Table 2
Pharmacokinetic properties and likely extent of postmortem redistribution for selected drugs of abuse

Drug/drug class	Common dose (mg)	Usual blood levels (mg/l)[a]	Main active metabolite or bio-marker[b]	V_D (l/kg)	$T_{1/2}$ (h)	Extent of redistribution[c]	Selected references
Amphetamine	10–100	0.2	None	3–5	4–30	Low	[107]
Methamphetamine	50–2000	0.2	Amphetamine (~10%)	3–4	10–30	Low	[168,169]
MDMA	50–250	0.3	MDA	Moderate	~8	Moderate	[170,171]
MDA	50–250	0.4	None	Unknown	–	Moderate	[170]
MDEA	50–200	0.5		Unknown	–	Moderate	[110,114]
MBDB	50–200	0.5		Unknown	–	Moderate	[118,170]
PMA	50–100	0.2	None	Unknown		Moderate	[119–121]
Heroin	10–100	–	Morphine, 6-AM	See morphine	<0.1	Low to moderate	[161,172,173]
Morphine	10–100	0.5	None, but bio-conversion from glucuronides	2–4	2–4	Low to moderate	[18,51,99,174]
Methadone	10–120	1.0	EDDP is often measured in urine	3–5	15–72	Moderate	[97,164,175,176]
Codeine	8–60	0.2	Morphine (10%)	4	2–4	Low to moderate	[177]
Buprenorphine	<1–24	0.05	Norbuprenorphine	3–7	2–9	Low to moderate	[178,179]
Meperidine	50–200	1.0					[180]
Oxycodone	5–30	0.2					[181,182]
Tramadol	50–400	1.0	Hydroxy-metabolite (M1)	2–3	5–7	Low to moderate	[183–185]
Alprazolam	0.5–4	0.5	α-Hydroxy-alprazolam	1	6–22	Low	[186]
Diazepam	5–40	1.0	Nordazepam	0.5–2.6	20–50	Low	[187]
Flunitrazepam	1–2	0.05	7-Amino-flunitrazepam	3–6	11–25	Low	[188–190]
Oxazepam	15–60	1.0		0.5–2	4–15	Low	[191,192]
Temazepam	10–20	1.0	Oxazepam	1	5–15	Low	[193]
Zolpidem	10–20	0.5		0.6	2–4	Low	[4,194]
Cocaine	10–100	0.5	Benzoylecgonine, EME*	1–3	0.6	Low	[127,195,196]
THC	5–25	50	11-Carboxy-THC*	9–11	19–96	Low to moderate	[160,197,198]

[a] Maximum postmortem blood concentrations following usual doses, although higher concentrations can be achieved in particular situations.

[b] Bio-marker of parent drug.

[c] Refers to best estimate of author. 6-AM: 6-acetyl morphine, EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, EME: ecgonine methyl ester, MDMA: methylenedioxy-methamphetamine, MDA: methylenedioxy-amphetamine, PMA: *para*-methoxy amphetamine, THC: Δ^9-tetrahydrocannabinol.

concentration following disruption of cellular membranes. This process is particularly significant for drugs with high lipid solubility or high tissue concentrations relative to blood taken from the heart. Table 2 provides a summary of the volume of distribution and extent of redistribution for selected drugs of abuse.

The drug with the highest lipid solubility and volume of distribution of the substances shown in Table 2, tetrahydrocannabinol (THC) has surprisingly not showed consistent increases in blood concentration after death [92,93]. This has been more recently confirmed [85], despite data that shows reversible uptake into muscle and fat in humans [94]. If this is confirmed with further studies it is likely that redistribution is not simply due to drug gradients between tissues.

The drug with the next highest volume of distribution, methadone, does exhibit moderate increases in blood concentration after death ranging up to four-fold, although there is significant site to site variability [95,96]. Regression analysis on 31 subjects show a two-fold increase for males and a three-fold increase for females [97].

The more water-soluble morphine shows little change in blood concentration after death in humans [98,99], although increases have been demonstrated in rats [100]. Production of morphine from hydrolysis of glucuronides is likely to be a more significant factor potentially elevating morphine concentrations postmortem (see earlier).

Two-fold increases have been demonstrated for MA when femoral and heart blood specimens were compared [101–104]. This appears to be due to diffusion of drug from the pulmonary circulation into the left cardiac chambers [105]. MDMA and PMA have also been shown to undergo increases in blood concentration after death [5,106].

Benzodiazepines show variable changes in the immediate postmortem period, although the reported magnitude of any changes are generally low due to their relatively low volumes of distribution [9,13].

It is worth noting that while femoral blood and perhaps other peripheral bloods show fewer changes than blood taken from the thoracic and abdominal areas, it too will show higher concentrations of drugs following a postmortem period. These processes are not limited to blood. Liver and lung tissue show differences in the concentration of drugs depending on the nature of the drug and whether diffusion of drug has occurred from neighboring tissues or the blood supply. For example, the left lobe of the liver is more likely to exhibit elevated drug concentrations than the right lobe [3].

As with all drugs substantial site to site variability can occur. This is due to not only redistributive processes, but also due to differences in hematocrit, influences of other fluids and other factors affecting the quality of blood even in situations where significant putrefaction has not seemingly occurred [3,9,85,94].

6. Drug monographs

6.1. Amphetamines

This group of strong stimulants are based on the dexamphetamine nucleus, and include MA, MDMA (ecstasy), methylenedioxy-amphetamine (MDA), methylenedioxyethylamphetamine (MDEA), and other designer forms such as PMA, and *N*-methyl-benzodioxazoylbutanamine (MBDB) [107]. Their pharmacokinetics and metabolism are diverse as suggested from their chemical names. Their common doses, any active metabolite, half-lives and usual blood concentrations are shown in Table 2.

Oral use of MA typically produces postmortem blood concentrations of up to about 0.2 mg/l. Corresponding blood concentrations of amphetamine is similar or slightly higher than MA.

Neither MA or AM seem to be associated with many deaths. When this does occur it is more likely that the heart has been weakened in some way, e.g. hypertrophy, contraction bands, or a predisposition to arrhythmias with prolonged QT-syndrome [108–110].

MDMA produces peak levels of 0.4 mg/l at 2 h following an approx. 100 mg dose. Under conditions of a single oral dose of MDMA little MDA is detectable in blood [111]. Disproportionate rises in blood concentrations occur with increasing doses of Ecstasy. This may be a cause of toxicity in susceptible persons [112].

Single doses of 75 or 125 mg MDMA significantly increase blood pressure (up to 40 mmHg systolic blood pressure), heart rate (~30 beats/min), and pupillary diameter (mydriasis), but not body temperature. Maximum plasma concentrations of 75 and 125 mg MDMA doses were about 0.13 and 0.24 mg/l at 2.4 and 1.8 h, respectively. The terminal elimination half-lives were about 8 h for both high and low MDMA doses [113].

MDMA and indeed other amphetamines cause significant rises in systolic blood pressure (~40 mmHg) and heart rate (~30 beats/min). This may be dangerous in persons with compromised cardiovascular function or impaired cerebral blood flows. Significantly, under heat stress MDMA may cause precipitous rises in core body temperature leading to rhabdomyolysis, coagulopathies and kidney failure. Liver damage has also been seen with MDMA [114].

Deaths have been reported with other designer amphetamines including MDEA [110,114–117], MBDB [118]. Deaths reported from PMA seem to outweigh this designer amphetamine's street availability suggesting PMA may be more toxic again on the brain [106,119–126].

6.2. Cocaine

Cocaine shares many of the toxicological features of the amphetamines in that it is a potent stimulant of nerve function. It is an inhibitor of reuptake in dopamine and norepinephrine nerve terminals in the CNS as well as serotonin. Cocaine also acts as a local anesthetic and is still used medically in otolaryngological procedures.

Cocaine as the free base is insufflated ("snorted") or inhaled as a vapor (smoked), or injected intravenously (usually as the hydrochloride salt). In the USA and Europe, cocaine is one of more prevalent illicit drugs.

The pharmacokinetics of this drug has been studied in humans in controlled settings. The terminal elimination half life of cocaine ranges from about 40 min to 4 h, depending on dose [127]. Cocaine is rapidly metabolized to a range of hydrolytic substances of which BE and EME are most significant. The biologically active ethyl *trans*-esterification analog cocaethylene (CE) is found in significant amounts in tissues of persons co-consuming ethanol. The formation of cocaethylene is route dependent but does not occur postmortem suggesting the active involvement of enzymes to facilitate bio-transformation [128,129]. Anhydroecgonine methyl ester (methylecgonidine) is only formed during smoking of cocaine as a result of pyrolysis [127,130]. It has a different profile of activity to cocaine acting as a muscarinic agonist to lower blood pressure [131].

BE and EME are commonly used to identify past use of cocaine when the parent drug is no longer present in blood. The predominate species in urine is BE and EME, although about 1–9% is cocaine [132]. Detection times using a 300 ng/ml cut-off is about 1–4 days [133], although this can be about a week in long term users [134]. Oral use leads to greater amounts of EME and CE due to first-pass metabolism. In contrast to urine the predominant species in hair, sweat and oral fluid is the parent drug itself [47,54,135]. Depots of cocaine in tissue can result in detectability in oral fluid well beyond that expected based on its blood pharmacokinetic profile [133]. The pharmacokinetics of cocaine in these alternative specimens requires more evaluation before their use can be optimized.

Cocaine is a potent stimulant with commonly used doses ranging from about 10 to 100 mg. Tolerance can set in quickly leading to a rapid escalation of doses up to over

1 g daily. As with other illicit drugs covered here there is no defined "safe" or "therapeutic" blood concentration. Since postmortem hydrolysis continues to occur after death, measurement of cocaine concentrations is unlikely to yield useful interpretive information [136]. It appears the brain cocaine is more stable to hydrolysis than other tissues [2].

Excessive use of cocaine can lead to a number of life threatening conditions. Ischemic heart disease is typified by contraction bands and sudden arrhythmic death. Pathological core temperatures leading to rhabdomyolysis, intravascular coagulation, renal failure and convulsions can also occur [137–140]. Its use with alcohol and with heroin and other narcotics increases its toxicity significantly.

6.3. Benzodiazepines

The benzodiazepines are a large group of substances typified by diazepam and alprazolam, but with a significant difference in potency and physiochemical properties. Non-benzodiazepines acting on a similar receptor system include zolpidem, zopiclone and zalpelon. These latter drugs are becoming increasingly used due to their lower profile of side-effects. Benzodiazepines and their close relatives bind to the gamma-aminobutyric acid (GABA) receptor affecting chloride movement through ion channels. This results in a reduction in activity in a number of key areas in the CNS involved in arousal and emotions.

While these drugs have a large medical use, their ability to relax, induce sleep and to assist in coping with mood swings between use of harder drugs such as heroin, cocaine and amphetamines means they are widely used (and abused) in the drug seeking community. Their use in drug facilitated assault and their ability to increase crash risk on the road is also noteworthy. Consequently, toxicologists need to be able to detect these drugs in biological specimens and to understand their toxicology.

The pharmacokinetics varies substantially between members from short acting hypnotics oxazepam, zolpidem and midazolam to long acting anti-anxiety agents diazepam, alprazolam and flurazepam. Profiles of selected members are found in Table 2. Some members are metabolized to active substances, e.g. diazepam to nordiazepam, flurazepam to desalkyl-flurazepam, while most are metabolized by hydroxylation and/or glucuronidation.

From a toxicological perspective given their diversity in potency and structure very few laboratories would be able to measure all drugs in this class in one analytical method. Immunoassay screens will often have difficulty with the morphine potent members, e.g. lorazepam and triazolam, and will not detect the non-benzodiazepines such as zopiclone or zolpidem [141]. For this reason, a chromatographic screen is recommended to at least supplement the traditional immunoassay screen. Recently, the development of LC–MS as a routine toxicological tool a number of assays have been developed for the wider group of benzodiazepines [142–145]. This technique has the advantage of also allowing the simultaneous confirmation and quantification of the drugs in the specimen.

Blood concentrations of benzodiazepines provide some indication of the usage of the drugs in the recent past, providing the stability of the drug is taken into account (see earlier), particularly in decomposed tissue for all benzodiazepines and the nitrobenzodiazepines in all cases. With some exceptions, parent benzodiazepines are the usual target in blood, hair and solid tissues, although metabolites are targeted in urine. The 7-amino-metabolites of the nitrobenzodiazepines are formed postmortem and need to be targeted with the parent in all postmortem cases. Urinary concentrations do require prior hydrolysis to liberate the glucuronide metabolites of the diazepam family (temazepam, oxazepam) [141].

Poisonings associated with this class of drug are among the most common [107]. Numerous fatalities have been reported with benzodiazepines, particularly in persons with compromised cardio-respiratory function (i.e. elderly persons). They are also very often associated with opioid cases, such as heroin and methadone deaths, where they may play a significant role [146].

6.4. Cannabis

This perennial plant includes various sub-species of *Cannabis sativa* and is the most used illicit drug in many jurisdictions. The main active cannabinoid is Δ^9-tetrahydrocannabinol. Modern cultivars and strains including "skunk weed" have a THC dried weight content of over 20%, although, most forms of cannabis have THC yields of 2–8%. Sinsemilla cannabis with the flowering heads has a typical THC content of 7–14 %. The only other cannabinoids that show significant activity are Δ^8-tetrahydrocannabinol, Δ^9-tetrahydrocannabivarol and cannabinol.

Peak THC plasma concentrations in blood rapidly exceed 50 ng/ml within 15 min of smoking and can reach 200 ng/ml with higher THC-content cigarettes [147,148]. THC is rapidly distributed to fat and muscle due its low water solubility resulting in a rapid decline in blood plasma THC concentrations. The half-life of this distribution phase is less than 1 h and plasma THC concentrations greater than 10 ng/ml are uncommon after 1 h even after moderate to high doses of cannabis [149]. Since the blood to plasma distribution is about 0.5, this represents about 5 ng/ml in blood. However, data obtained postmortem suggests that the distribution of cannabinoids between whole blood and serum is variable [150].

While the terminal elimination half-life of THC is 3–13 days blood concentrations are usually below 2 ng/ml after a few hours of last use and only highly sensitive analytical methods are able to detected the terminal stages of drug elimination [151].

In traffic cases blood THC provides a better measure of recent cannabis use, than the urinary metabolite. Recent data suggest that drivers with a measurable THC concentrations (>1 ng/ml) have an elevated crash risk [152–154].