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Butane-related deaths in post-mortem investigations: A systematic review

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ABSTRACT

Volatile substance abuse is widespread among adolescents due to its easy availability and methods of consumption. Inhalant abuse represents a current problematic issue, causing significant morbidity and mortality due to direct toxicity on several target organs and displacement of gas which results in a lack of oxygen. This review aims to evaluate post-mortem and toxicological investigations in cases of suspected butane intoxication. We performed comprehensive research using the Preferred Reporting Items for Systematic Review (PRISMA) standards. Forty scientific papers fulfilled the inclusion criteria. A total of 58 cases of butane-related deaths were found. Among these, we found 11 cases of suicide (18%), 1 case of homicide (2%), 44 cases of accidental poisoning (76%), and 2 cases of work-related deaths (4%). Autopsy and post-mortem examinations were performed in 54 cases, whereas toxicological analyses were presented in 56 cases. In autopsy, pulmonary edema (51%) and poli-visceral congestion (59%) were the most common findings. When death by butane inhalation is hypothesized, autopsy and histological findings may be nonspecific, therefore toxicological investigations assume a crucial role along with attention to the methods used to collect biological samples.

1. Introduction

The term "inhalants" comprises a heterogeneous group of psychoactive substances often used for the production of typewriter correction fluid, cleaning fluids, spray paints, adhesives, and lighter fluids [1]. Most of these substances are simple hydrocarbons or substituted hydrocarbon compounds, such as butane, and represent the most inhaled substances of abuse. Whereas most drugs may have multiple intake routes, inhalants can be used only through the respiratory tract. The *National Survey on Drug Use and Health* (SAHMSA, 2020) shows that in 2019, 2.4 million people (0.9 percent) aged 12 or older used inhalants. This percentage was higher among adolescents, from 12 to 17 years old, and progressively decreased with age, unlike other illicit drug use [2].

Various volatile substances exert a euphoria-inducing response in humans. These substances can be found mostly in gas form, and toluene, benzene, ethyl chloride, xylene, butane, and chlorofluorocarbons are part of this group [3]. The inhalation of these substances for recreational purposes is a form of drug abuse that is becoming increasingly common, especially among the youngest. The first reason is that these substances can be easily found on the market, such as in air fresheners, glues, paints, and lighter refills, and, most of all, they have a low cost. The second reason is that the abuse of volatile substances is not recognized as an illegal form of abuse [4]. Indeed, this type of abuse form is very underestimated and therefore unregulated and under-researched. This leads to the evermore continuous expansion of this type of abuse, especially among adolescents who do not understand its danger. According to the *Monitoring the Future 2010*'s survey, volatile substances represent the second most commonly used substance of abuse (average of 14.9 percent) after marijuana (average of 15.7 percent) and thus higher than all the most widely known drugs [5].

Volatile substances are mainly hydrocarbons, which, once inhaled, are largely absorbed by the respiratory system. Once drawn in, they are partly exhaled, whereas the rest passes into the bloodstream and is metabolized in the liver. Hydrocarbons are processed through different steps: firstly, they are metabolized into alcohols, secondary and tertiary; then they are transformed into ketones and simpler forms of propane

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and butane [4]. Secondary alcohols such as isopropanol and *sec*-butanol are metabolized by alcohol dehydrogenase, whereas tertiary alcohols such as *tert*-butanol are metabolized at a microsomal level. The metabolism of degradation products leads to the formation of acetone and formaldehyde. In post-mortem investigations, the search for these substances is not recommended as they do not provide unequivocal interpretation and may distract from the diagnosis. Indeed, although pharmacologically active, they can be found in many other clinical conditions [6] and as a result of post-mortem degradation [7].

Even though all volatile substances have a depressant effect on the central nervous system, butane and, in particular, his isomer N-butane, seems to be the most active at this level [4]. However, the range of confidence between concentrations resulting in the intentional effect pursued by abusers and lethal concentrations is very narrow. Low doses are needed to achieve euphoric effects, but given the ease with which overdose is achieved, these are often accompanied by intoxication effects, such as confusion, behavioral disorders, hallucinations, and ataxia [8].

In addition, both the euphoric and the toxic effects have a rapid onset (of a few seconds), which is paired with a very short duration and recovery time (from 15 min to an hour) [9,10]. Intake of the gases is achieved by directly inhaling the substance that is released from the container (spray cans or air fresheners), or by snorting the gas placed in plastic bags or baggies, or sniffing tissues or cotton pads that are soaked in the liquid gas form [3]. Some of these methods of intake, such as taking the substance from a plastic bag, lead to the inhalation of not well-dosed amounts of gas. In this way, it is easier to take a higher, and consequently lethal, dose of the substance. Death usually occurs very rapidly after the intake of the substance (due to its rapid absorption and metabolization) and it is mainly due to asphyxiation, cardiac dysfunction, central nervous system depression, or allergic reactions [11,12]. Chronic abuse of the substance can also lead to death from kidney or liver failure or liver tumor development [12,13]. In addition, these substances are more popular among young people, including fertile females and therefore they are often taken also throughout pregnancy [14]. During pregnancy, such substances can lead to malformations in fetal development, as several of these (e.g., toluene) are teratogenic. Such substances may also cause intrauterine death [15].

Paying particular attention to butane, a saturated aliphatic hydrocarbon, $CH_3–(CH_2)_2–CH_3$, existing in the form of two isomers, n-butane, and isobutane. Both are found in small amounts in natural gas, and they are obtained from the distillation of crude oil and cracked gases. Butane is an odorless, colorless gas commonly used for cosmetic or industrial purposes. It is frequently found in hair sprays, air fresheners, aerosol deodorants, and lighter fluids or butane gas canisters. Butane gas used for "commercial use" has a typical composition of butane (60 %), isobutane (30 %), propane (9 %), and ethane (1 %) [16]. The current threshold limit value for occupational exposure, according to the National Institute for Occupational Safety and Health (NIOSH), is 880 ppm (2.38 mg/m^3), and the Immediately Dangerous to Life and Health value (IDLH) is 1,600 ppm [17]. Butane is also a drug of abuse. As an "inhalant", the method of its use as a drug is only restricted to inhalation. Nevertheless, it can be "sniffed" by breathing directly from containers, inhaled from bags or balloons (a practice known as "bagging"), or "huffed" from a piece of cloth in which it is placed. These methods of inhalation determine a progressive increase in vapor concentrations and, therefore, may imply a higher involvement in the abuse of volatile substances [1].

Once inhaled, butane is absorbed into the respiratory system and distributed in tissues rich in lipids, due to its high liposolubility [18]. Butane expresses its effect on various tissues by asphyxiation by displacing oxygen and increasing reactive oxygen species (ROS). It also depresses the central nervous system by enhancing glycine receptors and inhibiting N-methyl-d-aspartate (NMDA) receptors [19,20]. Acute butane intoxication occurs with inhalation of a high dose of the substance, resulting in euphoria, hallucinations, confusion, diplopia, nausea and/or vomiting, convulsions, ataxia, respiratory depression, and cardiac arrhythmias to death [21]. The effects may last from 15 to 45 min per single dose [3].

Death is usually caused by cardiac arrhythmias with ventricular tachycardia [22], ventricular fibrillation [23], vagal stimulation [24] and catecholamine release [25], respiratory center depression [3], *ab ingestis*, and laryngeal edema [26]. Intoxication can be accidental, caused by substance abuse, by inhalation, or for autoerotic purposes, but also for suicidal purposes. The homicidal hypothesis is also possible. However, in many surveys, it has been noted that volatile substance abuse -linked death numbers are more than likely underestimated. As described, the extremely high variability in the causes of death from butane inhalation raises several questions during investigative inquiries. Consequently, a systematic literature review is conducted to assess the described anatomopathological findings. The purpose of this systematic review is to serve as a reference for forensic pathologists and toxicologists in routine postmortem investigations in case of suspect of Butane-related deaths.

2. Materials and methods

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Review (PRISMA) standards [27]. A systematic literature search and a critical review of the collected studies were conducted. An electronic search of PubMed, Science Direct Scopus, Google Scholar, and Excerpta Medica Database (EMBASE) from database inception until January 2023 was performed. The search terms used in the title, abstract, and keywords were "butane", "butane gas", "autopsy", "death", "intoxication", "suicide", "homicide", and "accidental". The bibliographies of all located papers were examined and cross-referenced to identify relevant literature. A methodological assessment of each study was conducted according to the PRISMA standards, including the bias evaluation. The data collection process included study selection and data extraction. The following inclusion criteria were used: (1) original research articles, (2) reviews and mini-reviews, (3) case reports/series, (4) and only papers written in English. Non-English papers and papers regarding cases of survival after inhaling butane gas were excluded. This study was exempt from institutional review board approval, as it did not involve human subjects.

3. Results

This The search performed identified 296 articles, which were screened for duplicates. The reference lists of the allocated articles were then reviewed to identify still undetected literature. The resulting 277 references were screened based on their title and abstract to evaluate their relevance concerning the following:

- Circumstantial data evaluation.
- Post-mortem evaluation.
- Toxicological evaluation.
- Study design.

Fig. 1 represents the methodology of our search strategy.

A brief description and review of the literature on death by butane are shown in Table 1.

We identified 58 cases of butane-related deaths as a result of the harmful use or misuse of butane. The route of exposure was exclusively by inhalation, whether "sniffed", "huffed", or "bagged". The source of abuse was mainly butane canisters and lighter refill canisters. Among these 58 cases, the population was predominantly male (83 %), while only 10 cases were female (17 %). The case subjects' ages varied between 11 and 70 years, and the most impacted age group was the < 18-year-old (44,8%) population. There were 11 cases of suicide (19 %), 44 cases of accidental poisoning (76 %), and one suspected homicide. Two cases resulted from a work-related incident (2,5%) [37], of which the

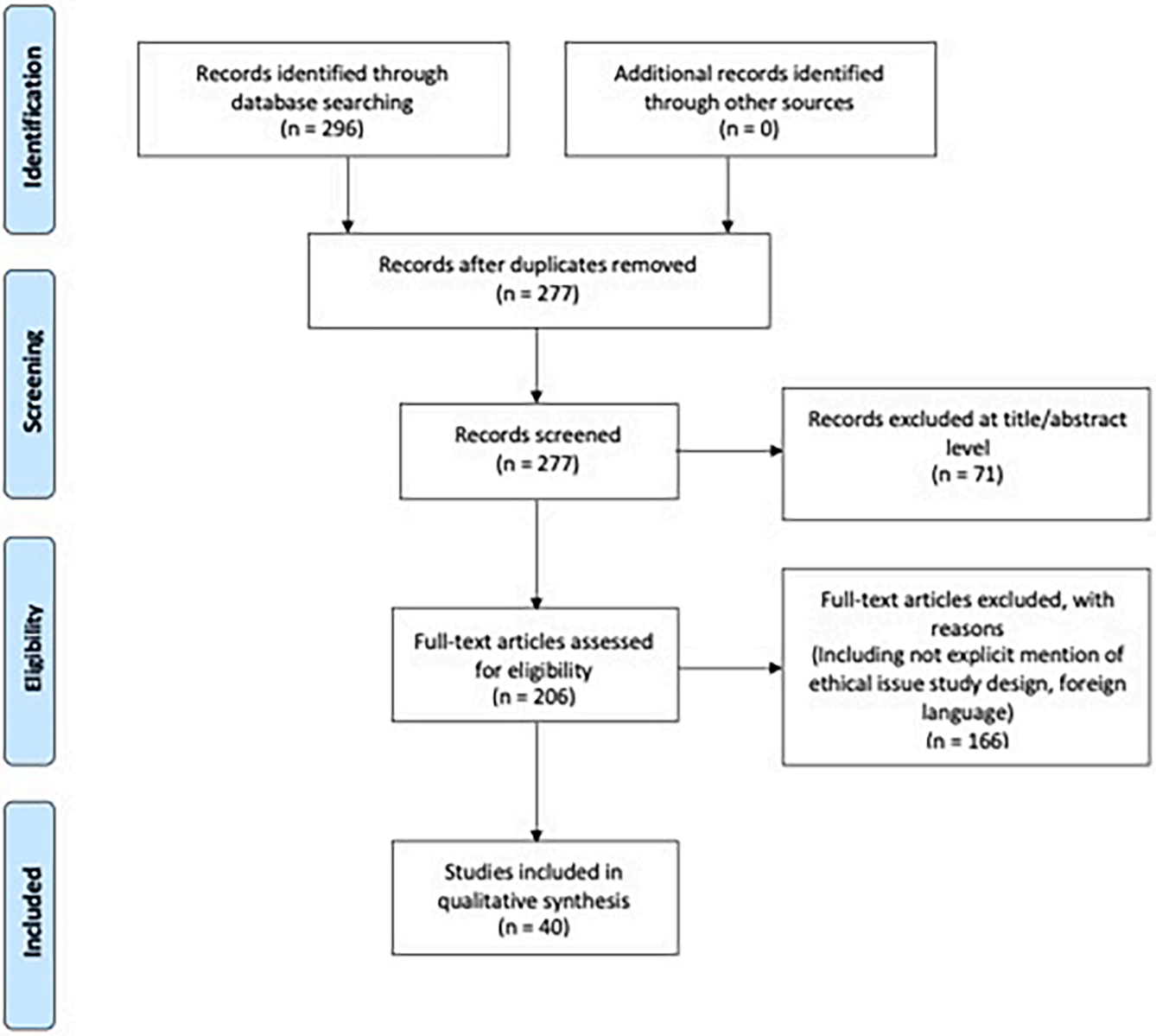

Fig. 1. Preferred Reporting Items for Systematic Review (PRISMA) flow chart – search strategy. A total of 40 studies fulfilled the inclusion criteria.

first concerns a 41-year-old male who was working 1.7 m underground to construct a new pipe connection without regulation gas masks and ventilation. He died of asphyxia due to anoxia. The second case was about a 34-year-old male who worked with his partner 1.3 m underground to construct a new pipe, lost consciousness, and died of asphyxia. Several case reports involved adolescents who inhaled butane from lighter refill canisters to achieve narcotics effects. To assist reading, the main characteristics of the subjects are summarized in Table 2.

Autopsy and post-mortem examinations were performed in 54 cases, whereas histopathological analysis was performed in 32 instances. The external examination did not show any peculiar findings. Autoptic discoveries were also unremarkable; the most common findings were congestion of the major organs (28 %), pulmonary edema (52 %), and petechiae (21 %). Regarding the histopathological analysis, the most common findings were the ones concerning pulmonary and cardiac tissue samples; showing hemorrhagic foci (16 %), edema (45 %), and congestion (24 %) in the lungs, while the heart tissue predominantly presented congestion (42 %), necrosis (21 %), and interstitial fibrosis (21 %).

In Fig. 2 histopathological findings in pulmonary tissues are depicted, while Fig. 3 shows the typical histopathological findings in cardiac tissue samples.

Toxicological investigations were performed in 56 cases and consisted mostly of screening of volatile substances by gas chromatography/mass spectrometry (GC/MS), and quantitative gas chromatography (GC). In 31 of these cases, quantitative toxicological analysis was carried out and two units were usually adopted to report butane concentrations, microliters per milliliter, and micrograms per liter. As shown in Table 3, the most common analysis performed is the quantification of butane in the blood (52 %). In all reported cases, blood concentrations were found to be higher than 100 μg/L in all butane-linked deceases. Brain and liver samples were used for butane determination in 22 cases (38 %), while quantification in lung samples was performed in 24 cases (41 %). Adipose tissue butane was quantified in 12 cases (21 %), although its levels in muscle tissue were estimated only in 5 cases (8.6 %). Lastly, gastric contents analysis was performed in 7 cases (12 %) and represent the second most common fluid used for quantification of butane after blood.

Table 1
Review of the literature on death caused by butane.

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
Ago et al. 2002 [28]	15M	Aerosol deodorant	Found unresponsive in a parking lot, resuscitated, vomited a large quantity of food. Died few hours later	Accidental	Slight abrasion and bruises on the head, neck, and shoulder. Lung's congestion and pulmonary edema; petechiae of the conjunctiva, pleural and pericardial surfaces, and under the scalp	Foreign material in the bronchioles. Congestion and edema of the lung. Congestion of the other organs	Fatal cardiac arrhythmia	Butane
Al-alousi et al. 1989 [29]	13M	Aerosol deodorant	Died after inhaling deodorant sprayed in a plastic bag for recreational purposes	Accidental	Congestion of the conjunctiva and vomit around the nose and mouth. Cerebral and pulmonary edema. Congestion of the liver, spleen, and kidneys	Cerebral edema, vacuolization and early perivascular demyelinization of the cerebral tissue. Cortical neuronal anoxic degeneration. Congestion and edema of the lung. Aspirated foreign material in the terminal bronchi and bronchioles. Congestion of the other organs	Asphyxia by inhalation of gastric contents	Butane and propane
Almulhim 2017 [30]	30M	Lighter refill canister	Found unconscious and had a seizure for over 30 min. 6 h later developed ventricular fibrillation and died after 45 min of resuscitation	Accidental	N/A	N/A	Fatal cardiac arrhythmia	N/A
Alunni et al. 2017 [31]	11M	Aerosol deodorant	Fainted in a parking lot. Died after 45 min of resuscitation	Accidental	Moderate cyanosis. Pulmonary edema, diffuse moderate congestion and cerebral edema	Pulmonary edema and serohemorrhagic or mucinous material rich in macrophages in the bronchial lumina. Centrilobular hepatic congestion, low-flow subendocardial cardiomyocyte necrosis and loss of Purkinje cells in the cerebellum	Isolated butane intoxication	Butane, isobutane, and limonene
	16F	Tissue soaked in deodorant	Type 1 diabetic suffered a grand mal seizure and died after resuscitation attempt	Accidental	Massive pulmonary edema with laryngeal regurgitation of food	Pulmonary edema and foreign material in the bronchial lumina. Dilation of the renal proximal convoluted tubule and low-flow cardiomyocyte necrosis. Hypoxic ischemic encephalopathy	Isolated butane intoxication	Butane, limonene
Aquila et al. 2020 [32]	30M	LPG cylinder tank	Found death in his house with a plastic bag wrapped around the head and connected to an LPG cylinder tank	Suicide	Advanced putrefaction, maggots in the nasal cavities and bloated abdomen. Pulmonary edema and congestion, sub-epicardial petechiae	N/A	Acute cardio-respiratory failure	Butane, alcohol, amphetamine, and ethanethiol
Bork et al. 2017 [33]	16M	Lighter fluid	Felt unwell playing football, was taken to the hospital where he died	Accidental	Congestion of major organs, pulmonary edema, foreign body aspiration compatible with food, petechial bleedings on the	Pulmonary edema and intra-alverolary fresh bleeding. Congestion of the other organs	Sudden death due to inhalant abuse	Butane, Propane, Isobutane, Tetrahidrocannabinol

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Table 1 (*continued*)

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
					surface of heart and lungs			
	14M	Lighter fluid	Felt unwell at home, was taken to the hospital where he died	Accidental	Bridging of the coronary artery, congestion of major organs, pulmonary edema and petechiae	Point fresh bleeding of the brainstem. Pulmonary edema and foreign body aspiration compatible with food content. Congestion of the other organs	Sudden death due to inhalant abuse	Butane, Propane, Isobutane
	16M	Lighter fluid	Found dead at home, lighter fluid tube found next to the corpse	Accidental	Congestion of major organs, pulmonary edema and petechiae	Focal interstitial fibrosis of the myocardium. Pulmonary edema and intra-alveolary fresh bleeding. Congestion of the other organs	Sudden death due to inhalant abuse	Butane, Propane, Isobutane, Tetrahidrocannabinol
	17M	Lighter fluid	Felt unwell while inhaling lighter fluid, died at the hospital while being treated	Accidental	Congestion of major organs, pulmonary edema and petechiae	Pulmonary edema and intra-alveolary fresh bleeding. Congestion of the other organs	Sudden death due to inhalant abuse	Butane, Propane, Isobutane
Bugra et al. 2018 [34]	15F	Lighter fluid	Found unconscious, cardiopulmonary arrest in transportation to the hospital where she died	Accidental	Subendocardial hemorrhagic area under the aortic valve to the interventricular septum	Contraction band necrosis, neutrophil infiltration of myocardial muscles fibers. Intra-alveolar hemorrhage and pulmonary edema	Cardio-pulmonary arrest	Butane
Durao et al. 2020 [16]	70M	Butane gas canister	Found dead in bed after inhaling butane gas by CPAP homemade adaptation	Suicide	Cyanosis of the extremities, petechial conjunctival, severe vascular congestion, and pulmonary edema	Pulmonary edema, acute marginal emphysema, and subpleural hemorrhages. Cardiac hypertrophy	Asphyxia through to butane inhalation	Butane, propane, tramadol, O-desmethyltramadol, N-desmethyltramadol, quetiapine, nor-quetiapine, and alcohol
El-Balkhi et al. 2015 [35]	15M	Lighter fluid	Fainted at home, resuscitation was performed but it was unsuccessful	Accidental	Hemorrhagic conjunctiva and cyanosis of the extremities. Food debris in the larynx	N/A	Cardiac arrhythmia	Butane and propane
Focardi et al. 2018 [36]	31M	Butane gas canister	Found in his prison cell next to a nylon bas and a canister of butane gas	Accidental	Congestion, sub-conjunctivae, subepicardial and mesothelium petechial	N/A	Acute asphyxia	N/A
Fuke et al. 2002 [25]	14M	Butane gas canister	Found collapsed after inhaling butane gas. Ventricular fibrillation was detected in the EKG, resuscitation was performed but he was pronounced dead in the hospital	Accidental	Poli-visceral congestion, severe pulmonary edema	Severe pulmonary edema	Cardiac arrhythmia	Butane, isobutane, and propane
Fukunaga et al. 1996 [37]	41M	LPG	Died 12 h after repairing an underground pipe connection	Accidental	Severe pulmonary edema and congestion. Total necrosis of the cerebellum cortex	N/A	Asphyxia from anoxia	Butane, propane, methane, and ethane
	34M	LPG	Fainted while sealing an LPG pipe, cardiorespiratory resuscitation was performed but not successful	Accidental	Petechial hemorrhages of the conjunctivae, thymus, epicardium, and lungs. Poli-visceral congestion	N/A	LPG poisoning	Butane, propane, methane, and ethane
Galante et al. 2022 [38]	43M	Butane gas canister	Found dead on the bed with a plastic bag over his head, connected with butane gas canister	Suicide	Wrist cuts for precedent suicide attempt. Pulmonary edema and congestion	Acute emphysema, edema, and hemorrhagic foci in the lungs	Asphyxia	Butane, methadone, and diazepam

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Table 1 (*continued*)

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
	40F	Butane gas canister	Found dead on the bed with a plastic bag over her head, connected with butane gas canister	Suicide	Pulmonary edema and congestion	Acute emphysema, edema, and hemorrhagic foci in the lungs	Asphyxia	Butane, methadone, and diazepam
Gioia et al. 2015 [39]	40M	Butane gas canister	Found unconscious on the bathroom floor of his cell, resuscitation was performed without results	Accidental	Pulmonary edema	Intra-alveolar edema	Cardiac arrhythmia	Butane, propane, chlorpromazine, and citalopram
Handlos et al. 2021 [40]	18M	Butane gas cylinder	Found in his car with a plastic bag around his neck and a tube leading to a butane gas cylinder	Suicide	Red mark around the neck. Pulmonary hyperinflation and pleural and subepicardial petechial hemorrhages. Poli-visceral congestion	N/A	Asphyxia due to upper airway obstruction and butane gas intoxication	Butane and propane
Hiquet et al. 2017 [41]	52F	Butane gas bottle	Found dead in the garage after suicide pact with the husband, with a butane gas bottle found on the back seat of the car	Homicide	Bruising on the neck, petechial hemorrhages of the upper eyelids, congested face. Signs of asphyxiation and superficial bruises of the tongue and thyroid cartilage	N/A	Asphyxiation through criminal poisoning	Butane
Ilhan et al. 2015 [42]	16M	Lighter refill canister	Found unconscious in the streets. In the hospital was determined ventricular fibrillation and died 1 h later	Accidental	Cyanosis of lips and nails. Edema of the brain and cerebellum. Compressed blood foaming fluid in the lung. Hyperemia of the trachea mucosa and abdomen and stomach mucosa	N/A	Cardiac arrhythmia	Butane
	17M	Lighter refill canister	Found dead on the kitchen floor	Accidental	Cyanosis of lips, nails, and ears. Foaming fluid in the lung sections and bronchi	N/A	Butane gas poisoning	Butane
Jackowski et al. 2005 [43]	19M	Kisag-gas cartridge	Found in bed with exposed genitals; an empty balloon and Kisag-gas cartridges found next to the corpse	Accidental	Foam at the mouth, oral cavity, larynx, trachea, and major bronchi. Massive edema of the brain and herniation of the cerebellar tonsils into the foramen magnum. Poli-visceral congestion	N/A	Cardiac arrhythmia	Butane, propane, isobutane, THC and THC-COOH
Kimura-Kataoka et al. 2015 [44]	29F	Butane gas cartridge	Found dead, face down, under a table at home. More than 50 butane gas cartridges were found in the house	Accidental	Petechiae on the conjunctiva, lungs, anterior neck, upper chest, and axillary regions. 6 regular scars from cigarette burns. Viscous fluid with fine foam in the trachea and bronchi. Poli-visceral congestion	Severe congestion of the organs. Deposition of fat tissue and adipose infiltration of the heart. Pulmonary edema and sinusoidal dilatation of the liver	Asphyxia due to anoxia	Butane, paroxetine, and trazodone
Kinoshita et al. 2016 [45]	30M	Butane gas canister	Found dead at home with history of volatile gas abuse	Accidental	Pulmonary edema and poli-visceral congestion	N/A	Butane poisoning	Butane, 2-butanol, 2-butanone, and t-butanol
Klitte et al. 2002 [46]	17F	Insect spray can	Found dead in the bed with an empty can of insect spray next to the corpse	Suicide	Agonal aspiration of gastric contents into the upper airways	N/A	Inhalation of insect spray	Butane, isobutane, ethanol, and alcohol
May 1995 [47]	18M	Lighter refill canister	Found unconscious after vehicle crash. Resuscitation was performed, with no results	Accidental	No trauma	N/A	N/A	Butane, propane, and 11-nor-delta tetra hydro cannabinol-9-carboxylic acid
	19M	Lighter refill canister	Collapsed after using drugs and	Accidental	N/A	N/A	N/A	

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Table 1 (*continued*)

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
			sprinting a short distance. CPR was performed and he was intubated. He died after 30Min					
Musshoff et al. 2006 [48]	30M	Plastic bag with butane/ propane canister	Found with a plastic bag over his head and upper body and butane/ propane gas canister. History of suicidal attempt by hanging	Suicide	Decomposition of the arms and head	N/A	Unclear	Butane and propane
Novosel et al. 2011 [49]	25M	Lighter refill canister	Found dead in an abandoned restaurant	Accidental	No trauma. Poli-visceral congestion, pulmonary and brain edema	Diffuse intra-alveolar hemorrhagic edema of the lung. Interstitial fibrosis and periarterial areas of intramural artery branches of the heart	Asphyxia	Butane and diazepam
	14M	Lighter refill canister	Found unconscious in a park, resuscitation was attempted with no success	Accidental	Superficial abrasions. Poli-visceral congestion, pulmonary edema. Brain edema and herniation of the cerebellar tonsils into the foramen magnum	Diffuse intra-alveolar hemorrhagic edema of the lung. Interstitial fibrosis and periarterial areas of intramural artery branches of the heart. Coagulation necrosis and contraction band necrosis of the myocardium	Asphyxia	Butane
Petekkaya et al. 2016 [50]	16M	Lighter refill canister	Collapsed during gas inhalation, died in the hospital	Accidental	Pin traces on the inside of both elbows and left wrist. Petechiae under the scalp, edema and hyperemia of brain, cerebellum and brain stem. Pulmonary edema and congestion, with foamy liquid in the bronchi and bronchioles	Edema and fresh intra-alveolar hemorrhage in the lung, and extravasated red blood cells in the parenchymal fat tissues. Congestion of the other organs	Asphyxia due to butane-induced toxicity	Butane
Romolo et al. 2017 [51]	29M	Camping gas stove	Found unconscious in his cell next to a camping gas stove. CPR was attempted with no success	Accidental	Subepidermal petechial hemorrhages on the rear region of the chest. Poli-visceral congestion. Emphysematous bubbles of the left lung	Stretched and wavy myocells. Thickening of the tunica media of the arterioles. Focal areas of perivascular fibrosis. Subpleural blebs, peripheral emphysematous areas in the lungs, and pulmonary edema. Intensive congestion of the liver and kidneys	Butane-induced hypoxia	Butane, propane, diazepam, nordiazepam, oxazepam, and temazepam
Rossi et al. 2012 [52]	25M	Camping gas stove	Found unconscious by the toilet of his cell with a plastic bag around his head. CPR was performed with no results	Accidental	Poli-visceral congestion, fluid brownish blood, and pulmonary and cerebral edema	Cerebral and pulmonary edema. Congestion of the other organs	Asphyxia	Butane and propane
	50M	Butane/ propane gas cylinders	Found lying on the bed of his cell, with a cellophane bag tied around his neck. CPR was	Accidental	Poli-visceral congestion, fluid brownish blood, and pulmonary and cerebral edema	Cerebral and pulmonary edema. Congestion of the other organs	Asphyxia	Butane and propane

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Table 1 (*continued*)

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
			performed without success					
Sasao et al. 2015 [53]	18F	Camping gas stove	Found dead in her room. The previous night she consumed alcohol and inhaled gases. History of volatile substance abuse	Accidental	Pulmonary and cerebral edema	N/A	Butane poisoning	Butane, isobutane, ethanol, phenobarbital, diazepam, and clotiazepam
	28M	Butane cartridge	Found dead in his house. History of depression, suicidal thoughts, and volatile substance abuse	Accidental	Pulmonary edema and frothy liquid in the mucosa of the bronchi	N/A	Butane poisoning	Butane, isobutane, and ethanol
	34M	Butane cartridge	Found dead in his house. History of volatile substance abuse	Accidental	Initial putrefaction. Pulmonary edema	N/A	Butane poisoning	Butane and isobutane
Sato et al. 2017 [54]	18M	Lighter refill	Found unconscious at home. He was taken to the hospital and successfully resuscitated. Diagnosed with anoxic encephalopathy followed by cardiac arrest after 16 days	Accidental	Purulent sputum in the bronchus. Near circumferential subendocardial ischemia of the left ventricle	Infiltration of inflammatory cells into the alveoli, and bronchi in the lung. Hemorrhage, necrosis, and fibrosis in the heart	Hypoxic encephalopathy and cardiac arrest due to butane gas intoxication	Butane and isobutane
Shields et al. 2005 [55]	17M	Butane gas canister	Found unresponsive on the couch in his home. A can of butane and a pornographic magazine near the corpse	Accidental	Petechiae of the face, neck, and thymus. Pulmonary edema and poli-visceral congestion	N/A	Asphyxia via inhalation of butane	Butane, benzodiazepines, cannabinoids, and amphetamines
Shintani-Ishida et al. 2018 [56]	23M	Butane gas cartridge	Found dead in the living room with ten used gas cartridges and two plastic bags near the corpse	Accidental	Pulmonary edema and pleural effusions. Chicken fat clot in the right atrium	Edema and congestion in the lungs	Butane poisoning	Butane, isobutane, and carbamazepine
	17M	Lighter refill canister	Found dead in the living room. His mother started CPR until the arrival of the ambulance crew, with no success	Accidental	Hemorrhages of the left sternocleidomastoid muscle and right sternothyroid muscle. Pleural petechiae and poli-visceral congestion	Pulmonary edema	Butane poisoning	Butane, isobutane, and propane
Siegel et al. 1990 [57]	11M	Typewriter correction fluid	Found collapsed in the bathroom of a movie theater. CPR was performed with no success	Accidental	No evidence of organic disease or anatomic cause of death	N/A	Butane poisoning	Butane
Sironi et al. 2016 [58]	12M	Air freshener	Found unconscious with a plastic bag around his head with white foam dripping from the mouth	Accidental	Poli-visceral congestion. Lung petechiae and pulmonary edema	Cerebral and pulmonary edema	Anoxia due to butane poisoning	Butane, isobutane, and propane
	14M	Lighter refill canister	Found unconscious in a public garden, was resuscitated, and arrived at the hospital in a comatose state. Died 12 h later after sudden onset bradycardia	Accidental	Poli-visceral congestion. Lung petechiae and pulmonary edema	Cerebral and pulmonary edema	Anoxia due to butane poisoning	Butane, isobutane, propane, and tetrahydrocannabinolic acid
Sugie et al. 2004 [59]	24M	Volatile liquid cans	Rushed out of his room, ran down the staircase, and	Accidental	Poli-visceral congestion	N/A	Cardiac arrhythmia	Butane, isobutane, and propane

(*continued on next page*)

Table 1 (*continued*)

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
			collapsed. He died at the hospital					
	14M	Lighter oil in vinyl bags	Inhaled the gas, kicked one of his friends in the abdomen and collapsed. Died despite resuscitation	Accidental	Poli-visceral congestion	N/A	Cardiac arrhythmia	Butane, isobutane, and propane
Tanaka et al. 2010 [60]	23F	Butane gas canister	Collapsed after getting out of friend's car, she was in cardiopulmonary arrest at the time of arrival at the hospital. History of volatile substance abuse	Accidental	Contusion of the forehead. Poli-visceral congestion	Moderate fragmentation of the myocardium and large amount of lipofuscin deposits. Marked congestion, edema, and intra-alveolar hemorrhages in the lung	Cardiac arrhythmia	Butane
Tanaka et al. 2012 [61]	N/AM	Lighter refill and plastic bag	Collapsed on a vacant lot, transferred to the hospital in cardiac arrest. CPR was unsuccessful	Accidental	Pulmonary congestion and frothy fluid in the trachea	Congestion, edema, and intra-alveolar hemorrhages in the lung	Cardiac arrhythmia	Butane, isobutane, and propane
Uchida et al. 2015 [62]	11F	Aerosol antiperspirant	Found lying face down on a pillow, holding a can of aerosol deodorant. History of abuse in several months prior to death	Accidental	Poli-visceral congestion, severe hemorrhages of the trachea, liver cell destruction and lipid deposition	Severe lipid deposits and liver cells degeneration	Cardiac arrhythmia	Butane, isobutane, propane, and isopentane
Ventura et al. 2017 [63]	22M	Butane gas	Fatal butane-gas overdose in male inmates. History of attempted suicide	Suicide	Pulmonary congestion and edema	Capillary congestion, edema, and alveolar hemorrhage in the lung. Diffuse intermyofibrillar edema of the myocardium	Acute butane gas poisoning	Butane
	25M	Butane gas	Fatal butane-gas overdose in male inmates. History of attempted suicide	Suicide	Cyanosis and conjunctival petechiae. Pulmonary edema	Capillary congestion, edema, and alveolar hemorrhage in the lung. Diffuse intermyofibrillar edema of the myocardium	Acute butane gas poisoning	Butane
	23M	Butane gas	Fatal butane-gas overdose in male inmates. History of attempted suicide	Suicide	Cyanosis, and hyperemic sclera and conjunctivae. Pulmonary edema and congestion. Petechial hemorrhages of pleura and pericardium	Capillary congestion, edema, and alveolar hemorrhage in the lung. Diffuse intermyofibrillar edema of the myocardium	Acute butane gas poisoning	Butane
	33M	Butane gas	Fatal butane-gas overdose in male inmates. History of attempted suicide	Suicide	Petechiae of the pleural surfaces. Pulmonary congestion and edema	Capillary congestion, edema, and alveolar hemorrhage in the lung. Diffuse intermyofibrillar edema of the myocardium	Acute butane gas poisoning	Butane
Wilkerson et al. 1998 [64]	20F	Aerosol air freshener	Found dead in a remote island barracks after inhaling air freshener through a towel	Accidental	N/A	N/A	N/A	Butane
	27M	Lighter refill canister	Found dead in his barracks. History of abuse of volatile substances	Accidental	N/A	N/A	N/A	Butane

(*continued on next page*)

Table 1 (*continued*)

References	Age/ Gender	Source of abuse	Brief case description	Mode of Death	External Examination and Autopsy Findings	Histopathological findings	Cause of Death	Post-Mortem Toxicological analysis
Winek et al. 1997 [65]	22M	Butane fluid canister	Found unresponsive with a can of butane fluid near the corpse	Accidental	Foam in the bronchi. Congestion and edema of the conjunctivae, tracheal mucosa, and lungs	N/A	Asphyxia due to butane inhalation	N/A

Table 2
Main characteristics of the cases included in the review.

Characteristics		Suicide	Homicide	Accidental	Work-related	Total
Sex	Male	9	0	37	2	48
	Female	2	1	7	0	10
Age	0–18	1	0	25	0	26
	19–30	4	0	17	0	21
	31–50	2	0	3	2	7
	>50	1	1	0	0	2
	Unspecified	0	0	1	0	1
Source of Abuse	Aerosol deodorant	0	0	7	0	7
	Lighter refill	0	0	19	0	19
	Butane canister	4	1	16	0	21
	LPG	1	0	0	2	3

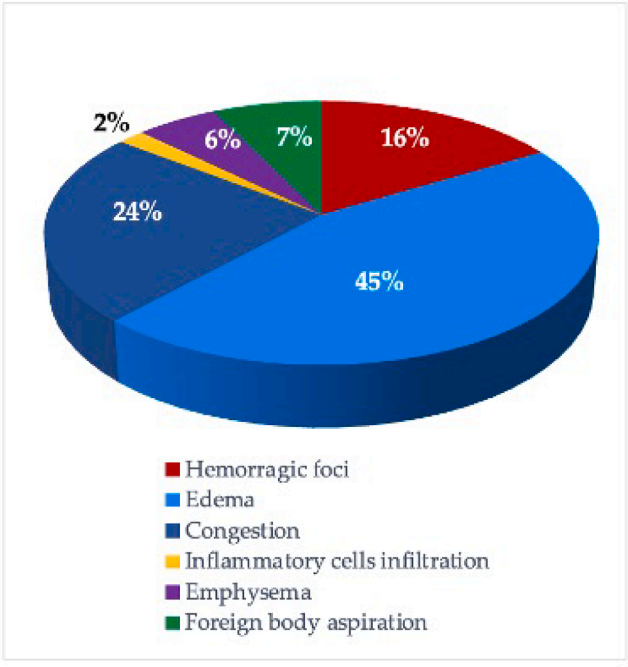

Fig. 2. The graphic shows the percentages of the most common histopathological findings in pulmonary tissue samples.

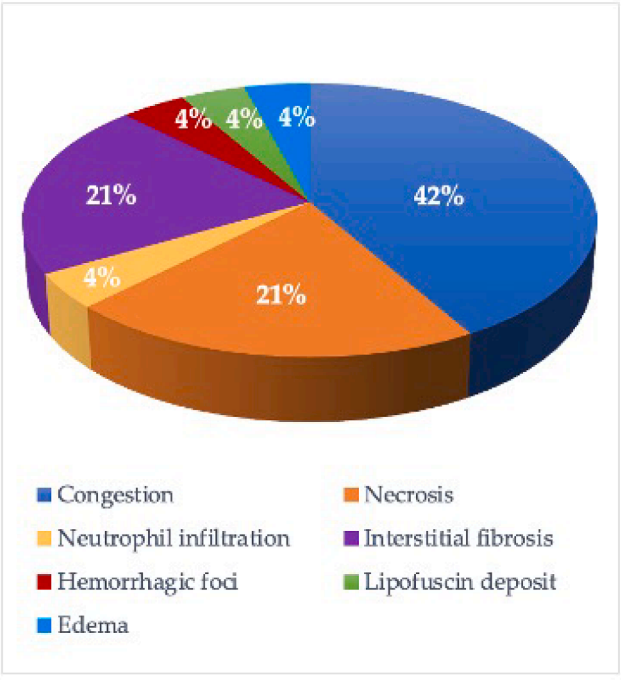

Fig. 3. The graphic shows the percentages of the most common histopathological findings in cardiac tissue samples.

Table 3 reports the different types of substances found in toxicological analysis besides butane. As shown, butane is often discovered with propane (40 %), and isobutane (34 %). Nevertheless, subjects were also under the influence of other substances of abuse, such as cannabinoids (12 %), alcohol (7 %), benzodiazepines, and antidepressant (15.5 %).

4. Discussion

Butane is an odorless, colorless gas commonly used as a solvent and domestic fuel. In fact, it is used as liquefied gas in cigarette lighters, camping stoves, gasoline and fuel gas, gas lamps, spray paints, and some air fresheners and deodorant. It is also becoming more and more widely employed as a drug of abuse, especially among adolescents, for whom the prevalence of volatile substance abusers ranges from 2 to 20 % of the general population. This phenomenon is explained by the easy availability of volatile substances in general and of butane in particular, given that their sale and detention are not regulated and also because of their economic viability.

Butane is absorbed rapidly through multiple tissues and has an

Table 3
Different types of substances found in toxicological investigations.

Toxicological findings		Suicide	Accidental	Total
Inhalants	Butane	11	45	56
	Isobutane	1	19	20
	Propane	1	22	23
Substances of abuse	Cannabinoids	0	7	7
	Amphetamine	1	1	2
	Methadone	1	0	1
	Alcohol	2	2	4
Psychoactive drugs	Benzodiazepines	2	3	5
	Antidepressant	0	2	2
	Antipsychotic	0	3	3
	Anesthetics	0	1	1

elective tropism for the brain, spleen, liver, and kidney due to its lipophilic properties. Aliphatic hydrocarbons, such as butane, are primarily absorbed through the respiratory tract, and partly expelled through exhale [4]. A minor part is metabolized in secondary and tertiary alcohol in the liver and then oxidized in ketone. In particular, N-butane can be found in organs and blood in its original form, or as 2-butanol, 2-butanone, and methyl-ethyl-ketone [66]. Minimal exposure to butane determines the rapid onset of euphoria and disinhibition as in asphyxia induced by hanging [67,68]. Those sought-after psychedelic effects, however, are often accompanied by hallucinations, ataxia, and behavioral disturbances like those related to ethanol, delusions, and confusion [4]. Shortly after the onset of the acute symptoms, the subject experiences anoxia, tachycardia, hallucinations of all senses, ataxia, dissociation, hypoxia, tinnitus, nystagmus, and dizziness. These acute effects start 5 min after exposure and may last between 15 and 45 min. Its effects depend on the duration, quantity, and concentration of butane inhalation. Volatile substance abuse determines dose-dependent effects similar to those of hypnosedatives. Seizure, coma, and sudden death could be the life-threatening result of higher doses [63].

Moreover, chronic exposure to butane is associated with neurological, psychiatric, hematological, renal, pulmonary, and cardiovascular effects [69,70]. The clinical manifestations to be expected in abusers who have survived an episode of acute intoxication are cardiac (dysrhythmias, direct myocardial toxicity, myopericarditis, etc.) and neurological (ataxia, optic atrophy, sensorineural hearing loss, dementia, peripheral neuropathy, tremor, loss of motor control, etc.) [56,57].

Among the 58 cases of death due to butane inhalation identified in our research, and comprehensive of almost four decades of literature, there were only 11 suicides. Still, most cases were accidental deaths of chronic users or abusers of butane.

The exact mechanism of death that can occur after inhaling butane is still not completely understood. Cardiac arrhythmia is considered the most probable cause of death by inhalation of butane and overall volatile substances, followed by anoxia, respiratory depression, and vagal inhibition [71][44,70,72,73]. Butane also exerts effects on the central nervous system: in the beginning, inhalation of butane can cause excitatory effects on the central nervous system, followed by depressant effects. N-butane and isobutane have particular repercussions on the central nervous system comparable to that of an anesthetic or narcotic [63]. A low concentration of butane gas seems to cause suppression of the central nervous system while at higher concentrations it may act as a narcotic [37].

Epidemiologically, it is reported that direct toxic effects include only 51 % of the death related to butane, followed by plastic bag asphyxia (21 %), aspiration of gastric contents (18 %), injuries following traffic accidents, hanging, and drowning [28].

Novosel et al. hypothesized that inhaling butane could sensitize the myocardial cells to adrenaline, leading to a fatal arrhythmia due to the sudden increase of this hormone in particular situations. For example, events such as sudden fear, hard muscular exercise, running, or sexual activities immediately after the inhalation of butane could result in fatal arrhythmia [49]. It is suggested that auditory and visual hallucinations experienced by inhalant abusers may also provoke disturbing fear and abruptly increase the level of adrenaline [74]. Moreover, it has been assumed that inhalation of a mixture of butane and propane could lead to a massive catecholamine release, thus causing ventricular fibrillation [39]. Congestion of the internal organs and within the mucosae may indicate a primary cardiac reason [43]. Anoxia is the result of the total depletion of oxygen by other gases, and it is usually associated with bagging or inhaling volatile substances from a plastic bag. In this instance, the individual, as a direct effect of the inhalants, tends to lose consciousness and becomes incrementally more challenging to remove the bag, resulting in anoxia and thus causing death [44]. Jackowski et al. reported a case of hypoxia due to butane poisoning; they detected edema of the brain and hypothesized it may be caused by hypoxia on the grounds of respiratory depression or as a direct toxic effect of butane [43]. Klitte reported a case of a young female suicide by inhaling insect spray; an autopsy examination found agonal aspiration of gastric contents into the upper airways [46].

In all case reports, toxicological analysis and circumstantial data had crucial importance in defining the cause of death. Uchida et al. described a case of accidental intoxication by aerosol deodorant. The diagnosis was made by determining butane in blood samples, using quantitative gas chromatography/mass spectrometry [62]. Fuke et al. reported a case of a young male abuser of butane that died after sudden muscular exercise; they performed a quantitative gas chromatography analysis on blood, brain, and lung tissues. Butane levels were in the range of fatal cases; nevertheless, since the victim ran, these values were considered not to determine a sedative effect on the central nervous system [25].

To facilitate the post-mortem investigations in the case of suspected death due to butane inhalation overdose we provide the following recommendations. Firstly, a thorough crime scene investigation needs to be performed. The forensic pathologist presents at the scene of the crime must carefully examine the location and the corpse. In particular, he should look for the presence of lighter refill canisters, butane gas canisters or camping stoves, air fresheners, or aerosol deodorants as well as plastic bags, balloons, or cloths the subject might have used to inhale volatile substances. Moreover, the first examination of the body should evaluate the presence of conjunctival petechiae, lips, or nails cyanosis, and signs of trauma. This research could be ineffective as most butane gas victims do not show any external signs. Furthermore, the investigator should collect information on the victim's habit, history of drug abuse, and history of depression or suicide attempts. If some of these factors are present, death due to butane abuse can be reasonably suspected.

During the external examination forensic pathologist should look for the presence of petechiae of the conjunctiva, cyanosis, or abrasions. The latter seems to be linked to the sudden loss of consciousness, typical of inhalant abuse. Regrettably, the absence of evident pathognomonic data, revealed by this review of the literature, limits the suggestions for specific research to be conducted during autopsy. Still, sampling of the different matrices (blood, vitreous humor, urine, lung, brain, fatty tissue, and other organs) appears to be paramount to carrying out toxicological investigations.

Butane determination is challenging due to its elimination process between the intoxication period and the moment of death. It is eliminated from organs and tissues and evaporates naturally after death and before sampling or analysis. Currently, there isn't a consistent method for butane determination; therefore, a standardized protocol should be implemented.

The following recommendations should be used when collecting samples when there is a suspect of butane poisoning:

- The collection of samples should be performed using gastight vials.
- Multiple matrix samples should be collected.

- Samples should be analyzed as soon as possible after collection.
- Samples should be stored at a temperature between −20 °C and −30 °C, if analyses cannot be performed promptly [75,41].

It is recommended to collect gas samples from the bronchi, reducing the possibility of contamination by exposing the main bronchi in situ without manipulation of the respiratory tract [75]. One of the most used matrices for the research of butane is blood. However, butane concentrations in blood and their interpretation are questionable considering the influence of metabolic enzymes, gender differences, and possible exposure to alcohol or other drugs [16]. Concentrations in the blood can also be significantly reduced because of resuscitation attempts [33]. Moreover, butane clearance from blood appears to be very rapid, so much so that its concentration in the blood tends to decrease very rapidly. Sasao et al. reported on three cases of butane poisoning and observed in all three that liver samples had high concentrations of butane. Therefore, they suggested liver samples be viable substitutes whenever blood isn't available [53]. Because of the lipophilic nature of butane, it is more likely retainable and stored in lipid-rich organs such as the brain, spleen, liver, and kidney. Hence, sampling of cerebral material, and those organs rich in lipids, is especially important to detect volatile substances. Bugra et al stated that collecting cerebral samples to perform the toxicological analysis is paramount because of butane's lipophilic nature, but also because of the enclosed environment of the central nervous system, which acts by slowing down the release of these kinds of substances after death [34]. As a consequence, some studies suggest using a butane's brain/blood concentration ratio as it might be useful to presume the circumstances and timing of death. This ratio, according to El Balkhi et al, ranges from 0.75 to 4.45. This is a practice usually employed in those cases of intoxication by toluene, to estimate blood toluene concentrations at the time of death [33]. However, the scientific community is in disagreements about the usefulness of the brain/blood ratio in the evaluation of deaths from butane: in actuality, Shintani-Ishida et al., in their work, found that there is no correlation between the brain/blood ratio of butane and survival time. To support that assumption, they reported an interesting experiment conducted on baboons who received ^{11}C-labeled butane via inhalation. These tests demonstrated that the passage of butane through the blood–brain barrier appears to be inefficient, thus resulting in an uneven distribution of the substance in the brain [54].

According to Sato et al., adipose tissue should be the first choice for analysis whenever the subject survived for a long period after exposure to butane gas [54]. A higher ratio of fatty tissues to blood butane concentration could be compatible with a long survival time [58]. In particular, Shintani-Ishida et al. individuated a fat/blood ratio of 20 in the case of a man who survived hours after butane inhalation. In contrast, it was 14 or less in case of acute death [56]. Such results allowed authors to identify a value of 20 for those cases that can be considered borderline between an acute and a non-acute decease. Homogeneous concentrations of the gas in different matrices are believed to be an indication of rapid diffusion, but also the absence of accumulation or elimination of butane. Moreover, the absence of butane in the vitreous humor and a minimum amount of it in the urine could indicate that death occurred relatively quickly after inhalation [52]. Concerning the research of butane metabolites, this process often seems to be unreliable. As stated by Statheropoulos et al., lastly, some volatile organic compounds, such as 2-butanone, can be found by cause of the early stages of human decomposition [76].

The study of histological specimens using traditional staining and immunohistochemical techniques is necessary to suspect the pathological mechanism supported by VSA. Hypoxic-ischemic brain damage due to gas inhalation or baggig has been associated with a specific 'butane inhalation encephalitis' [8,10,44,77,78]. Purkinje cells in the cerebellum and perineuronal satellitosis lesions have been described. In addition, the study of cardiac specimens may be useful in revealing early ischaemic damage in cardiac death due to the increased action of catecholamines [34]. Conversely, the study of airways and lung parenchyma can reveal pulmonary oedema and congestion, rupture of septa with alveolar hemorrhages and aspirated amorphous material, mucus, neutrophils, eosinophils, and mast cells [21]. These findings are also useful in survival cases, where they can be helpful in dating pneumonias from butane or other volatile solvents that lead to the subject's death later. Several cases have been described as sudden death syndrome. In these cases, where the pathophysiological mechanisms occur in a very short time, the assessment of the causal sequence is complex [21]. Especially when the mechanism is mixed, hypoxic and from butane intoxication, as in the case of buggig. Many of the different microscopic findings are non-specific [35], however, it can be used in conjunction with other relevant information to distinguish chronic abuse from recent intake. In chronic abusers, both Hypoxic-ischemic brain damage and repeated infarctions can lead to death.

5. Conclusions

This work reviewed 58 cases of sudden death due to butane inhalation, whether it was used as a substance of abuse, with a suicidal purpose, or in a work environment. It showed that, when butane intoxication is suspected, the diagnosis of death may be difficult to be carried out. The investigation must include a thorough crime scene analysis, autopsy, and specific toxicological analysis has to be performed on samples stored in sealed vials. While investigating the scene of a crime the pathologist must pay attention to all the elements that can support the hypothesis of death due to butane inhalation. These include the presence of butane gas canisters, lighter refill canisters, aerosol deodorant or air fresheners, and plastic bags, cloths, or tubes connected to the canisters. Circumstantial data may offer crucial information too. The autopsy may provide unspecific macroscopic and microscopic findings, such as congestion of visceral organs, pulmonary edema, and signs of myocardium necrosis. Toxicological investigations can have a critical role, even though butane levels can be affected by perimortem, post-mortem, and decomposition phenomena. Another limitation that makes it difficult to interpret toxicological results is the lack of a threshold that can be associated with severe toxicity. It is established that butane is eliminated from organs and tissues after death and evaporates before sampling or analysis. Therefore, this kind of analysis should be conducted rigorously, and samples should be collected limiting the contamination as much as possible, especially when collecting gas samples from the bronchi. The specimens should also be stored properly and analyzed as soon as possible to reduce the evaporation and dispersion of the gas. The novelty of our investigation resides in tackling the intricate task of determining the toxicological thresholds and lethal concentrations of butane contributing to fatal outcomes. Similar to other substances, butane intoxication and fatalities are identified through the correlation between gas inhalation and clinical/postmortem evidence. Furthermore, this work highlights the relevance of early autopsy investigation and collaboration with the toxicology laboratory to reduce significant post-mortal alteration in the samples to be analyzed.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S.H. Dinwiddie, Abuse of inhalants: a review, Addiction 89 (1994) 925–939.
[2] Substance Abuse and Mental Health Services Administration. (2021). Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/, (n.d.).
[3] S.E. Bowen, M.O. Howard, E.L. Garland, Inhalant Use Disorders in the United States, in: Neuropathology of Drug Addictions and Substance Misuse, Elsevier, 2016: pp. 931–942. doi: 10.1016/B978-0-12-800212-4.00085-6.
[4] M.-P.-L.-A. Bouche, W.E. Lambert, J.F.P. Van Bocxlaer, M.H. Piette, A.P. De Leenheer, Quantitative determination of n-propane, iso-butane, and n-butane by headspace GC-MS in intoxications by inhalation of lighter Fluid*, J. Anal. Toxicol. 26 (2002) 35–42, https://doi.org/10.1093/jat/26.1.35.
[5] L. D. Johnston, P. M. O'Malley, J. G. Bachman, and J. E. Schulenberg, Monitoring the future national survey results on drug use, 1975–2009, vol. 1, secondary school students (NIH Publication No. 10-7584). Bethesda, MD: National Institute on Drug Abuse, 2010., (n.d.).
[6] D.K. Molina, A characterization of sources of isopropanol detected on postmortem toxicologic analysis, J. Forensic Sci. 55 (2010) 998–1002, https://doi.org/10.1111/j.1556-4029.2010.01386.x.
[7] S.W. Ragsdale, Deep-sea secrets of butane metabolism, Nature 539 (2016) 367–368, https://doi.org/10.1038/539367a.
[8] R.J. Flanagan, M. Ruprah, T.J. Meredith, J.D. Ramsey, An introduction to the clinical toxicology of volatile substances, Drug Safety 5 (1990) 359–383, https://doi.org/10.2165/00002018-199005050-00005.
[9] C.E. Anderson, G.A. Loomis, Recognition and prevention of inhalant abuse, Am. Fam. Physician 68 (2003) 869–874.
[10] R.J. Flanagan, R.J. Ives, Volatile substance abuse, Bull. Narc. 46 (1994) 49–78.
[11] R.T. Shepherd, Mechanism of sudden death associated with volatile substance abuse, Hum. Toxicol. 8 (1989) 287–291, https://doi.org/10.1177/096032718900800406.
[12] R. Wick, J.D. Gilbert, P. Felgate, R.W. Byard, Inhalant deaths in South Australia: a 20-year retrospective autopsy study, Am. J. Forensic Med. Pathol. 28 (2007) 319–322, https://doi.org/10.1097/PAF.0b013e31815b48b0.
[13] R. Meadows, A. Verghese, Medical complications of glue sniffing, South. Med. J. 89 (1996) 455–462, https://doi.org/10.1097/00007611-199605000-00001.
[14] K.M. Kuczkowski, The effects of drug abuse on pregnancy, Curr. Opin. Obstet. Gynecol. 19 (2007) 578–585, https://doi.org/10.1097/GCO.0b013e3282f1bf17.
[15] G.L. Arnold, R.S. Kirby, S. Langendoerfer, L. Wilkins-Haug, Toluene embryopathy: clinical delineation and developmental follow-up, Pediatrics 93 (1994) 216–220.
[16] C. Durão, F. Pedrosa, R.J. Dinis-Oliveira, Suicide by inhalation of butane gas through a homemade adaptation of a continuous positive airway pressure (CPAP) face mask, Forensic Sci. Med. Pathol. 16 (2020) 732–734, https://doi.org/10.1007/s12024-020-00271-y.
[17] The National Institute for Occupational Safety and Health, NIOSH Pocket Guide to Chemical Hazards. https://www.cdc.gov/niosh/npg/npgd0068.html, (n.d.).
[18] P. Cugini, When science becomes technology: epistemological and ethical consequences of the adduction, Clin. Ter. 166 (2015) 9–11, https://doi.org/10.7417/CT.2015.1799.
[19] S.J. Kile, C.C. Camilleri, R.E. Latchaw, B.R. Tharp, Bithalamic lesions of butane encephalopathy, Pediatr. Neurol. 35 (2006) 439–441.
[20] D. Cerretani, M. Neri, S. Cantatore, C. Ciallella, I. Riezzo, E. Turillazzi, V. Fineschi, Looking for organ damages due to anabolic-androgenic steroids (AAS): is oxidative stress the culprit? Mini-Rev. Org. Chem. 10 (2013) 393–399.
[21] D. Harris, Z. Mirza, Butane encephalopathy, Emerg. Med. J. 22 (2005) 676–677.
[22] S. Wason, W.B. Gibler, M. Hassan, Ventricular tachycardia associated with non-freon aerosol propellants, JAMA 256 (1986) 78–80.
[23] D. Williams, S. Cole, Ventricular fibrillation following butane gas inhalation, Resuscitation 37 (1998) 43–45.
[24] H. Tsoukali, A. Dimitriou, N. Vassiliades, Death during deliberate propane inhalation, Forensic Sci. Int. 93 (1998) 1–4.
[25] C. Fuke, T. Miyazaki, T. Arao, Y. Morinaga, H. Takaesu, T. Takeda, T. Iwamasa, A fatal case considered to be due to cardiac arrhythmia associated with butane inhalation, Leg. Med. 4 (2002) 134–138, https://doi.org/10.1016/S1344-6223(02)00004-4.
[26] H. Anderson, B. Dick, R. Macnair, J. Palmer, J. Ramsey, An investigation of 140 deaths associated with volatile substance abuse in the United Kingdom (1971–1981), Hum. Toxicol. 1 (1982) 207–221.
[27] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P.A. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ 339 (2009) b2700–b, https://doi.org/10.1136/bmj.b2700.
[28] M. Ago, K. Ago, M. Ogata, A fatal case of n-butane poisoning after inhaling anti-perspiration aerosol deodorant, Leg. Med. 4 (2002) 113–118, https://doi.org/10.1016/S1344-6223(01)00063-3.
[29] L.M. Al-Alousi, Pathology of volatile substance abuse: a case report and a literature review, Med. Sci. Law 29 (1989) 189–208, https://doi.org/10.1177/002580248902900304.
[30] K.N. Almulhim, Fatal butane toxicity and delayed onset of refractory ventricular fibrillation, SMJ 38 (2017) 1250–1254, https://doi.org/10.15537/smj.2017.12.20811.
[31] V. Alunni, Y. Gaillard, F. Castier, M.-D. Piercecchi-Marti, G. Quatrehomme, Death from butane inhalation abuse in teenagers: two new case studies and review of the literature, J. Forensic Sci. 63 (2018) 330–335, https://doi.org/10.1111/1556-4029.13520.
[32] I. Aquila, C. Ricci, M.A. Sacco, S. Gratteri, L. De Aloe, C.C. De Pasquale, P. Ricci, The role of ethanethiol in deaths from acute poisoning by gas mixtures: a suicide case involving a decomposed corpse and a review of the literature, Med. Leg. J. 88 (2020) 199–204, https://doi.org/10.1177/0025817219891948.
[33] T. Bork, O. Celbis, S. Petekkaya, B.S. Oner, E. Samdanci, Sudden death in relation to inhaling lighter fluid in adolescents, Romanian J. Leg. Med. 25 (2017) 379–383.
[34] A. Bugra, T. Das, Postmortem diagnosis of myocardial infarction due to butane gas intoxication in a child: a case report, Am. J. Forensic Med. Pathol. 40 (2019) 81–83, https://doi.org/10.1097/PAF.0000000000000435.
[35] S. El Balkhi, C. Coutaz-Fluck, F. Moreau, F. Paraf, J.-M. Gaulier, Is it worth carrying out determination of n-butane in postmortem samples? A case report and a comprehensive review of the literature, Int. J. Legal Med. 130 (2016) 1223–1229, https://doi.org/10.1007/s00414-015-1260-9.
[36] M. Focardi, B. Gualco, G. Norelli, Accidental death in autoerotic maneuvers, Am. J. Forensic Med. Pathol. 29 (2008) 64–68, https://doi.org/10.1097/PAF.0b013e3181651b79.
[37] T. Fukunaga, H. Yamamoto, A. Tanegashima, Y. Yamamoto, K. Nishi, Liquefied petroleum gas (LPG) poisoning: report of two cases and review of the literature, Forensic Sci. Int. 82 (1996) 193–200, https://doi.org/10.1016/S0379-0738(96)01995-0.
[38] N. Galante, G. Gentile, S. Tambuzzi, R. Zoja, Suicide pacts in the Milan district (Italy): a retrospective autopsy-based study with literature review, J. Forensic Leg. Med. 86 (2022) 102319, https://doi.org/10.1016/j.jflm.2022.102319.
[39] S. Gioia, M. Lancia, M. Bacci, F. Suadoni, A fatal case of acute butane-propane poisoning in a Prisoner under psychiatric treatment: do these 2 factors have an arrhythmogenic interaction, thus increasing the cardiovascular risk profile? Am. J. Forensic Med. Pathol. 36 (2015) 251–253, https://doi.org/10.1097/PAF.0000000000000194.
[40] P. Handlos, R. Obadálková, R. Papoušek, Regarding "suicide by inhalation of butane gas through a homemade adaptation of a continuous positive airway pressure (CPAP) facemask", Forensic Sci. Med. Pathol. 17 (2021) 177–178, https://doi.org/10.1007/s12024-020-00287-4.
[41] J. Hiquet, E. Christin, F. Tovagliaro, J.-M. Gaulier, V. Dumestre-Toulet, S. Gromb-Monnoyeur, A rare case of poisoning with a volatile substance: quantitative determination of n-butane in postmortem tissue, J. Forensic Sci. 62 (2017) 549–552, https://doi.org/10.1111/1556-4029.13302.
[42] R. Ilhan, A. Artar, C. Butun, F.Y. Beyaztas, Butane gas inhalation resulting in death: two case reports, Med. Sci. 4 (2015) 2938–2946.
[43] C. Jackowski, W. Römhild, B. Aebi, W. Bernhard, D. Krause, R. Dirnhofer, Autoerotic accident by inhalation of propane-butane gas mixture, Am. J. Forensic Med. Pathol. 26 (2005) 355–359, https://doi.org/10.1097/01.paf.0000188076.54147.07.
[44] K. Kimura-Kataoka, J. Fujihara, T. Yasuda, H. Takeshita, Fatal butane inhalation from gas cartridges: a case report and literature review, Romanian J. Leg. Med. 23 (2015) 115–120.
[45] H. Kinoshita, N. Tanaka, A. Takakura, M. Kumihashi, J. Mostofa, A. Ito, S. Kimura, K. Tsutsui, Y. Nagasaki, S. Masubara, Detection of butane metabolites as an indicator of butane abuse, Romanian J. Leg. Med. 24 (2016) 216–218.
[46] Å. Klitte, J.D. Gilbert, R. Lokan, R.W. Byard, Adolescent suicide due to inhalation of insect spray, J. Clin. Forensic Med. 9 (2002) 22–24, https://doi.org/10.1054/jcfm.2001.0483.
[47] C.R. May, Sudden death following butane inhalation, Emerg. Med. 7 (1995) 93–95.
[48] F. Musshoff, S.A. Padosch, L.A. Kroener, B. Madea, Accidental autoerotic death by volatile substance abuse or nonsexually motivated accidents? Am. J. Forensic Med. Pathol. 27 (2006) 188–192, https://doi.org/10.1097/01.paf.0000188167.70732.9d.
[49] I. Novosel, Z. Kovačić, S. Gusić, L. Batelja, M. Nestić, S. Seiwerth, J. Škavić, Immunohistochemical detection of early myocardial damage in two sudden deaths due to intentional butane inhalation. Two case reports with review of literature, J. Forensic Leg. Med. 18 (2011) 125–131, https://doi.org/10.1016/j.jflm.2010.12.003.
[50] S. Petekkaya, N. Ayaz, M. Doğan, M. Oruç, B.S. Öner, C. Göktürk, A. Çelebi, A.E. Budak, Ö. Soylu, O. Celbiş, A case of sudden death due to lighter refill gas ınhalation, (2016).
[51] F.S. Romolo, N.M. di Luca, C. Ciallella, E. Bottoni, P.A. Fiore, S. Cappelletti, N. Giuliani, M. Augsburger, V. Varlet, Volatile lipophilic substances management in case of fatal sniffing, J. Forensic Leg. Med. 52 (2017) 35–39, https://doi.org/10.1016/j.jflm.2017.08.005.
[52] R. Rossi, F. Suadoni, L. Pieroni, F. De-Giorgio, M. Lancia, Two cases of acute propane/butane Poisoning in Prison: acute propane/butane poisoning, J. Forensic Sci. 57 (2012) 832–834, https://doi.org/10.1111/j.1556-4029.2011.02003.x.
[53] A. Sasao, K. Yonemitsu, Y. Ohtsu, S. Mishima, Y. Nishitani, Quantitative determination of n-butane metabolites in three cases of butane sniffing death,

Forensic Sci. Int. 254 (2015) 180–184, https://doi.org/10.1016/j.forsciint.2015.07.032.
[54] T. Sato, H. Nishioka, K. Tsuboi, M. Katagi, A. Miki, T. Saito, S. Abe, M. Nomura, M. Kitagawa, H. Tsuchihashi, K. Suzuki, Detection of butane gas inhalation at 16 days after hypoxic encephalopathy: a case report, Leg. Med. 29 (2017) 34–37, https://doi.org/10.1016/j.legalmed.2017.09.005.
[55] L.B.E. Shields, D.M. Hunsaker, J.C. Hunsaker, C.V. Wetli, K.D. Hutchins, R. M. Holmes, Atypical autoerotic death: Part II, Am. J. Forensic Med. Pathol. 26 (2005) 53–62, https://doi.org/10.1097/01.paf.0000153995.07817.9f.
[56] K. Shintani-Ishida, H. Tsuboi, H. Ichioka, H. Ikegaya, Comparison of postmortem butane distribution between two fatal butane poisoning cases, Leg. Med. 35 (2018) 69–72, https://doi.org/10.1016/j.legalmed.2018.09.008.
[57] E. Siegel, S. Wason, Sudden death caused by inhalation of butane and propane, N. Engl. J. Med. 323 (1990) 1638.
[58] L. Sironi, A. Amadasi, R. Zoja, Recreational inhalation of butane and propane in adolescents: two forensic cases of accidental death, Forensic Sci. Int. 266 (2016) e52–e58, https://doi.org/10.1016/j.forsciint.2016.05.028.
[59] H. Sugie, C. Sasaki, C. Hashimoto, H. Takeshita, T. Nagai, S. Nakamura, M. Furukawa, T. Nishikawa, K. Kurihara, Three cases of sudden death due to butane or propane gas inhalation: analysis of tissues for gas components, Forensic Sci. Int. 143 (2004) 211–214, https://doi.org/10.1016/j.forsciint.2004.02.038.
[60] N. Tanaka, H. Kinoshita, R. Haba, M. Jamal, E. Ohkubo, K. Ameno, An autopsy case of butane gas abuse, Soud Lek 55 (2010) 44–45.
[61] N. Tanaka, H. Kinoshita, M. Jamal, M. Kumihashi, K. Tsutsui, K. Ameno, An autopsy case of fuel gas abuse, Rom. J. Leg. Med. 20 (2012) 195–196.
[62] K. Uchida, K. Unuma, K. Uemura, A fatality in a child with severe fatty liver due to n-butane and isopentane poisoning resulting from long-term inhalation of an antiperspirant aerosol, Forensic Sci. Med. Pathol. 11 (2015) 631–632.
[63] F. Ventura, R. Barranco, M.C. Landolfa, M. Gallo, A.G. Castiglione, G.F. Orcioni, F. De Stefano, Fatal poisoning by butane sniffing: a forensic analysis and immunohistochemical detection of myocardial hypoxic damage, J. Forensic Leg. Med. 51 (2017) 57–62.
[64] J.A. Wilkerson IV, M.P. Burton, Inhalation of volatile substances: an emerging threat to readiness? Mil. Med. 163 (1998) 343–345.
[65] C.L. Winek, W.W. Wahba, R.M. Huston, Accidental death due to inhalation of butane, J. Anal. Toxicol. 21 (1997) 323.
[66] S. Tsukamoto, S. Chiba, T. Muto, T. Ishikawa, M. Shimamura, Study on the metabolism of volatile hydrocarbons in mice. Propane, n-butane, and iso-butane, J. Toxicol. Sci. 10 (1985) 323–332, https://doi.org/10.2131/jts.10.323.
[67] A. Maiese, A.C. Manetti, P. Santoro, F. Del Duca, A. De Matteis, E. Turillazzi, P. Frati, V. Fineschi, FOXO3 depletion as a marker of compression-induced apoptosis in the ligature mark: an immunohistochemical study, IJMS 24 (2023) 1396, https://doi.org/10.3390/ijms24021396.
[68] A. Maiese, F. Spina, G. Visi, F. Del Duca, A. De Matteis, R. La Russa, M. Di Paolo, P. Frati, V. Fineschi, The expression of FOXO3a as a forensic diagnostic tool in cases of traumatic brain injury: an immunohistochemical study, Int. J. Mol. Sci. 24 (2023), https://doi.org/10.3390/ijms24032584.
[69] U. Horoz, A Rare type of burn injury due to butane gas inhalation abuse, Ulus Travma Acil Cerrahi Derg (2016), https://doi.org/10.5505/tjtes.2016.37999.
[70] M. dell'Aquila, A. Maiese, A. De Matteis, R.V. Viola, M. Arcangeli, R. La Russa, V. Fineschi, Traumatic brain injury: estimate of the age of the injury based on neuroinflammation, endothelial activation markers and adhesion molecules, Histol. Histopathol. 36 (2021) 795–806, https://doi.org/10.14670/HH-18-319.
[71] M. Vahabzadeh, B. Mégarbane, A two-decade review of butane toxicity as a substance of abuse, Basic Clin. Pharma Tox. 131 (2022) 155–164, https://doi.org/10.1111/bcpt.13760.
[72] A. Maiese, F. Iannaccone, A. Scatena, Z. Del Fante, A. Oliva, P. Frati, V. Fineschi, Pediatric abusive head trauma: a systematic review, Diagnostics (Basel) 11 (2021), https://doi.org/10.3390/diagnostics11040734.
[73] A. Maiese, P. Frati, F. Del Duca, P. Santoro, A.C. Manetti, R. La Russa, M. Di Paolo, E. Turillazzi, V. Fineschi, Myocardial pathology in COVID-19-associated cardiac injury: a systematic review, Diagnostics (Basel) 11 (2021) 1647, https://doi.org/10.3390/diagnostics11091647.
[74] E.L. Garland, M.O. Howard, Phenomenology of adolescent inhalant intoxication, Exp. Clin. Psychopharmacol. 18 (2010) 498.
[75] E. Bottoni, P.A. Fiore, S. Cappelletti, P.E.Y. Petrasso, M. Straccamore, Volatile substance related deaths: a simple and safe autopsy procedure for sampling and preserving aliphatic hydrocarbons, Clin. Ter. 169 (2018) e231–e234, https://doi.org/10.7417/CT.2018.2084.
[76] M. Statheropoulos, A. Agapiou, C. Spiliopoulou, G. Pallis, E. Sianos, Environmental aspects of VOCs evolved in the early stages of human decomposition, Sci. Total Environ. 385 (2007) 221–227, https://doi.org/10.1016/j.scitotenv.2007.07.003.
[77] F. Del Duca, A. Maiese, F. Spina, G. Visi, R. La Russa, P. Santoro, M.S. Pignotti, P. Frati, V. Fineschi, Idiopathic pulmonary hemorrhage in infancy: a case report and literature review, Diagnostics (Basel) 13 (2023), https://doi.org/10.3390/diagnostics13071270.
[78] C. Izzo, A. Monica, G. De Matteis, S. De Biasi, A. De Chiara, A.M. Pagano, E. Mezzetti, F. Del Duca, A.C. Manetti, R. La Russa, M. Di Paolo, A. Maiese, Not Only COVID-19: Prevalence and Management of Latent Mycobacterium Tuberculosis Infection in Three Penitentiary Facilities in Southern Italy., Healthcare (Basel) 10 (2022). doi: 10.3390/healthcare10020386.