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Review

The forensic limits of hair drug testing: a critical assessment of drug intake and hair concentration relationships

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ABSTRACT

Hair analysis is widely used in forensic toxicology to establish drug exposure, offering a long detection window and non-invasive sampling. This review provides a critical assessment of whether a dose-concentration relationship between drug intake and concentrations measured in hair exists and if such a relationship would be suitable for forensic purposes. A systematic search as conducted to identify controlled studies that were published across illicit substances and pharmaceuticals. The results reveal substantial variability in reported correlations. While some pharmaceuticals (e.g., clozapine, methadone) show moderate associations, most illicit drugs, including heroin, codeine, amphetamine, cannabis, and GHB, show weak or inconsistent relationships. Overlapping concentration ranges between low and high doses, combined with confounding factors such as melanin content, sweat contamination, cosmetic treatments, and methodological inconsistencies, undermine the reliability of dose estimations. Although controlled administration studies provide more robust data, ethical constraints limit their scope. Current evidence indicates that hair analysis can confirm exposure but cannot accurately quantify dose or distinguish intentional ingestion from passive contact. Future research should focus on standardizing analytical protocols, correcting for melanin content, and exploring pharmaceuticals with predictable dosing patterns. Overall, hair should be regarded as a qualitative indicator of exposure rather than a quantitative measure of drug intake.

1. Introduction

Since the 1960′s there has been an increase of the use of hair in forensic toxicology as an alternate matrix for analysis of toxins, such as mercury. In 1979, Baumgartner et al., (1979) [1] published a paper on the detection of diamorphine in human hair with the use of radioimmunoassay (RIA); this sparked a surge of publications on the use of hair to detect therapeutic or illicit drugs. Thereafter, hair became commonplace for drug screening in the workplace due to its advantages, such as a less invasive sample collection; assessment of drug use patterns and a more stable matrix for detection due to no metabolism or excretion [2]. Hair also provides a larger detection window than conventional methods. Therefore, it can be a reliable source for ante-mortem drug information [3]. Drugs, such as cocaine, nicotine and opiates have even been found in pre-Columbian mummies. Musshoff [4] detected nicotine in the hair of three out of 70 pre-Columbian mummies. However, it is possible that, due to transport and handling, this could be due to external contamination, a major limitation in hair analysis [5,6].

1.1. Drug incorporation

Much of the incorporation of drugs into the hair matrix is unknown; it is proposed that drugs bind to pigments, such as eumelanin and pheomelanin, in the hair shaft as strong correlations have been noted between melanin and drug concentration in hair [7,8]. Rollins *et al.,* [9] investigated the effects of hair colour on the incorporation of codeine in 42 subjects and found that subjects with black hair had significantly higher concentrations of codeine, 15-fold higher than those with lighter or dyed hair. Furthermore, out of the black hair, Asian hair had higher concentrations than Caucasian hair. The authors attribute this to the total melanin content, as Asians, on average, had a higher melanin concentration [10]. The findings of the studies correlating drugs to melanin indicate that there is a strong bond between melanin and basic drugs, such as that of amphetamine. By normalising data with the concentration of melanin, the bias of hair colour could be removed [5]. Thus, the most common mechanism of drug incorporation is thought to be via passive diffusion of the drug from the circulating blood, as shown in Fig. 1. A large mass of capillaries exists at the hair follicles base within

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the scalp. As the follicle cells die, they coalesce together to become strands of hair, encasing the drug diffused from the capillaries by binding to keratin and/or melanin. [7,11,12]. Drugs are also indicated to be incorporated into hair via sweat and sebum, which frequently contain drugs in concentrations higher than that of blood [13].

1.2. . Limitations of hair analysis

One of the largest limitations of hair analysis is the interpretation of the results and the possibility of obtaining a false negative or positive [5]. Several studies have shown that treatment, such as bleaching or dying may reduce the concentration of drugs in hair [14,15]. Baeck *et al.*, [16] suggests that repeated washing reduced the concentration of amphetamine by up to 27.8% and that dying the hair reduced the concentration by up to 36.9%. Furthermore, Yegles *et al.*, [17] showed that bleaching drastically reduced the concentration of heroin by 89% and cocaine by 25%. There are many factors that can influence the concentration of drugs, even in some cases to below the limit of detection, causing a false negative result [18]. The presence of the drug does not indicate intentional consumption. Uhl *et al.*, [19] shows that the cannabis metabolite 11-*nor*-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) was present in the hair of a child and people who had not smoked cannabis. As high as 6.6 ng/mg of hair of THC-COOH was present in hair. This indicates that it is impossible to distinguish between passive exposure and intentional consumption. This is also supported by Kintz *et al.*, [20] who also finds THC-COOH in hair of 2 to 24 months old children who may have been exposed to cannabis prior to their death. a cannabis-dependant mother. Papaseit *et al.*, [21] also reported finding benzoylecgonine in children's hair from passive exposure of crack cocaine by their parents.

1.3. Dose-concentration

There is disagreement in the hair testing society of whether the dose of a drug consumed relates to the concentration that is obtained in hair, [5,6,22]. This gap in knowledge has tried to be filled by myriad studies. Many of these studies, however, are not controlled experiments, opening them up to numerous sources of inaccuracy. For example, Skopp *et al.*, [23] reports that there is a significant correlation coefficient (r) at 0.71, between the amount of cannabis consumed and the concentration of cannabinoids in the hair of 12 cannabis users, based on their consumption over the previous three months. However, Moosmann *et al.*, [24] argues that even though cannabinoids can be detected in hair, it does not prove that cannabis has been consumed. The study encouraged to consider other methods of incorporation, such as sweat and second-hand smoke. Another major question regarding cannabis studies is determining the concentration of cannabis. It is unlikely they were all consuming the same batch/strain of cannabis, so there is likely to be a significant difference in the levels of tetrahydrocannabinol (THC) in the cannabis itself [25]. Depending on how THC is extracted from the cannabis plant, or if the plant is smoked there will be variation. A recent study by Lorenzetti *et al.*, [26] found that street cannabis had a potency varying between 4.48% and 12.00% with regards to THC content. Not only is this a broad range, but there is also a high chance that they would not be ingesting the same form or strain and thus the same potency, in every dose [27]. In addition, it is highly unlikely that all participants could accurately recall every instance of drug use over a three-month period, l*et al*one the precise quantities consumed. Consequently, studies relying on self-reported dosing data should be interpreted with caution, as such information is inherently prone to recall bias and inaccuracies [28].

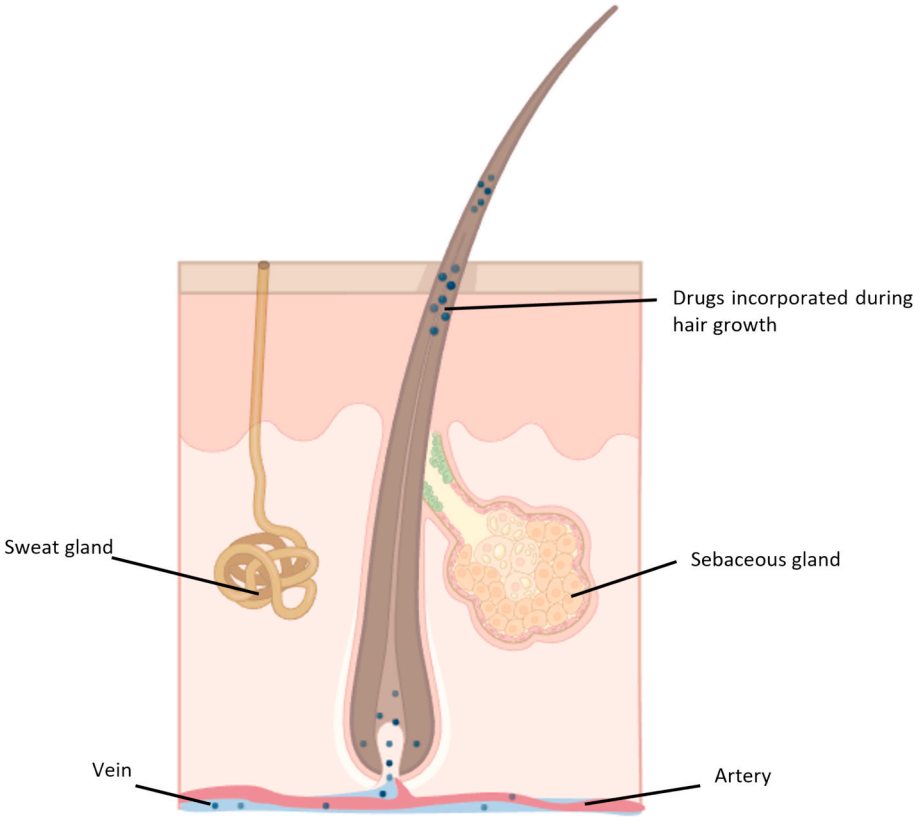

Fig. 1. Diagram showing the passive diffusion of drugs into hair. Drugs circulating in the capillaries become trapped in the hair shaft via passive diffusion from the underlying capillaries.

1.4. Aim

The objective of this paper is to provide a comprehensive and current review of the literature concerning dose-concentration relationships across a range of psychoactive substances and pharmaceuticals. These include cocaine; opiates (illicit and pharmaceutical); cannabis; amphetamine, gamma-hydroxybutyric acid; and a range of pharmaceutical agents, including antiretroviral drugs used in the management of human immunodeficiency virus (HIV), anti-seizure medications for epilepsy, and antidepressants for mood disorders. This review aims to evaluate whether a dose-concentration relationship exists between drug intake and concentrations detected in hair, and to assess the potential forensic applicability of such a relationship [29].

2. Methodology

Given that the primary aim of this review is to assess the relationship between experimentally verified drug intake and concentrations detected in hair, the inclusion criteria were restricted to studies involving controlled administration or experimentally verified dosing. To minimise bias, studies based solely on self–reported dosing were excluded, as were publications presenting only qualitative findings or those not using hair as the analytical matrix. Substances were selected based on their relevance to forensic toxicology and the existence of controlled–administration data, which led to the inclusion of cannabinoids, cocaine, opiates, amphetamine–type stimulants, and selected pharmaceuticals. A systematic literature search was performed using PubMed, ScienceDirect, and Scopus covering all available years from each database's inception up to November 2025. Boolean operators were applied to combine key terms, such as 'dose', 'concentration', 'response', 'hair', and 'analysis', with specific drug classes, including cannabis, cocaine, opiates, amphetamines, and pharmaceuticals. To ensure the quality and relevance of the retrieved studies, filters were applied to include only peer-reviewed journal articles. The search was limited to peer-reviewed publications written in English. Studies were first screened at the level of title and abstract, and those meeting the broad criteria of controlled dosing, quantitative reporting, and relevance to hair analysis proceeded to full-text evaluation. Only studies with quantitative data that correlated an established dose with the hair concentrations were selected to ensure that the final selected studies are robust enough to understand the pattern of drug incorporation into hair.

3. Results

Table 1 summarizes the findings from the reviewed literature, including administered dose ranges, corresponding hair concentrations, analytical workflows, and reported correlation statistics across multiple drug classes. Since the 1990 s, only a limited number of controlled studies have investigated the association between drug dose and hair concentration, highlighting the scarcity of robust evidence in this area. The table highlights the considerable methodological variation between studies, including differences in washing procedures, extraction approaches, instrument platforms, and sample masses used for analysis. There are a few studies report moderate to strong correlations between administered dose and measured hair concentration, while others demonstrate weaker or non-significant associations, underscoring the complexity of interpreting dose-concentration relationships in hair.

3.1. Heroin

Three studies were found describing a dose-concentration relationship between heroin doses and concentrations in hair, all of which follow a maintenance programme over the course of three months to one year. The parent drug heroin, or the metabolite, 6-mono-acetylmorphine (MAM), was reported to be the most abundant in hair. Concentration ranges were reported to be from 0.05–14.36 ng/mg of hair with doses ranging from 120–780 mg/day. No correlation was seen by Kintz, *et al.*, [30] ($r = 0.32$) or by Girod & Staub [31] ($r = 0.01$). Musshoff *et al.*, [32] reported a statistically significant correlation ($r = 0.66$, $p = <0.0001$).

3.2. Methadone

A total of eight controlled dose-concentration studies were found pertaining methadone. All the literature reports that methadone was the major analyte in hair. However, metabolites, 2-ethyl-l,5-dimethyl-3,3-diphenylpyrolinium (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-l-pyroline (EMDP) are also usually reported. The concentration ranges of the studies were from 0–78.1 ng/mg of hair with doses ranging from 20–7400 mg/day. No correlation is observed in Girod & Staub [33]; Goldberger *et al.*, [34]; and Paterson *et al.*, [39] who report correlation coefficients of 0.1022, 0.1019, and 0.2263, respectively. Correlation was reported in Lucas *et al.*, [35]; Moeller *et al.*, [37]; and Musshoff *et al.*, [38] who report coefficients of 0.8187, 0.630, 0.760, and 0.602, respectively. No statistical information was provided in Marsh *et al.*, [36].

3.3. Codeine

Three of the five studies: Scheidweiler *et al.*, [41]; Ropero-Miller *et al.*, [42]; and Goullé *et al.*, [44] give correlation coefficients (r) of 0.430, 0.439, and 0.539, respectively. Whereas Joseph *et al.*, [40] does not state any statistical analysis was carried out and Kronstrand *et al.*, [43] only studied one dose. Codeine was reported to be the primary analyte in hair; traces of acetyl codeine were also noted in Joseph *et al.,* [40]. Concentration ranges of 0.03–8.1 ng/mg of hair have been reported from doses ranging from 30–120 mg/day of codeine.

3.4. Buprenorphine

Both buprenorphine and nor-buprenorphine were reported to be found in hair, with buprenorphine being the most abundant. Only two dose-concentration relationship studies were found in the literature with a concentration range of 0.0003–0.59 ng/mg of hair with doses from 0.2 to 4 mg/day. Skopp *et al.*, [45] reports a correlation coefficient of 0.8051, which is statistically significant (<0.001). Kintz *et al.*, [46] produces no statistical analysis.

3.5. Cannabis

Only one study was found describing oral Δ^9–tetrahydrocannabinol (THC) dosing and its relationship to cannabis concentration in the hair. Huestis *et al.*, [47] uses two subjects who received oral doses of THC (0–14.8 mg) over 10 weeks. 11–nor–9–carboxy–Δ^9–tetrah ydrocannabinol (THCCOOH) was the only metabolite detected (0–0.1 pg/mg), and the reported correlation between dose and THCCOOH concentration ($r = –0.1912$) was weak.

3.6. Cocaine

The parent drug cocaine was reported to be more prevalent in hair with some studies reporting high benzoylecgonine concentrations in some subjects. Four studies were found denoting dose-concentration relationships with concentration ranges of 0.11–4.72 ng/mg of hair and doses ranging from 32–825 mg/day. Joseph *et al.*, [40] Joseph et al., (1999) and Ropero-Miller *et al.*, [42] show correlation coefficients of 0.45 and 0.43 respectively whilst Henderson *et al.*, [57] and Scheidweiler *et al.*, [41] do not produce any statistics.

3.7. Amphetamine and methamphetamine

Polettini *et al.*, [48] conducted a controlled dose-concentration study on methamphetamine, reporting hair concentrations ranging from 0.13

Table 1
Results of the literature search for dose-concentration relationship between drugs and hair. A total of 36 individual dose-concentration assessments were found across 29 individual studies were found involving a controlled administered dose with a human subject and a concentration obtained in hair. *P*-value shows a statistically significant correlation at < 0.05, where p-values have been reported following correlation analysis.

Dose range (mg/day)	Hair Concentration Range (ng/mg of hair)	No. of subjects	Correlation Coefficient (r)	P-Value (*p*)	Reference
Heroin					
210 – 780	0.05 – 6.83	46		<0.0001	[32]
			0.6587		
	1.86 – 14.36	20	0.3226	0.1654	[30]
141 – 715.4					
120 – 750	0.3 – 10.5	43	0.01	0.9493	[31]
Methadone					
					[33]
15 – 230	0.7 – 43	26	0.1022	0.6193	
					[34]
20 – 60		20	0.1019	0.6690	
	0.0 – 15.0				
55 – 100		8	0.8187	0.0129	[35]
	2.45 – 78.1				
480 – 7400	1.42 – 10.63	23	–	–	[36]
					[37]
25 – 70	0 – 42	5	0.63	0.2546	
30 – 250	0.25 – 13.29				[38]
		41	0.760	<0.001	
20 – 165	2.6 – 63.2	60		0.1140	[39]
			0.2263		
Codeine					
60–120 (per 70 kg)			–	–	[40]
	1.1 – 3.1	5			
75–150 (per 70 kg)	1.109 – 3.151				[41]
		10	0.43	<0.05	
60–120 (per 70 kg)	0.71 – 8.7	8	0.4394	0.2760	[42]
100	0.057 – 0.566	9	–	–	[43]
30 – 60	0.06–5.74	22	0.539	0.03	[44]
Buprenorphine					
	0.0003–0.238	18	0.851	< 0.05	[45]
2.2 – 12					
0.2 – 4.0	0.02 – 0.59	14	–	–	[46]
Cannabis (THC)					
0 – 14.8	0 – 0.1				[47]
		38	−0.1912	<0.05	
Amphetamines					
40 – 80					[48]
	0.17 – 5.3	7		0.1829	
			0.4582		
50	0.07 – 12.5	9	–	–	[49]
Cocaine					
75—150 (per 70 kg)	1.7—27	8	0.4394	0.2760	[42]
75—–150 (per 70 kg)	2.379 – 4.721	10	–	–	[41]
75 – 150 (per 70 kg)	1.8 – 3.2	5	–	–	[40]
32—–825	0.11 – 4.02	25	–	–	[50]
Clozapine					
	0.17 – 34.24	22	0.542	<0.0001	[51]
200 – 700					
150 – 425	167 – 59.2	16	0.8047	0.001	[52]
8.3 – 62.5		12	0.91	0.0002	[53]
	0.16 – 3.05				
Tenofovir					
2 – 7		18	–	–	[54]
	0.012 – 0.053				
Amitriptyline					
0.13 – 2.08	0.61 – 11.0	25	0.0451	0.8305	[55]
Maprotiline					
0.21 – 3.07	1.4 – 40	13	0.3783	0.2025	[55]
Carbamazepine					

(*continued on next page*)

Table 1 (*continued*)

Dose range (mg/day)	Hair Concentration Range (ng/mg of hair)	No. of subjects	Correlation Coefficient (r)	P-Value (*p*)	Reference
		40		0.0019	[56]
200 – 1000	13.58 – 24.23		0.476		
Valproic Acid					
	5.81–9.63	40	0.717	<0.0001	[56]
200 – 3000					
Phenytonin					
100—400		60	0.883	<0.0001	[56]
	6.55 – 16.76				
Chlorpromazine					
	1.6 – 27.5	16	0.8047	0.001	[52]
100 – 500					
GHB					
3—9	1.56 – 2.69	19	0.3	0.1	[14]
34—377	6.3 – 239.6	30	–	0.45	[15]

Abbreviations: GHB, gamma-hydroxybutyrate; THC, Tetrahydrocannibinol.

to 0.54 ng/mg and a correlation coefficient of 0.4582 in subjects administered doses between 40 and 80 mg. The second study by Jakobsson & Kronstrand, [49] showed a concentration range between 0.07 – 12.5 ng/mg in hair with subjects being dosed with 50 mg up to three months.

3.8. Gamma Hydroxy Butyrate (GHB)

The first study by Nebel *et al.*, [14] states that GHB concentrations can be seen in hair in patients using GHB to treat narcolepsy, as the average concentration observed was 1.86 ng/mg, with the correlation coefficient being 0.30. The subjects were dosed with concentrations between 3—9 g a day for up to 148 months. Results were not statistically significant ($p = 0.100$). As seen in Table 1, the second study by Van Elsué *et al.*, [15] has a higher statistical significance ($p = 0.450$) as concentrations in hair were seen between 6.3–239.6 ng/mg. Subjects ingested between 34–337 g a day for up to 120 months.

3.9. Pharmaceuticals

A wide range of studies was found investigating dose-concentration relationships with various pharmaceuticals: anti-depressant [55], anti-retroviral [54], anti-seizure [56] and anti-psychotic drugs [51–53]. Statistically significant correlations are found in all the pharmaceutical drugs, except for the anti-depressants' amitriptyline ($r = 0.0451$) and maprotiline ($r = 0.3783$). No statistical analysis was carried out by Liu *et al.*, [54] regarding anti-retroviral drugs.

4. Discussion

There is much discrepancy within the literature regarding dose and concentration between drugs and hair, with the published literature on each drug giving conflicting results. Some studies demonstrated an apparent dose-concentration relationship between drugs and hair, whilst others find no correlation. Even amongst the more rigorously executed studies, sample sizes are frequently too small to support robust conclusions, while others rely on long-term cohorts of heavy drug users in whom the likelihood of undisclosed illicit consumption is high, undermining any attempt to link administered dose with hair concentration [23]. Moreover, substantial methodological variability exists across studies. For example, the Society of Hair Testing (SoHT), recommends that samples need to be stored in a dark area at room temperature. They suggest swelling can occur in frozen/refrigerated environments, leading to drug loss. [22,58]. However, in Polettini *et al.*, [48]), Huestis *et al.*, [47], and Joseph *et al.*, [40] it is stated in their methodology the hair samples were frozen to −30°C prior to analysis. No information can be found on how much of the drug would be lost if frozen/cooled. However variability in pre–analytical handling, including storage, washing, digestion methodology, derivatisation, and analytical instrumentation, almost certainly contributes to the inconsistent dose-concentration findings reported across the literature [59].

4.1. Cannabis and amphetamines

The only controlled studies examining drug intake-hair concentration relationships for cannabis and amphetamines are those conducted by Huestis *et al.*, [47]; Polettini *et al.* [48]; and Jakobsson & Kronstrand [49]. These experiments show notable methodological limitations and interpretive limitations. They both employ a small number of subjects, who are dependent on cannabis or methamphetamine and carry the study over the course of 10 weeks, expecting abstinence from the drugs. This allows for the permittance numerous unmonitored behaviours that could distort results. Huestis *et al.*, [47] concluded that delta 9-THC is not incorporated into hair following oral administration. However, this conclusion was based on a study involving only two participants, who received oral THC tablets. This raises concerns regarding statistical robustness and the validity of generalising these findings. In addition, only THC and its metabolite (THC–COOH) were measured, and extremely low concentrations near analytical limits of detection increase the likelihood of false–negative interpretations. Polettini *et al.* [48] used seven subjects, only four of whom took low and high doses of methamphetamine. No linear relationship could be found ($r = 0.4582$) and there was a large overlap in the range of low and high doses. This overlap suggests that analytical variability, melanin content, segment length, and timing of sample collection may have influenced the results as much as, if not more, the ingested dose [43,60]. Jakobsson & Kronstrand [49] similarly inconsistent findings following a 50 mg oral dosing of amphetamine. The controlled-dose study stated the samples presented two patterns regarding segmental analysis; either the concentration in hair decreased towards to proximal end or it increased, demonstrating inconsistent patterns. The authors provide no explanatory mechanism for these opposing trends, and because the publication does not supply numerical raw data for each segment, it is not possible to perform an independent statistical assessment of dose–concentration relationships. Given the prevalence of these substances in patterns of misuse, the relative scarcity of controlled studies, and the inconsistent findings within them, it is shown that there is a limited reliability of hair analysis for quantifying intake of cannabinoids or amphetamines, especially at low doses.

4.2. Heroin

Across the three controlled heroin–maintenance studies reviewed the findings consistently show that dose cannot be reliably inferred from hair opiate concentrations, even when heroin administration is medically supervised [30–32]. The variability observed across these studies underscores the significant influence of methodological, biological, and behavioural factors on opiate incorporation into hair, even under highly controlled condition [32]All three studies were carried out on maintenance patients using pharmaceutical heroin, and all employed GC–MS as the quantification method, although the sample size, duration, length of hair segment, and analytes varied across the studies. Kintz et al., [30] used segments of hair samples from 20 patients, each measuring 4 cm (~100 days), while Girod & Staub [31]employed segments of hair samples from 43 maintenance patients and 74 illicit users, each measuring 3 cm, and Musshoff et al., [32] used 1 cm proximal segments from 46 patients over 12 months. A notable limitation across the three heroin dose-concentration studies is their extended duration, ranging from four to twelve months. Given that these investigations were conducted with individuals experiencing opioid dependence, the potential for unsupervised or illicit consumption outside the prescribed dosing regimen is substantial. These individuals are at high risk of unsupervised heroin use, and any unreported intake would fundamentally confound dose-concentration interpretations. This issue is illustrated by Musshoff *et al.*, [32], in which three participants did not receive prescribed heroin, having been transitioned to a methadone substitution. Nonetheless, low concentrations of heroin and its metabolites were detected in their hair. The presence of heroin in participants who were no longer prescribed it strongly suggests additional illicit consumption. This discrepancy highlights the need for greater transparency in statistical reporting to ensure the robustness and reproducibility of findings.

4.3. Codeine

Most identified studies (n = 5) examine broadly comparable dosing regimens over similar timeframes and with comparable cohort sizes. Despite this methodological alignment, the reported hair concentration ranges vary between studies. This variability suggests that factors beyond administered dose, such as individual metabolic differences, hair characteristics, and analytical methodology, may influence the measured concentrations [6,12,22]. Joseph *et al.*, [40] used a highly controlled inpatient model, collecting weekly whole–scalp shavings from five African–American males over 10 weeks. Codeine dosing was alternated with cocaine, allowing clear identification of incorporation timelines. The authors state that the concentration found in hair is dependent upon the dose. However, they only explain the data for unwashed hair. No mention of a correlation is provided for the washed hair samples, which found, on average, 44% reduced concentrations of codeine and cocaine. No statistics were performed to find out if a correlation did exist with any statistical significance; it is hard to ascertain a dose-concentration relationship from this data with no graphs or evidence to support this. Ropero-Miller *et al.*, [42] states that there is a dose-concentration relationship with a high variability between the doses following a controlled study using eight subjects. Subjects were taking low (60 mg/70 kg) and high (120 mg/70 kg) doses of codeine over a 10-week period. The low doses range from 0.71-5.7 ng/mg of hair, which has a large overlap with 1.8–8.7 ng/mg of hair found with the high doses, proving it is difficult to distinguish between high and low dose use. This large inter-individual dose variability in data is also seen in Scheidweiler *et al.*, [41]. Scheidweiler et al., also further highlighted methodological sensitivity by employing LC–MS/MS, which offers greater sensitivity and selectivity than the GC–MS approaches used in the other studies. Despite this advantage, they likewise observed a wide range of codeine concentrations and major overlap between dose conditions. Analytical sensitivity did not reduce population variability; instead, it revealed how strongly incorporation depends on individual metabolism and hair structure. Overall, the comparative evidence makes clear that codeine incorporation into hair is not linearly or reliably dose–dependent.

4.4. Methadone

Methadone was found to have the highest number of studies conducted. Several features are broadly similar across the studies. All examined individuals enrolled in methadone maintenance programmes, typically with daily supervised doses [61]. All of the studies detected both methadone and 2–Ethylidene–1,5–dimethyl–3,3–diphenylpyrrolidine (EDDP) in hair with high frequency, and all adopted segmental hair analysis to represent recent exposure. A major differentiator between all of these is analytical technique used. Marsh et al. (1995) relied on radioimmunoassay (RIA), an older technology with limited specificity, making its quantitation prone to cross–reactivity. In contrast, Moeller et al. [37] and Goldberger et al., [34] used broad GC–MS panels that detected methadone effectively but were not designed for precise dose–response interpretation. Later work by Lucas et al., [35], Girod & Staub [33], and Paterson et al., [39] employed selective GC–MS or GC–MS/SPME, enabling more reliable quantification. Four of the eight studies describe a correlation, however, only two of which have statistical significance in their correlations. All the studies that have a positive correlations [35,37,38] indicate that whilst it is not possible to obtain concentrations from unknown samples, it can be ascertained whether a subject has been consuming low or considerable amounts. Despite reported correlations, the substantial overlap in concentration ranges across dose groups indicates that the data do not allow for clear differentiation between low and high dosing. Paterson *et al.*, [39] states that there is a significant difference between the concentrations in female and male hair. Females had a correlation coefficient of 0.0619 whereas males have a correlation coefficient of 0.3153. Although this may be attributable to the increased likelihood of cosmetic treatments and the sample size, it is noteworthy that only 31% of participants were female. Furthermore, the presence of metabolites was not explored in this study. Studies finding correlation, such as Musshoff *et al.*, [32], find a stronger correlation using the total methadone and metabolite concentration. The statistical analysis of the pooled data from the literature shows a weak correlation coefficient of 0.3329. This does, however, show statistical significance ($p = 0.0011$). This suggests a general trend of increasing concentration with higher doses. However, the data reveal considerable variability, making it impossible to reliably distinguish between high and low usage. In some cases, individuals receiving a high dose exhibit lower concentrations of methadone in their hair, than those administered a low dose. As with the previous opioids, the central finding is consistent. Although methadone and EDDP are reliably detected in hair, the relationship between administered dose and resulting concentration is highly inconsistent. This inconsistency likely reflects variation in analytical methods, decontamination protocols, metabolite inclusion, hair mass analysed, participant characteristics, and study duration. Overall, methadone hair testing provides strong qualitative confirmation of exposure but has limited quantitative value for dose estimation.

4.5. Cocaine

Ropero-Miller *et al.*, [42] reported that a 150 mg/kg cocaine dose yielded approximately twice the concentration of cocaine was observed in the hair when compared to the 75 mg/kg dose. However, this pattern is evident in only around half of the dataset. The significant overlap in the range of concentrations for low and high doses makes any conclusion with regard to the actual dose consumed highly unreliable. Significant overlap in the range of concentrations for low and high doses means that the estimation of doses is highly unreliable. This is similar to the findings of Joseph et al., [40], where despite controlling for alternate doses of cocaine/codeine, significant intra-subject and inter-subject variability

were observed with some subjects showing marginal increases in peak concentrations of hair even when doses are doubled.

Henderson *et al.*, [57] similarly found inconsistent dose-concentration relationships when using isotopically labelled cocaine–d5 to eliminate confounding from prior drug use. The authors conclude that cocaine is more rapidly absorbed into non-Caucasian hair as they had more cocaine present than Caucasian. However, there were only four non-Caucasian subjects to 21 Caucasian subjects, given the low number of subjects used in the study, this conclusion is statistically weak. The limited representation of minority hair types makes the conclusion weaker, especially when compared with Joseph et al., [40] who also observed large inter–subject variability but attributed this to multiple mechanisms of incorporation, including sweat/sebum and diffusion into the hair root, rather than race alone. Overall, only two of the four studies show any clear dose-concentration relationship, but even then, only at the group mean level, not at the individual level. Although cocaine exposure in hair samples is readily detected, the literature clearly shows that hair analysis cannot accurately determine the quantity of cocaine used, even under tightly controlled clinical conditions.

4.6. GHB

The gamma-hydroxybutyrate (GHB) studies further reinforce the overall conclusion that hair concentrations do not correlate with dose. Both Van Elsué *et al.*, [15] and Nebel et al., [14] show that although repeated intake can elevate levels above endogenous values, no relationship exists between the amount consumed and the concentration measured in hair. There is extensive overlap between endogenous, therapeutic, and chronic–use ranges. Nebel et al., [14] examining patients taking 3–9 g nightly, found concentrations typically within endogenous variability and unrelated to either dose or duration. Similarly, Van Elsué *et al.*, [15] reported no association between daily intake (30–336 mL/day) and hair concentrations, despite values ranging from 6.3 to 239.6 ng/mg in dependent users. Both studies also highlighted the unpredictable reductions caused by cosmetic treatments such as dyeing or bleaching. Overall, the GHB literature mirrors that of other drugs, whereby even under well–documented exposure conditions, dose discrimination of single–use events remain impossible.

4.7. Pharmaceuticals

There appears to be a stronger correlation between pharmaceutical dosage and hair concentration, which may reflect the lower likelihood of misuse or erratic consumption patterns associated with prescribed medications. However, several salient methodological limitations are evident within these studies, including small sample sizes, inadequate control of confounding variables, and inconsistent analytical protocols. These flaws collectively undermine the reliability of the reported associations and highlight the need for more rigorous, standardized research designs. Kintz *et al.*, [46] states there is a dose-concentration relationship between buprenorphine and hair. However, they did not wash the hair prior to analysis, casting doubt on the accuracy of the results through contamination. The same lack of a wash procedure is observed by Kronstrand *et al.*, [53] and Liu *et al.*, [54]. The high correlations observed in these studies could be attributed to contamination by sweat or drug residue from hands, artificially inflating dose-concentrations of drugs in hair correlations. Shen *et al.*, [52] infers that Cirimele *et al.*, [51] had a weak correlation because of the wash procedure used. However, there is a more noticeable difference between the two studies, other than the procedure. In Shen, all the subjects were black haired Japanese patients, compared to a varied hair colour subjects in Cirimele *et al.*, [51]. Rollins *et al.*, [9] reported that drugs are more likely to be incorporated into black hair, and more likely to be incorporated into Asian hair due to higher melanin content [61,62]. The strong correlations observed in Shen *et al.*, [52] likely reflect pigmentation effects rather than methodological superiority. Therefore, it is expected that there is a good correlation shown between both the doses of chlorpromazine and clozapine and hair concentration in Shen et al., (2002)with all black-haired participants.

4.8. Melanin content

A consistent theme across the reviewed studies is the correlation between melanin content in hair and drug concentration. Polettini *et al.*, [48], Scheidweiler *et al.*, [41] (Scheidweiler et al., (2005) and Kronstrand *et al.*, [43] report a direct association between melanin levels and drug incorporation, suggesting that pigmentation plays a significant role in drug binding within the hair matrix. Furthermore, Henderson *et al.*, [50], Kronstrand *et al.*, [43], Ropero-Miller *et al.*, [42], Shen *et al.*, [52], Musshoff *et al.*, [32], Huestis *et al.*, [47] and Liu *et al.*, [54] consistently demonstrate that darker or black hair incorporates higher concentrations of drugs compared to lighter-coloured or chemically treated hair. This phenomenon is often attributed to the affinity of basic drugs for eumelanin, which is more abundant in darker hair, thereby influencing drug deposition and retention [60,62]. However, exceptions exist. For instance, Kintz *et al.*, [30] found no significant effect of hair colour on the incorporation of heroin or methadone, indicating that the interaction between melanin and drug molecules may be compound specific. These findings underscore the importance of considering hair pigmentation as a potential confounding factor in forensic toxicology, particularly when interpreting quantitative results for dose estimation or comparative analysis [63].

5. Conclusion

The relationship between drug dose and hair concentration remains highly inconsistent across the literature. Although modest correlations have been reported for certain pharmaceuticals such as methadone and clozapine, no meaningful association has been demonstrated for heroin, codeine, buprenorphine, amphetamine, GHB, or cannabis. Findings across all drug classes consistently show substantial overlap in hair concentrations between low- and high-dose groups, preventing reliable retrospective dose estimation. The critical review presented in this work highlights that inconsistencies arise not solely from analytical variation but from fundamental biological processes. For example, sweat contamination has been identified as a major source of variability among individuals consuming identical doses. Adjusting for melanin content may improve accuracy; however, external influences such as washing, bleaching, dyeing, ultraviolet exposure, and heat treatment further complicate interpretation. Much of the literature concludes by advocating for additional research into dose-concentration relationships. Controlled administration studies provide more reliable insights into dose-concentration dynamics, yet ethical constraints limit their scope and frequency. Future research should prioritize pharmaceuticals that are less commonly abused and incorporate corrections for melanin concentration to refine interpretative models. The present review aimed to evaluate whether a dose-concentration relationship exists that could enable estimation of consumed dose from hair analysis. No such relationship was identified. At best, hair testing can confirm exposure to a substance, but it cannot distinguish intentional ingestion from passive, nor can it quantify the amount consumed. Consequently, hair analysis should be regarded as a qualitative indicator of exposure rather than a quantitative measure of dose.

CRediT authorship contribution statement

Daniel Preece: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Abigail Jones:** Writing – review & editing, Investigation.

Declaration of competing interest

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Appendix A. Supplementary data

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