



HAL
open science

Is there an interest for hair analysis in non-intentional pediatric cannabis intoxication?

Isabelle Claudet, Sophie Breinig, Michel Lavit, Lucas Ricco, Camille Brehin,
Souleiman El Balkhi

► **To cite this version:**

Isabelle Claudet, Sophie Breinig, Michel Lavit, Lucas Ricco, Camille Brehin, et al.. Is there an interest for hair analysis in non-intentional pediatric cannabis intoxication?. *Forensic Science International*, 2020, 313, pp.110377 -. 10.1016/j.forsciint.2020.110377 . hal-03491546

HAL Id: hal-03491546

<https://hal.science/hal-03491546>

Submitted on 18 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Is there an interest for hair analysis in non-intentional pediatric cannabis intoxication?

Isabelle Claudet^{a,b}, MD, Sophie Breinig^c, MD, Michel Lavit^d, Pharm.D., MD, Lucas Ricco^a,
MD, Camille Brehin^{a,e}, MD, Souleiman El Balkhi^f, Pharm.D.

Affiliations: ^aPediatric Emergency Department, Children's Hospital, CHU Toulouse, France; ^bUMR 1027, Inserm, Paul Sabatier University, UPS, Toulouse, France; ^cPediatric Intensive Care Unit, Children's Hospital, CHU Toulouse, France ; ^dLaboratory of Toxicology, CHU Toulouse, France; ^eUMR 1416, Inserm, IRSD, Toulouse, France; and ^fLaboratory of Toxicology, Children's Hospital, CHU Limoges, France.

Address correspondence to: Prof. Isabelle Claudet, Urgences Pédiatriques, Hôpital des Enfants, 330, avenue de Grande-Bretagne, TSA 70034, 31059 Toulouse cedex 9, France.
claudet.i@chu-toulouse.fr

Running title: Hair analysis and non-intentional cannabis intoxication

Funding Source: none

Word count: 3481 (abstract included)

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest: The authors have no conflicts of interests to disclose.

Abbreviations: CPS – Child protective services; GC-MS – Gaseous chromatography-Mass spectrometry; LC-MS/MS – Liquid chromatography coupled with tandem mass spectrometry; $\Delta 9$ -THC – $\Delta 9$ -tetrahydrocannabinol; THC-COOH – 11-nor-9-carboxy- $\Delta 9$ -tetrahydrocannabinol; PED – Pediatric emergency department; SoHT – Society of Hair Testing

Abstract

Background and Objectives: The incorporation of drugs in the hair of young children differs from that of adults and the metabolism of cannabis cannot be the same. Our primary objective was to analyze the distribution of the different cannabinoids in children's hair samples. The secondary objective was to correlate the intensity of toxic environmental exposure to cannabinoid metabolite levels.

Methods: This was a prospective, single-center, observational pilot study of a pediatric cohort. Included subjects were all children less than 6 years of age admitted to a tertiary pediatric emergency unit for proven cannabis intoxication during the reference period. A hair strand was sampled within 12 hours of emergency admission.

Results: Forty-one pediatric patients were consecutively enrolled. Hair analysis showed that 34 children were positive for Δ 9-THC (range 0.06-284.4 ng/mg); 41% of them were also positive for THC-COOH (range 0.26-2.76 pg/mg). Depending on the Δ 9-THC concentration (>1 ng/mg), 39% of the children could be considered exposed to an intensely toxic environment. The rate of THC-COOH detection steadily increased from 2015 to 2018 (18%, 40%, 50%, 58% for each consecutive year). Children intensely exposed weighed less on admission ($p=0.02$), had more comatose presentations ($p=0.02$), and more previous social issues (75% versus 12%, OR 22.0, $p=0.0002$).

Conclusion: Hair testing in this context indirectly shows the intensity of children's toxic environmental exposure by the cannabinoid metabolite threshold. This was very helpful during the collegial examination of the toddlers' environment and led to a full investigation and to appropriate decisions concerning social measures.

Key words – hair testing, cannabis, hashish, intoxication, pediatric

Introduction

France has one of the highest rates of cannabis consumption in the world despite its prohibition. Users are mainly young adults who consume the resin form (hashish). Cannabis resin remains readily accessible and is becoming increasingly potent due to the increasing Δ 9-tetrahydrocannabinol (Δ 9-THC) concentrations (12% in 2011, 25% in 2016) (Graph 1). We previously reported in a French national study that this change led to an increase in the presentation of non-intentionally intoxicated infants to pediatric emergency and intensive care units [1]. Over the past 15 years, these pediatric admissions have become worryingly more frequent and more severe. Consequently, we think that it is important to find a way to detect children with intensely toxic environmental and/or daily exposure. The assessment of this risk is possible only when intoxicated toddlers are referred to child protective services. Parents must be informed of the procedure and that social workers will conduct an in-depth, long-term investigation. This investigation is usually followed by a home visit by a pediatric nurse. However, parents have the right to refuse this intervention. Many emergency physicians or pediatricians do not even report such cases of intoxication, arguing that they have insufficient proof of parental consumption levels. For these reasons, we decided to conduct a study to determine whether hair analysis could help to improve the assessment of at-risk environments (heavy consumers) and the implementation of appropriate social measures.

Objectives – Considering that the absorption of drugs in young children's hair differs from adults' hair and that the metabolism of cannabis cannot be the same in this particular population, our primary objective was to analyze the distribution of the different cannabinoids in the hair samples of presumably exposed children. The secondary objective was to correlate the intensity of toxic environmental exposure to the Δ 9-THC level and the concomitant detection of 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol (THC-COOH). We also aimed to describe the influence of hair testing on the choice of social measures in terms of child protection.

Study design – This is a single-center, prospective, observational study of a pediatric cohort.

Setting and study participants – Between December 6, 2014 and December 11, 2018, all children under 6 years of age admitted with proven cannabis intoxication (compatible clinical symptoms and positive toxicological screening) to our tertiary pediatric emergency department during the reference period were eligible. Compatible clinical symptoms for the diagnosis of “intoxicated” children were any acute neurological symptom(s) (drowsiness, ataxia, hypo- or hypertonia, seizures, coma, altered consciousness, agitation, euphoria ± mydriasis) occurring in a previously healthy, afebrile toddler with no prior medical history. Patients over 6 years of age, asymptomatic patients (exposed but not intoxicated) and those with suspected but unproven cannabis intoxications were not included.

As of December 2014, the hair of all children with proven cannabis intoxication was analyzed. Within 12 hours after emergency admission, a hair strand was sampled from the posterior vertex of each patient. Twenty milligrams of hair are required to measure cannabinoid levels. The hair sample was mailed to the regional toxicology laboratory with hair analysis expertise (Limoges). A month later, a joint consultation (pediatric emergency physician and a social worker) was systematically held in order to present hair results to the parents and to make the most appropriate decision in terms of child protection and the need to resort to an addiction team.

The general data collected per patient were: demographic data (age, gender, weight, date and time of admission, mode of transportation); clinical data (vital signs on admission, Glasgow Coma Scale [GCS] score); clinical symptoms; intoxication-related data (time and mode of exposure, estimated ingested amount, place of intoxication, form of cannabis [resin, cannabis cigarette, edible products (“space cake”, “space cookies”, candies, chocolate bars)], liquid [e-cigarette]); data related to examinations: blood tests, lumbar puncture, head CT scan, electrocardiogram (EKG), electroencephalogram (EEG), toxicological tests (blood, urine, hair); disposition (home, general pediatric ward, intensive care or resuscitation unit

[mechanical ventilation required]); notion of parental consumption and outcome (date and time of discharge from the emergency unit, total hospitalization period, social issues [isolated parent, family violence, social deprivation, previous social measures], social measures [child protective services, alert information, reporting to the juvenile/family court judge, foster care]). The severity criteria were: coma (unarousable, unresponsive), seizures, respiratory failure (apnea and/or respiratory rate < 10th percentile for age, and/or tracheal intubation), hypotension (systolic blood pressure < 5th percentile for age), hypertension (systolic blood pressure > 95th percentile for age), bradycardia (pulse rate < 80 bpm [age ≤ 1 year]; pulse rate < 60 bpm [age 1-6 years]), and a Poisoning Severity Score (PSS) of 3 [2]. For hair analysis, specific collected data were hair strand length, type of analysis (global or by segmentation), the presence of cannabis metabolites (11-nor-9-carboxy- Δ 9-tetrahydrocannabinol [THC-COOH], Δ 9-tetrahydrocannabinol [Δ 9-THC], cannabinol [CBN], cannabidiol [CBD]) and their concentrations. Children were considered positive when Δ 9-THC and THC-COOH values were over the limits of quantification (respectively, 50 pg/mg and 0.2 pg/mg) as recommended by the Society of Hair Testing (SoHT). By applying the results of a preliminary study that determined the threshold of exposure intensity and significant systemic absorption [3], patients were divided in two groups: intense environmental exposure (Δ 9-THC > 1 ng/mg) and low to moderate environmental exposure (Δ 9-THC < 1 ng/mg).

Laboratory analysis strategies – Urine drug testing could be performed by automated immunochemical (IC) methods as soon as urine samples were available. IC screening methods detected THC-COOH, with a cut-off set at 50 μ g/L. Positive results were confirmed with chromatography methods (LC-MS/MS with a limit of quantification [LOQ] of 1 μ g/L). With the LC-MS/MS method, the detection of the most important cannabinoids was possible (namely, THC, 11-OH-THC and THC-COOH). This improved the estimation of the period between the intake of cannabis and the sampling moment. In some cases, a general unknown

screening with GC-MS or LC-MS/MS was performed to rule out the presence of other drugs besides cannabis.

Hair analysis

The hair strand was analyzed globally or divided in two to four segments depending on the hair length. Hair samples were decontaminated by a gentle mixing of samples in two glass tubes containing 10 ml water for 2 min each, followed by two 1-min baths in 10 ml of dichloromethane. The hair samples were then washed and finely cut (1–2 mm long, using perfectly decontaminated scissors) before being introduced in a 15 ml glass tube to which the internal standards solutions were added. After the addition of 1 ml of NaOH 1N to approximately 20 mg of the samples, 50 μ L of internal standards were added and the tube was heated in a boiling water bath for 10 min. After total hydrolysis, samples were cooled and 1 mL of acetic acid 20% was added. Samples were left at room temperature for 5 min and 7 mL of hexane/ethyl acetate (90/10 ; v/v) were added. Hair samples were vortex-mixed for ten seconds and centrifuged at 3000 rpm for 5 min. Supernatants were then dry evaporated à 30°C under N₂ flux before reconstitution with 20 μ l of a mixture of acetonitrile and formate buffer and injection into the LC–ESI-MS/MS system. A hybrid API 5500 QTRAP (Quadrupole/Quadrupole/Ion Trap) mass spectrometer (AB Sciex, Courtaboeuf, France) was used for detection and quantification with negative electrospray ionization mode was used for the analysis of cannabinoids. The limit of quantification (LOQ) was 0.05 ng/mg for THC, cannabidiol (CBD) and cannabinol (CBN). THC-COOH had a lower LOQ at 0.0002 ng/mg. Briefly, the method was successfully validated with a correlation coefficients higher than 0.99 (for the following ranges: 0.0002–20,000 ng/mg for THC-COOH; 0.05–10 ng/mg for THC, CBD and CBN) and intra and inter-assay accuracies below 15% for the all compounds. This method has already been published [4].

Statistical analysis – For statistical analysis, data were entered in Microsoft Excel tables (Microsoft Corp, Redmond, WA). The analysis was performed with StatView 5.1 (SAS Institute Inc., Cary, NC) and EpiInfo 6.04fr (VF, ENSP-Epiconcept, Paris, France). In the descriptive analysis, data are presented as mean \pm SD, median with extreme values, or with 95% confidence intervals where appropriate, unless otherwise indicated. To compare qualitative variables, a χ^2 test (Mantel-Haenszel) was used and a 2-tailed Fischer's exact test if the expected value was <5 . For quantitative independent variables, a paired student t test was used. A nonparametric Kruskal-Wallis test was performed in case of non-normal distribution. Statistical significance was considered at $p < 0.05$.

Ethical and regulatory considerations – The data recorded during this research were subject to electronic processing at the Toulouse University Hospital Pediatric Emergency Department (PED) in accordance with law no. 78-17 of January 6, 1978 regarding Data Processing, Data Files and Individual Liberties, amended by law 2004-801 of August 6, 2004. At the time of the study, toxicological analysis of hair strands were excluded from the French bioethics law and did not require approval from an ethics committee, parental acceptance or non-opposition.

Results – Main characteristics – During the study period, 41 pediatric patients were consecutively enrolled. The male/female ratio was 1:1.4 (male, $n=17$). The mean age was 1.5 ± 0.5 years; the mean weight was 10.9 ± 1.3 kg. When the time of intoxication was known (83%), it occurred most often during the afternoon between 12:00 AM and 6:00 PM (53%). The mean time period between intoxication and hospital admission was $5h55min \pm 3h31min$. The principal place of intoxication was the parental home (73%). The main form of cannabis that was ingested was hashish (97%). One child ate a “space cake”.

Table 1 summarizes the main characteristics of the population and the features of intoxication. Forty-four percent of the children were in a coma on admission; six patients had prehospital seizures. Eight patients were diagnosed with respiratory failure. Basic metabolic panel blood tests performed on all patients revealed abnormalities ($n=19$). These included high blood

glucose levels (n=10), hyponatremia (≤ 130 mmol/l) (n=6), and functional kidney failure (n=7). Additional procedures included a head CT scan (n=14), lumbar puncture (n=6), EEG (n=2), and abdominal ultrasound (n=1). In addition to cannabis detection by IC assays, blood and/or urine toxicological screening was performed in 33 cases. Three other molecules were isolated in three children (diazepam, acetaminophen and caffeine). Paracetamol was allegedly being given to treat hyperthermia, and benzodiazepines were detected in a child who had received diazepam to stop seizures. Parents could not explain the caffeine detection.

Most of the children were hospitalized (90%). Four patients were admitted to the pediatric intensive care unit and one child required assisted ventilation for 12 hours. Twenty-two (54%) different children met at least one severity criteria. Forty-one percent of the children had a PSS score of 3 (2015-2016: 41%; 2017-2018: 46%). Sixteen families initially conceded that they were cannabis consumers (father n=10, mother n=3, both parents n=3). During the hospital stay, the social worker met all families and social issues were identified in 15 families (37%). These included social deprivation (n=4), previous interaction with child protective services (CPS) in 6 other families (with effective educative measures for 4 of them), and isolated or single-mother households for 5 children. At the time of the follow-up consultation, families who initially denied being cannabis consumers or who gave no explanation for the cause of the intoxication finally admitted cannabis use when confronted with the hair results. Social or legal measures included a referral to CPS for all cases; a written report of special concern was made for 32 children, 13 cases were reported to the juvenile court judge, 4 children were placed in foster care by court order and 3 families were subject to a complaint filed with the police department.

Results of hair analysis – Table 2 summarizes the hair results with the different metabolites present and their concentrations. Considering the consensus of the SoHT and the recommended limit of quantification (LOQ), 34 children (83%) were positive for Δ^9 -THC (LOQ >0.05 ng/mg, range 0.06-284.4 ng/mg) and 14 (41%) were also positive for THC-

COOH (LOQ >0.2 pg/mg, range 0.26-2.76 pg/mg). Patients were divided into two groups according to the Δ^9 -THC concentration (over or below 1 ng/mg) (Table 3), and 39% of the children could be considered exposed to an intensely toxic environment (Δ^9 -THC > 1 ng/mg). Fifteen children had blood measurements of cannabis metabolites and they were all positive for THC-COOH: THC blood concentration (range 0.5 – 138 ng/ml), 11-OH-THC (range 0.7 – 34.6 ng/ml) and THC-COOH (range 11 – 122.6 ng/mL).

Comparative analysis – Comatose and non-comatose patients did not differ when their main characteristics and the hair distribution of cannabinoids were compared. In terms of the level of environmental exposure, children with intense environmental exposure (Δ^9 -THC > 1 ng/mg, n=16) weighed less on admission (10.1 ± 0.9 kg versus 11.4 ± 1.2 kg, $p=0.006$), had more comatose presentations (56% versus 20%, OR 5.1 (1.3–20.7), $p=0.02$) and had more previous social issues (75% versus 12%, OR 22.0 (4.2–115.0) $p=0.0002$). The prematurity rate of our cohort was higher (12%) than the French national prematurity rate (7.5%), without any significant difference.

Discussion – Currently, the increase of admissions in emergency services for pediatric non-intentional cannabis intoxication is alarming. This phenomenon is observed in all countries, regardless of whether cannabis has been legalized or not [5-9]. In terms of child protection, it is therefore essential to use all available resources to determine whether children are regularly and intensively subjected to a toxic environment, especially to avoid resultant health risks, such as potential neurological sequela.

Compared with adults, children's hair is thinner and more porous, and the risk of contamination from sweat and environmental smoke is greater [4,10,11]. During certain periods, the growth rate of children's hair can differ from the usual growth of 1 cm per month, which starts at the age of one year [12]. Due to children's hair properties, hair analysis interpretation that has been proven in adults cannot always be applied to children. On the other hand, the maturity of liver enzymes is gradually acquired after birth. Cytochromes P450,

involved in the conversion of THC into THC-COOH, are partially or completely immature (e.g. CYP2C activity is not functional at birth and reaches 30% after the first year of life), and this can lead to an underestimation of toxic exposure. The immaturity of enzyme activity can also affect UDP-glucuronyltransferase, leading to a decrease in the conjugation of THC-COOH and can facilitate hair absorption, with a theoretically higher concentration for the same amount of THC absorbed when compared with adults [13,14]. Therefore, before interpreting hair analysis results, physicians should be aware of these differences and be warned about the difficulties interpreting blood or hair analysis in young children [15-22].

In adults, it has been proven that the presence of THC alone in hair indicates that the subject lives in a contaminated environment, but the detection of THC-COOH argues for active use of cannabis [9,15]. To reduce contamination from passive exposure, the SoHT has recommended applying a decontamination procedure to wash out external pollutants (including an initial organic solvent followed by aqueous washes) [23,24]. Even with the SoHT recommended application to decontaminate hair strands before analysis [23], it has been established that contamination issues should still be considered in the interpretation of the final results.

Environmental exposure in children should lead to a profound investigation of the contextual circumstances [25]. THC-COOH screening has been suggested for differentiating passive and active users (in children it was thought to be an indirect indication of caregiver or parental use) [15,18,23]. In intoxicated children, the presence of THC-COOH in hair is inconsistent, even when the intoxication is proven by blood and/or urine detection of cannabinoid metabolites with chromatography/mass tandem spectrometry analysis. The absence of THC-COOH could be explained by the absence of cannabis intake over the past months. A segmented analysis is of no interest in such non-intentional intoxications since the purpose is more to determine the risk of high environmental exposure and not to date or prove chronic drug administration, as in pediatric forensics or cases of abuse [11,21,26,27].

In our study, the majority of patients' hair tested positive for Δ^9 -THC (83%), which indicates that they were living in contaminated areas and/or surrounded by cannabis users. THC-COOH

was detected in 41% of the cases, which is not very uncommon. There was no significant relation between the findings of THC-COOH in hair and the severity of presentation (47% in comatose children vs. 36% in non-comatose patients, $p=0.48$). However, we observed that the rate of THC-COOH detection increased steadily from 2015 to 2018 (18%, 40%, 50%, 58% for each consecutive year, $p=0.09$, OR 3.1 [0.8-11.8]). This could be related to the increase in resin THC content (cf. Graph 1).

From a previous study conducted in Limoges, France, the authors were able to determine that the hair THC concentration threshold ($> 1\text{ng/mg}$) could reflect intense environmental exposure [3]. When this threshold was reached and associated with the presence of THC-COOH, this meant significant systemic absorption [3]. Our study is the first to apply such thresholds, finding that 39% ($n=16$) of our intoxicated patients were living in an environment with intense exposure. Compared with other intoxicated patients, children who met intense environmental exposure criteria ($n=16$) weighed less on admission, but their birth weight was not lower. Compared with the French national rate (7.5%), we also had a greater proportion of premature children (12%) in our cohort, which could be related to the mothers' exposure to cannabis smoke during pregnancy, as it was the father who conceded use [29]. However, we cannot completely rule out that the mothers were also users during pregnancy.

In case of suspected child abuse, it is very difficult to distinguish a child with environmental cannabis contamination from one to whom cannabis is being administered for purposes of sedation or who is being self-poisoned by consuming remaining hashish present at home or in the living area [16,23]. Some authors have suggested screening for the non-psychoactive precursor of THC (THCA-A), which is a marker of external contamination, while THC-COOH is an indicator of THC absorption [11]. In case 28, the hair THC level was very high with the absence of THC-COOH, suggesting several manual contaminations by caregivers/parents. THCA-A is found in cannabis smoke, but it is not present following

absorption due to the extensive metabolization to THC and THC-COOH. Therefore, its detection suggests external contamination [11].

Positive results should be very cautiously interpreted. They should be taken into consideration by a cross-disciplinary study group including: 1) physicians or pediatricians who are familiar with the medical file (clinical presentation) and past medical history, especially previous admission for a domestic accident; 2) social workers who have information concerning the socioeconomic situation and preexisting social measures; and 3) analytical and clinical toxicologists with expertise in hair analysis.

Bias and limitations – This study concerned our center, which does not reflect what is being done on a national level. However, during the Marie-Jeanne study [1], we had interviewed each center regarding their practices concerning hair analysis in such cases and it appeared that we were by far the largest center in terms of annual demands (80%).

Among the 41 hair samples analyzed in our study, disparities in hair color were observed. Although several studies have shown that melanin in hair appears to play a binding role for at least some commonly abused drugs, these findings have not been sustained when larger numbers of subjects were analyzed. This has been demonstrated for THC-COOH and cocaine [30,31].

Conclusion – Without hair analysis, many pediatric forensic or abuse cases would not have been resolved. Rejecting hair testing because of some drawbacks would be a loss of opportunity in many cases. This paper highlights that hair testing in this context leads to parental admission of cannabis use and that the intensity of toddlers' exposure can be indirectly predicted by hair cannabinoid concentrations. Hair testing results are also helpful during the follow-up consultation with parents, as an appointment with an addictions team could be suggested. We also demonstrated that intensely exposed children had more serious clinical and biological manifestations and weighed less, leading to more severe presentations (comatose status). Collegial examination of the toddler environment through a full

investigation leads to appropriate decisions concerning the social measures that are in the best interest of the child[32].

Contributor's statement page

X developed the project and the study design, analyzed results, interpreted data, and drafted the initial manuscript.

X collected data and critically reviewed and revised the manuscript.

X did the follow-up consultations.

X performed toxicological analyses and critically reviewed and revised the manuscript.

All the listed authors contributed to data collection and substantially participated in data analysis. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

- 1 Claudet I, Mouvier S, Labadie M, et al. Unintentional Cannabis Intoxication in Toddlers. *Pediatrics*. 2017;140. pii: e20170017.
- 2 Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino J. Poisoning severity score. Grading of acute poisoning. *J Toxicol Clin Toxicol*. 1998;36(3):205-13.
- 3 Winckel M, Dulaurent S, Morichon J, Gaulier J-M. CANHAIRKID (evaluation of hair analysis in the diagnosis of significant cannabis exposure among children): preliminary results. *Toxicol Anal Clin*. 2015;27:S18-9. Available at <https://www.em-consulte.com/revue/TOXAC/27/2S/table-des-matieres/> (2019/04/17)
- 4 Dulaurent S, Gaulier JM, Imbert L, Morla A, Lachâtre G. Simultaneous determination of Δ^9 -tetrahydrocannabinol, cannabidiol, cannabinol and 11-nor- Δ^9 -tetrahydrocannabinol-9-carboxylic acid in hair using liquid chromatography-tandem mass spectrometry. *Forensic Sci Int*. 2014;236:151-6.
- 5 Richards JR, Smith NE, Moulin AK. Unintentional Cannabis Ingestion in Children: A Systematic Review. *J Pediatr*. 2017;190:142-52.
- 6 Wang GS, Le Lait MC, Deakyne SJ, Bronstein AC, Bajaj L, Roosevelt G. Unintentional Pediatric Exposures to Marijuana in Colorado, 2009-2015. *JAMA Pediatr*. 2016;170(9):e160971.
- 7 Heizer JW, Borgelt LM, Bashqoy F, Wang GS, Reiter PD. Marijuana Misadventures in Children: Exploration of a Dose-Response Relationship and Summary of Clinical Effects and Outcomes. *Pediatr Emerg Care*. 2018;34(7):457-62.
- 8 Noel GN, Maghoo AM, Franke FF, Viudes GV, Minodier PM. Increase in emergency department visits related to cannabis reported using syndromic surveillance system. *Eur J Public Health*. 2019;29(4):621-5.

- 9 Thomas AA, Mazor S. Unintentional Marijuana Exposure Presenting as Altered Mental Status in the Pediatric Emergency Department: A Case Series. *J Emerg Med.* 2017;53(6):e119-e123.
- 10 Berthet A, De Cesare M, Favrat B, et al. A systematic review of passive exposure to cannabis. *Forensic Sci Int.* 2016;269:97-112.
- 11 Wang X, Drummer OH. Review: Interpretation of drug presence in the hair of children. *Forensic Sci Int.* 2015;257:458-72.
- 12 Kintz P. Contribution of in utero drug exposure when interpreting hair results in young children. *Forensic Sci Int.* 2015;249:314-7.
- 13 Hakkola J, Tanaka E, Pelkonen O. Developmental expression of cytochrome P450 enzymes in human liver. *Pharmacol Toxicol.* 1998;82(5):209-17.
- 14 Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol.* 2018;84(11):2477-82.
- 15 Kintz P, Ameline A, Eibel A, et al. Interpretation of Cannabis Findings in the Hair of Very Young Children: Mission Impossible. *Curr Pharm Biotechnol.* 2017;18(10):791-5.
- 16 Moosmann B, Roth N, Auwärter V. Finding cannabinoids in hair does not prove cannabis consumption. *Sci Rep.* 2015;5:14906.
- 17 Moosmann B, Roth N, Hastedt M, Jacobsen-Bauer A, Pragst F, Auwärter V. Cannabinoid findings in children hair - what do they really tell us? An assessment in the light of three different analytical methods with focus on interpretation of Δ^9 -tetrahydrocannabinolic acid A concentrations. *Drug Test Anal.* 2015;7(5):349-57.
- 18 Cuypers E, Flanagan RJ. The interpretation of hair analysis for drugs and drug metabolites. *Clin Toxicol (Phila).* 2018;56(2):90-100.

- 19 Hill VA, Schaffer MI, Stowe GN. Carboxy-THC in Washed Hair: Still the Reliable Indicator of Marijuana Ingestion. *J Anal Toxicol*. 2016;40(5):345-9.
- 20 Boroda A, Gray W. Hair analysis for drugs in child abuse. *J R Soc Med*. 2005;98(7):318-9.
- 21 Alvarez JC, Lasne L, Etting I, et al. Hair analysis does not allow to discriminate between acute and chronic administrations of a drug in young children. *Int J Legal Med*. 2018;132(1):165-72.
- 22 Chatterton C, Turner K, Klinger N, Etter M, Duez M, Cirimele V. Interpretation of pharmaceutical drug concentrations in young children's head hair. *J Forensic Sci*. 2014;59(1):281-6.
- 23 Cooper GA, Kronstrand R, Kintz P; Society of Hair Testing. Society of Hair Testing guidelines for drug testing in hair. *Forensic Sci Int*. 2012;218:20-4.
- 24 Duvivier WF, Peeters RJ, van Beek TA, Nielen MW. Evidence based decontamination protocols for the removal of external Δ^9 -tetrahydrocannabinol (THC) from contaminated hair. *Forensic Sci Int*. 2016;259:110-8.
- 25 Pélissier F, Claudet I, Pélissier-Alicot AL, Franchitto N. Parental cannabis abuse and accidental intoxications in children: prevention by detecting neglectful situations and at-risk families. *Pediatr Emerg Care*. 2014;30(12):862-6.
- 26 Pichini S, García-Algar O, Alvarez AT, et al. Pediatric exposure to drugs of abuse by hair testing: monitoring 15 years of evolution in Spain. *Int J Environ Res Public Health*. 2014;11(2):8267-75.
- 27 Levy S, Siqueira LM; Committee on Substance Abuse, Ammerman SD, Gonzalez PK, Ryan SA, Siqueira LM, Smith VC. Testing for drugs of abuse in children and adolescents. *Pediatrics*. 2014;133(6):e1798-807.

- 28 Kirkham TC. Cannabinoids and appetite: food craving and food pleasure. *Int Rev Psychiatry*. 2009;21(2):163-71.
- 29 Grant KS, Petroff R, Isoherranen N, Stella N, Burbacher TM. Cannabis use during pregnancy: Pharmacokinetics and effects on child development. *Pharmacol Ther*. 2018;182:133-51.
- 30 Mieczkowski T. Assessing the Potential of a "Color Effect" for Hair Analysis of 11-nor-9-carboxy-delta(9)-tetrahydrocannabinol: Analysis of a Large Sample of Hair Specimens. *Life Sci*. 2003 Dec 12;74(4):463-9.
- 31 Mieczkowski T. Assessing the potential for racial bias in hair analysis for cocaine: examining the relative risk of positive outcomes when comparing urine samples to hair samples. *Forensic Sci Int*. 2011;206(1-3):29-34.
- 32 Tsanaclis L, Andraus M, Wicks J. Hair analysis when external contamination is in question: a review of practical approach for the interpretation of results. *Forensic Sci Int*. 2018;285:105-10.

Table and graph legends

Graph 1. Change in THC concentration (results obtained from the analysis of products seized by French customs), and comatose presentations among non-intentional cannabis intoxicated children.

Table I. Main characteristics of non-intentional cannabis intoxicated pediatric patients (n=41).

Table II. Results of hair analysis with cannabis metabolite concentrations.

Table III. Hair detection of cannabinoid metabolites in comatose and non-comatose patients (percentage in column).

Graph 1 – Change in hashish THC concentration (results obtained from the analysis of products seized by French customs <https://www.ofdt.fr/BDD/sintes/LePointSINTES04.pdf>), and comatose presentations among non-intentional cannabis intoxicated children

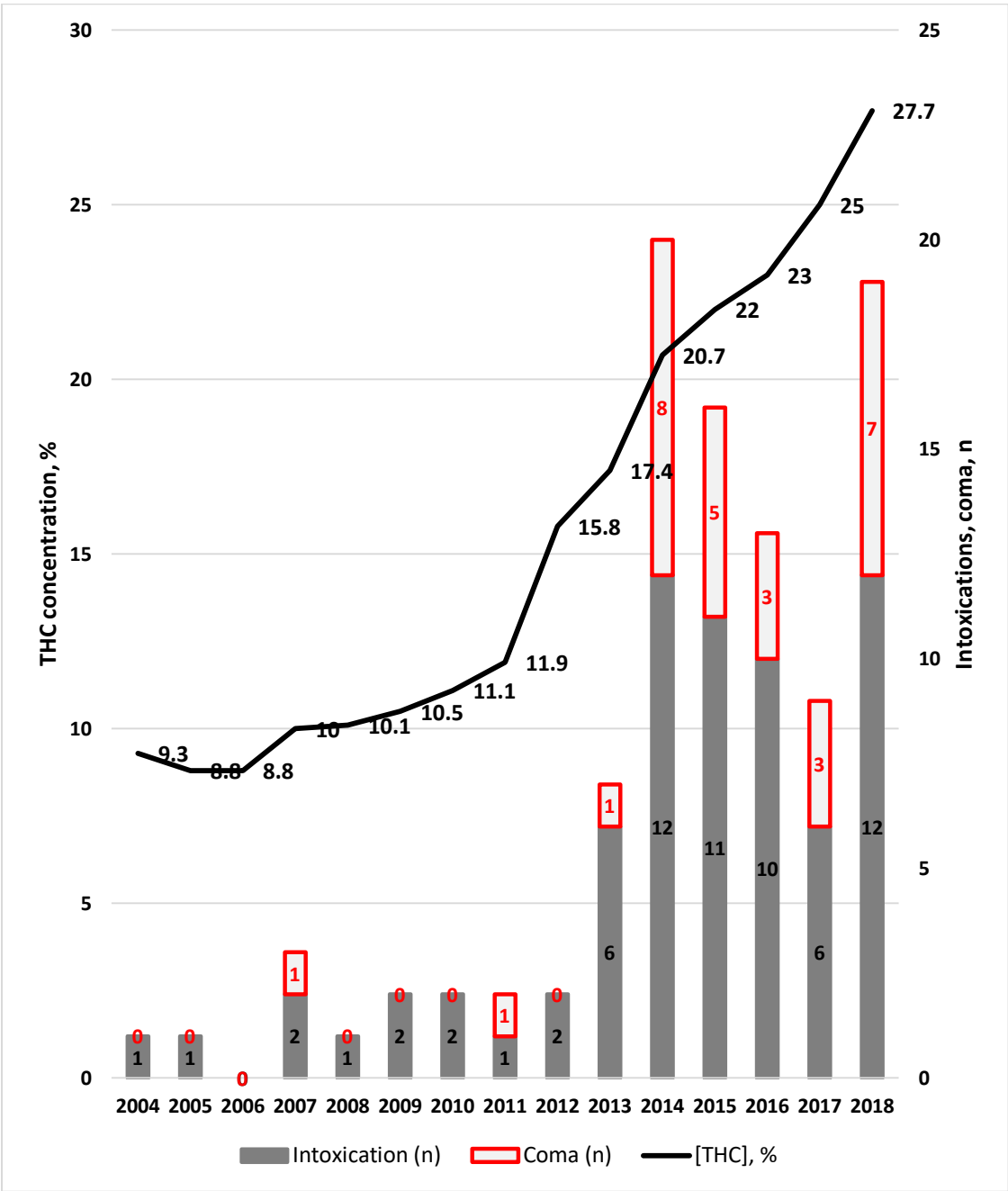


Table 1 – Main characteristics of non-intentional cannabis intoxicated pediatric patients (n=41)

Population characteristics, n (%)	p
Males	17 (41)
Mean age , years (SD) [range]	1.5(0.5) [0,9-4.0]
-male (n=17)	1.7(0.7) [0.9-4.0]
-female (n=24)	1.3(0.3) [0.9-2.8]
Age group	
0-11 months	9(22)
12-23 months	27(66)
24-35 months	3(7)
≥36 months	2(5)
Mean weight , Kg(SD) [range]	10.9(1.3)[8.4-17.5]
-male	11.4(1.2) [9.0-17.5]
-female	10.6(1.2) [8.4-14.8]
Term of birth	
Term≥ 37 weeks of gestation	26(63)
Prematurity	5(12)
Non specified (Ns)	10(25)
Referral mode	
-spontaneous	30(73)
-family physician, pediatrician	11(27)
Transportation mode	
-sanitary (firefighters, ambulances) or medical transportation (physician on board)	12(29)
Weekend admission	16(39)
Time of admission	
8:00AM-11:00AM	3(5)
12:00AM-5:00PM	19(46)
6:00PM-11:00PM	18(44)
12:00PM-7:00AM	3(5)
Location of intoxication	
Home	30(73)
Public area	6(15)
“Friends”	4(10)
Others*	1(2)
Hospitalization	37(90)
-PICU	4(10)
Clinical presentation	
Neurological	
-coma	19
-drowsiness	18
-hypotonia	16
-seizures	6
-agitation	5
-ataxia	5
Cardiovascular	
Tachycardia	18
Hypotension	4
Hypertension	2
Ophthalmological	
Mydriasis	24
Conjunctival hyperemia	6
Myosis	1
Respiratory failure	8
(hypoventilation, apnea)	1
Assisted ventilation	

TemperatureHyperthermia ($\geq 38.5^{\circ}\text{C}$)

4

Hypothermia ($< 36^{\circ}\text{C}$)

0

*nanny, grandmother

Table 2 – Results of hair analysis with cannabis metabolite concentrations

Case	Sex, age(mths)	Hair strand length (cm)	Segments* (n)	THC-COOH (pg/mg)	Δ 9 THC (ng/mg)	Cannabinol (ng/mg)	Cannabidiol (ng/mg)	Coma	Year
1	♂,16.5	2	1	0	0.08	0	0.08	Yes	2014
2	♀,11.3	2	1	0	0.08	0	0.08	No	2014
3	♀,16.7	6	1	0	0	0	0	Yes	2015
4	♂,11.6	4	2	2.73 2.76	1.26 1.45	0.36 0.51	0.63 0.86	Yes	2015
5	♀,19.7	4	2	0.38 0.37	0.24 0.24	0.12 0.18	0.12 0.17	No	2015
6	♀,19.3	6	3	0 0	0 0.1	0 0	0 0.07	No	2015
7	♀,12.2	5	1	0	0.36	0.48	1.22	No	2015
8	♂,15.8	4	2	0 0	1.17 1.25	0.28 0.31	1.12 1.34	Yes	2015
9	♀,14.0	6	3	0 0	0.07 0.06	0 0	0.06 0.05	No	2015
10	♀,26.7	3	1	0	0.8	0.32	0.35	No	2015
11	♀,12.4	2.5	1	0	0	0	0	No	2015
12	♂,20.4	4	2	0 0	0.42 0.6	0.14 0.22	0.25 0.44	Yes	2015
13	♂,14.4	2.5	1	0	0	0	0	Yes	2015
14	♂,32.2	4.5	1	0	0.06	0.08	0	No	2016
15	♂,17.3	5	2	0.6 1.22	0.42 0.54	0.19 0.4	0.09 0.08	Yes	2016
16	♀,20.5	5	1	0	0.23	0	0	No	2016
17	♀,14.2	6	2	0.37 0.56	1.04 1.87	0.56 0.79	1.04 1.27	No	2016
18	♂,18.4	4	1	0.59	1.65	0.32	0.86	No	2016
19	♂,18.3	2	1	0	1.34	0.23	0.96	No	2016
20	♀,15.5	11	1	0	0.58	0.28	0.18	Yes	2016
21	♂,15.0	8	1	0	0	0	0	Yes	2016
22	♀,13.5	3	1	0	0.48	0.12	0.09	No	2016
23	♀,10.7	2	1	1.1	7.02	1.26	3.6	No	2016
24	♀,34.0	9	1	Positive**	Positive	Positive	Positive	Yes	2017
25	♀,10.0	3	1	0	1.5	0.47	0.72	No	2017
26	♀,10.2	4	2	0.79 1.2	0.77 1.73	0.19 0.39	0.42 0.91	No	2017
27	♂,10.0	2	1	0	1.46	0.22	1.44	Yes	2017
28	♀,16.9	12	1	0	284.44	76.34	69.27	Yes	2017
29	♂,12.1	5	2	1.54 1.91	0.79 2.16	0.83 2.47	0.5 1.13	No	2017
30	♂,21.0	6	2	1.26 1.51	9.1 14.38	2.69 2.7	0.9 0.91	Yes	2018
31	♂,12.4	4	1	0	0.23	0.05	0.14	No	2018
32	♂,48.2	4	1	0	0	0	0	No	2018
33	♂,10.8	4	1	6	0	0	0	No	2018
34	♀,10.7	10	1	0.34	0.97	0	0.11	Yes	2018
35	♀,13.6	10	1	0	0.18	0.4	0	Yes	2018
36	♀,17.2	6	1	0.52	1.13	0.1	0.32	Yes	2018
37	♀,17.2	6	1	0.5	1.39	0.14	0.45	Yes	2018
38	♂,43.4	5	1	0	0.13	0	0	No	2018
39	♀,13.0	5.5	1	0.26	4.11	0.51	0.76	No	2018
40	♀,16.9	21	4	0 0 0	0.35 0.75 0.85	0 0.12 0.13	0.07 0.08 0.09	Yes	2018

				0	1.05	0.13	0.12		
41	♀,11.3	6	1	1.78	3.89	0.5	0.63	Yes	2018

*When the analysis was made on several hair segments, the first results are from the segment closest to the scalp (proximal segment) toward the last segment (distal hair strand) – **Due to a technical problem, only qualitative results have been provided.

Table 3 – Hair detection of cannabinoid metabolites in comatose and non-comatose patients (percentage in column)

Cannabinoid presence, n(%)	Comatose (n=19)	Non-comatose (n=22)	Total (n=41)	p
Δ9-THC > 1ng/mg	8(42)	8(36)	16(39)	0.71
Δ9-THC ≤ 1ng/mg	11(58)	14(64)	25(61)	0.71
No Δ9-THC	3(16)	4(18)	7(17)	0.84
No THC-COOH	10(53)	14(64)	24(59)	0.48

*The cut-off value for detection is 0.2pg/mg according to the Society of Hair Testing (SoHT)