, 20.0% and 8.3%, respectively, as shown in **Figure 6** (Raverta et al., 2016).

Figure 6: Percentage of hair samples from smokable cocaine users that tested positive for adulterants, and number of adulterants in each sample



Pawlik et al. (2015) studied the presence of adulterants in blood in heart cavities, femoral veins, and lung tissue in 11 forensic cases of cocaine users. Phenacetin, lidocaine, diltiazem, levamisole, and hydroxyzine were found, with elevated concentrations in the lung.

Knuth et al. (2018) analyzed 10 forensic samples of brain tissue in which cocaine was found to be present. Levamisole, lidocaine, hydroxyzine, and phenacetin were also found to be present in these samples. Both levamisole and hydroxyzine were found in high concentrations.

5.2. ADULTERATION OF SYNTHETIC DRUGS AND NEW PSYCHOACTIVE SUBSTANCES

MDMA has a serotonergic agonist effect, explained by stimulation of the release and inhibition of presynaptic serotonin reuptake, and also by inhibition of the activity of the monoamine oxidase A enzyme (MAO-A), responsible for the degradation of serotonin. It also has an agonist effect on the 5-HT 2A receptors. MDMA also increases the synthesis of dopamine and the release of norepinephrine. Serotonin, norepinephrine, and dopamine thus build up in the synaptic clefts (Ministerio de Sanidad, Política Social e Igualdad de España, 2011). **Table 8** gives details of the toxic syndromes caused by stimulant drugs.

The entactogenic properties (greater empathy with the environment and intensification of sensory perceptions) are explained by a combined mechanism of action of serotonin and dopamine.

The adulteration of pills with other ATS with greater serotoninergic potency is common, as is the associated use of other drugs such as alcohol and cocaine. These practices, combined with strenuous dancing in closed or poorly ventilated environments, increase the risk of acute complications from using MDMA. Methoxyamphetamines such as PMA and PMMA show greater affinity for serotonin receptors (5-HT-2A) (Jang, 2015).

The serotonin syndrome caused by ATS is characterized by disorders of consciousness (general restlessness or psychomotor agitation) accompanied by neuromuscular changes (hypertonia, trismus, seizures) and dysautonomia, initially tachycardia and arterial hypertension with the risk of cardiovascular collapse. Hyperthermia is a frequent sign, both due to direct toxic action and because of the conditions of the setting referred to above. Other complications include dehydration, rhabdomyolysis, acute renal injury, and disseminated intravascular coagulation (Sternbach, 1991; Dunkley et al., 2003; Boyer & Shannon, 2005; Isbister, Buckley, & Whyte, 2007).

Fatal cases have been described of hyponatremia secondary to the toxic effect of ATS and to a considerable intake of water without replenishment of mineral salts (Balanzó Fernández & Martínez Poveda, 2002; Galicia, Alonso, & Nogué, 2014; Jang, 2015) .

The toxic syndromes produced by stimulant drugs (cocaine, phenylethylamines) are shown in **Table 8.**

Table 8: Toxic syndromes in overdose of stimulant drugs

Sympathomimetic syndrome	Serotonin syndrome
Mydriasis Tachycardia Arterial hypertension Cardiac arrhythmias Chest pain (myocardial ischemia due to coronary artery spasm) Cerebral infarction or hemorrhaging	Disorders of consciousness - agitation, confusion, coma Muscle disorders - rigidity, myoclonia, trismus, seizures

Trembling Convulsions	Dysautonomia - hyperthermia, changes in heart rate and arterial pressure, sialorrhea, vomiting and diarrhea, urinary incontinence

The adulterants of ecstasy and MDMA increase the risk of acute poisoning via different mechanisms. They may:

- potentiate the toxic effect of MDMA (by adrenergic/noradrenergic and/or serotoninergic stimulation).
- have a later/slower onset of action or not have the same "desired" effects (entactogenic), which leads to higher doses being used.

This chapter describes some of these adulterants in which cases or series of cases have been reported with toxic or even fatal effects **(Table 9)**. On occasion, a number of individuals were affected by the use of the same substance, other than MDMA.

5.2.1. PMA and PMMA

PMMA does not produce the psychoactive effects that are typical of MDMA, such as empathy, introspection, and a feeling of well-being in oneself and with others. MDMA users, expecting these effects, may assume that the dose is very low and take more pills. This, together with its longer latency at the onset of action, has been associated with reports of fatalities. The effects allegedly "sought" occur at the same time as the toxic effects. Higher serotonin action with PMA and PMMA has also been reported (WHO Expert Committee on Drug Dependence, 2015).

The fatalities reported due to use of MDMA pills replaced by or adulterated with PMA/PMMA involved hallucinations, seizures, tachycardia and arterial hypertension, cardiac dysrhythmias, changes in the electrocardiogram suggestive of myocardial ischemia, hyperthermia, rhabdomyolysis, acute renal injury, liver failure, and respiratory distress (Becker et al., 2003; Caldicott et al., 2003; Johansen et al., 2003; Refstad, 2003). In some cases, the clinical presentation was a multiple organ failure secondary to a serotonin syndrome (Lurie et al., 2012; Vevelstad et al., 2012; Nicol et al., 2015).

There was a high rate of mortality in a series of cases involving PMA/PMMA in the same setting where they were used (Caldicott et al., 2003; Nicol et al., 2015; WHO Expert Committee on Drug Dependence, 2015).

In many cases, death occurred in the same location where the substance was used or in the ambulance on the way to the hospital, showing the rapidity of onset and of the aggravation of the toxic effects and complications following the use of methoxyamphetamines (Nicol et al., 2015).

Laboratory exams showed alterations such as hypoglycemia, hypernatremia or hyponatremia, hyper or hypokalemia, hypocalcemia, elevated creatine phosphokinase due to muscle damage, and alterations that are evidence of renal injury and/or toxic hepatitis (Caldicott et al., 2003; Refstad, 2003; Nicol et al., 2015).

Analytical toxicology shows the presence of PMA and PMMA in urine, blood, or organs in forensic cases, on occasion associated with the presence of MDMA, alcohol, or metabolites of other drugs (cocaine) (Becker et al., 2003; Lurie et al., 2012); however, in some cases there is evidence only of the presence of methoxyamphetamines referred to above (Caldicott et al., 2003; Refstad, 2003).

Evidence from these case reports and case series shows that the substitution and/or adulteration of MDMA with PMA/PMMA significantly increase the risk of overdose and death.

Consequently, there have been reports of presentations in pills and crystals (molly) with high MDMA content (Head, 2016; Uruguayan Early Warning System on Drugs, 2018). The increase in the level of purity is associated with higher risk of MDMA overdose.

5.2.2. SYNTHETIC CATHINONES

Some synthetic cathinones have been found in adulterations or substitutions of ecstasy or MDMA. Fatal cases have been described of serotonin syndrome involving methylone and butylone (Warrick et al., 2012). A study of 48 individuals attending a rave party whose hair samples were analyzed showed that of those who said they had never used synthetic cathinones or any other NPS other than MDMA, 41.2% tested positive for butylone, methylone, and alpha-PVP or alpha-pyrrolidinovalerophenone, also known as “flakka” (Palamar et al., 2016).

5.2.3. PIPERAZINES

Cases have been described of acute poisoning by piperazines, replacing MDMA in ecstasy pills. The cases were characterized by agitation, dissociative symptoms, tachycardia, arterial hypertension (as a consequence of sympathetic stimulation), bruxism, and seizures (Wood et al., 2007, 2008).

5.2.4. OTHER

A) Caffeine

Caffeine is frequently reported as an adulterant of MDMA. It has been demonstrated in experimental models that simultaneous administration of caffeine significantly increases the acute toxicity of MDMA in rats, with effects such as hyperthermia and tachycardia, as well as higher death rates. It is also suggested that caffeine may increase the long-term neurotoxicity induced by MDMA and mediated by serotonin (Vanattou-Saïfoudine, McNamara, & Harkin, 2012).

B) Derivatives of 2 C phenylethylamines

The case was reported of an adult who ingested one capsule of ecstasy that contained fluoroamphetamine and 25C-NBOMe instead of MDMA, resulting in seizures. Both substances were found in the capsules seized (ACTINOS, 2016; UNODC, 2017c).

C) Brodifacoum as an adulterant of synthetic cannabinoids

In the first half of 2018, a number of cases were reported in the U.S. state of Illinois that presented elements of hemorrhagic syndrome (easy bruising, significant bleeding from minor wounds, gingivorrhagia, hematemesis, enterorrhagia, hematuria) and increased INR, suggesting the use of synthetic cannabinoids, in the absence of exposure to known coumarins. Brodifacoum was found in part of this series in blood; it is a superwarfarin rodenticide of high anticoagulant potency and a very prolonged half-life, which was recognized as an adulterant of synthetic cannabinoids (Centers for Disease Control and Prevention, 2018; Moritz et al., 2018).

Table 9: Case reports or case series of adulterations of ecstasy and new psychoactive substances

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
Becker et al., 2003 (Forensic case)	Germany	MDMA P.O.	PMMA PMA	Male 22 yrs	Hallucinations, seizures, respiratory distress, death	N/R	Severe cerebral edema and congestion of internal organs (autopsy histopathology)	PMMA blood + (0.85 mg/L) PMMA urine + (10.22 mg/L) PMA blood + (0.61 mg/L) PMA urine + (6.37 mg/L) AMPH blood+ (0.21 mg/L) ANF urine + (2.39 mg/L) BZE blood+ (<0.01 mg/L) BZE urine + (0.02 mg/L) OH (% o) blood+	N/R

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
								(0.46 mg/L) OH (% o) urine + (1.18 mg/L)	
Caldicott et al., 2003	Australia	MDMA P.O.	PMA	Female 20 yrs	General malaise, tachycardia, hypertension, mydriasis, nystagmus, trismus, agitation, polypnea, seizures, hyperthermia, OI/MVA. ECG: sinus tachycardia, anterolateral ST depression, lower T wave inversion	Neutrophilia, elevated CPK, slight respiratory acidosis	N/R	PMA urine +	N/R
Johansen et al., 2003 (Casos forenses)	Denmark	MDMA P.O.	MDMA PMMA PMA	Male 20 yrs	Hallucinations, hyperthermia, arrhythmia, cardiorespiratory arrest, death	N/R	Pulmonary and cerebral edema, splenomegaly, slight sclerosis of the coronary arteries (autopsy histopathology)	PMMA liver+ PMMA blood + (3.3 mg/kg) PMA liver+ PMA blood + (3.4 mg/kg) MDMA blood + (1.6 mg/kg)	N/R

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
								THC blood + OH blood + (0.066%)	
		MDMA P.O.	PMMA PMA	Male 20 yrs	Paranoia, muscle spasms, coma, multiple organ failure, death	N/R	Cerebral edema and vasculitis (autopsy histopathology)	PMMA liver+ PMA liver+ PMA blood + (0.02 mg/kg) AMPH blood + (0.02 mg/kg)	N/R
		MDMA P.O.	MDMA PMMA PMA BZE	Male 24 yrs	Diaphoresis, agitation, anxiety, hetero-aggressive behavior, hyperthermia, death	N/R	Severe cerebral edema, congestion of internal organs (autopsy histopathology)	PMMA liver+ PMMA blood + (0.68 mg/kg) PMA liver+ PMA blood + (0.78 mg/kg) MDMA blood + (0.08 mg/kg) BZE blood+ (0.08 mg/kg) OH blood +	N/R

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
								(0.029%)	
Refstad, 2003	Norway	MDMA P.O.	PMMA PMA	Male 16 yrs	Inappropriate behavior (patient found naked in a wood). Hyperthermia, tachycardia, mydriasis, seizures, coma. Required OI (due to ongoing seizures). Ventricular fibrillation, death	Hypoglycemia Hypocalcemia Hyperpotassemia	Centrolobulillar hepatic necrosis, autolytic changes in cerebellum (autopsy histopathology)	PMMA blood + PMA blood +	N/R
Wood et al., 2007	United Kingdom	MDMA P.O. AMPH	BZP	Female 18 yrs	Collapse, seizures, agitation, mydriasis, tachycardia, hypertension. Asymptomatic after 12 hours	N/R	N/R	BZP blood + (2.5 mg/L)	BZP +
Wood et al., 2008	United Kingdom	MDMA P.O.	TFMPP BZP	Male 18 yrs	General malaise, euphoria, nausea, weakness, dissociative symptoms, agitation, bruxism, tachycardia, mydriasis, inducible clonus	N/R	N/R	TFMPP blood+ (0.0467 mg/L) TFMPP urine + BZP blood + (0.263 mg/L) BZP urine +	N/R

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
		MDMA P.O.	TFMPP BZP	Male 18 yrs	Agitation, anxiety, dissociative symptoms, bruxism, tachycardia, mydriasis, inducible clonus	N/R	N/R	TFMPP blood+ (0.0467 mg/L) TFMPP urine + BZP blood + (0.263 mg/L) BZP urine +	N/R
		MDMA P.O.	TFMPP BZP	Male 19 yrs	Nausea, vomiting, general malaise, difficulty walking, dissociative symptoms, verborrhea, slight tachycardia, mydriasis	N/R	N/R	TFMPP blood+ (0.0467 mg/L) TFMPP urine + BZP blood + (0.263 mg/L) BZP urine +	N/R
Lurie et al., 2011	Israel	N/R	PMMA PMA	Series of 29 cases: 24 fatal (mean ages: 27 +/-5 yrs)	Headache, tremors, seizures, mydriasis, coma, diaphoresis, acute respiratory failure, arrhythmias, MI, hyperthermia, rhabdomyolysis, acute renal failure, liver injury	N/R	N/R	PMMA blood + (2.72 mg/L) PMMA urine + (2.72 mg/L) PMA blood + (0.35 mg/L) PMA urine + (0.35 mg/L)	

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
								MDMA blood + MDA blood + Cocaine HCl blood + Ephedrine/pseudoephedrine blood + THC blood + Cathinone derivatives blood + Opiates	
Warrick et al., 2011	United States	MDMA P.O.	Methylone Butylone	Female 24 yrs	Fever, coma, tachycardia, polypnea, hypertension, tremors, mydriasis hyperreflexia, sustained clonus, DIC, lactic acidosis, multiple organ failure, death. Cause of death: serotonin syndrome	Hypernatremia, hipopotassemia, elevated CPK, lactic acidosis, renal insufficiency, anemia, plaquetopenia, elevated transaminases levels, lower fibrinogen	Generalized coagulopathy Hepatic steatosis Anoxic encephalopathy (autopsy histopathology)	Methylone urine + Butylone urine +	Powder extracted from 1 capsule: Total weight: 619 mg Methylone + (422 mg) Butylone + (53 mg)

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
Vevelstad et al., 2012	Norway	MDMA P.O.	PMMA PMA MA AMPH	Series of 34 cases: 12 fatal cases (mean age: 30)	Hyperthermia, trembling, hyperactivity, muscle spasms, seizures, hallucinations, cardiac arrest, coma, multiple organ failure, death. Cause of death: serotonin syndrome and excessive catecholamine activity	N/R	Pulmonary edema and congestion of other organs, hemorrhaging of nasal and gastric mucus, petechial hemorrhaging of various organs (autopsy histopathology)	PMMA blood + (2.02 mg/L) PMA blood + (0.09 mg/L) MA blood + (0.13 mg/L) AMPH blood + (0.05 mg/L)	N/R
		MDMA P.O.	PMMA PMA MA AMPH	22 non-fatal cases (mean age: 27)	N/R	N/R	N/R	PMMA blood + (0.10 mg/L) PMA blood + (0.01 mg/L) MA blood + (0.43 mg/L) AMPH blood + (0.19 mg/L)	N/R

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
Nicol et al., 2015	Canada	MDMA P.O. Cocaine HCl inh.	PMMA MDMA COC BZE MA	Series of 27 fatal cases (mean age: 24)	Tachycardia, polypnea, respiratory insufficiency, hyperthermia, multiple organ failure, arrhythmia, shock, cardiac arrest, death. In 17 patients: serotonin syndrome	Hyperkalemia, elevated creatininemia, elevated AST, elevated CPK, hypoglycemia, hepatic injury, coagulopathy	N/R	PMMA blood + (2.84 mg/L) Other substances blood+ PMA, MDMA, MDA, MA, AMPH, COC, BZE	N/R
Palamar et al., 2016	United States	MDMA P.O., powder and crystals, unknown bath salt, ethcathinone, methcathinone	MDMA Butylone Methylone	Series of 48 cases (ages: 18-25)	N/R	N/R	N/R	MDMA hair + Butylone hair + Methylone hair + Alpha-PVP hair + 5/6-APB hair + 4-FA hair +	N/R

Study	Country/ countries	Type of substance "used" and route of administration *	Substance found **	Case report(s) ***	Clinical manifestations/ Complications ****	Laboratory *****	Histopathology	Analytical toxicology ******	Analysis of the substance used
ACTINOS 2016	Australia	MDMA P.O.	Fluoroam-phetamine 25C-NBOMe	Adult, N/R	Convulsions	N/R	N/R	N/R	Capsules: Fluoroamphe-tamine 25C-NBOMe
Moritz et al., 2018	United States	Synthetic cannabinoids	Brodifaco um	Series of 4 cases, N/R	Unexplained hemorrhagic syndrome	INR between 5 and higher than 20 (normal: less than 1.1)	N/R	N/R	Brodifacoum

* MDMA=3,4-methylendioxymethamphetamine (ecstasy); Cocaine HCl=cocaine hydrochloride; AMPH=amphetamine; P.O.=ingested; inh=inhaled.

** PMA=paramethoxyamphetamine; PMMA=paramethoxymethylamphetamine; BZE=benzoylecgonine; COC=cocaine; MA= methamphetamine; MDAI=5,6-methylendioxy-2-aminoindane; 2-AI=2-aminoindane; BZP=1-benzylpiperazine; TFMPP=1-(3-trifluoromethyl phenyl) piperazine.

*** yrs=years of age.

**** OI=orotracheal intubation; MVA=mechanical ventilation assistance; ECG=electrocardiogram; MI=myocardial infarction; DIC= disseminated intravascular coagulation; N/R=not reported.

***** CPK=creatine phosphokinase; AST=aspartate aminotransferase.

****** OH=ethanol; THC=tetrahydrocannabinol; MDA=methylenodioxyamphetamine; Alfa-PVP=alfa-pyrrolidinovalerophenone 5/6-APB (1-(benzofuran-5-yl)-propan-2-amine and 1(benzofuran-6-yl)-propan-2-amine; 4-FA=4-fluoroamphetamine.

5.3. ADULTERATION OF OPIUM, OPIATES, AND OPIOIDS

5.3.1. Adulteration of opium and health effects

There have been numerous reports of lead poisoning among users of opium. Authors have indicated that lead contamination and adulteration of opium is one of the major health problems among chronic users in countries in the Middle East such as Iran (Alinejad et al., 2018).

Higher levels of lead in blood have been reported among opium users compared to a control group of non-users in the same neighborhood in Tehran. A number of authors have described case reports or series of cases of lead poisoning with very high levels of lead in blood, with a mean of 80 micrograms/dl, as well as several reports of levels much higher than 100 micrograms/dl (Jalili, & Azizkhani, 2009; Hayatbakhsh et al., 2017; Alinejad et al., 2018; Soltaninejad & Shahina, 2018).

There is a statistically significant association between levels of lead in the blood and the form of using opium or its route of administration; levels are higher when the opium is ingested rather than smoked. Higher levels of lead in blood have also been reported when the dose of opium is larger. Studies on levels of lead in blood and the association with the time of use are controversial (Alinejad et al., 2018; Soltaninejad & Shahina, 2018).

In the province of Kerman, Iran, a study in the first half of 2016 evaluated 249 opium users, most through ingestion (71.9%), with levels of lead in blood in the range of 51.7 to 119 micrograms/dl, mean of 80 micrograms/dl, and clinical manifestations such as abdominal colic (86.9%), constipation (75.8%), and anorexia (71.5%) (Hayatbakhsh et al., 2017).

Levels of lead in blood in excess of 80 micrograms/dl are associated with difficult-to-treat anemia, kidney disease, polyneuropathy, digestive symptoms, and serious neurobehavioral changes (Alinejad et al., 2018). Acute poisoning with levels greater than 100 micrograms/dl has been reported, characterized by severe encephalopathy, with seizures and coma, and in some cases, death (Soltaninejad & Shahina, 2018).

Lead may affect the children of women who use opium, either through intrauterine exposure or through breastfeeding. A child may be involuntarily exposed to lead by inhaling the smoke produced by the burning of opium being smoked in the home (Alinejad et al., 2018).

With regard to thallium as an adulterant of opium, cases of thallium poisoning have been reported. A study of 150 chronic users of opium in Iran showed the presence of thallium in urine in 15% of the cases; the levels of thallium in the urine of chronic users of opium were higher than in the control group. Some of these individuals presented with clinical manifestations compatible with thallium poisoning, such as ataxia, sweating, and constipation (Ghaderi et al., 2015).

5.3.2. Adulterants of heroin and health effects

The type of adulterant of heroin is a factor that impacts the likelihood of developing complications, which in some cases may be fatal.

A study conducted in the city of Vienna, Austria, analyzing 415 samples of heroin seized in 1999, showed purity ranging between 0% and 47%, with diluents such as lactose and with a predominance of caffeine and paracetamol as adulterants. The authors did not find a relationship between the heroin-related deaths and the presence of adulterants (Risser et al., 2007). The evolution of the adulterants or methods used has significantly increased morbidity and mortality attributable to some adulterants such as fentanyl and derivatives over the last decade (DEA, 2016b).

5.3.2.1. CLENBUTEROL

Clenbuterol is a β_2- adrenergic agonist, which is banned for human use in countries like the United States but is used as a veterinary bronchodilator in horses, for example. Bodybuilders have used it for its sympathomimetic, anabolic, and lipolytic effects, alone or together with androgenic steroids. Acute clenbuterol poisoning may cause nausea, vomiting, tachycardia, arterial hypotension, hyperglycemia, hypokalemia, and metabolic acidosis with hyperlactatemia (Hoffman, Kirrane, & Marcus, 2008; Wingert et al., 2008).

Occurrences have been described ever since 2005 of cases of heroin adulteration (Centers for Disease Control and Prevention, 2005), in which users who snort or inject

heroin presented clinical pictures compatible with acute clenbuterol poisoning, confirmed by analytical studies in some of the cases. Some serious cases presented with myocardial injury (Hieger et al., 2016; Hoffman et al., 2008). Some authors report a neuromuscular syndrome in heroin users characterized by muscle spasms, tremors, hyperreflexia, and elevated levels of serum creatine phosphokinase (CPK), translating into muscle injury (Manini et al., 2008).

Forensic cases have been reported of heroin users in which clenbuterol were detected in samples of blood, urine, or organs. Other drugs or their metabolites were also found in these cases (ethanol, cocaine, fentanyl, methadone, codeine, hydromorphone), and it was therefore not possible to attribute the cause of death exclusively to the presence of the heroin/clenbuterol combination (Wingert et al., 2008).

The reported clinical manifestations and complications due to acute clenbuterol toxicity in adulterations of heroin are detailed in **Table 10.**

Table 10: **Clinical manifestations and complications reported due to acute clenbuterol poisoning in adulterations of heroin.**

Clinical manifestations
Nausea, vomiting
Headache
Mydriasis
Anxiety, agitation
Palpitations, tachycardia
Arterial hypotension
Chest pain, changes in the electrocardiogram, myocardial ischemia
Pulmonary edema
Muscle spasms, tremors, hyperreflexia, damage to skeletal muscle
Hyperglycemia, hypokalemia
Lactic acidosis

5.3.2.2. XYLAZINE

Xylazine was synthesized as an antihypertensive drug in 1962; it is structurally related to phenothiazines, tricyclic antidepressants, and clonidine. It is currently used for sedation in veterinary medicine, and is known popularly in places such as Puerto Rico as "horse anesthetic" (Ruiz-Colón et al., 2012). The name may vary in different contexts since it is used in other countries to refer to ketamine. In Puerto Rico, it is an adulterant that was frequently found in samples of heroin (36%–37% in 2006-2007, a figure that doubled in some communities in 2012). Although it has been found in the analysis of forensic cases of heroin and other drugs such as cocaine, its toxic effects (central nervous system depression, respiratory depression, bradycardia, hypotension, hyperglycemia) appear to have a synergistic effect with heroin, aggravating cases of overdose, and are linked to some fatalities reported (Ruiz-Colón et al., 2014). Lesions in puncture sites (phlebitis, cellulitis, superinfected ulcers) have also been reported due to the combination of heroin and xylazine (Torruella, 2011).

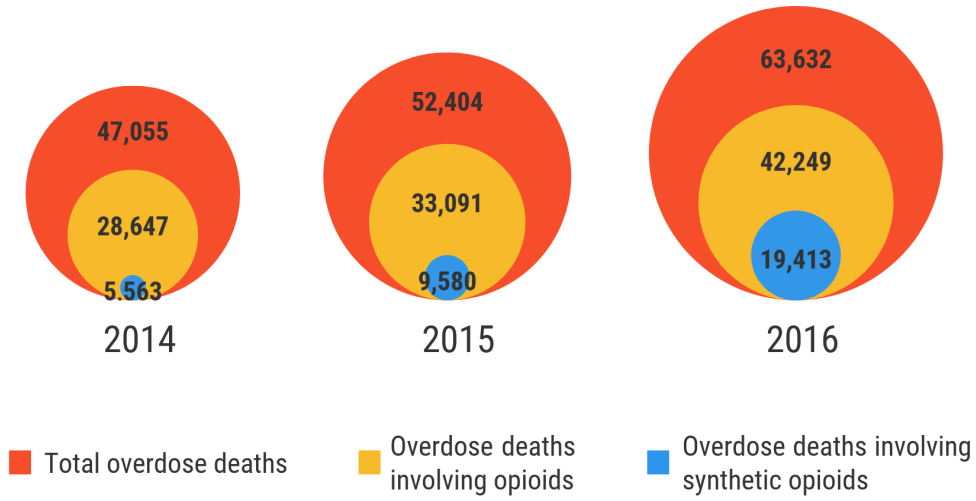
5.3.2.3. FENTANYL AND DERIVATIVES

Opioids are the principal cause of overdose in the United States. In 2015 the Centers for Disease Control and Prevention (CDC) reported 33,091 deaths from opioid overdose. Synthetic opioids, including fentanyl and derivatives, were responsible for 9,580 of the deaths, representing an increase of 72.2% over previous years (DEA, 2017a). Another DEA report found that deaths due to overdose of fentanyl increased from 550 in 2013 to 2,000 in 2014-2015 (DEA, 2017b).

Heroin-related deaths also rose significantly between 2010 (3,036) and 2014 (10,574). The high death rate is attributable to the presence of fentanyl mixed with powder heroin, in some cases sold as ¨heroin¨ (DEA, 2016b).

A more recent report from the CDC attributed 63,632 deaths in the United States to drug overdose during 2016. Of these, 19,413 were related to the use of synthetic opioids, particularly fentanyl, representing an increase of 110% over 2015 (**Figure 7**). The report notes that people who sell heroin, fentanyl, or fentanyl-adulterated heroin are often unaware of the composition of the product they are selling (DEA, 2018c). Currently, the term *China White*, associated with high-purity heroin, may be heroin adulterated with fentanyl (Ciccarone, Ondocsin, & Mars, 2017; DEA, 2018c).

Figure 7: Overdose deaths in the United States



As to the type of synthetic opioid involved, O´Donnell et al. (2017) reported 5,152 deaths in 10 U.S. states related to opioid use in the second half of 2016. This study noted that fentanyl was present in 14% of the deaths, followed by carfentanyl (7.6%), furanyl-fentanyl (3.5%), and acetylfentanyl (2.9%).

Some authors' studies describe the limitations of using qualitative and quantitative techniques to detect fentanyl in emergency room patients with opioid overdose, which means that figures on overdose admissions and deaths may be underestimated (Slavova et al., 2017). Fentanyl has a very rapid onset of action; it is distributed in tissues, and almost 99% is eliminated from plasma in one hour when administered intravenously, with an elimination half-life of 219 minutes (Suzuki & El-Haddad, 2017). This may limit the ability to detect it in such settings.

Overdose from synthetic opiates and opioids is characterized by depression of consciousness (which may evolve rapidly into coma), myosis, respiratory depression, bradycardia, and arterial hypotension. Pulmonary edema may occur. Death often occurs as the result of apnea and cardiorespiratory arrest/failure (Suzuki & El-Haddad, 2017). The initial treatment is based on the administration of naloxone as an antidote, requiring high doses in the case of fentanyl overdose due to the high potency of its *mu* opioid receptors.

Given the context in which overdose occurs, the presence of fentanyl in fatal cases is frequently associated with the simultaneous detection of other drugs. Wong et al. (2008) describe, in seven forensic cases in which death was caused by overdose, the presence in blood and urine of xylazine and fentanyl in all cases, and 6-acetylmorphine (heroin metabolite) in six of the cases. Cocaine and other common adulterants of heroin and cocaine were also found in some cases (Wong, Curtis, & Wingert, 2008).

Algren et al. (2013) describe a significant increase in mortality attributable to fentanyl as a heroin adulterant at the beginning of 2005, as well as the occurrence of 101 fatalities due to overdose of fentanyl-adulterated heroin in Wayne County, Michigan, between July 2005 and May 2006. Unlike the cases involving fatalities due to overdose of heroin without fentanyl (n=90), a higher prevalence was found in women over the age of 44. This suggests possible greater vulnerability to and severity of fentanyl overdose among women than among men, due to toxicokinetic and/or toxicodynamic aspects that are not clearly established. Pulmonary edema was found in 77% of the cases, with no significant differences between the two groups (Algren et al., 2013).

Forensic case reports or case series describe fatalities due to derivatives or analogues of fentanyl, such as acetylfentanyl (McIntyre et al., Trochta et al., 2015; Lee et al., 2016). In a series of 72 cases, fentanyl was also found in post-mortem blood at levels significantly higher than those reported in cases of deaths with therapeutic doses. The presence of 6-acetylmorphine, morphine, and cocaine metabolites was prevalent in that series. Other opioids such as oxycodone, hydrocodone, hydromorphone, and methadone were also found (Lee et al., 2016). Although the high levels of fentanyl and analogues in blood link them to the fatalities described, some limitations are evident in these forensic reports, such as the high prevalence of the use of multiple substances (evidenced by the analytical studies), and the unconfirmed hypothesis that fentanyl was consumed in the form of adulterated heroin, or in combination with it, in order to enhance its effects.

Fentanyl-adulterated heroin has also been reported in Australia. Rodda et al. (2017) detected fentanyl in blood in nine forensic cases out of 4,200 toxicology analyses of deaths in Victoria in 2015, of which 168 corresponded to heroin-associated overdose. The presence of 6-acetylmorphine in blood was also found in all nine of the cases mentioned. The substance used was analyzed in one case and was identified as a mix of

heroin with fentanyl. It was confirmed that in the majority of cases, the users were injecting heroin.

Case reports showed adulterations with fentanyl and other opioids used as analgesics (Vo et al., 2016; Edison et al., 2017).

Sutter et al. (2016) described the cases of 18 patients seen due to severe acute opioid toxicity, having received a usual dose of a formulation of hydrocodone and paracetamol tablets. The 18 patients died, 17 of them after receiving large doses of naloxone over a prolonged period (26-39 hours). The patients' blood tested positive for fentanyl in all cases, with plasma levels of between 7.9 and 162 ng/mL (mean = 52.9 ng/mL) in 13 of them. Analysis of the tablets showed a concentration of fentanyl of 600–6,900 microg/tablet. (Sutter et al., 2017). Other authors say that the mean in fatalities due to fentanyl reported in therapeutic doses was 5.2–28 ng/mL (Lee et al., 2016), clearly lower than that reported in this study. Fentanyl is highly liposoluble. It is deposited in the adipose tissue and then recirculates in the blood and is distributed in tissue, which may explain the need for naloxone for long periods of time, or a worsening of the clinical picture after an apparent improvement. Repeated doses tend to accumulate in tissue and may also prolong the overdose picture (Suzuki & El-Haddad, 2017). Fentanyl activates at under 100 micrograms, and can be fatal in doses of 2 mg (DEA, 2018a).

The "informal" preparation of pills or tablets in the illicit market, where the methods for weighing the active principle are imprecise, significantly increases the risk of overdose, given that the concentration of fentanyl or derivatives in a tablet is extremely variable and unpredictable. Errors in calculating the dose and users' lack of experience with these substances mean that this practice may have fatal consequences (UNODC, 2017c).

Table 11 shows case reports or case series in which the adulteration of opiates or opioids with fentanyl and derivatives was suggested or confirmed.

5.3.2.4. OTHER

Quinine (analgesic and anti-inflammatory, antimalarial) and **quinidine** (antiarrhythmic) have been reported as adulterants of heroin, mimicking its bitter taste and, because of their hypotensive effect, simulating the sought-after effects of heroin. There is a report

of a patient with a cardiac conduction disorder following the intravenous injection of heroin adulterated with quinine/quinidine (indistinguishable in the analytical study that was conducted). Both substances may cause cardiac conduction disorders shown in the ECG as a prolonged QRS or QT interval, or due to an atrioventricular block. The limitation of this report is the user's concomitant use of methadone, which may also cause some changes in myocardial conduction (Phillips et al., 2012).

Barbera et al. (2013) describe five forensic cases that examined the possible causes of death by overdose in users of cocaine or heroin. **Dextromethorphan**, a synthetic opioid with an agonist effect on *mu* receptors and an antagonist effect on N-methyl-D-aspartate (NMDA) receptors, appears in three of these cases as a heroin adulterant. The authors suggest a synergic effect, with the risk of respiratory depression increasing by means of the two mechanisms described. Death may also be related to the intravenous form of use in these cases. Caffeine, described in some reports as an adulterant of heroin, was found in one case. Injecting **caffeine** intravenously may contribute to changes in heart rate and cardiotoxicity.

The adulteration of heroin with **anticholinergics such as scopolamine or atropine** has been described since the 1990s, with outbreaks of mass poisonings characterized by an anticholinergic syndrome in heroin users. Users may present with signs of opiate overdose, such as depression of consciousness, myosis, and respiratory depression, and following the administration of naloxone, a previously "masked" anticholinergic syndrome appears, characterized by agitation, mydriasis, tachycardia, acute urine retention, hyperthermia, and seizures in serious cases (Wang et al., 2002).

Table 11: Case reports or case series of adulterations of fentanyl and analogues/derivatives

Studies	Country/ countries	Type of substance suspected and route of administration *	Substance in fact found**	Case report(s)	Clinical manifestations Complications ***	Laboratory	Histopathology	Analytical toxicology ****	Analysis of the substance used
Wong et al., 2008 (Forensic cases)	United States	Heroin IV and other drugs (alcohol and other, non-specified)	Xylazine, fentanyl, 6-AM, morphine	Series of 7 fatal cases	Cardiac arrest, death	N/R	N/R	Xylazine blood + Xylazine urine + Fentanyl blood+ Fentanyl urine+ 6-AM blood + 6-AM urine + Morphine blood+ Morphine urine+ COC blood+ COC urine+ BZE blood+ BZE urine+ PCP blood+ PCP urine+	N/R
Algren et al., 2013	United States	Heroin	Fentanyl, COC (50%), BZE, morphine,	Series of 101 fatal cases	N/R	N/R	Pulmonary edema in 77% of the cases (histopatholog	Fentanyl blood+ (0.02 ug/ml) COC blood+	N/R

Studies	Country/ countries	Type of substance suspected and route of administration *	Substance in fact found**	Case report(s)	Clinical manifestations Complications ***	Laboratory	Histopathology	Analytical toxicology ****	Analysis of the substance used
			6-AM, methadone, codeine, hydrocodone, and oxycodone				y autopsy)	BZE blood+ Morphine blood + 6-AM blood + Other: methadone, codeine, hydrocodone and oxycodone blood +	
Mc Intyre et al., 2015 (Forensic case)	United States	Heroin IV	Acetylfentanyl	Male 24 years	Found in a coma. Syringe with needle, tourniquet with rubber band. Death	N/R	3 recent punctures on left forearm. Pulmonary edema and congestion (histopatholog y autopsy)	Acetylfentanyl blood+ (0.26 mg/L) Acetylfentanyl Liver + (0.001 mg/kg) Acetylfentanyl Vitreous + (0.24 mg/L) Acetylfentanyl Urine + (2.6 mg/L)	N/R

Studies	Country/ countries	Type of substance suspected and route of administration *	Substance in fact found**	Case report(s)	Clinical manifestations Complications ***	Laboratory	Histopathology	Analytical toxicology ****	Analysis of the substance used
Lee et al., 2016 (Forensic cases)	United States	Heroin (44%), fentanyl (36%), other opioids (32%), cocaine (14%), benzodiazepines (14%)	Fentanyl, acetylfentanyl, COC, morphine	Series of 72 fatal cases (average age: 41.5)	N/R	N/R	N/R	Fentanyl blood+ (0.0098 mg/L) Fentanyl urine+ Acetylfentanyl blood + COC blood and urine + Morphine blood and urine + Other: oxycodone, hydrocodone, hydromorphone, methadone, codeine blood and urine + Benzodiazepines blood and urine +	N/R
Quintana et al., 2016	Spain			Series of 4 samples and effects described by users					

Studies	Country/ countries	Type of substance suspected and route of administration *	Substance in fact found**	Case report(s)	Clinical manifestations Complications ***	Laboratory	Histopathology	Analytical toxicology ****	Analysis of the substance used
		Heroin	Ocfentanil, caffeine, paracetamol	User No. 1 (sex and age not specified)	Sample not tested prior to being sent for analysis	N/R	N/R	N/R	Ocfentanil Caffeine Paracetamol
		Heroin	Ocfentanil, caffeine, paracetamol, heroin	User No. 2 (sex and age not specified)	"Major effect, similar to very strong heroin, very rapid onset, short duration. Followed by one hour of lesser effect"	N/R	N/R	N/R	Ocfentanil Caffeine 27% Paracetamol 33% Heroin 16%
		Heroin	Ocfentanil, caffeine, paracetamol, heroin	User No. 3 (sex and age not specified)	"Major effect, similar to very strong heroin, very rapid onset, short duration. Followed by one hour of lesser effect"	N/R	N/R	N/R	Ocfentanil Caffeine 26% Paracetamol 29% Heroin 3%
		Heroin	Ocfentanil, caffeine, paracetamol	User No. 4 (sex and age not specified)	Analgesia, nausea	N/R	N/R	N/R	Ocfentanil Caffeine Paracetamol

Studies	Country/ countries	Type of substance suspected and route of administration *	Substance in fact found**	Case report(s)	Clinical manifestations Complications ***	Laboratory	Histopathology	Analytical toxicology ****	Analysis of the substance used
Sutter et al., 2016	United States	Hydrocodone tablets/ paracetamol P.O.	Fentanyl	Series of 18 cases (ages 16-59)	Opiate overdose. Several needed cardiopulmonary resuscitation, intubation, and mechanical ventilation with bag valve mask. 17 cases required IV bolus administration of naloxone, 4 continuous IV infusion of naloxone. One death	N/R	N/R	Fentanyl blood+ (0.0529 mg/L) Other: Fentanyl, norfentanyl, hydrocodone, norhydrocodone, oxycodone, promethazine, cocaine, levamisole, trazodone, MA, AMPH, dihydrocodeine, cyclobenzaprine in urine +	Pills: Fentanyl: 600-6900 ug per pill
Rodda et al., 2017 (Forensic cases)	Australia	Heroin, methadone	Morphine, fentanyl, 6-AM, methadone	Series of 9 fatal cases (average age: 37)	Death	N/R	N/R	Fentanyl blood+ (0.018 mg/L) Fentanyl urine+ Morphine blood + (0.08 mg/L) Morphine urine + Codeine blood + 6-AM blood +	Powder, syringe & spoon found on the scene: Heroin + Fentanyl +

Studies	Country/ countries	Type of substance suspected and route of administration *	Substance in fact found**	Case report(s)	Clinical manifestations Complications ***	Laboratory	Histopathology	Analytical toxicology ****	Analysis of the substance used
								6-AM urine + Other: methadone, AMPH, MA, THC, COC, BZE, GHB, benzodiazepines fluoxetine, quetiapine, paracetamol, buprenorphine, diphenhydramine, promethazine in blood and urine +	

* IV=intravenous; P.O.=by mouth.

** 6-AM: 6-acetylmorphine; COC: cocaine; BZE: benzoylecgonine.

*** N/R=not reported; OTI=orotracheal intubation.

**** PCP=phencyclidine; AMPH=amphetamine; MA=methamphetamine; THC=tetrahydrocannabinol; GHB=gamma-hydroxybutyric acid.

5.3.3. CASES OF DESOMORPHINE OR "KROKODIL"

"Krokodil" refers to a form of homemade, intravenous desomorphine, a mix of different forms of codeine with other highly toxic chemical agents. It appeared more than 10 years ago in countries like Russia and Ukraine (Booth, 2013), and then spread to other countries such as Georgia, Uzbekistan, and Kazakhstan. It emerged a heroin substitute on account of its low cost in those countries. Due to Russian emigration to other countries, cases have been reported in Poland, Czech Republic, France, Belgium, and Norway, among others (Alves et al., 2015).

Krokodil is a liquid presentation, brownish in color. Its name comes from the appearance of the skin at the injection sites and surrounding areas, which is roughened and grayish-green. Desomorphine is synthesized from codeine, in two stages: extraction of the codeine from the tablets (which is sometimes mixed with other analgesics like acetyl salicylic acid and paracetamol), and subsequent synthesis of desomorphine. The homemade synthesis uses both domestic and industrial use products, in very unsafe conditions. The products used include red phosphorus, iodine, organic solvents such as aromatic and aliphatic hydrocarbons, corrosive agents such as alkaline solutions, and strong acids (Florez et al., 2017).

There are descriptions of cases in the United Kingdom and in the United States where krokodil may be sold as heroin. In fact, cases have been reported among injecting heroin users. It is also suggested that heroin may be contaminated with krokodil (Gahr et al., 2012; Alves et al., 2015).

The effects resulting from the contamination with these extremely toxic agents may be divided into local and systemic effects:

- local: discoloration of the skin, thrombophlebitis, ulcers, abscesses, necrosis, and gangrenous lesions at the puncture sites, which may lead to amputation of the limb and death due to superinfection (Gahr et al., 2012; Alves et al., 2015).
- systemic: vascular lesions, rhabdomyolysis, osteonecrosis, multiple organ failure, liver and kidney lesion, hypothyroidism, endocarditis, and infectious complications such as pneumonia and meningitis, with a high rate of death. Neurobehavioral and cognitive changes may occur as a result of chronic use (Alves et al., 2015; Florez et al., 2016).

Local inflammatory and necrotic lesions are caused by the corrosive agents involved. Osteonecrosis of the jaw is related to the toxic effect of red phosphorus (Ruggiero et al., 2004; Poghosyan et al., 2014). Hypothyroidism and muscle injury are associated with the use of iodine (Matiuk, 2014). Neurological changes (encephalopathy, behavior changes, cognitive disorders) may be caused by exposure to hydrocarbons, including gasoline, which in some countries still contains lead (Florez et al., 2016).

Reports have shown an increase in communicable diseases such as HIV infection and hepatitis C. Although the highest prevalence may be due to the route of administration and the sharing of equipment, the extension and severity of the local lesions predispose to these infections (Booth, 2013).

5.4. ADULTERATION OF CANNABIS AND ITS DERIVATIVES

The effects of the adulterants found in cannabis and its derivatives may increase the psychoactive effect of cannabis and/or cause toxic effect on the user's health.

McPartland, Blanchon, & Musty (2008) describe a series of cases in which marijuana users voluntarily adulterated the marijuana with tobacco and anticholinergic and cholinergic agents to obtain a greater psychoactive effect. Tobacco may, because of the presence of nicotine, exercise a synergic effect on the cannabinoid system by increasing the number of receptors and endogenous ligands, boosting THC effects such as sedation and its analgesic properties (McPartland, 2008); however, the use of smoked marijuana and tobacco increases the risk of respiratory diseases in users. The combination with anticholinergics (atropine, scopolamine) that contain *Datura* plants increases the risk of undesired effects (dry mouth, tachycardia, arterial hypertension, hallucinations). In addition, the association with cholinergic agents such as organophosphate pesticides may lead to acute poisoning as the result of inhaling, which manifests itself in vomiting, diarrhea, bronchospasm, bradycardia, and arterial hypotension (McPartland, Blanchon, & Musty, 2008).

While lead may be present in the soil where cannabis plants are grown and be a source of contamination, two 2008 studies reported a series of cases of lead poisoning in marijuana users, with compatible clinical manifestations (cephalea, abdominal colic, Burton's line on gums, polyneuropathy, anemia) and very high levels of lead poisoning. In these cases, the marijuana was adulterated with lead to increase its volume. This was

the only series reported with these characteristics, involving a total of 35 patients (Busse, Omidi, Timper et al., 2008; Busse, Fiedler, Leichtle et al., 2008).

Smoking is the most common way to use marijuana; this has implications for the toxic effects both of smoked cannabis (via the products of combustion) and of the adulterants present. The contamination with glass beads reported by the U.K. Department of Health in 2007 was associated with medical consultations for lesions in the mouth and respiratory symptoms (Department of Health, 2007; McLaren et al., 2008). Delourme et al. (2009) reported one case with these characteristics, as well as another case of a 33-year-old individual who presented with acute pneumonitis resulting from the use of marijuana adulterated with industrial sand.

There have also been reports of pneumoconiosis due to the consumption of smoked marijuana adulterated with talc, which manifests itself in acute symptoms of fever, dyspnea, and ventilatory insufficiency, resulting in chronic pulmonary interstitial lung disease with the presence in biopsies of particles of silica, aluminum, and other minerals. The particles found are smaller than those found in cases of pulmonary granulomatosis resulting from intravenous injection of drugs (Scheel et al., 2012).

With regard to microbiological contamination, the carcinogenic effect of some *Aspergillus flavus* mycotoxins has been demonstrated, which might have implications for the chronic user. Cases of pulmonary aspergillosis have also been described in inmunodepressed subjects (McLaren et al., 2008).

5.5. ADULTERATION OF LSD

Cases have been reported in recent years of serious poisoning, including fatalities, by 25x-NBOMe-type new psychoactive substances (Shanks, Sozio, & Behonick, 2015).

Derivatives of 2 C phenylethylamines (25x-NBOMes) have played a significant role as substitutes for classic hallucinogens such as LSD and tryptamines. In many cases, they are sold on stamps or blotters like LSD, and users are confused about their similar presentation (Wood et al., 2015). There are reports of cases of overdose due to these substances in that context, with prevalent clinical manifestations such as agitation, confusion, mydriasis, hyperthermia, tachycardia and arterial hypertension, seizures, rhabdomyolysis, and hepatic and renal injury (Armenian & Gerona, 2014; Suzuki et al., 2015; Gee et al., 2016).

Cases of LSD overdose are rare, unlike what occurs with 25x-NBOMe, whose affinity to the 5HT2-A receptors is significantly greater; as a result, a dose of 50 micrograms taken sublingually produces psychoactive effects. In a review of 20 overdose cases, 20% of users thought that they were using LSD. Three of these cases had a fatal outcome (Suzuki et al., 2015).

These substances are not detected by the normal screening tests available in emergency departments, which may delay diagnosis. For this reason, a high level of clinical suspicion is important in beginning treatment early in an effort to reduce morbidity and mortality due to acute poisoning with these substances.

5.6. ADULTERATION OF ALCOHOLIC BEVERAGES

Alcoholic beverages have a varying percentage of ethyl alcohol (ethanol) depending on how they are prepared (fermentation, distillation). There are circumstances in which drinks are adulterated with toxic alcohols other than ethanol, such as methanol and ethylene glycol, to lower their cost (Wiener, 2015; Kraut & Mullins, 2018). Such adulterations cause mass poisonings with a high rate of morbidity and mortality of those affected. The next section describes mass methanol poisonings that are the result of these adulterations.

5.6.1. METHANOL

Methanol is an industrial alcohol that is used to synthesize other chemical substances such as formaldehyde and methylated compounds. It is used as a solvent for varnishes, lacquers and removers, antifreeze for car radiators, and fuel for model airplanes.

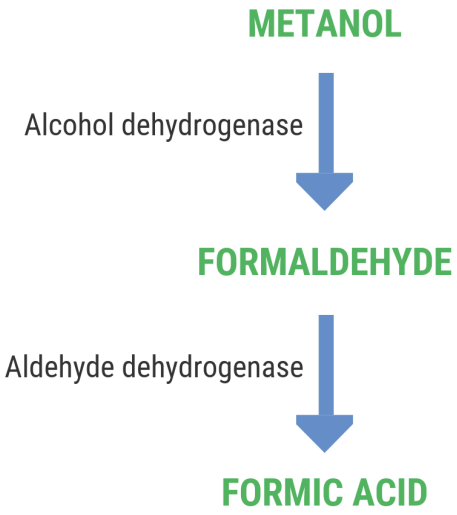
Mass poisonings due to methanol used as an adulterant in alcoholic beverages are often true epidemics because of the number of people involved. Such events are termed "poisoning epidemics" and have been described in the scientific literature since the middle of the 20th century (Wiener, 2015).

Mass methanol poisonings have continued to occur in recent years, mainly in developing countries or in countries with a high level of social vulnerability, where ethyl alcohol is very expensive.

Ingesting 15-30 ml of 100% methanol may cause a serious acute poisoning (Pinilla Ruesca, 2013).

Acute poisoning is characterized by depressed consciousness or "state of drunkenness" (as occurs with any consumption of alcohol), although it may not be significant particularly when chronic alcohol drinkers have developed tolerance. The toxicity of methanol is related to its metabolism (**Figure 8**). Its initial metabolic pathway is similar to that of ethanol via the alcohol dehydrogenase enzyme (alcohol ADH) with the formation of formaldehyde and then formic acid, which is responsible for severe metabolic acidosis, with high anion gap and osmolar gap. This is frequently resistant to conventional treatment, which causes multiple complications that may that may cause the death of the person involved (Wiener, 2015; Hovda, McMartin, & Jacobsen, 2017).

Figure 8: Methanol metabolism and its relationship to toxicity



Methanol is associated with gastrointestinal and respiratory symptoms, as well as loss of visual acuity that may evolve into blindness (methanol optic neuritis), neurological changes that affect the central and peripheral nervous systems (Gee & Martin, 2012; Giovanetti, 2013; Hovda, McMartin, & Jacobsen, 2017). Cerebral changes found in imaging studies have been described, such as putaminal necrosis and cerebral hemorrhaging. Methanol has also been related to Parkinsonism as a sequela in individuals who survive the acute poisoning (Jarwani et al., 2012; Wiener, 2015; Hovda, McMartin, & Jacobsen, 2017).

Diagnosis tends to be delayed in serious poisonings in individuals or in the initial stages of a mass poisoning, which increases morbidity and mortality. Diagnostic confirmation may be done by analyzing the adulterated beverage, and in patients by measuring levels

of methanol in blood or of formic acid in urine (Hovda, McMartin, & Jacobsen, 2017). These studies require techniques that are rarely available or accessible in countries where these epidemics occur. Another limitation is the length of time needed to detect methanol in blood, which is 2-4 hours (Wiener, 2015).

Treatment of acute poisoning requires the use of ethanol as an antidote to compete with the methanol metabolism and reduce the synthesis of toxic metabolites. Fomepizole, which inhibits the alcohol ADH enzyme, is also used. Sodium bicarbonate is also administered to treat metabolic acidosis. Hemodialysis is used to help eliminate methanol and its toxic metabolites from the body.

In terms of the period under review in this study, the World Health Organization in 2014 published an alert describing numerous toxic epidemics due to methanol adulterations of alcoholic beverages in countries such as Cambodia, Czech Republic, Ecuador, Estonia, India, Indonesia, Kenya, Libya, Nicaragua, Norway, Pakistan, Turkey, and Uganda. Between 40 and 800 individuals were affected in each instance, with death rates of up to 30% (WHO, 2014).

Table 12 describes some of these epidemics, based on the systematic and descriptive review that was conducted.

Table 12: **Outbreaks of methanol poisoning resulting from adulterations of alcoholic beverages reported in the literature and in the press**[†]

Year	Location of the incident	Individuals affected	Deaths
2001	San Salvador, El Salvador	More than 200	123
2001	Parnü, Estonia	154	68
2001	Bombay, India	More than 120	27
2002	Norway	59	17
2003	Botswana	More than 45	9
2005	Kenya	174	49
2006	Nicaragua	801	48
2006	Ural Mountains, Russia	60	3

Year	Location of the incident	Individuals affected	Deaths
2008	Karnataka & Tamil Nadu, India	285	150
2009	Gujarat, India	More than 275	136
2009	Uganda	77	27
2009	Bali/Lombok, Indonesia	45	25
2009	Kampala, Uganda	189	89
2011	Los Ríos, Ecuador	More than 770	51
2011	Western Bengal, India	More than 370	170
2011	Haiti	40	18
2011	Kolkata, India	More than 167	143
2012	Orissa, India	100	31
2012	Cambodia	367	49
2012	Tegucigalpa, Honduras	48	24
2012	Czech Republic	121	41
2013	Tripoli, Libya	1066	101
2013	Rafsanjan, Iran	694	8
2014	Central Kenya	341	100
2014	Western Kenya	126	26

† Adaptation of Zhang et al., 2012; Pinilla Ruesca, 2013; Hassanian-Moghaddam et al., 2015.

An outbreak of poisoning in Estonia in September 2001 was described as starting with the sale of alcoholic drinks with concentrations of methanol that ranged between 50% and 100%. Poisoning was confirmed in 154 patients, 68 of whom died. Twenty of the survivors presented with sequelae. Metabolic acidosis and coma were the principal manifestations in serious cases. The autopsies showed multiple organ failure. Cerebral edema and hemorrhaging were the most common findings (Paasma et al., 2007). In a subsequent study, Paasma, Hovda, & Jacobsen (2009) reported on a six-year follow-up of patients who had survived the outbreak. That follow-up found more deaths (some

from alcoholic poisoning) and long-term sequelae that had not been diagnosed years earlier, predominantly cognitive changes and visual disorders.

Hovda et al. (2005) described the outbreak that occurred in Norway in 2002-2004. The adulterated liquor came from another part of Europe and consisted of 20% methanol and 80% ethanol. The study reported 59 confirmed cases of methanol poisoning, with 17 deaths. Severe metabolic acidosis was the initial clinical presentation in a significant number of cases, which suggests that the hospital consultation was delayed. Five of the 42 survivors presented with sequelae, particularly changes in vision (Hovda et al., 2004; Hovda et al., 2005).

Jarwani, Motiani, & Sachdev (2013) conducted a retrospective study of 178 cases of methanol poisoning in Gujarat, India, in 2009, resulting from drinking illegal alcoholic beverages (given that alcohol use is prohibited in that area). The reported complications were neurological and gastrointestinal symptoms, metabolic acidosis, and changes in vision.

A mass poisoning was reported in August 2012 in the Czech Republic, following the production of 10,000 liters of alcoholic beverages adulterated with varying percentages of methanol (20% to 66%), contained in bottles of rum, vodka, and other distilled beverages sold on the black market and in legal liquor stores. The study described 121 cases of methanol poisoning, with 41 deaths (20 before reaching the hospital). Thirty percent of the survivors presented with visual and neurological sequelae (Zakharov et al., 2014).

Rostrup et al. (2016) described methanol poisoning outbreaks that occurred in Libya (2013) and Kenya (2014). In Tripoli, Libya, 1,066 cases of poisoning were reported; the diagnosis based on the clinical manifestations was delayed and the possibilities of treating with an antidote were limited. The death rate was 10%. The sequelae in survivors were predominantly visual. Two outbreaks were reported in Kenya involving 341 and 126 patients, with a death rate of 29% and 21% respectively.

In Islamic countries, mass methanol poisonings are often associated with drinking homemade beverages and spirits that are manufactured illegally in social and cultural settings in which drinking alcohol is prohibited. That was the case in Rafsanjan, Iran, in May 2013, where 694 presumed methanol poisonings were reported. There were eight

deaths in which the analytic confirmation was able to be done in blood (Hassanian-Moghaddam et al., 2015).

6. CHALLENGES AND PROSPECTS

Evidence from both systematic and descriptive reviews shows that there is a broad spectrum of substances used as adulterants. The purity of the drugs that are most frequently used is highly variable and depends on the region or epidemiological context. Drug adulteration is constantly changing, with an overall trend toward a decline in the purity of most drugs over the past 10 years.

Some points to consider:

- Although diluents are inert substances or so-called inactive ingredients that do not cause acute poisoning in most cases, evidence suggests their possible association with chronic complications, depending on some of the variables such as the form of use or route of administration (e.g., intravenous, smoked).
- Some adulterants enhance a drug's psychoactive effects and may contribute to its addictive potential.
- While some adulterants are associated with a significantly higher risk of overdose and death due to acute poisoning (e.g., fentanyl in cocaine or heroin, adulterants of MDMA and LSD, adulterations of NPS), others are related to complications that appear following chronic use in subjects who may be genetically predisposed (e.g., levamisole in cocaine).
- The dose and time of exposure are factors to be considered when referring to the toxic effects of adulterations.
- Deaths in the studies analyzed appear to be related to the drugs involved, to poly drug use, and to the dose consumed. Clear examples here are fatal cases associated with adulterations of MDMA with PMA/PMMA, or of heroin and other opioids with fentanyl and its derivatives.

Considering the gaps in knowledge, it would seem necessary to conduct a standardized analysis of chemical composition and expand it to include a broader spectrum of substances using similar protocols with more representative samples in the various countries and regions, to obtain a complete chemical characterization of the drugs analyzed.

The quality of the information and evidence available on the harms to health caused by some adulterants varies widely. Many reviews refer to acute, chronic, or long-term toxicity (e.g., carcinogenesis) of the individual substance, but these effects have not been demonstrated in users. That is the case with phenacetin, which is currently prevalent as an adulterant of some drugs such as cocaine. It is a substance of recognized toxicity, but very few studies refer to the harms it may cause in combination with cocaine. In this case, the dose and time of exposure may be determining factors. Prevention and toxicovigilance are essential in reducing the harms that may occur as it evolves.

While the most frequent adulterations of some substances are well known, the emergence of NPS has led to gaps in knowledge about the drugs being used and their composition. Analytical research protocols *in situ* (e.g., at rave parties) as well as in specialized laboratories are needed in order to produce that information. Coordination among supply control agencies and those organizations that have access to samples obtained directly from users appears to be needed to achieve common objectives. Early warning systems in the different countries are fundamental to such coordination, as they are sources of information and a means of immediate communication about possible adulterations or related clinical cases. Such information should be worldwide, and not limited to scientific or medical circles but rather available to the entire community and to the general public.

In the current context of legalization or regularization of the marijuana market in a number of different countries, more rigorous research must be conducted on possible contamination by pesticides used on crops, and their possible effects on cannabis use -- particularly smoked cannabis, given current evidence linking adulterations of marijuana with respiratory disease.

Studies of the toxic health effects of adulterants and their association with the drug that is used are based on experimental studies, and essentially on case reports and case series. Epidemiological context, clinical presentation, complications (as seen clinically and in histopathology), and analytical confirmation are the basic pillars in analyzing the toxicity of an adulterant or an adulterant/drug combination.

Case reports are essential in understanding the harms to health, but some limitations are apparent:

- Number of individuals included in the studies. Many of the studies on adulterants have been done on a small scale, which makes it difficult to draw broad conclusions.
- Methodology. In many cases, the studies are retrospective observational studies that do not have a protocol for data collection or information search.
- Difficulties in the field of analytical toxicology in the clinical cases reported. These include time elapsed between the onset of the toxic effect or illness and the taking of the sample; the toxicokinetic and toxicodynamic characteristics of each adulterant; interactions with other drugs; and lack of proper equipment or techniques for confirmatory qualitative and quantitative analysis.
- Resources available. A lack of resources for research, education, and treatment can have negative repercussions, particularly for developing countries.

While drugs are a widely recognized public health problem, drug adulteration is a serious and often overlooked side effect that warrants more attention, resources, and cooperation.

The first step is greater awareness. Health professionals, the community, and most importantly drug users should understand the risks inherent not only in the drugs they are using but in the substances commonly used as adulterants. Some of these carry potential chronic, long-term toxic effects of their own.

Hospitals need to have trained personnel, the necessary material resources, and the means to communicate immediately with local laboratories to identify the adulterants. Early diagnosis makes for better treatment and reduces morbidity and mortality.

Addressing this public health problem effectively will require developing research and action protocols and strengthening networks involving government agencies (e.g., early warning systems), clinical and forensic laboratories, nongovernmental organizations with access to users, as well as universities and toxicology centers.

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