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Toxicological findings in a fatal multidrug intoxication involving mephedrone

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Abstract

The distribution of mephedrone in the body fluids and tissues of a subject found dead after the concomitant intake of cocaine and mephedrone is reported. Mephedrone (4-methylmethcathinone) is a designer drug of the phenethylamine family that is able to cause central nervous system stimulation, psychoactivity and hallucinations and that is becoming popular among youth as a recreational drug. Mephedrone has been available in Europe since 2007, and it is sold through the internet and by local shops as bath salt or plant food.

In the case reported here, a 25-year-old man was found dead in the apartment of a friend after a night spent in several local clubs. A fragment of a blue diamond-shaped pill was found in the pocket of the trousers worn by the decedent. During the autopsy, no evidence of natural disease or trauma was found to account for this death. Blood, urine and gastric content samples were collected and submitted for toxicological analysis. Moreover, bile, brain, lung and hair samples were collected as additional matrices. The content of the pill was submitted to a general screening analysis in order to determine its composition.

Mephedrone was detected in the blood, urine, gastric contents and in the additional matrices using an expressly validated GC/MS method. The blood and urine concentrations were 1.33 mg/L and 144 mg/L, respectively. Contextually, cocaine and cocaethylene were found in the blood and urine specimens. The distribution of mephedrone in the body organs was evaluated by analyzing the brain, bile and lung specimens. Hair analysis revealed a past exposure to mephedrone, ketamine, MDMA and cocaine. Sildenafil was identified as the main component of the blue, diamond-shaped pill. The quantitative determination of mephedrone in several body fluids and tissues provides significant knowledge about the distribution of this new drug of abuse in the human body after massive ingestion.

Keywords

Mephedrone; Distribution; GC/MS; Forensic toxicology; Intoxication

1. Introduction

Mephedrone (4-methylmethcathinone) is a designer drug that is structurally similar to cathinone, which is the active ingredient of the *Khat* plant. Mephedrone was first synthesized in 1929 as a ring-substituted cathinone; its structure is closely related to that of the phenethylamine family [1]. Mephedrone produces stimulant psychoactive effects similar to those induced by amphetamines, methamphetamines, cocaine and MDMA, including hallucinations. For this reason, mephedrone is becoming increasingly popular as a recreational drug, mainly among youths, though its use is reported in several population groups, including young adults, mid-to-late adolescents and older adults [2] and [3]. Mephedrone is made available from several sources, such as street drug dealers, smart shops and internet suppliers. It is sold as a white or slightly yellowish powder or fine crystals under different names, including '4-MMC', 'bubbles', 'meow meow', and 'M-Cat' [4]. The most common routes for recreational use are inhalation (snorting) and oral ingestion, but due to its high water solubility, mephedrone is also taken by rectal insertion and intramuscular or intravenous injection [5]. Mephedrone abuse is associated with serious side effects, including increasing heart rate, chest pain, agitation, irritability and dizziness [5], [6], [7] and [8]. Although several cases of acute and lethal intoxication were reported in the literature [5], [6], [7], [8], [9], [10], [11], [12], [13], [14] and [15], little is still known about the correlation between its blood concentration and its effects. Furthermore, most routine drug screening procedures do not include synthetic cathinones, preventing clear knowledge of the real consumption of these new drugs within the population and the connection between the abuse of new psychoactive substances and road and work accidents [16].

2. Case report

A 25-year-old man (weight 63 kg, height 165 cm) was found dead in the apartment of a friend, where he lay face down in a bed, in the condition of rigor and livor mortis. In the room, an empty glass with alcohol smell and a fragment of a blue, diamond-shaped pill were found; no evidence of violence was observed. The decedent's friend reported to the police that they had spent the previous night together in several local clubs, drinking a high quantity of alcohol and consuming cocaine. He also reported that his friend was a frequent consumer of new designer drugs, and he had with him a white crystal of unknown substance. The white crystal was not found at the crime scene. The death was reported to the public prosecutor who took jurisdiction of the case. To investigate the cause of death, he ordered a post-mortem examination and toxicological analysis.

2.1. Autopsy findings

The autopsy findings were irrelevant, except for a general pulmonary edema and multi-visceral congestion. The body appeared well-nourished, and the internal examination presented no evidence of natural disease or trauma to account for his death. All of the organs were normal. To execute the inherent toxicological analyses, heart blood, urine, gastric contents, brain, bile, lung and hair (length: 3 cm) specimens were collected during the post-mortem examination. Peripheral blood was not collected. All of the samples were stored at $-20\text{ }^{\circ}\text{C}$ before the analysis.

3. Experimental

3.1. Chemicals and reagents

Mephedrone hydrochloride solution (0.1 mg/L as free base) was provided by the 'Istituto Superiore della Sanità' – National Institute of Health (ISS, Rome, Italy). Amphetamine-D₆ was purchased from LGC Promochem (Milan, Italy). Sodium hydrogen carbonate (NaHCO₃), sodium carbonate (Na₂CO₃), sodium phosphate dibasic dihydrate (Na₂HPO₄·2H₂O), potassium phosphate monobasic (KH₂PO₄), methanol, *t*-butyl methyl ether (TBME), trifluoroacetic acid (TFA) trifluoroacetic anhydride (TFAA) and β -glucuronidase (from *Escherichia coli*) were obtained from Sigma–Aldrich (Milan, Italy). Phosphate buffer was prepared by dissolving 4.63 g of KH₂PO₄ and 11.75 g of Na₂HPO₄·H₂O in 1 L of deionized water, and the carbonate buffer was prepared by dissolving 2.12 g of Na₂CO₃ and 6.72 g of NaHCO₃ in 1 L of deionized water. Deionized water was obtained from a Milli-Q system (Millipore Corporate Headquarters, Billerica, USA).

3.2. Sample preparation for fluids and tissues

General screening analysis was executed on 2 mL of urine, buffered at pH 7.4 with 2 mL of 0.1 M phosphate buffer and deconjugated with the addition of 30 μL of β -glucuronidase from *E. coli* prior to incubating the mixture at 55 $^{\circ}\text{C}$ for 1 h. The sample was subsequently extracted under alkaline conditions (pH 9.6) by adding 2 mL of a 0.1 M carbonate buffer and then 10 mL of TBME. After shaking the mixture in a multimixer for 10 min, the organic layer was separated and dried under a gentle flow of nitrogen. The resulting residue was reconstituted with 50 μL of methanol. Lastly, a 1 μL aliquot was injected (splitless mode) into the gas chromatography/mass spectrometry (GC/MS) system. In addition, the blood sample was screened with an updated method for the detection of more than ninety pharmaceutical drugs and metabolites, including LSD and GHB, routinely employed in our laboratory [17]. For mephedrone quantitation in the blood, urine, gastric contents, bile and homogenized tissues, 2 mL (or 1 g) of samples were added with the internal

standard (amphetamine-D₆, final concentration of 250 ng/mL or 500 ng/g) and basified with 2 mL of 0.1 M carbonate buffer and 2 drops of NaOH 1 N. After extraction with 10 mL of TBME, the organic layer was dried under a nitrogen flow, and the dry residue was derivatized with 50 µL of TFAA for 30 min at 65 °C. The resulting residue was reconstituted with 50 µL of TBME, and a 1 µL aliquot was injected (split ratio of 10:1) into the GC/MS system operating in the selected ion monitoring (SIM) mode.

3.3. Sample preparation for hair analysis

Hair analysis was performed on the entire length of the hair lock (3 cm). Approximately 100 mg of hair was twice-washed with dichloromethane and methanol (3 mL each, vortex mixed for 3 min). After complete removal of the solvent wash, the hair was dried at room temperature by a gentle nitrogen flow and subsequently cut with scissors into 1–2 mm segments. For mephedrone quantitation, the hair sample was fortified with 5 µL of an amphetamine-D₆ solution used as the internal standard at a final concentration of 0.5 ng/mg. After the addition of 2 mL of methanol, the sample was incubated at 55 °C for 15 h without stirring. Lastly, the organic phase was collected in a new test tube and 30 µL of TFA was added. The solvent was dried at 55 °C under a nitrogen stream, and the dry residue was derivatized with 50 µL of TFAA for 30 min at 65 °C. The resulting residue was reconstituted with 50 µL of TBME and a 1 µL aliquot was injected (split ratio of 5:1) into the GC/MS system operating in the SIM mode. Moreover, qualitative and quantitative hair analyses for the detection of (1) the most common drugs of abuse and (2) synthetic cannabinoids were performed by means of analytical methods used in our laboratory and described elsewhere [18] and [19].

3.4. Sample preparation for pill analysis

The blue diamond-shaped pill was subjected to systematic analysis for the detection of drugs and toxic substances. The pill (total weight: 271 mg) was pulverized in a mortar, and 150 mg of the resulting powder was dissolved in 5 mL of methanol. After sonication in an ultrasound bath for 1 h at 55 °C, a 1 µL aliquot of methanolic solution was injected into the GC/MS system with the mass spectrometer acquiring the spectra in the full scan mode (40–650 amu).

3.5. Apparatus and methods

Preliminary screening analyses for amphetamines, tricyclic antidepressants, barbiturates, benzodiazepines, cannabinoids, methadone, cocaine and opiates were performed on urine by the enzyme multiplied immunoassay technique (EMIT, Abbott Laboratories, IL, USA). The ethanol

concentration in the blood, urine and gastric contents was determined by headspace-GC–MS. Screening analysis for unknown substances was performed using a 6890 N GC apparatus (Agilent Technologies, Milan, Italy) equipped with a 17 m fused-silica capillary column (J&W Scientific HP-5) with a 0.2 mm inner diameter and a 0.33 μm film thickness. Helium was employed as the carrier gas at a constant pressure of 23.24 psi. The GC oven temperature was set at 90 °C for 1 min and then raised to 180 °C with a 30 °C/min heating rate. The oven temperature was maintained at 180 °C for 7 min and then raised to 315 °C with a 15 °C/min heating rate. The GC injector and transfer line were maintained at 280 °C. Full scan spectra in the interval 40–650 amu were acquired using a 5975 inert mass-selective detector (Agilent Technologies, Milan, Italy) operating in the EI mode at 70 eV. The qualitative identification of the underivatized compounds was performed by comparing the full scan spectra obtained with those recorded in the updated spectra libraries (PMWTox2, SWGDRUG version 1.7, AAFS2013, CaymanSpectraLib). The screening for the determination of pharmaceutical drugs and metabolites, GHB and LSD in blood was conducted by means of an updated UHPLC-MS/MS method used in our laboratory and described elsewhere [17].

Table 1. Validation data for the detection of mephedrone in blood and urine.

Matrix	Linearity range (mg/L)	Determination coefficient (R^2)	Mephedrone					
			LOD (mg/L)	LOQ ^a (mg/L)	Precision (CV%)		Accuracy (bias%)	
					0.1 mg/L	1.0 mg/L	0.1 mg/L	1.0 mg/L
Blood	0.1–1.5	0.995	0.006	0.02	1.8	2.0	+18.9	–1.1
Urine	0.1–1.5	0.996	0.006	0.02	3.0	2.0	+12.3	+4.5

^aCalculated LOQ

For the mephedrone confirmation analysis, a dedicated GC–MS procedure was developed and validated, as follows. A 6890 N gas chromatograph from Agilent Technologies (Milan, Italy) equipped with a J&W HP-5 capillary column, 17 m \times 0.200 mm \times 0.33 μm was used. Helium was employed as the carrier gas at a constant pressure of 25.00 psi. The GC oven temperature was set at 85 °C for 2 min and then raised to 110 °C with an 8 °C/min heating rate. The oven temperature was then raised to 300 °C with a 30 °C/min heating rate. The total run time was 14.5 min. The GC injector and transfer line were maintained at 250 °C.

The chromatograph was coupled to a 5975-inert MSD from Agilent Technologies (Milan, Italy) with EI at 70 eV. Quantitative determination of mephedrone was performed on its TFA-derivative by monitoring the diagnostic ions at m/z 119 (target ion), 154 and 91 (qualifiers), whereas for the internal standard (amphetamine- D_6), the diagnostic ions at m/z 144, 123 and 93 were chosen.

3.6. Method validation

The method was validated by investigating the following parameters: linearity, selectivity, identification limit (LOD), quantitation limit (LOQ), precision and accuracy. Blood and urine were chosen as the target matrices for method validation. The linear calibration models were checked by analyzing (three replicates) blank samples (blood and urine) spiked with mephedrone standard solution at final concentrations of 0, 0.10, 0.20, 0.50, 0.75, 1.0 and 1.5 mg/L. Whenever the effective drug concentration exceeded the calibration range, the samples were diluted to fit the quantitation interval considered in the curve. The dilution integrity was evaluated by spiking each matrix at a mephedrone concentration 1.5 times the highest calibration point (1.5 mg/L) and diluting the resulting solution twice and ten times with blank matrix. These samples were analyzed along the standard calibration curve, and the accuracy was considered satisfactory within the interval $\pm 20\%$ around the expected value.

For each matrix, ten different blank samples were prepared, as described above, in order to test the selectivity of the whole analytical procedure. The occurrence of possible interferences from endogenous substances was checked by monitoring the signal-to-noise ratio (S/N) for the characteristic selected-ion chromatograms at the expected retention time of mephedrone. The LOD was estimated as the analyte concentration whose response provided a signal-to-noise (S/N) ratio of 3, as determined from the least abundant qualifier ion. The S/N ratio at the lowest concentration (0.1 mg/L) was used to extrapolate the theoretical LOD. The calculated LOD for both matrices was experimentally confirmed by analyzing urine and blood samples spiked with mephedrone at the LOD concentration.

Table 2. Mephedrone concentrations in post-mortem specimens and other findings.

Sample	Concentration (mg/L)	Other findings
Blood	1.33	Ethanol: 0.13 g/L Cocaethylene: 18 ng/mL Cocaethylene: 18 ng/mL Lidocaine, phenacetin, paracetamol, levamisole Benzoylecgonine: not tested
Urine	144	Ethanol: 0.43 g/L Benzoylecgonine: 34.5 mg/L Cocaine: 6.97 mg/L Cocaethylene: 3.10 mg/L Lidocaine, paracetamol, levamisole
Gastric content	4.52	Ethanol: 0.23 g/L
Bile	1.29	–
Lung	0.79 (mg/kg)	–
Brain	0.89 (mg/kg)	–

Sample	Concentration (mg/L)	Other findings
Hair	0.25 (ng/mg)	Cocaine: 0.78 ng/mg Benzoylcegonine: 0.49 ng/mg Ketamine: 1.90 ng/mg MDMA: 0.23 ng/mg

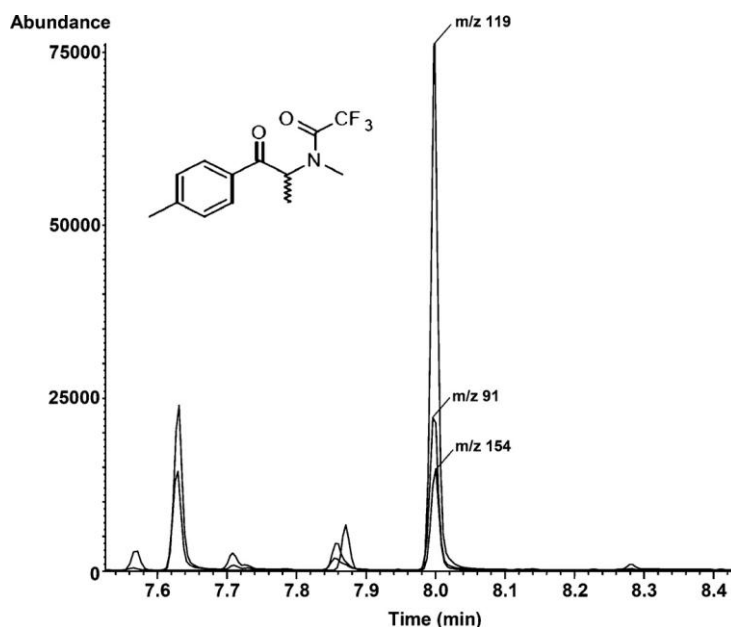


Fig. 1. GC-SIM-MS chromatograms resulting from the detection of mephedrone in the victim's blood.

The LOQ values were estimated as the analyte concentration whose response provided an S/N value equal to 10. The LOQ generally corresponds to the lowest concentration that provides a useful signal along the calibration curve. Within-batch precision (expressed as the percent variation coefficient, CV%) and accuracy (expressed as bias %) were assessed by extracting and analyzing, for each tested matrix, a series of five samples fortified at 0.10 and 1.0 mg/L.

For hair analysis, a calibration curve in the interval 0.2–2.0 ng/mg was constructed, and two quality control samples obtained by spiking blank hair with mephedrone at final concentrations of 0.2 and 1.0 ng/mg were tested separately in order to roughly estimate the method accuracy.

4. Results and discussion

4.1. Validation results

The calibration plots showed good linearity in the range 0.10–1.5 mg/L, with a determination coefficient of 0.995 and 0.996 in blood and urine, respectively. The SIM chromatograms from 10 negative samples of blood and urine showed no interfering signals (i.e., S/N ratio lower than 3) at the retention time of mephedrone, indicating that the method is selective and free from matrix interferences. The three ions monitored in the SIM protocol, together with the retention time, provided at least 4 identification points. The substantial stability of their relative abundance proved compliant for the unambiguous identification of mephedrone in the assay, in agreement with the CE/2002/657 decision guidelines [20]. The calculated LOD was 0.006 mg/L for both blood and urine, and the LOQ was 0.02 mg/L. This estimated value is smaller than the lowest calibration point, arbitrarily fixed at 0.10 mg/L for both matrices. The LOD values were experimentally confirmed by analyzing in triplicate a blank matrix sample (blood and urine) spiked with mephedrone at the estimated LOD concentration. The within-batch data on the precision and accuracy are reported in Table 1. The results show a satisfactory repeatability because the CV% falls in the interval 1.8–3.0% for mephedrone spiked in blood and urine at both the 0.10 and 1.0 mg/L concentrations. In the tested matrices, the accuracy (expressed as percent bias) varied from –1.1 to +18.9%, showing that all experimental values were below the acceptable bias limit of $\pm 20\%$ at the 0.10 and 1.0 mg/L concentrations.

4.2. Toxicological findings

The presence of mephedrone was confirmed in all specimens; all of the toxicological results are reported in Table 2. Fig. 1 depicts the GC–SIM–MS profiles obtained from the heart blood sample for the detection of mephedrone, which was quantified at a concentration of 1.33 mg/L. Mephedrone was uniformly distributed among the lungs and brain at a concentration of approximately 0.8–0.9 mg/kg. Higher amounts of mephedrone were detected in urine (144 mg/L) and bile (1.29 mg/L), indicating the occurrence of extensive drug excretion before death. High concentrations of the drug were also detected in the gastric contents, confirming its ingestion before death. Other analytical findings indicated the recent intake of cocaine and ethanol, consistent with the declarations of the decedent's friend. Hair analysis revealed past exposure to mephedrone (0.25 ng/mg), ketamine (1.90 ng/mg), MDMA (0.23 ng/mg) and cocaine (0.78 ng/mg). Sildenafil was identified as the main component of the pill fragment, but this substance was not detected in any biological specimen.

Presently, several death cases have been attributed to mephedrone intoxication, either alone or in association with other drugs, but reference toxic and lethal concentrations in body fluids and organs are not yet available for mephedrone. In the literature, a case of a non-fatal intoxication related to mephedrone was reported by Wood et al.; the drug concentration in the plasma was 0.15 mg/L [3]. In a recent study, Cosbey et al. reported a total of 32 non-fatal impaired driving cases in which mephedrone was found alone or together with other drugs or alcohol in Northern Ireland [9]. When mephedrone was the only drug detected (9 cases), the blood concentration was in the interval of 0.08–0.66 mg/L. In the remaining 23 cases, mephedrone was found along with other drugs at blood concentrations ranging from 0.01 to 0.74 mg/L. The most common symptoms observed were hyperactivity, agitation, glazed eyes, dilated pupils and slurred speech. Fatal cases involving mephedrone are summarized in Table 3. Mephedrone was detected at blood concentrations within the range of 0.13–0.50 mg/L in the cases when another drug played a key-role in the fatal event, namely morphine [10], methadone [11] and GHB [12]. In these cases, the death was attributed to “multidrug intoxication”. In one case, where the death was attributed to the “adverse effect of mephedrone on a atherosclerotic coronary artery disease”, mephedrone was detected alone in femoral blood at 0.98 mg/L [11].

Table 3. Mephedrone blood concentration in fatal intoxications.

Case	Year	Blood (mg/L)	Site ^a	Other relevant findings	Cause of death	Refs.
Presented	2013	1.33	h	Cocaine 18 ng/mL, cocaethylene 18 ng/mL, ethanol 0.13 g/L	Mephedrone intoxication	–
1	2010	0.5	n/a	Morphine 0.6 mg/L	Multi-drug intoxication	[10]
2	2010	22	n/a	Amphetamine 0.34 mg/L, diazepam <0.1 mg/L, nordiazepam <0.1 mg/L	Mephedrone intoxication	[15]
3	2010	3.3	n/a	None	Mephedrone intoxication	[15]
4	2011	0.98	f	Atropine/naloxone	Effect of mephedrone on coronary disease	[11]
5	2011	2.24	f	3-TFMPP (3-trifluoromethylphenylpiperazine)	Mephedrone intoxication	[11]
6	2011	0.13	f	Methadone 0.3 mg/L, diazepam, nordiazepam, olanzapine, chlorpromazine metabolite	Multi-drug intoxication	[11]
7	2011	5.1	f	Cocaine 7 ng/mL, MDMA 11 ng/mL, oxazepam <0.1 mg/L, midazolam 6 ng/mL	Fatal excited delirium by mephedrone	[13]
8	2012	0.5	h	GHB 288 mg/L	Multi-drug intoxication	[12]
9	2013	5.5	n/a	None	Mephedrone intoxication	[14]
10	2013	2.10	n/a	Ethanol 0.19 g/L	Mephedrone intoxication	[9]
11	2013	1.94	n/a	3-TFMPP 0.02 mg/L, diazepam 0.11 mg/L	Mephedrone	[9]

Case	Year	Blood (mg/L)	Site ^a	Other relevant findings	Cause of death	Refs.
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intoxication

^af: Femoral blood, h: heart blood, n/a: data not available.

In a case of fatal excited delirium after the use of mephedrone, a concentration of 5.1 mg/L was determined in the femoral blood, and low levels of cocaine, MDMA, oxazepam and midazolam were also found in the same sample [13]. The mephedrone blood concentration was between 1.94 and 22 mg/L in six cases where “mephedrone intoxication” was reported as the cause of death [9], [14] and [15]. In two cases, mephedrone was the only drug detected in the blood, at levels of 3.3 and 5.5 mg/L [14] and [15].

In the present case, the heart blood concentration of mephedrone was slightly lower than in the cases previously reported, where no other drugs were found to play a role in the intoxication. On the other hand, the mephedrone blood concentration determined in the present case is higher than in the reported non-fatal mephedrone intoxications. The presence of low levels of ethanol, cocaine and cocaethylene in the blood may have partially contributed to the fatal event. The potential synergic effect of multiple drugs intake, even at low levels, on mephedrone toxicity is not known. The presence of lidocaine, phenacetin, paracetamol and levamisole in the biological fluids confirmed the recent intake of cocaine because these molecules represent the most common adulterants used in cocaine powder. Lastly, the presence of mephedrone in the hair sample indicates that the decedent had previously been exposed to the same drug on more than one occasion. Assuming that the hair growth rate ranges from 1.0 to 1.3 cm/month [21], a consumption of mephedrone in the three months before the death could be presumed. This finding is consistent with the statement of the decedent’s friend, reporting that he was a consumer of new designer drugs. Few literature data regarding hair samples are available, making it difficult to interpret the hair result. Martin et al. reported 13 cases in which mephedrone was detected in hair samples at concentrations between 0.2 and 313.2 ng/mg [22], whereas Shah et al. reported a single case of a positive mephedrone hair sample at a lower concentration (21.11 pg/mg) [23]. Unfortunately, no additional data (e.g., frequency of consumption) were collected in these studies, so there is poor knowledge on the correlation between the frequency (and dosage) of mephedrone intake and hair concentration. In our case, the level of mephedrone appears relatively low if compared with existing data [22], leading to the conclusion that the deceased was likely not a heavy consumer of mephedrone.

5. Conclusions

In the fatal case reported here, the concomitant intake of mephedrone, cocaine and ethanol suggests that their synergic pharmacological effects likely accounted for the death. Among the

three substances found in the blood, only mephedrone appears to be present at a concentration compatible with acute intoxication conditions, possibly leading to death. Quantitation of mephedrone in several body fluids and tissues contributes new information about the distribution of this chemical in the human body after massive ingestion.

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