

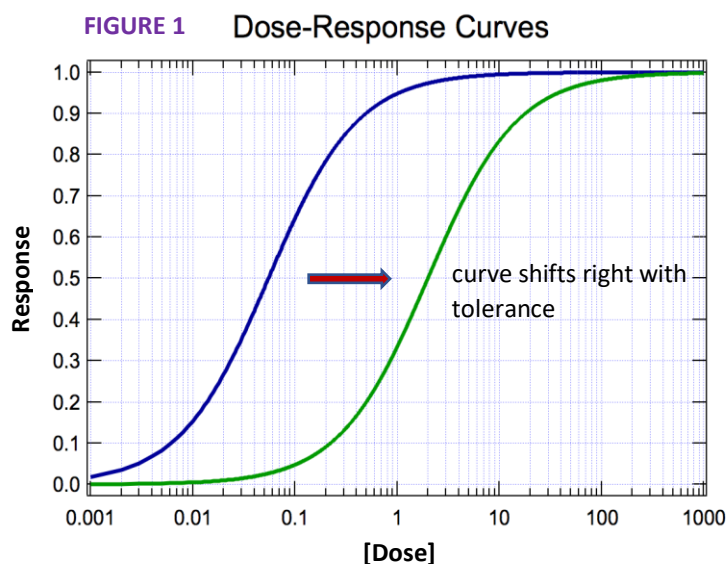
Tolerant or Intolerant?

Learning from studying drug concentrations in the living and the dead.

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INTRODUCTION

Tolerance is defined as a person's diminished response to a drug when that drug is used repeatedly, and the body adapts to its continued presence. From a physiological standpoint, this means that larger quantities of the drug are required to obtain the desired effects. This can be achieved by using increased and/or more frequent dosages or by adding drug(s) to the dosing regimen (Ref. 1). Dose-response curves are simple and practical ways to visualize the concept of tolerance. No matter the mechanism by which a drug exerts its effects (e.g., receptor binding, chemical interaction, etc.) the drug concentration at its intended site of action controls its endpoint effect. Dose-response curves are plotted with dose in log form on the x-axis and quantifiable effect (response) on the y-axis. The main parameters that can be identified by dose-response curves are drug potency based on the location of the curve along the x-axis, the dose required for maximal efficacy, and changes in response per unit dose (Ref. 2). A rightward shift of the curve indicates the development of tolerance. (Figure 1).



BEST PRACTICES FOR THE INTERPRETATION OF TOXICOLOGY RESULTS

In 2019, the American Academy of Forensic Science Standards Board (ASB) published the consensus-based document *Guidelines for Opinions and Testimony in Forensic Toxicology* (Ref. 3). Sections 5.2 and 5.3 address best practices for the interpretation of drug concentrations by toxicologists. Specifically, the first sentence of Section 5.3.i states that "A toxicologist should not opine as to the effects of a drug or combination of drugs on a specific individual without the context of a given case." Without the appropriate training to interpret analytical results in relation to the functioning of the body, the inherent risk exists that a postmortem case will be misdiagnosed. Some main factors that should be considered when forming an opinion concerning drug effects include but are not necessarily limited to:

- 1) Pharmacodynamic effects
- 2) Interval between the time of drug use and death – especially in patients who survived for a period before death
- 3) Normal rates of metabolism and elimination
- 4) Disease or conditions that can impact hepatic and/or renal elimination
- 5) Presence of drugs that can produce additive or synergistic effects
- 6) Drug interactions
- 7) Tolerance or sensitization
- 8) Postmortem redistribution
- 9) Drug stability
- 10) Autopsy findings

WHAT TOLERANCE IS AND IS NOT

Drug tolerance is a pharmacological concept that describes the reduced reaction to a drug following its repeated use. Its development occurs through distinct mechanisms which may work alone or together (Figure 2). While drug tolerance is predictive of chronic drug use, drug dependency or drug addiction (substance use disorder) is not inherently associated with it. Drug dependence is the physical need to have the drug acting within the body because the body has become accustomed to its continued presence (Ref. 4). One example is the patient who decides on their own to

discontinue taking their antidepressant medication. As the blood concentration decreases, symptoms such as irritability, headache, nausea, and dizziness begin to appear and worsen. This is because the body was “dependent” on the antidepressant and without it, the effects of withdrawal are felt by the patient. In contrast, drug addiction is a chronic, relapsing disorder characterized by compulsive drug-seeking behavior despite negative outcomes such as loss of employment, damage to relationships, and the potential for significant legal consequences. An example is a person that was prescribed an opioid painkiller following a sporting injury. The use of the medication produces positive feelings of euphoria that are pleasurable and desirable. With time the injury heals and even though the drug is no longer needed, the person cannot stop using the drug although no medical benefit exists. The National Center for Drug Abuse Statistics reports that more than 20 million people over the age of 12 in the United States have substance use disorder (Ref. 5).

What are the types of drug tolerance?

The operational definition of tolerance is a decrease in effect following repeated or prolonged administration of a specific dose.

Cross Tolerance -Exposure to one drug can produce tolerance to other similar acting drugs

Metabolic Tolerance -Reduction in amount of drug which reaches site of action

Functional Tolerance -Reduction in the reactivity of sites of drug action

FIGURE 2

TOLERANCE AND THE PRACTICE OF FORENSIC PATHOLOGY

Forensic pathologists are tasked with determining the cause and manner of death, which inevitably includes some amount of toxicology testing to exclude and/or identify any drug present at the time of death. Even though a drug overdose may appear obvious based on the scene, it is prudent to consider how tolerance applies to the interpretation of toxicology results. Tolerance is dynamic in nature and can change, even in a short amount of time, based on several endogenous and exogenous variables (Figure 3). One complexity of toxicology is that analysis only shows what is in the sample at the time of collection or testing, it does not reveal the duration or pattern of drug use. It is, therefore, evident that the pharmacodynamic impact of a drug concentration on an individual in the absence of case-specific information is almost impossible to determine with any degree of certainty.

TOLERANCE IS DYNAMIC

Tolerance decreases if:

▪ the drug use is stopped, or the dosage is reduced ▪ the drug is changed to a similar but less potent drug ▪ there is inconsistent access to the drug ▪ the person is placed in an environment where drug use is restricted such as in a rehabilitation facility ▪

Tolerance increases if:

▪ the drug use or the dosage is increased ▪ the drug is changed to a similar but more potent drug or if another similar drug is added ▪ there is continued access to the drug such as in a palliative care situation ▪

Tolerance decreases or increases if:

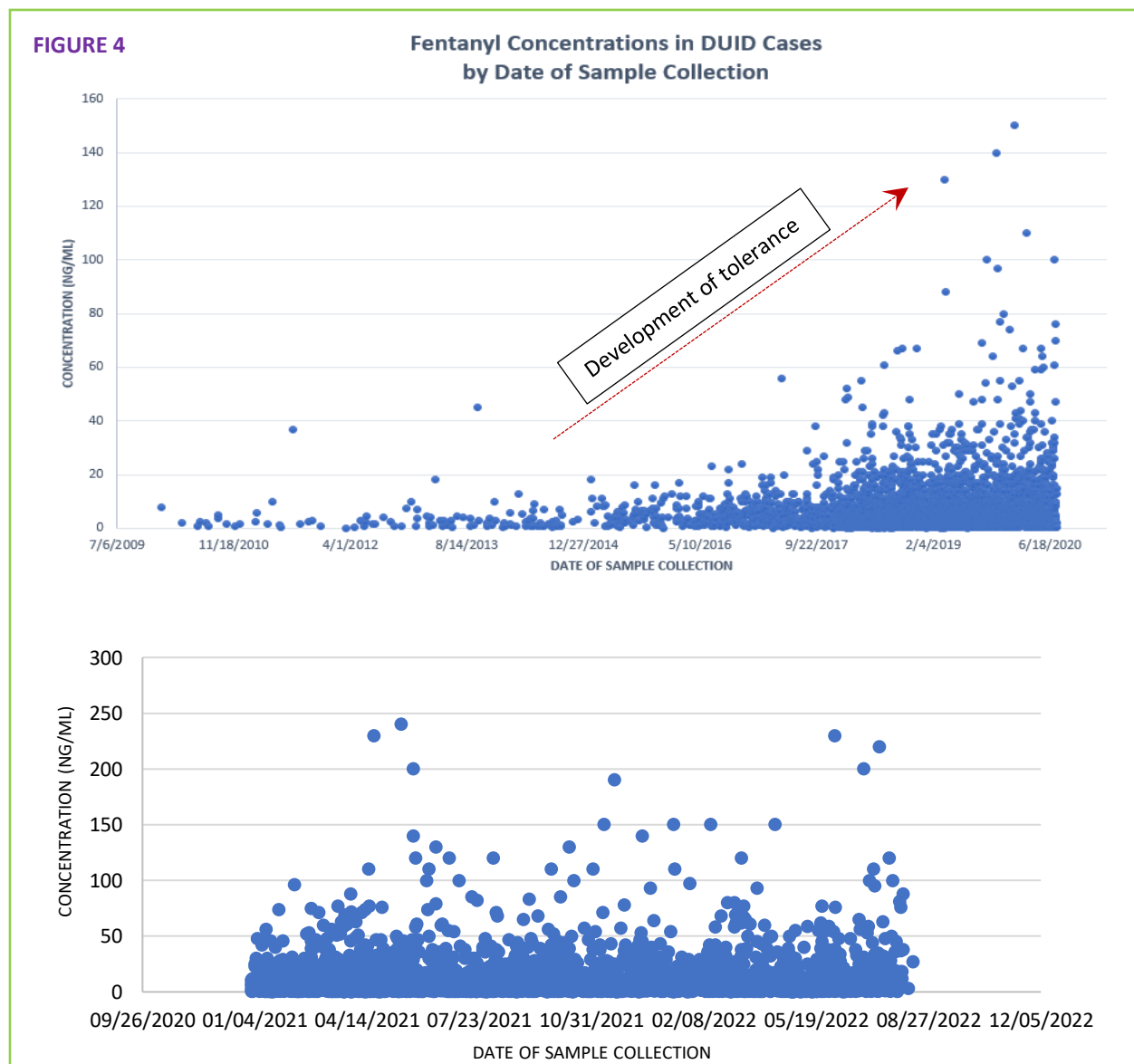
▪ there are unpredictable changes in drug purity ▪ there is an unexpected change in drug formulation ▪ there is intermittent access to the drug ▪

FIGURE 3

Appropriate interpretation of toxicological results begins with understanding which drugs and concentrations are therapeutic and which are not. One common approach is to compare reported case concentrations with published concentrations that have been associated with therapeutic, toxic, and lethal outcomes. While this is a good starting point, a thorough toxicology interpretation should not end here.

THE DRUG EPIDEMIC AND TOLERANCE

In 2021, a record number of Americans – 107,622 – died from drug intoxication. This represents an increase of nearly 15% from the 93,655 deaths estimated in 2020. Furthermore, overdose deaths from synthetic opioids (primarily fentanyl) and psychostimulants (primarily methamphetamine) continued to increase in 2021 as compared to 2020 (Ref. 6). These are alarming numbers that justify ongoing intervention at all government levels. Toxicologists who review human performance impairment (DUID) results have seen drug concentrations begin to dramatically increase around 2015 in living individuals to levels that on the surface could readily be associated with lethal outcomes. As an example, the data depicted in Figure 4 shows the upward trend in fentanyl concentrations from 2010 through the lockdown phase of the COVID-19 pandemic and then more consistent but overall greater concentrations from 2021 to August 2022. These charts provide a clear image of what the development of tolerance looks like.



LESSONS TO BE LEARNED FROM FENTANYL AND METHAMPHETAMINE CONCENTRATIONS IN THE LIVING

In a series of cases, submitted for DUID testing over 12 months, fentanyl concentrations in blood ranged from 0.22 to 230 ng/mL (n = 2322) and 5.1 to 8100 ng/mL (n = 3464) for methamphetamine. Methamphetamine concentrations >1000 ng/mL (n=175) ranged from 1100 ng/mL to 8100 ng/mL. A comparison between these concentrations and concentrations found in postmortem cases over the comparable period shows similar frequency distributions. In the fentanyl postmortem cases (n=37789), concentrations ranged from 0.20 ng/mL to 3900 ng/mL with 88% of these cases were < 41 ng/mL. In the methamphetamine cases (n=25243), concentrations ranged from 5.0 to 250,000 ng/mL with 76% of these cases < 1100 ng/mL. Frequency distributions are shown in Figures 5 and 6.

FIGURE 5

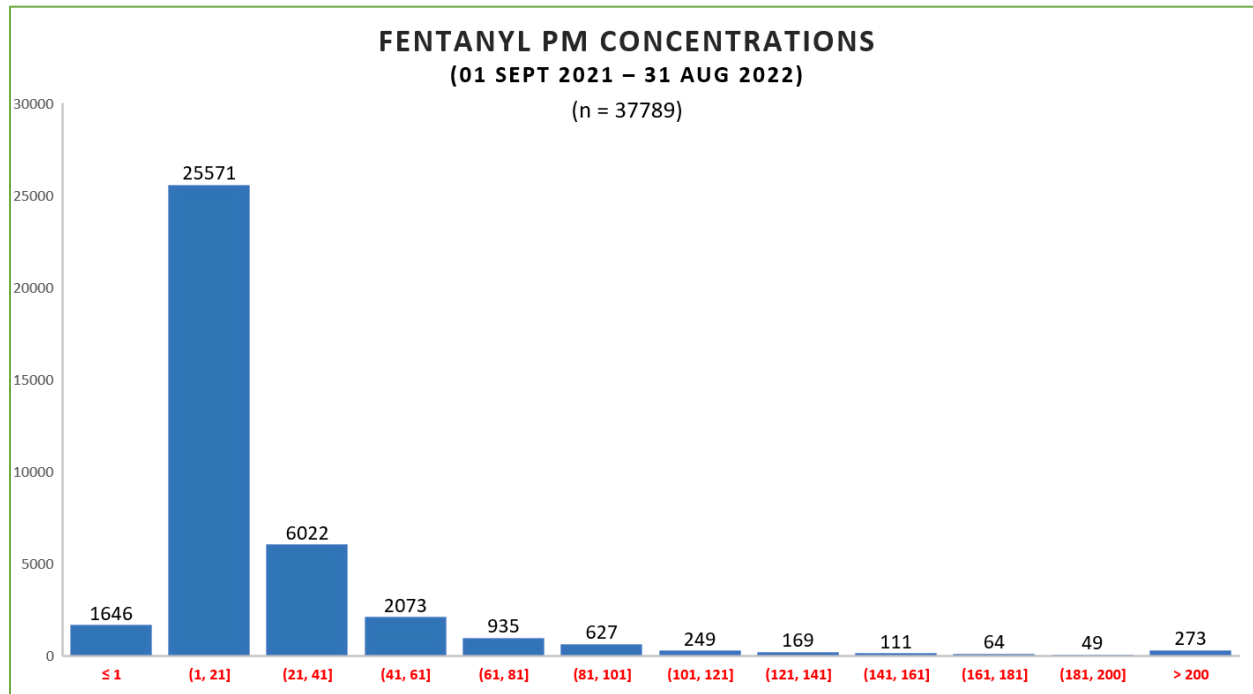
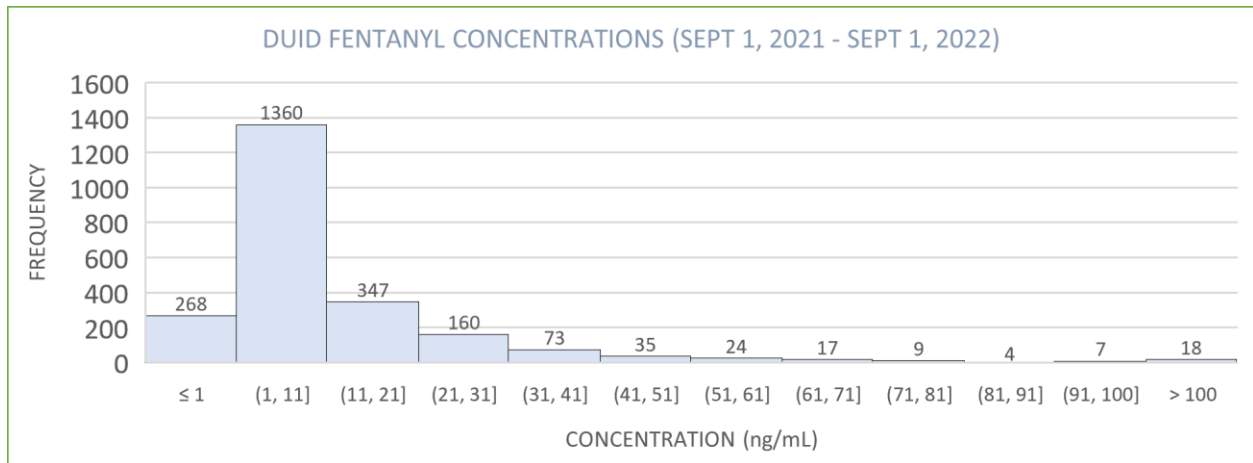
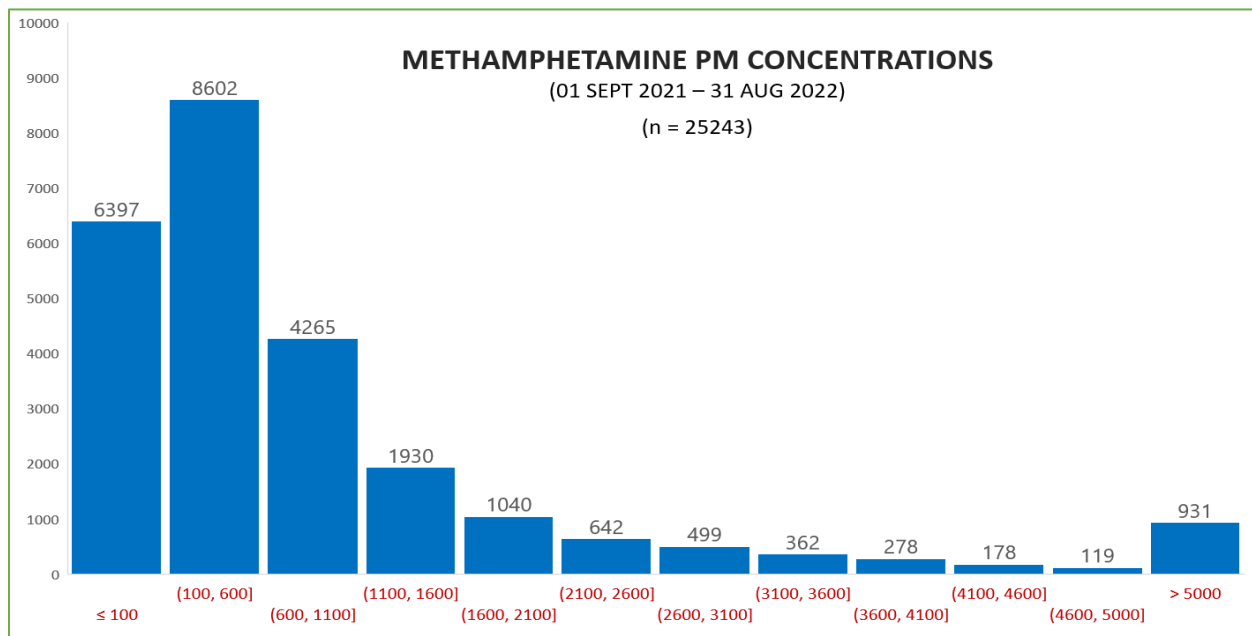
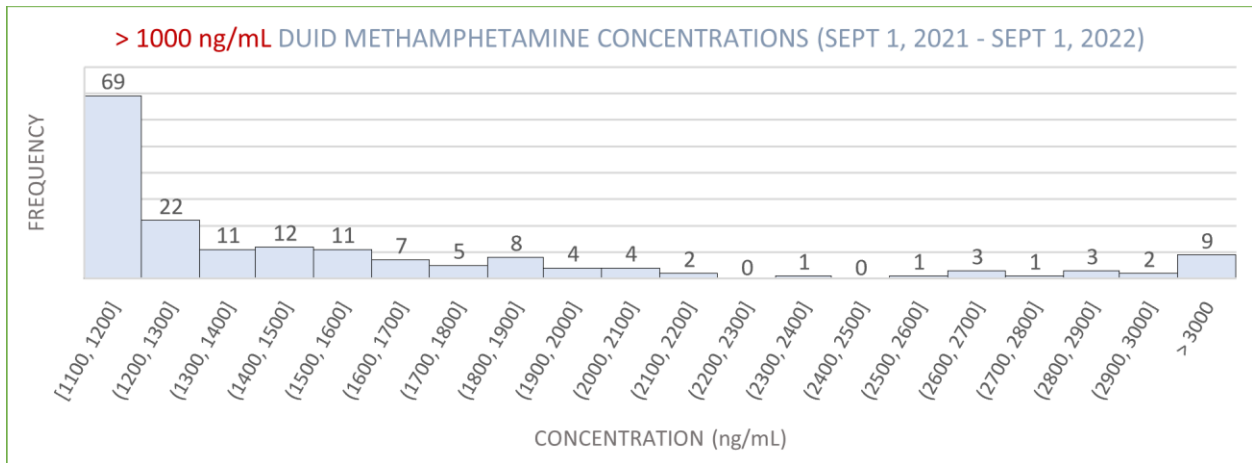
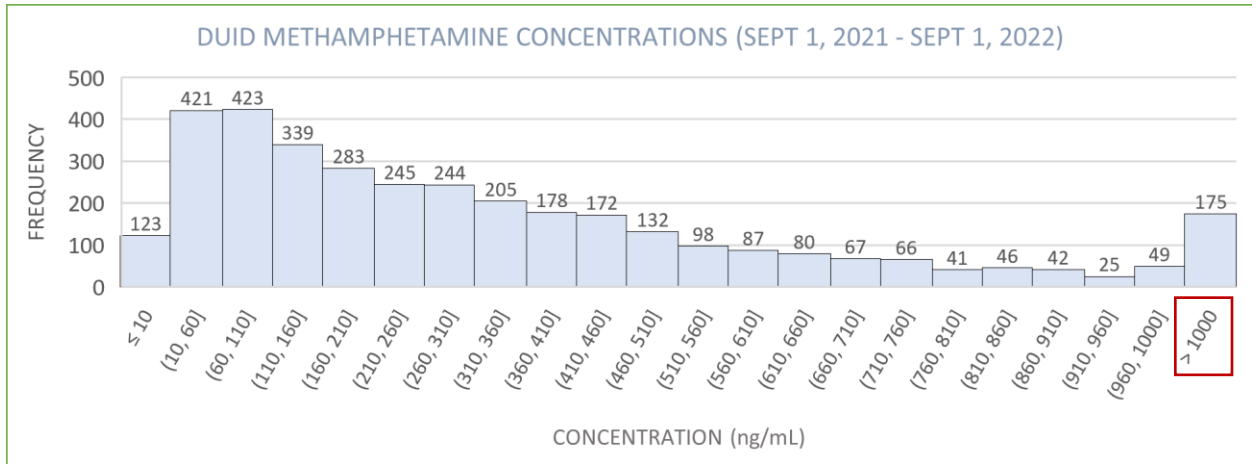


FIGURE 6



CONCLUSIONS AND DISCUSSION

Drug tolerance is when a person's body becomes less responsive to a drug after repeated use. Modifying the drug regimen is one strategy that can help to achieve therapeutic benefits or other desired effects. Improvement of drug efficacy can occur by increasing the drug dosage, switching the route of administration, for example, from oral ingestion to intravenous injection, or by adding a drug to augment the effects of the first drug. Drug tolerance progresses to dependence and addiction in some individuals.

Within the last two decades, toxicologists have witnessed the crossover from prescription opioids to heroin to fentanyl, the proliferation of novel drugs and analogs, upticks in the presence of adulterants such as xylazine and levamisole in the drug supply, and extremely elevated drug concentrations in some people being investigated for DUID. The latter means there are tolerant individuals that have active drugs within their system well above concentrations that may be considered fatal to drug-naïve individuals. Epidemiological data demonstrate that within the last decade the number of accidental, substance-related deaths has increased to epidemic proportions. Evidence at the scene and on the body helps to triage the case and ascertain if the death warrants an autopsy. Different opinions about how to work up suspected drug fatalities, the autopsy versus external exam requirement, and death certification of cases with positive drug findings exist among medical examiners. The data shows that no matter the approach, it is important to consider the role of drug tolerance when developing death investigation protocols and interpreting toxicology results.

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