The IACFT Gazette

Volume 1 Issue 1
April 2023

International Alliance of Clinical and Forensic Toxicologists

Bringing Excellence
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Atlantic Technological University

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Young Scientists Committee

This is our newest committee currently chaired by Chinyere Williams and co-chaired by Geraldine Dowling. Those wishing to serve on this exciting committee please contact **info@iacft.online**

Welcome to the IACFT Gazette

There is much to celebrate regarding IACFT and from this perspective we are happy and honoured to publish the inaugural issue of the IACFT Gazette, a professional magazine with two issues per year that include peer reviewed articles, news items and anything else our editors feel the need to share with our membership. Even more exciting, we are pleased to announce the imminent release of the IACFT Gazette Podcast, coming soon to a computer, tablet or smartphone near you.

IACFT is a collective of scientists from around the world who serve their local communities as best as they can but who don't always have the time or budget to attend professional meetings in remote parts of the world to present their research or to learn the latest developments in the field. We strive to build productive relationships and make a positive impact with all of our pursuits informed by comprehensive empirical studies and high quality data.

I hope everybody who attended previous IACFT meetings enjoyed not only the scientific content but the exceptional discussions. The meeting organisers, speakers and sponsors must be congratulated for holding these meetings prior to and during the pandemic in multiple languages. The free multilingual meetings were virtually attended by participants from 65 countries. Downloadable recordings of these meetings are available on demand for one year after each meeting on the website of the Center for Forensic Science Research and Education (CFSRE). After that they are accessible by our members on our website www.IACFT.online

There is much to celebrate regarding IACFT and from this perspective it was decided to produce two issues of the Gazette magazine per year for professional membership, academics, researchers and students in clinical and forensic toxicology disciplines and a subsequent podcast series.

The partners of IACFT, including those in industry and the higher education sector, are diverse communities and as such inclusion remains high on the IACFT Gazette's agenda. It is fundamental that a welcoming environment is provided for all, where everyone feels valued, respected and appreciated. In going forward together, we foster inclusion and celebrate diversity in all aspects of forensic and clinical toxicology research, education and service provision.

The IACFT Gazette is published in digital format only and shared online and therefore papers include a variety of media elements including audio and visual files, a range of image formats and interactive hyperlinks to websites and other online resources.

We hope you enjoy the first issue of the IACFT Gazette and please feel free to give feedback or suggestions.

Happy Reading!

Geraldine
E: Geraldine.Dowling@atu.ie

Guidelines for IACFT Authors

The IACFT Gazette chief editor is Dr Geraldine Dowling and along with numerous review editors and language editors welcome articles from membership. The format for the IACFT Gazette articles must follow the following guidelines.

Artwork/Pictures:
The artwork if present should be sent in a separate file.

The artwork files should be in an acceptable format (JPEG or high quality PDF).

Tables:
Tables should be present in a separate file (JPEG, word or Excel).

Tables should be shown consecutively in accordance with their appearance within the original piece of work. Footnotes to tables if present should be added below the table and give them with superscript lowercase letters.

References:
Reference style (Forensic Sciences Research).

Please follow the reference style outlined here https://files.taylorandfrancis.com/tf_NLM.pdf

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Examples
Reference to a journal publication:

[1] Meneton P, Jeunemaitre X, de Wardener HE, et al. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev. 2005;85:679–715.

Reference to a book:
[2] Wenger NK, Sivarajan Froelicher E, Smith LK, et al. Cardiac rehabilitation. Rockville (MD): Agency for Health Care Policy and Research (US); 1995.

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Academic Partners

We would like to acknowledge funding from the Atlantic Technological University, Teaching & Learning Centre (Sligo, Ireland) - Supported through the National Forum Strategic Alignment for Teaching & Learning Enhancement Fund 2022. This funding is designed to encourage IACFT professionals, academics, researchers and students to publish interesting, exciting, unusual or otherwise noteworthy material in the IACFT Gazette using Universal Design for Learning (UDL) and Community Based Learning (CBL) pedagogies that facilitate the sharing of information in multiple formats with students and professionals thus making IACFT accessible even to those with non traditional learning behaviours and to everyone irrespective of toxicology career stage. To this extent, the IACFT Gazette welcomes feedback on how to improve our accessibility and inclusivity for all.

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IACFT wishes to acknowledge our Academic and Educational partners who help us bring free virtual knowledge to every part of the world.

Case study

Driving under the influence of drugs

André Dion and Tamaro Diallo[1]
Montréal Forensique (Québec), Canada

Driving under the influence of drugs is a road safety and public health issue. The drugs most commonly found in motor vehicle drivers in Quebec [1] are CNS stimulants, depressants and cannabis.

In Quebec, drug recognition evaluation officers (DREs) are trained by a police academy to use a protocol that consists of twelve steps to identify seven classes of drugs (CNS depressants, CNS stimulants, cannabis, inhalants, dissociative substances, hallucinogens, and narcotics/analgesics) [2]. A positive classification allows for the collection of biological specimens. In Quebec, urine is the most widely used specimen.

This typical case describes a situation in a road safety context, and while not intended to be exhaustive, is intended to provide a better understanding of the issues involved in assessing driving under the influence of one or more drugs.

A driver smoked three joints of cannabis in the afternoon followed by a light meal around 12:00 p.m. He did not have any alcohol. Around 12:00 a.m., the police received a call about erratic driving. They intercepted the car around 12:40 a.m. They smelled cannabis coming from the vehicle. They also noted that the driver was agitated, had a lack of attention as well as red eyes. At first, these signs and symptoms are not specific to any one drug and could be caused by different drugs, a medical condition or other factors. The police officers then proceed to take the driver to the police station where a DRE conducted various tests on him. At 2:33 a.m., the officer came to the conclusion that the driver was impaired by cannabis. He requested two urine samples around 3:15 a.m. for toxicological analysis by a forensic laboratory. The samples were analyzed thirty-three days later and the results indicated "THC-COOH detected" and "methamphetamine detected", without numerical values or uncertainty calculations. In other words, no concentration was revealed for the detected drugs. The same report states that the presence of THC-COOH may or may not indicate recent cannabis use and that the presence of a substance in the urine indicates only that administration (or exposure) of that substance has occurred.

The DRE assessment [3] involves vertical and horizontal nystagmus, lack of eye convergence, pupil diameter, pupil response to light, heart rate, blood pressure, and body temperature. Different classes of drugs can have CNS and/or peripheral effects via changes involving neurotransmitters and their receptors. These changes impact, among other things, an individual's vital signs, abilities and behavior and can be observed during a drug recognition evaluation.

Cannabis (DRE category: cannabis) is usually smoked or ingested. Being a fat-soluble substance, it can be found in the blood and urine in conjugated or unconjugated form over a long period of time. It disrupts the endocannabinoid system primarily via CB1 receptors. The effects can include a feeling of euphoria or relaxation, an alteration in the perception of time, a lack of concentration, a decrease in understanding and memory, a change in mood that can cause panic

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or paranoia. It can also cause tachycardia, red eyes, dry mouth or throat, increased appetite, decreased blood pressure [4].

Methamphetamine (ERD category: stimulant), is absorbed orally and is mainly excreted unchanged in the urine and a small portion is converted into amphetamine. Amphetamines are also metabolized by the liver and some of these metabolites are involved in amphetamine psychosis. It disrupts neurotransmitters such as serotonin (5-HT), norepinephrine (NE) and dopamine (DA)[4]. The effects can cause dizziness, agitation, headache, and tremors that can progress to confusion, anxiety, hallucinations, cardiac arrhythmia, hypertension, hyperthermia, circulatory collapse, convulsions, and coma [5]. Some of these signs and symptoms may be observed, such as pupil dilation (mydriasis) for stimulants, during the drug recognition evaluation protocol.

The behavior of a drug becomes complex, from the first minutes of its consumption because of the toxicodynamic and toxicokinetic processes that influence the effects caused by the substance. The progression of the effects according to the dose does not always follow a linear dose-effect relationship. However one should expect a curve called hysteresis, as it is the case with methamphetamine and cannabis.

In the present case, the analyses were performed on urine, not blood. The drug detection windows in urine are generally wider and do not necessarily reflect the presence of these drugs in the blood at the time of the events. It is also difficult to establish a level of intoxication with the presence of both substances solely in urine samples. Without definitely contradicting the toxicology results, the DRE findings do not show any stimulant category (e.g., methamphetamine). Additionally, the analytical results do not specify the isomeric or chiral forms of the detected substances, which have different impairment effects on an individual.

The assessment of driving impairment must take into account a combination of elements including, but not limited to, topography of consumption, observation of vehicle operation by various witnesses, observation of the driver, consumption cues, symptomatic tests at interception, statements by the driver during questioning, opinion of the DRE officer, and toxicology results. Knowledge of the DRE protocol and documented results in combination with the limitations of the extraction and toxicology methods are relevant and useful for the interpretation of this case.

Finally, it is important to remember that the effects of any drug may vary according to several factors: the individual, the dose absorbed, the route of absorption, the degree of addiction (tolerance), the presence of impurity(ies) and the circumstances surrounding the administration (e.g. environment, pre-existing medical or psychiatric condition, drug dependencies, emotional state and concomitant use of other drugs).

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Keywords: Drugs and driving, driving, symptomatic testing, forensic toxicology, drug recognition evaluation, DRE, traffic safety, cannabis, methamphetamine

Acronyms: DECP: Drug Evaluation Classification Program, DRE: Drug Recognition Expert, ERD: ***Evaluateur en reconnaissance de drogues***, CNS: Central Nervous System

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Novel/New Psychoactive Substances; an African Perspective

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The abuse of prescription drugs and psychoactive substances is considered a global healthcare menace that continues to plague many nations and developing countries and Africa is no exception. According to the United Nations (UN), there are over 28 million drug users from Africa with about 37,000 people dying annually from its use. This problem has further been complicated by the emergence and proliferation of new/novel psychoactive substances (NPS) as the continent comes second in terms of trafficking and the consumption of illicit drugs [1].

NPS can be defined as substances of abuse in a pure or prepared state that are not controlled by either the 1961 or 1971 convention on narcotic or psychotropic substances respectively. The street names for such substances may include spices, bath salts, legal highs, herbal incense, etc [2,3]. Broadly speaking, NPS are classified as hallucinogens, stimulants and depressants or as natural, synthetic and semi-synthetic (origin). Alternatively, they can be classified as legal medicine based on their therapeutic properties or as illicit substances [4].

A United Nations Office on Drugs and Crime (UNODC) report in 2017 confirmed the emergence of NPS; synthetic cannabinoids, ketamine, piperazine, plant-based substances and others classified as miscellaneous in 18 African countries [5]. Data from UNODC Early Warning Advisory (EWA) shows 1,047 reported individual NPS in 2020, a meteoric rise from what was seen in 2009 (131) and 2019 (542) suggesting a probable increase in the use of these substances in Africa as well. Unfortunately, data pertaining to the use of these NPS in Africa is lacking [6]. These NPS are used purposely for the euphoric, therapeutic and/or functional effects that they produce and are more potent than traditional drugs with much higher associated health risks including high reported morbidity and mortality rates [7].

Reports of NPS in Africa

Synthetic Cannabinoids

These are substances that react with cannabinoid receptors and produce cannabimimetic-like effects similar to that of Δ9-tetrahydrocannabinol in cannabis. Initially developed as a research tool to investigate endocannabinoids and the therapeutic relevance of cannabinoids, these substances have currently been repurposed recreationally and are one of the most abused NPS [8]. Togo and Egypt reported the emergence of synthetic cannabinoids in 2008 and 2010 respectively. Egypt has reported the presence of two main synthetic cannabinoids- Stroox and Voodoo, a 100 times as potent as natural cannabis and currently, five similar synthetic cannabinoids have been reported. Other countries reporting the appearance of synthetic cannabinoids include South Africa, Nigeria, Mauritius, Sierra Leone, the Seychelles and Comoros islands of the Western Indian Oceans [9,10].

Plant Based NPS

NPS from plant origin consists of varying species such as stramonium, sauveolens and metel made up of different alkaloids including scopolamine responsible for psycho-activity. Dhatura is a highly hallucinogenic and poisonous plant. Severe intoxication can lead to paralysis and respiratory blockade causing death. It that grows near waste sites around the world and hence is readily available and economically convenient [11,12]. Dhatura has been commonly abused and used in Africa especially Nigeria for initiation into cults and criminal organizations and also used as an incapacitant during robbery [13]. Khat or Catha edulis is a flowering plant native to some African countries and the Arabian Peninsula where it is commonly chewed. Cathinone– an amphetamine-like stimulant of the autonomic sympathetic nervous system- is a major alkaloid

Large seizure of tramadol by Libyan authorities. Courtesy; Quartz Africa

in khat and it produces the euphoric effects and excitement after khat ingestion [14]. It is mainly abused in East Africa particularly, Ethiopia -where it is argued to have originated but also Kenya, Somalia, Uganda, Tanzania, Malawi, Djibouti, Congo and further southern in South Africa and Madagascar. It has enjoyed a quasi-legal status in major cultivating sectors in Africa especially Kenya due to its agricultural prominence [15, 16]. Other psychoactive plants of African origin that are notoriously abused may include Sceletium tortuosum and Tecomaria capensis predominantly used in South Africa and Tabernanthe iboga used by the people of Gabon and other West African countries [17].

Tramadol

Tramadol is a 4-phenyl-piperidine analogue of codeine which has agonistic interaction with μ-opioid and γ-aminobutyric acid receptors thereby producing its analgesic effects. It has fewer side-effects, a lesser potency and therefore a low potential of abuse as compared to other opium analogues [18].

Recent literature however paints a picture of widespread abuse of tramadol in North and West African countries due to the ease of accessibility to the medication particularly resulting from its low cost, porous prescription monitoring systems and restrictions and inability to control unprescribed use as well as prescribed abuse [19].

Methamphetamine

Commonly known as crack or speed, methamphetamines are one of the most commonly abused synthetic chemicals worldwide. They act on dopaminergic receptor causing massive release of dopamine which can trigger the generation of reactive oxygen species thereby leading to many debilitating effects associated with its use [20].

The production, marketing and consumption of methamphetamine now appears to have taken shape particularly in South Africa, Nigeria and others including eSwatini, Lesotho, Botswana, Mozambique, Malawi, Zambia, Uganda, Kenya, Ghana, Cote D'Ivoire, Guinea, Senegal [21, 22].

Crystal Meth. Courtesy; Global Initiative.

Others

The presence of a number of NPS such as ketamine (dissociative anesthetics), piperazine (anthelminthics) and ecstasy among others have been reported in some African countries. There are also reports of concoctions or cocktails of traditional and novel substances notably gutter water found in Nigeria (mixture of tramadol, cannabis, codeine and vodka), monkey-tail in Nigeria or laka in Ghana -(a mixture of locally produced gin and parts of the cannabis plant)- that produce euphoria and psychosis and thus should be classified as NPS [23, 24]. This concomitant drug intake may significantly increase the effect(s) of one or more component of the drugs leading to more pronounced/heightened pharmacodynamic effects and possibly increased risk of toxicity and/or fatality.

Conclusion

There is far less research on the emergence and use of these novel/new psychoactive substances in Africa and hence the socio-economic, cultural, clinical/health and pathological implications of the use of these substances within the African context have not been fully explored.

Another challenge is the complexity and difficulty associated with the analysis and identification of NPS. Most African nations simply are not equipped to deal with this challenge logistically speaking or are constricted by budgetary or financial capacity restricting such mandated facilities to focus primarily on "traditionally prohibited drugs". The availability of highly trained personnel to tackle this issue within the continent is also another conundrum. Analysis of wastewater can prove a useful means of gathering information on the use of NPS and may prove a useful means of an early warning system, however without the logistics or budget or personnel not much can be done.

Also, the ease of smuggling these NPS and other traditional psychoactive substances through established routes across the continent and the impact of COVID-19 to other parts of the globe with Asia being the main destination exposes the porosity of policing of contraband. There is a need to understand the role of digitization and the internet particularly the dark-web and social media platforms in potentially facilitating the distribution of such substances across Africa. Major efforts from diverse international and regional bodies will be needed in fighting this menace. One such notable effort was the operation Lionfish launched by INTERPOL involving over 32 African countries and some Middle Eastern nations which saw the seizure of more than 4.5 million tramadol tablets and over 30 kilos of methamphetamine among other illicit drugs and bootlegged items [25].

This however barely scratches the surface of the NPS predicament as it buds in the continent and more needs to be done by all parties involved.

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Career Spotlight: Professor Pascal Kintz

President of X-Pertise Consulting
Head and Senior Toxicologist at the Institute of Legal Medicine in Strasbourg, France

Prof Pascal Kintz has a degree in Pharmacy (1985), a Diplôme d'Etudes Approfondies in Molecular Pharmacology and a PhD in Toxicology (1989) from the Université Louis Pasteur in Strasbourg. He was Associate Director of the Institute of Legal Medicine of Strasbourg and Associate Professor of Legal Medicine until the end of 2004. Then, he was Head of the Scientific Affairs at ChemTox, a private laboratory in Strasbourg, France (2005-2010). Currently, he is a consultant in toxicology, President of his own company, X-Pertise Consulting and Senior Toxicologist and Head of the Laboratory at the Institute of Legal Medicine at the University of Strasbourg, where he is also a Professor of Legal Medicine.

His main topics of interest include: alternative specimens with a special focus on hair and oral fluid, pharmacology of drugs of abuse, drug metabolism, postmortem toxicology, drug-facilitated crimes and doping control both for human and animals.

He is active in several national and international scientific societies, such as Société Française de Toxicologie Analytique, SFTA (President 1997-2003), The International Association of Forensic Toxicologists, TIAFT (President 2005-2008) and the Society of Hair Testing, SoHT (Founding Member in 1995, President 2008-2012).

He received the TIAFT Award for Excellence in 2001, the SFTA Grand Prix in 2003, the IATDMCT Irving Sunshine Award in 2011. He received the TIAFT Alan Curry Award in 2015. In 2021 he was honoured by the French Academy of Medicine (Prix Elisabeth Taub).

He is an expert for Justice in Pharmacology / Toxicology and blood alcohol determination and an expert certified by the Gesellschaft für Toxicologische und Forensische Chemie (Germany) and Eurotox.

Prof Kintz has published more than 380 papers in peer-reviewed journals and 8 books, including 5 in English. He is editor-in-chief of Toxicologie Analytique & Clinique (Elsevier) and regular reviewer for Journal of Chromatography, Journal of Analytical Toxicology, Forensic Science International, Clinical Chemistry, Drug Testing and Analysis, Forensic Toxicology and Therapeutic Drug Monitoring.

Did you always hope to work in toxicology? What did you do in school to prepare yourself for those opportunities?

I was not prepared to be a forensic toxicologist. This was an opportunity during my last year of my studies. There was a position advertised and I was interested.

What work did you do following your initial undergraduate and postgraduate training if applicable trainings undertaken?

I studied toxicology with foreign scientists and colleagues namely Robert Wennig in Luxembourg, Hans Maurer, Hans Sachs and Manfred Moeller in Germany and they all pushed me to do hair analysis of drugs. However 30 years later, I am so thankful to these people.

What do you most enjoy about your work?

And at the end, what remains? Papers, books, passionate discussions! Transmission of knowledge is the most important task. In your career if able to explain something (solving analytical problems or interpretation issues) in simple words to your students or your colleagues it supports being able to present your findings to a court. Continuous questioning is of paramount importance to maintain/enhance scientific knowledge and helps to maintain a positive mind and remain open to the evolution of the world and enhances communication.

For me, the final success of a professional career is when a student after his/her PhD thesis asks or a long-term position in forensic toxicology.

What piece of advice would you give to a current science/toxicology student/ early stage practitioner?

Irrespective of the pressure of colleagues, always document each item of a report with a literature reference. It is well known that the same result can be read in 2 different ways so using peer-reviewed data is the key to discuss opposable views and cannot be simply dismissed by the respondent. I learnt that all possible explanation to document the findings is acceptable pending support from literature. Therefore, I deeply encourage all the active scientists to use the literature review to be able to retrieve citations.

What might you do differently now that you have had all the experiences you have had if you had the chance to do it again?

Do not focus on the opinions of your national colleagues but try to find the recognition outside your country, mainly by participating to international meetings and by publishing your research. However, do not forget to publish in your own country in your native language and not only in international journals in English. This will help your national reputation and spread your work as the local language is more suitable for lawyers, judges and policemen, who are your final clients.

Always be modest, keep up-date with the latest scientific papers, ask as much as possible the right questions and do not say "I know" but evaluate other possible parameters and express your doubt ...

What do you like to do in your free time?

Diving, diving ... and diving again !!

The US Opioid Crisis Since COVID-19

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The US opioid crisis spread in three waves, starting in 1997 with the unprecedented promotion of a controlled opioid analgesic. Purdue Pharma spent over $200 million dollars in 2001 alone, promoting their patented controlled release formulation of oxycodone as less addictive, while also providing financial support to researchers, universities, professional pain management societies, and the Federation of State Medical Boards [1]. Historically reserved for treatment of pain in terminal patients, by 2002, the number of prescriptions of oxycodone for non-malignant chronic pain had increased 10 fold, from 670,00 to 6.2 million [2]. In 2010, there were 251 million opioid prescriptions written in the US [3] and the number of deaths due to overdose of prescription opioids reached 21,089 [4]. The new opioid addict was young, white, middle class, and lived in rural rather than urban areas. In response to the crisis, Purdue Pharma released an abuse resistant formulation of OxyContin in 2009. Over the next 3 years there was over a 45% decrease in past month abuse of Oxycontin [5]. However, the problem of opioid addiction remained.

At the same time prescription opioids abuse was escalating, the distribution of heroin in the US was undergoing a transformation. Employing a marketing scheme more comparable to a pizza delivery service than the strong arm techniques utilized by the established cartels, the Xalisco Boys had infiltrated Reno, Nevada and spread into the Midwest and Appalachia. By 2010, black tar heroin was being sold for one third to one half the cost of prescription opioids in the same regions hardest hit by the first wave of the opioid crisis. A cheap convenient source of heroin was primed to fill the need created by the release of abuse resistant formulation of OxyContin [6]. In the second wave of the opioid crisis (2010-2013) heroin overdose deaths increased by 250%.

In 2013, while Xalisco Boys were distributing black tar heroin in the Midwest, fentanyl was being detected in the white powder heroin sold by the Sinaloa Cartel on the east and west coasts [7] Fentanyl was not being diverted from legitimate sources, but was being shipped from China through the US mail and standard shipping companies [8] China had been a source of novel psychiatric substances (NPS) since 2008, when Spice and Bath Salts were hitting Europe and North America. Fentanyl is easily synthesized from inexpensive precursors and clandestine manufacturers of NPS quickly transitioned to fentanyl and fentanyl analogs such as furanylfentanyl, acetylfentanyl and carfentanil. One kilogram of fentanyl could be shipped via the US Postal Service or FedEx to the US where it could be divided into over 650,000 individual doses worth millions of dollars on the street. Fentanyl precursors were also exported to Mexico, where the cartels used crude methods to produce fentanyl that was smuggled over the southern border into the US [9]

The number of heroin addicts is relatively small in the US. The preferred drugs of abuse in 2010 were marijuana 77%, psychotherapeutics 32%, cocaine 7%, methamphetamine 1.5%, and heroin 0.88% [10] However, heroin is much deadlier drug, accounting for 8% of the drug overdose deaths in that same year. The new and reintroduced fentanyls were many times more potent than heroin. In the third wave of the opioid crisis, overdose deaths from fentanyl accounted for over 46% of the 70,237 drug overdose deaths in 2017 [1] From 2015 through 2018, China controlled fentanyl, 23 fentanyl analogs, and the two fentanyl precursors NPP and 4-ANPP, adding them to the Measures for the Listing of Non-pharmaceutical Narcotic Drugs and Psychotropic Substances. Drug penalties are severe in China and as each analog was scheduled, it would disappear. As the scheduled fentanyls disappeared, they were

quickly replaced with new analogs. Still, in 2018, drug overdose deaths decreased to 67,367, although fentanyl and analog deaths increased by 10%. Finally, China controlled all fentanyl analogs in 2019 and closed manufacturers, web sites, and enforced existing shipping regulations[11]

The effect was a dramatic increase in fentanyl adulterated counterfeit pills being marketed as prescription opioids or stimulants. According to the DEA, 40% of the counterfeit pills contained a lethal dose of fentanyl at 2 mg or more. Between May through September of 2022, more than 10,000,000 counterfeit pills containing fentanyl were seized in the United States, along with approximately 980 pounds of fentanyl powder [12]

Drug overdose deaths increased slightly in 2019 to 67,697. With the COVID pandemic disrupting commercial distribution chains in late 2019 and early 2020, early data indicated a decrease in drug seizures in the United States. Unfortunately, by the end of 2020 there was 35% increase in the number of drug overdose deaths (91,799) [13] and a 55% increase in fentanyl deaths (56,516)[1]. The increase has been attributed to several factors such as increase in drug use due to isolation, opioid dosing in isolation without friends or family to administer Naloxone, user is unaware of taking fentanyl and a decrease in availability of drug treatment services [14] In 2021, the number of deaths was 107,622, still an estimate at the time of publication. Natural, semi-synthetic, synthetic opioids and methadone accounted for 78,154 of those deaths. The data for 2022, available through May indicates the numbers will continue to rise.

Ultimately, COVID-19 did not have a significant impact on fentanyl availability in the US, although the manufacture and distribution has changed dramatically. In 2021, fentanyl was still being shipped directly to the US from China, although at a much reduced rate and the focus is no longer on new fentanyl analogs. As all fentanyls were now scheduled in China, there has been a shift to the manufacture and export of precursor chemicals. Four precursors identified to date include 4-AP, 4,4-piperidinediol, 1-BOC-4ANPP, and 1-BOC-4-piperidone [15] The precursors are shipped to clandestine manufacturers in Mexico and increasingly to India, where they are used to manufacture fentanyl, which is then smuggled into the US. As Chinese suppliers create more international partnerships, there is concern that synthetic opioids may become a global concern [16]

This project was supported by Award No. 2019-R2-CX-0019, awarded by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice. The opinions, findings, and conclusions or recommendations expressed in this publication/program/exhibition are those of the author(s) and do not necessarily reflect those of the Department of Justice.

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[1] Deaths are reported as over-dose of synthetic opioids, which is dominated by fentanyl and fentanyl analogs.

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The Role of a Forensic Practitioner in Sexual Offence Investigations in England and Wales

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The Epidemiology of Sexual Offence Crimes in England and Wales

Clinical Forensic Medicine involves the detection, collection and preservation of evidence in cases typically involving both medical and legal considerations [1]. In light of the rising numbers of sexual offences in England and Wales between 2002 and 2020, the investigation of these offences remains a challenge for healthcare professionals and clinical forensic practitioners (Figure 1) (Office for National Statistics, 2021). Alarmingly, police-recorded offences are likely to under-represent the total number of victims as a consequence of a lesser 'willingness to report' and consistently reported low conviction rates for crimes of this nature [2]. Under the Sexual Offences Act of 2003, sexual offences are considered to be a variety of crimes including non-consensual sex crimes such as rape and sexual assault, exploitation crimes with a sexual agenda and sexual crimes against children such as grooming or child sexual abuse (Sexual Offences Act 2003, 2021). Drug-facilitated sexual assault and female genital mutilation (FGM) can also be deemed sexual assault crimes and are therefore investigated by a clinical forensic practitioner using standardised protocols. This paper will cover the current protocols for sampling and retaining evidence from these cases and some of the caveats associated with clinical forensic investigations of crimes of this nature.

Primary Considerations in Sexual Offence Investigation (SOI)

Sexual offence crimes can have overwhelming and devastating impacts on victims, highlighting the importance of bringing justice to complainants. However, false allegations do occur. This presents a pertinent requirement for precision and care in the examination and the collection evidence, for both complainants and suspects of a sexual assault investigation (SAI). The primary role of clinical forensic medicine is medical care for the patient, including the diagnosis and management of physical and emotional trauma. Additional roles of the forensic clinician include the collection and preservation of evidence, which is paramount to suspect elimination and prosecution [4].

The Medical Forensic Examination

A typical response to sexual assault allegations involves the collection of physical evidence through the undertaking of a clinical forensic examination [5]. Clinical Forensic professionals must treat patients in this setting with compassion and care, considering the potentially very traumatic nature of these crimes. Examiners must not inadvertently cause complainants further distress or emotional trauma during the retrieval of evidence. For this reason, forensic examiners must have a sufficient level of training, consistent across the field. There are suggestions within published literature that a caveat to Clinical Forensic Medicine in SAI is the lack of consistency in terms of training and professional background of examiners dealing with complainants in cases of this nature. Consequently, the outcomes of these cases in the Criminal Court may be compromised due to failure to properly detect, retrieve or document crucial evidence [6]. Any professional who may encounter sexual assault victims should have an extensive understanding of the health problems that may incur following sexual assault, and the subsequent protocol for the handling of these cases. All primary assessments of sexual assault victims should be performed by doctors or nurses with specialist knowledge of both chronic and acute health problems caused by sexual assault and substantial practice and training in the handling of these circumstances [4]. Key considerations upon medical examination are the immediate care e.g., post-exposure

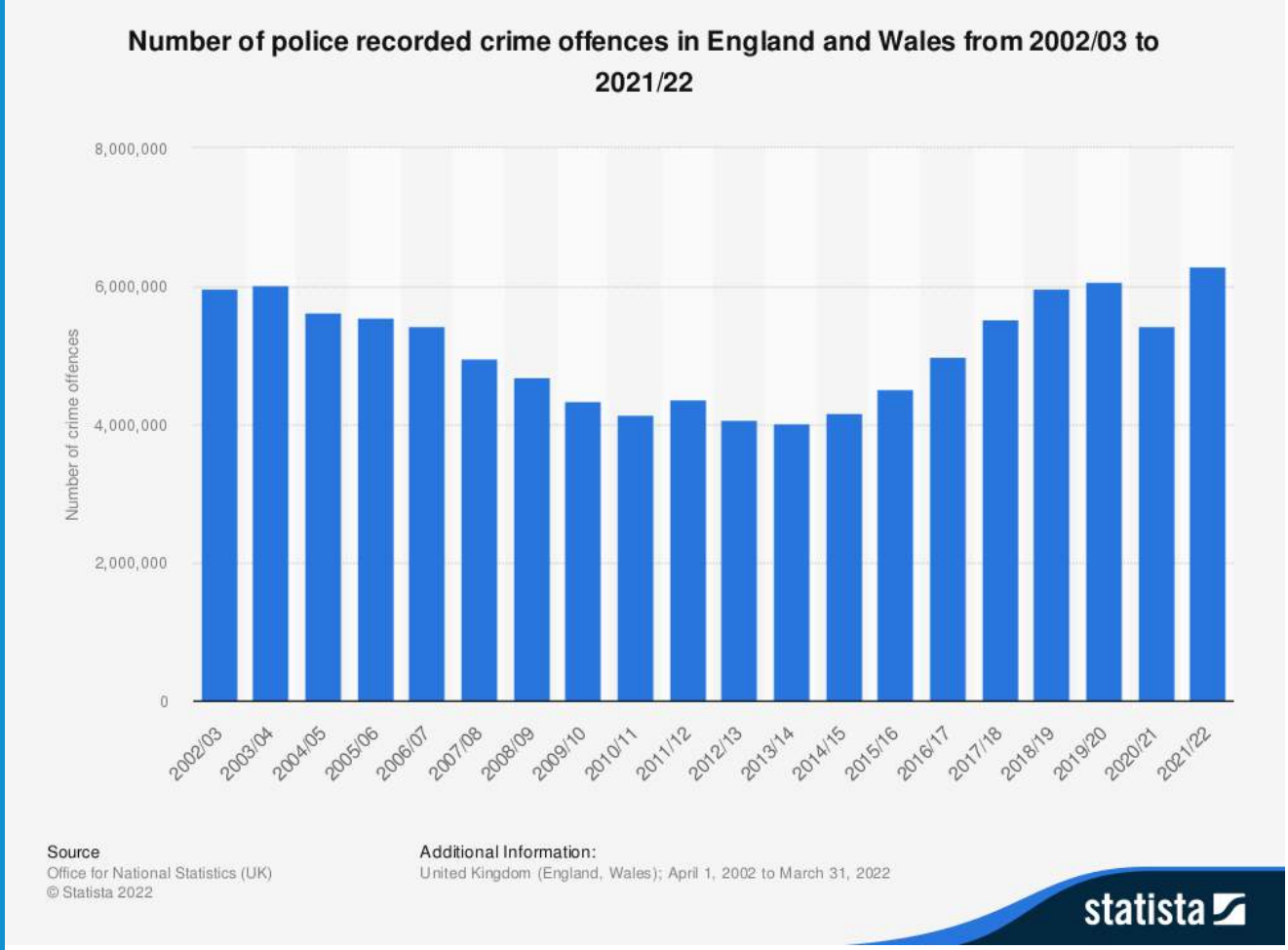

Figure 1: Bar chart presenting the numbers of reported sexual offences in England and Wales. The chart presents a net rise in the number of recorded sexual offences between 2002/3 and 2020/21, with a more pronounced growth in cases from 2013/14. The highest number of recorded offences was 164, 000, in the period of 2018/19. Data published by Office for National Statistics, 2022. Image reproduced with permission from [3].

prophylaxis, the timing and location of the medical examination, consent, detailed history of the allegation, as well as medical, sexual, drug and alcohol history. It is also important for a physician to document any lack of accurate and continuous memories of the incident and to respectfully communicate with and reassure the complainant that this could be an indicator of drug-induced memory impairment, rather than falsification or misreporting of information by the complainant. Additional considerations are the handling of photographic documentation and notes, which ensure that evidence is not lost before the case can be taken to court.

Sampling and evidence collection

A detailed history of the alleged assault should be taken by an appropriately trained nurse, doctor, police officer or forensic medical examiner. Clinical forensic practitioners should advise on which biological samples are to be taken and how. Subsequently, a clinical forensic practitioner should undertake or supervise the sampling process, subject to consent. Any clothing associated with the alleged offence may be taken as evidence, in conjunction with biological samples from the skin (typically the neck, breasts, genitalia and nails are swabbed) and body cavities for DNA evidence. Possible contamination during forensic sampling can be minimised through the implementation of double gloving throughout the sampling process and when handling specimens and evidence. Precise placement, sequential ordering, and appropriate labelling, when coupled with the use of masks and PPE throughout the examination furthermore reduce the risk of contamination of the specimens. Urine and blood specimens can be useful for testing the presence of drugs and alcohol for toxicology analysis. Combings or cuttings from the pubic hair and the examination and documentation of any internal or external genital injuries are also included within set protocol [5] [7]. Problematically, many sexual assaults leave little evidence in terms of genital injury and often any injury that did occur will heal very quickly [8, 9]. This highlights the importance of taking evidence as soon as possible following reporting of an alleged offence, whilst avoiding subjecting the complainant to a distressing or pressured environment.

Retaining evidence for forensic analysis

Physical evidence and biological specimens must be secured by a chain of custody as an improper protocol at this stage of investigation can be detrimental to the admissibility of physical evidence in the respective court case. Following professional guidelines, the details of the clinical forensic practitioner who undertook the sampling process should be documented and their gloves

retained as evidence. Relevant supportive documents such as body diagrams, forensic medical examination forms and statements should be concurrently made. Photography plays a vital role in documenting evidence of injury which might be later relied on in court. A lack of supporting documentation and/or a lack of a clear chain of custody can have implications for an early collapse of the case in court, which can lead to miscarriages of justice. SAI is characterised by a well-documented poor conviction rate in England and Wales, typically due to lack of substantial evidence against suspects. Therefore, when clinical forensic practitioners are collecting evidence, they must abide by all regulations and guidelines to ensure that credible evidence for the adjudication of a case is not lost, contaminated, or diminished in legal value.

Conclusion

The basic principles of SAI are immediate patient care, the timing and place of the examination, consent, history and detailed photographic documentation that is confidentially retained. Key considerations for a clinical forensic practitioner are preventing evidence contamination and retaining a clear chain of custody to support a fair court case [4]. Problems in these investigations can occur at any stage between medical examination, forensic analysis through to trial. Whilst the very nature of these investigations deems adjudication of such cases lengthy and sometimes difficult processes, quality standards must be followed by healthcare professionals who share specific and consistent training in SAI, to avoid hindrance to the trial and miscarriages of justice.

Acknowledgements

Parts of this paper comprised coursework in the module Clinical Forensic Medicine, of the Master's in Forensic Medical Sciences at Queen Mary University of London.

The author wishes to acknowledge the academic guidance of Professor Nikolas P Lemos and Dr Sajeel Shah.

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Career Spotlight: Professor Serap Annette Akgür

Director of Ege University, Institute on Drug Abuse, Toxicology and Pharmaceutical Science, İzmir/Turkey
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Serap Annette AKGÜR, received her medical degree from Ankara University School of Medicine and completed her residency in medical pharmacology from Ege University School of Medicine Department of Pharmacology. She also completed her PhD degree at Ege University School of Medicine, Department of Forensic Medicine. Her current position is Professor at Ege University Institute on Drug Abuse, Toxicology and Pharmaceutical Sciences.

She is an active and contributing member to The International Association for Forensic Toxicologists (TIAFT) as a regional representative for Turkey, European Workplace Drug Test Society (EWDTS) board member, The International Forum of Drug and Alcohol Testing (IFDAT) legal committee member and also The International Alliance of Clinical and Forensic Toxicologists (IACFT) board member. She is the President of the Society of Forensic and Clinical Toxicology in Turkey. Her main topics of interest include: workplace drug testing, driving under the influence of drugs, toxicological analysis for the drug abuse patients and probationers.

Did you always hope to work in toxicology? What did you do in school to prepare yourself for those opportunities?
The fundamental relationship between toxicology and medical pharmacology is a fact. But I realized that I wanted to advance my training in forensic toxicology when I was working as a pharmacologist in the forensic medicine department.

What work did you do following your initial undergraduate and postgraduate training if applicable trainings undertaken?
While I was working in the department of forensic medicine, I saw the importance of the existence of psychoactive drugs and abused substances in forensic cases. I thought that training programs in this field should be enriched in the national struggle against substance abuse and addiction. With this in mind, I ensured the establishment of the "Institute of Drug Abuse, Toxicology, and Pharmaceutical Science", which is the first academic organization to provide education in this field in Turkey. I had the chance to develop in the kitchen of this institute, which brings together experts from many disciplines such as psychiatrists, psychologists, lawyers, practitioners, public health specialists, biologists, chemists, biochemists, physiologists, pharmacologists etc. The fact that, I take part in the meetings and workshops of the scientific associations has greatly contributed to the development of this structure. For a quarter of a century, I have gained experience in explaining situations such as which substances have been used for how long, how often and in what way, as part of the struggle against substance abuse and addiction.

What do you most enjoy about your work?
The fact that graduates from our programs at our institute take an active role in institutions in this field and in judicial expertise in our country is one of the things that makes me happy. I am also proud that our institute is among the reference institutions in this field and in forensic toxicology.

What piece of advice would you give to a current science/toxicology student/ early stage practitioner?
Since there are few people working in the field of forensic toxicology in my country, they should understand the importance of receiving postgraduate education in this field and they should do their professional jobs in accordance with the laws of the country and within the framework of up-to-date scientific data. Being a member of national and international professional organizations or societies that are working in this area will enable them to easily reach people working in this field.

What might you do differently now that you have had all the experiences you have had if you had the chance to do it again?
Despite many unfair interventions, I would continue my progress with perseverance and patience building national and international cooperation and collaborations. I would put more effort into the national recognition and visibility of our corporate work also.

What do you like to do in your free time?
Everything can be verified by history and I would like to take stronger steps into the future by learning about past civilizations and studying historical places and artifacts.

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Cosmology in Crisis

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Cosmology is a branch of science concerned with the origin and evolution of the Universe. Experiments are currently giving funny results which is a good sign that paradigm shift is underway.

One of the hottest topics in physics today is an apparent 10% discrepancy in the Hubble constant H0, namely the rate of expansion of the Universe. This disagreement is of interest to astronomers, particle physicists and data scientists. The central protagonists are Adam Riess (Johns Hopkins), who notched up a Nobel prize in 2011 for the discovery of accelerated late-time expansion, aka dark energy, and the Planck Collaboration, a community of scientists that analysed the data from the European Space Agency's Planck satellite. This would be a David and Goliath narrative if not for the fact that Riess has a shiny medal and the band of rebellious scientists he leads has been steadily growing in number in recent years as the statistical significance of the anomalies has ticked up.

The roots of the current turmoil date back to the early 2000s. Then, a predecessor to the Planck Satellite, NASA's Wilkinson Microwave Anisotropy Probe (WMAP) [1], had produced visually stunning maps of the Cosmic Microwave Background (CMB), essentially the earliest light in the Universe. The CMB light or radiation permeates deep space, so that the Universe is a relatively balmy -270 °C (3 degrees above absolute zero). From temperature fluctuations or anisotropies in the CMB, typically measured in millionths of a degree Celsius, we make inferences of cosmological parameters, including H0. There is also a temperature anisotropy at the level of a thousandth of a degree Celsius, but being much larger than the other fluctuations, this is interpreted as an effect due to the motion of our solar system with respect to the CMB. We subtract this larger fluctuation to analyse the smaller fluctuations, and this fixes the CMB as the rest frame of the Universe.

Unfortunately, one cannot extract information from the CMB without assuming a cosmological model. The current working model is the Lambda-CDM or ΛCDM model, which is built on the assumptions that dark energy is described by the cosmological constant Λ in Einstein's field (gravity) equations and that dark matter is slowly moving or cold dark matter (CDM).

Viewed objectively, 95% of the ΛCDM model is theoretically poorly understood, but it represents the model with the fewest parameters that provides a good fit to CMB observations. One of the great successes of this model is that many observable data sets agree that the Universe is approximately 30% matter and 70% dark energy. However, the CMB is special; it provides the most stringent constraints on the parameters and the constraints are currently at the sub-percent level. For example, through the ΛCDM model, the Planck collaboration infer the Hubble constant to be $H0 = 67.4 \pm 0.5$ km/s/Mpc (0.7% error) [2]. What this number means in practice is that for every megaparsec (1 megaparsec or Mpc is a typical distance between galaxies) that a galaxy is further away from us, it is on average receding from us 67.4 km/s quicker. Here, it is beyond question that the Universe is expanding, since virtually all light is shifted ("redshifted") to longer wavelengths and such a coincidence can only be explained by the expansion of spacetime.

Leveraging the great statistical power of the CMB, cosmologists produced a successful model of the Universe with tightly constrained parameters. The small errors make the model extremely predictive. Cosmologists started to view cosmology as a "precision science", and attention turned to feats that may even impress particle physicists. To that end, cosmologists decided to use their new model to constrain the sum of the neutrino (a weakly interacting particle) masses. Even today, particle physicists have been unable to nail down this number, so there was considerable promise that the cosmology community could beat the particle physics community to the result. Interestingly, something else happened around 2000. The Hubble Space Telescope, under the stewardship of Wendy Freedman (Chicago), was employed to produce the first modern determination of the same parameter, $H0 = 72 \pm 8$ km/s/Mpc (11% error) [3]. While the errors are considerably larger, this determination is completely independent of the cosmological model, so it is complementary to the CMB, and it involves building a distance ladder in the local Universe. In subsequent years, Planck, following on from WMAP, raised the precision on this determination, which forced the astronomy community and Riess to respond.

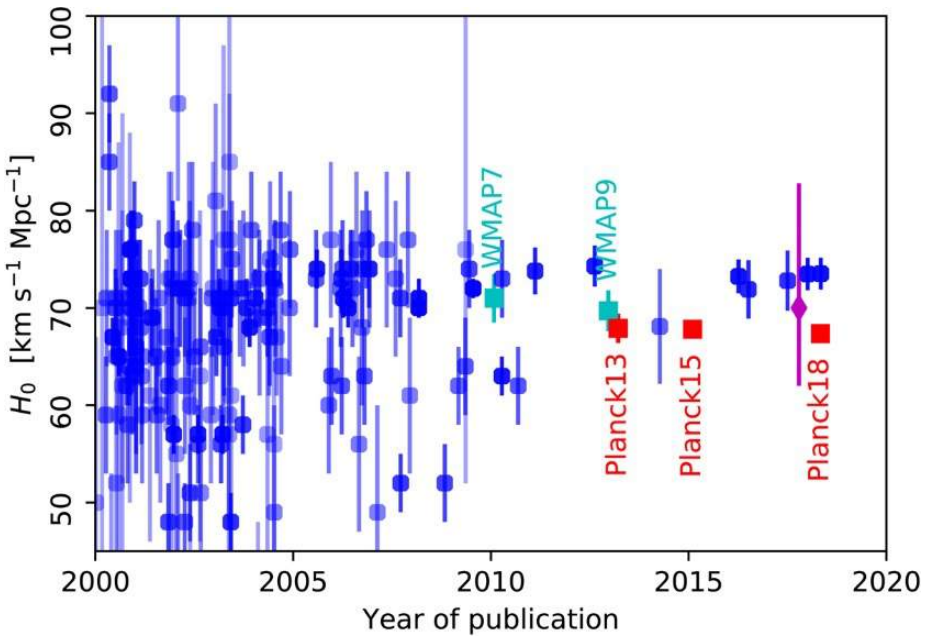

Figure 1: Historical determinations of the Hubble constant since 2000. The Planck determinations in red are discrepant with distance ladder determinations in blue. Earlier WMAP determinations are in cyan, while magenta denotes a determination based on gravitational waves, an emerging observational technique. Credit ESA/Planck collaboration.

Fast forward to the end of 2021 and Riess' Supernovae H0 for the Equation of State (SH0ES) collaboration has combined geometric parallax with Cepheid variables (pulsating stars) and Type Ia supernovae (exploding stars) to announce a new determination of the Hubble constant, H0 = 73 ± 1 km/s/Mpc [4]. The first two techniques were known to Edwin Hubble, and modulo Type Ia supernovae, which were only developed in the 1990s, this is traditionally how one infers astronomical distances. On the assumption of Gaussian errors, this marks a 5σ discrepancy with Planck, where 5σ is traditionally the threshold for a discovery in particle physics. In recent years, independent groups have re-analysed both the Planck and SH0ES results, finding that there is no obvious systematic. Moreover, other groups working with complementary distance indicators in the local Universe, including Wendy Freedman's group, have arrived at determinations in the range H0 ≈ 70 km/s/Mpc to H0 ≈ 76 km/s/Mpc [5-8]. On the flip side, CMB can be replaced with Big Bang nucleosynthesis (BBN), a model describing how heavier elements are formed from Hydrogen in the early Universe, and one arrives at H0 ≈ 67 km/s/Mpc [9], so the Planck determination looks robust. It is possible that gravitational waves may emerge as an important probe that settles the debate, but there is considerable speculation and scientific hype.

The absence of any obvious experimental systematic turns our attention to the ΛCDM model, the standard model of cosmology since the late 1990s. On the face of it, one can view Planck's determination of H0 as a prediction, one that misses the mark by 6 km/s/Mpc, or a little under 10%. While this is admittedly close, since the 2000s cosmologists have been promoting "precision cosmology" based on errors at the 1% level, so 10% no longer cuts the mustard. Apparently, something is missing from the cosmological model. However, this is too quick for a considerable portion of the community and there is still hope that observational systematics may yet reconcile these numbers. In recent years theorists have been working earnestly on proposals for the missing ingredient and the front running idea involves introducing dynamical dark energy to the early Universe. The proposal is admittedly contrived and despite not working, it remains the best idea from a bad lot. Curiously, the ideas being introduced to alleviate the problem may be uglier than any shortcomings with the working model.

Interestingly, there is one more anomaly that has largely gone overlooked by the cosmology community and for good reason; it is an unspeakable anomaly in many circles. Virtually all modern cosmology, be it statistics or techniques, rests upon the Cosmological Principle, which assumes that the Universe is homogenous (same at all places) and isotropic (same in all direction) at large scales, typically assumed to be 100 Mpc. Cosmology textbooks lay out this assumption on the first page. In the words of Nobel laureate Steven Weinberg, this assumption comes down to pragmatism: "The real reason for our adherence to the Cosmological Principle is not that it is surely correct, but rather, that it allows us to make use of the extremely limited data provided to cosmology by observational astronomy." Scientifically, it is of course imperative to test this assumption whenever possible and we should not shy away from the possibility that one could get the "wrong" result, the result that forces us to rewrite the whole field!

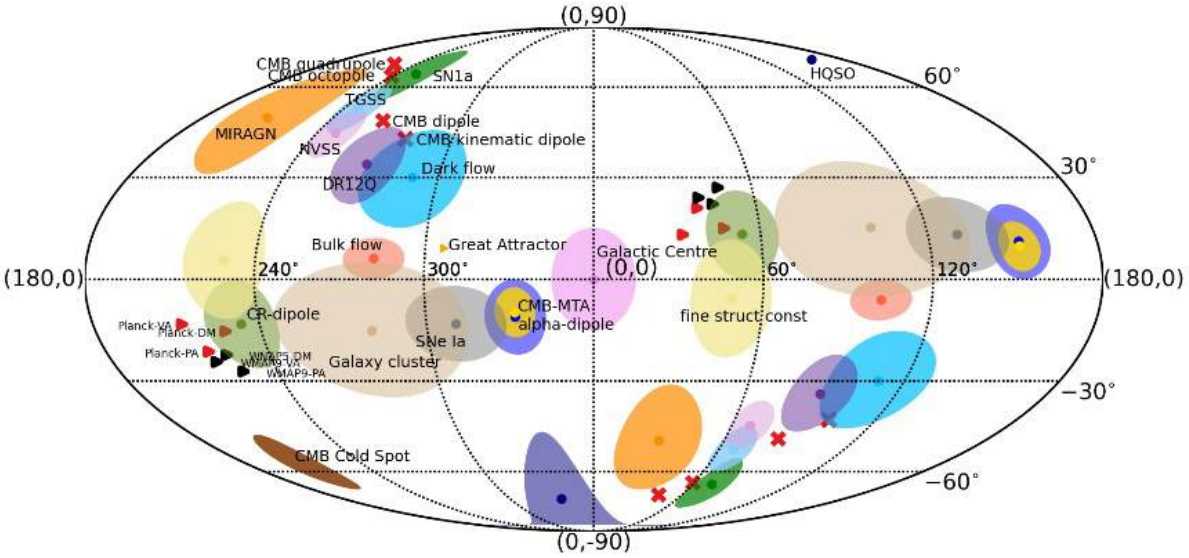

Figure 2: Various anisotropies in the Universe. At least one of these anisotropies is expected as it allows us to define a rest frame for the Universe, which is traditionally taken to be the CMB dipole. Figure reproduced from [14].

As touched upon earlier, the solar system should be in motion with respect to the CMB, otherwise it is difficult to understand why the magnitude of a given temperature fluctuation exceeds the others by a factor of 1000. In 1984 Ellis & Baldwin proposed a test for the rest frame of the Universe [10]. Conceptually, the idea is simple, but requires a large number of astronomical sources. Given a million radio galaxies or quasars (QSOs) on the sky, by studying subtle shifts in their position on the sky, one can infer our velocity with respect to the radio galaxies or QSOs. One needs to assume that the radio galaxy or QSO sample is isotropically distributed, but if this is not the case, then the Cosmological Principle is broken from the outset. Curiously, since 2011 a difference in our velocity inferred from the CMB and our velocity inferred from radio galaxies has emerged. This was first noted by Ashok Singal [11], but since, independent groups have confirmed the anomaly and now we find the same discrepancy in radio galaxies [12], which are observed terrestrially, and QSOs observed by satellite [13]. There are very few shared systematics between these two experimental setups, yet they agree with the CMB on the direction of motion, but do not agree with the CMB on the speed with which we are moving. Taken at face value, these results naively imply an anisotropic Universe. What makes this observation more compelling is that a host of other observations at different redshifts or epochs return anomalies that appear consistent. Tellingly, there is now enough material for a substantial review of these unexpected results [14].

If the observable Universe is no longer consistent with the Cosmological Principle, then there is no expectation that H0 is a constant. In essence, it can vary across the sky, and it is plausible that astronomical data has already exceeded the precision whereby these variations in H0 can be seen, even in tried and tested cosmological distance indicators, such as Type Ia supernovae. Regardless of the outcome, modern cosmology appears to be in turmoil and the resolution to this process has the potential to radically change how we understand the Universe and our place in it.

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Eoin Ó Colgáin is a mathematical physicist at ATU Sligo interested in anomalies in cosmological data sets. He steered the first international review [14] that (either foolhardily or bravely) questions the prevailing narrative that the Universe is isotropic & homogeneous at large scales.

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The Detection of Bisphosphonates in Racehorses by Eoghan Feane

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Introduction

It is of the upmost importance to uphold the integrity of horse racing with appropriate anti-doping controls to ensure races are won based on merit, to ensure the health of the horse and rider and to protect the integrity of the breeding industry. While there is no global governing body for horse racing, most racing authorities consider the guidelines and regulatory framework established by the International Federation of Horseracing Authorities (IFHA) when formulating processes for laboratory testing. Article 6A of the International Agreement on Breeding, Racing and Wagering published by the IFHA define prohibited substances as 'substances capable at any time of causing an action or effect, or both an action and effect, within one or more of the following [listed] mammalian body systems' but does not identify individual drugs or compounds as prohibited substances.
In contrast to the situation in horse-racing, the International Equestrian Federation/The Fédération Equestre Internationale (FEI) is the sole governing authority for all international equestrian events and produces a list of specific prohibited substances (the Equine Prohibited Substances List (EPSL)). There are two categories of prohibited substances in this FEI list, namely banned substances and controlled medications. Banned substances have no legitimate use and have a high potential for abuse. Controlled medications provide a therapeutic benefit as a medicine but may impact equine performance negatively or positively. According to the latest FEI list of banned substances and controlled medications for 2023, there are 7 bisphosphonate compounds which are included in the banned list. These include alendronate, ibandronate, neridronate, olpadronate, pamidronate, risedronate and zoledronate (Figure 1). The other two bisphosphonates, tiludronic acid and clodronic acid, are licensed for treatment of specific conditions in horses and fall into the category of controlled medications. These products are licensed under the names 'Tildren' TM and 'Osphos' TM to treat skeletal diseases, mainly podotrochlosis (navicular syndrome), in horses older than 3 (Tildren) or 4 (Osphos) years of age.

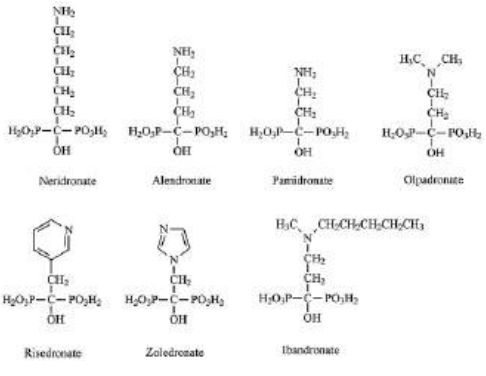

Figure 1: Examples of chemical structure of N-containing bisphosphonates [1].

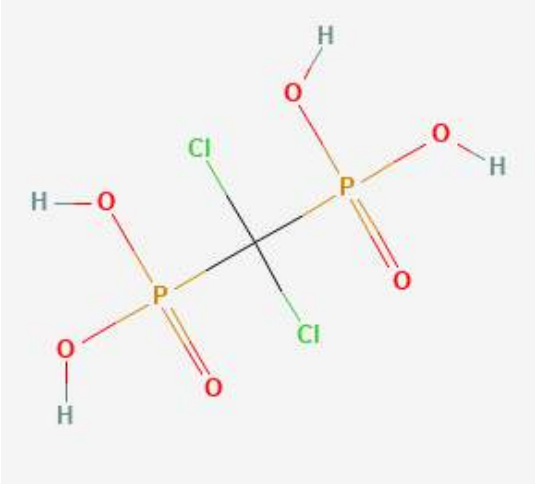

Figure 2: Chemical Structure of Clodronic acid [2].

Clodronic Acid (Figure 2)
Molecular Weight:
244.89 g·mol^{-1}
Chemical Formula: $CH_4Cl_2O_6P_2$

Tiludronic acid (Figure 3)
Molecular Weight:
318.61 g·mol^{-1}
Chemical Formula: $C_7H_9ClO_6P_2S$

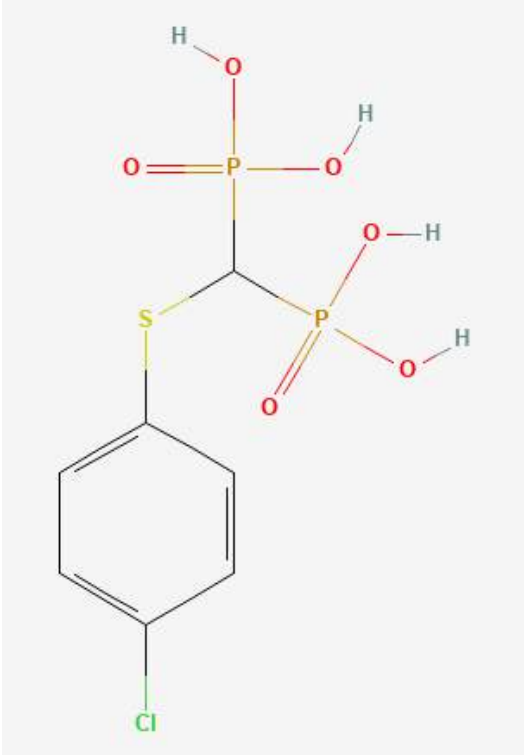

Figure 3: Chemical structure of Tiludronic acid [3].

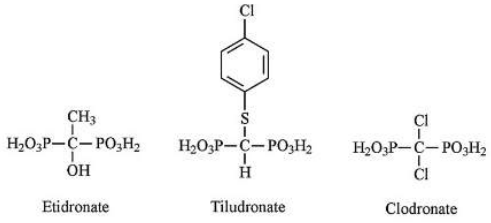

Figure 4: Examples of chemical structure of Non-N-containing bisphosphonates. Tiludronate and Clodronate are the two drugs approved for use in equine species [1]

Bisphosphonates are analogues of inorganic pyrophosphate (PPi), which are important mediators of bone metabolism. Biphosphonates were originally produced in the 1960's as a replacement for naturally occurring PPi [4]. Bisphosphonates main functionality is inhibiting osteoclast-mediated bone resorption [5]. Bisphosphonates bind to bone mineral and inhibit osteoclast activity [6]. Osteoclasts degrade bone mineral which initiates bone remodelling and resorption [7]. Bisphosphonates interfere with the natural healing process of bone suppressing remodelling.

Bisphosphonates may be classified as nitrogenous or non-nitrogenous in structure. The mechanisms of action for both types of bisphosphonates are proven [8,9] and are defined by their biochemical structure. The non-nitrogenous bisphosphonates (e.g. clodronate, etidronate and tiludronate, Figure 4) are similar in structure to PPi. They inhibit osteoclasts in several ways including resorptive activity, adhesion, differentiation, and recruitment. This can result in apoptosis or cell death. When these compounds are metabolised into osteoclasts, they interact with adenosine triphosphate (ATP). They are fused to ATP forming non-hydrolysable analogues, cytotoxic ATP. The build-up of cytotoxic ATP intracellularly can induce apoptosis effecting metabolism, cellular function and inhibiting morphology. The nitrogenous bisphosphonates function by inhibiting the mevalonate/cholesterol pathway which is responsible for cell signalling [10,11]. The nitrogenous bisphosphonates are considered to be more potent than the non-nitrogenous compounds.

Analytical Approaches

In the literature, there are a number of methodologies which have been applied to bisphosphonate detection over the years in human matrices, including techniques such as radioimmunossay to detect zoledronate acid [12] and batch spectrophotometry for the detection of alendronate, risedronate and etidronate [13]. Zacharis and Tzanavaras [1] outline a number of sample preparation and instrumental analytical techniques. In addition, ion chromatography mass spectrometry was utilised by Garcia et al. [14] to improve bisphosphonate analysis. The hydrophilic

properties of these compounds meant that only specific extraction and detection techniques were suitable based on the technologies available at a point in time. With the application of derivatisation during and post extraction, it led to the possibility of utilising more sensitive instrumentation. The derivatised form of bisphosphonates are more readily ionised in ESI positive mode which is ideal for mass spectrometric (MS) detection [15]. The greater hydrophobicity of the derivatives allows for liquid chromatography (LC) analysis with cation exchange and the widely used reverse phase LC (RPLC) chromatographic separation established in more recent methodologies [16,17,18].

As detection of these substances at very low levels is a priority for horse racing samples and for sale of horses below the age limit, LC-MS techniques combined with derivatisation have proven to be the most valuable approach. In order to prepare a sample for analysis via LC-MS methodologies it is essential to extract the target compound from the matrix. The optimised extraction technique for bisphosphonates involves clean-up steps (solid phase extraction (SPE)) prior to derivatisation. Zhu et al [15] was the first to define an approach for quantitation of nitrogenous bisphosphonates by LC-MS/MS following derivatisation with diazomethane. Diazomethane derived risedronate and alendronate were detected in human serum and urine at 0.2 ng/mL and 1 ng/mL respectively. A method using LC-MS/MS was developed for the analysis of a single bisphosphonate, tiludronate in equine plasma and urine [5]. The experimental work showed that urine was difficult to analyse due to matrix effects.

Popot et al. [5], Wong et al. [17] and Riggs et al. [16] all used the same anion exchange SPE cartridge to extract the compound(s) of interest. The use of a second cartridge for clean-up was established in the 2014 paper [5] which aided in binding lipids and other compounds that disrupted the bisphosphonate peaks on the analyser. The first multi-bisphosphonate method was developed in equine matrix by Wong et al [20] and the use of 2 SPE steps was continued in this method. Studies around optimisation of derivatisation are also described in the literature. Trimethyl orthoacetate (TMOA), trimethylamine oxide (TMO) and trimethylsilyldiazomethane (TMSD) as well as a number of other methylisation reagents were evaluated for derivatisation [5,16,17]. TMOA had poor yield of ibadronic acid as a derivatisation agent in plasma. For bisphosphonate methodologies in equine matrices, TMSD was most widely used [16,17,18].

The British Horse Racing Authority prohibits the use of bisphosphonates in horses below the age of 3 years and 6 months on animal welfare grounds. There is concern that the impact to bone remodelling in combination with the anti-inflammatory and analgesic effects of bisphosphonates may predispose horses to major skeletal injuries long-term [19,20]. Bisphosphonates must not be administered to horses on the day of racing or in the 30 days prior to racing.

A study conducted by Popot et al. [21] analysed the pharmacokinetics of tiludronic acid in horses based off a single dose of the drug at 1 mg/kg administered intravenously under field conditions. From this study it was estimated that 96% of horses would have plasma tiludronic acid concentrations below a screening limit of 10 ng/mL at 600 hours (25 days) post administration. The release of these compounds from bone can be sporadic and may be up- and down-regulated by many factors such as horse age and activity level. Consequently, the detection of bisphosphonates in urine and blood may be inconsistent and establishment of the half-life of the drug is made difficult. Riggs et al. [16] found detection of the bisphosphonate, tiludronic acid, in equine urine and plasma matrices is possible 3 years after administration to racehorses using a UPLC-High Resolution MS (HRMS). This work involved the analysis of samples from older horses and the limit of detection was 0.015 ng/ml in both matrices. Detection of tiludronate in urine was found to be less consistent than in plasma from this study. It may be possible to use less sensitive LC-MS methods in active racehorses where low levels of bisphosphonates may be acceptable compared to young horses where detection of any concentration is likely to be significant.

It is important to note that in equine species compared with humans only non-nitrogenous bisphosphonates are legal to treat in horses. The nitrogenous bisphosphonate class are not currently approved but could be used illegally. Development of multi-residue methods for the detection of a large number of bisphosphonates in a single method may be advantageous to the horse racing industry in cases where bisphosphonates licensed for human use may be abused in animals.

Future directions

Biomarkers, in the context of anti-doping, refer to substances produced in the body as a result of the administration of prohibited substances. Testing for the presence or quantity of biomarkers can be used to detect the effect of such prohibited substances on the body instead of testing for the presence of the drug itself or its metabolites [22].

'Omics' involves the study of all the components which make up an organism at a molecular level using various technologies. Omics includes several sub-disciplines which all can contribute to the potential generation of biomarkers; these include genomics, epigenomics, metabolomics and lipidomics. With the study of the different pathways and interactions in a population of

organisms at the DNA, protein and lipid level, etc. traits and characteristics can be observed, and quantitative biological molecules are defined from this as biomarkers [23].

Ohnuma et al. [24] outlines the potential for omics approaches in horses. Proteomics may be a challenging approach to use in horses as comprehensive protein databases for horses have not been established yet. The expression of proteins in horses also differs greatly to humans. Genomic approaches provide some logistical issues in terms of sampling and storage. With this in mind, metabolomic approaches show the most potential for investigating doping biomarkers in horses.

Doping control with conventional chemical testing restricts analysis to a limited number of targeted substances. The potential of utilising metabolomics and monitoring biomarkers associated with doping agents is a possible expansion of current doping detection capabilities.

Ohnuma et al [24] and other studies [25] have looked at analysing metabolomic pathways and alterations to biomarkers in horses. These studies have focused on the changes and regulation of metabolites from pre- and post-race samples. The aim is to establish a post-race biomarker database to understand the changes physiologically of horses in relation to racing. Establishing a baseline for the up and down regulated metabolites, fold changes and relevant pathways of a horse post racing is an important step in potentially identifying doping biomarkers.

Metabolomics studies involving equine plasma with the use of technologies such as HR-MS appears to be one of the most promising approaches for defining biomarkers in equine species. Kieken et al. [26] studied the impact of recombinant growth hormone on the metabolism of horses in plasma and urine samples using a HR-MS metabolomics approach. As there are so many variables between samples (gender, age, physical activity etc.), as well as differences in sample handling and analysis types there is a need for advanced statistics such as the Bayesian approach which can correct for variation between samples.

In the future the use of 'omics' techniques may be very helpful for the detection of bisphosphonate use within a set window of time. Studies conducted in humans have established that the effect of bone resorption can be detected months after administration of the drug through the use of specific biomarkers. In these cases, the human trials were conducted after long term treatment and with different bisphosphonate drugs than are currently prohibited for use in horses. Various biomarkers were identified for specific and sensitive assessment of the rate of bone formation and bone resorption [27]. It may be possible to identify similar biomarkers of bisphosphonate use in horses which could improve their detection compared with current analytical approaches which detect the drug residue. It is likely that the validation of biomarker-based methods will require extensive comparison with current decision limits and may be used in conjunction with, rather than instead of, such limits. Post administration of bisphosphonates, samples were analysed for biomarkers in a study by Tou at al. [28] which identified eicosanoid and corticosteroid ratios up- and down-regulated compared with the population reference limit. Corticosteroid ratios exceeded the population reference limit.

In conjunction with developments in omics techniques, proposals for the introduction of equine biological passports have also been made [29]. The Equine Biological Passport (EBP) is a record of biochemical or other biological test results over time for the individual animal. Generation of EBP's for horses may be challenging as both population data, as well as repeated readings, both from pre- and post-racing, for the individual animal are required. The use of biological passports has been established in humans [30] and would need a well-defined strategy for equine species whilst also remaining flexible. Some considerations include developing a population profile for horses focusing on numbers required, sampling techniques, software training, ethical access to research horses, defined suitable biomarkers and appropriate method validation plans. There are numerous benefits to establishing an EBP and it could change the way in which racing authorities currently battle doping in racing [29]. Establishment of a biological signature for horses could reduce the reliance on methods which detect specific prohibited substances. Furthermore, EBP approaches may act as a deterrent against the use of novel drugs where they have a similar mode of action to related currently prohibited drugs.

Conclusions

Bisphosphonates have the potential to be hugely beneficial to the general horse population; however, caution should be exercised to ensure their correct usage. Effective doping control of bisphosphonates in horse racing relies on the use of chromatographic and mass spectrometric techniques to detect low levels of precursor and product ions of prohibited drugs and their metabolites. In the analysis of bisphosphonates in horses, it is necessary to define an action level for horses above the threshold age and a separate limit for younger animals where the detection of even trace amounts is significant. The half-life and sporadic release of these compounds from bone also poses challenges in determining residue limits. Newer analytical approaches, such as metabolomics, may complement existing testing methods or, in time, may replace then entirely.

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Gas Chromatography Mass Spectrometry (GC-MS) and the Value of Free Online Databases

Rebecca McNamara, Atlantic Technological University, Ballinode, Sligo, F91 YW50, Ireland

Gas Chromatography - Mass Spectrometry (GC-MS) has been considered the gold standard technique for unknown drug separation and identification up until recently. Separation is now moving towards Liquid Chromatography (LC) techniques; notwithstanding, GC-MS can have a very positive impact on the separation and identification of unknowns in forensic and analytical settings. The value of this technique lies in the fact that data is easily obtainable, highly reproducible and its equipment often costs a fraction of other hyphenated techniques. This allows mass spectral reference data along with data from identified compounds to be combined in searchable online databases such as SWGDRUG, Response Project, MassBank [1][2].

An analytical facility has choices on which databases to employ as those could be created locally using in-house data and purchased data uploaded on the instrument's hard drive or could be downloaded from the web using data from the global online community. Purchased databases include NIST 20, which is the latest version of the NIST and has over 300,000 GC-Electron Impact Ionization (EI)-MS mass spectra [3].

Alternatively, online databases such as SWGDRUG, Response Project and Mass Bank are also available at no cost to users globally. They allow data extracted from GC-MS spectra to be searched in extensive libraries. The value of such databases cannot be overstated in the reduction of time and resources needed for the identification of an unknown compound.

A review of the current literature available surrounding GC-MS online databases allows us to draw the following inferences:

1. The availability of appropriate reference mass spectra and reference standards impacts time spent on identification.

If no reference spectra/standards are accessible, the knowledge and experience of the reviewing scientist is key in correctly identifying the unknown. Consequently, there can be a significant increase in time spent on spectral examination.

If a reference standard is available, repeat analysis is typically required to confirm the structure of a compound once one has been proposed. This further adds additional time and resources to an already lengthy analysis.

An example of the additional resources needed in the latter scenario described above can be seen in a case study where the authors carried out analysis on 10 unknown new psychoactive substances (NPS) [4]. No reference spectra or standards were available. Initially, the unknown compounds were subjected to GC-MS followed by UHPLC – QToF - MS for further characterization. GC-MS data suggested that 8 of the 10 unknown compounds were β-keto-phenylethylamines . The chemical structure of the β-keto-phenylethylamine group can be seen in Figure 1.

The value of GC-MS in this case was that it quickly notified the chemist of possible structures, narrowing down the possible class of compound being analyzed.

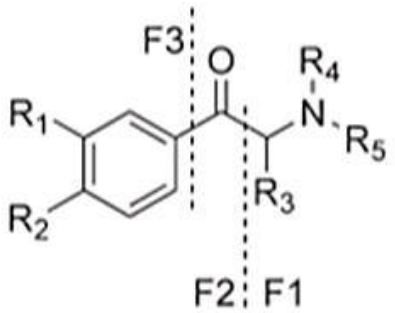


Figure 1: General fragmentation of β-keto-phenylethylamine group (Reitzel, et al., 2011

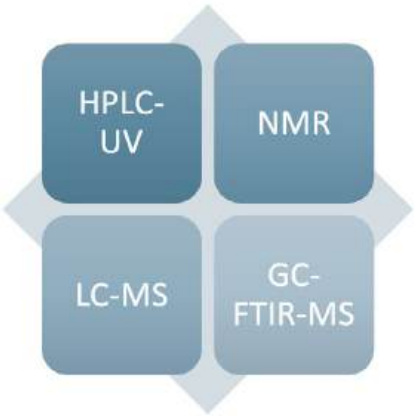
This supported the results of more specific analysis instrumentation - UHPLC – QToF – MS.

Despite this indication, the lack of actual reference spectra/standards resulted in further analyses being undertaken for compound confirmation/identification which highlights the issue that analysis is dependent on the availability of reference spectra/standards.

2. GC-MS is used in combination with other analytical techniques for unknown identification [5][6].

This is also implemented when no reference spectra are available. Greif et al, for example, used LC-HRMS in conjunction with GC-MS for the development of non-targeted screening of production waste samples from Leuckart amphetamine synthesis [7].

Along with this, Reitzel et al. [4] used UPLC-QTOF-MS in the analysis of NPS's in-conjunction with GC-MS data which provided suggested structures of the various unknowns.



The overall implication is that GC-MS cannot always be solely relied upon for identification as it is a less specific technique. It can be suitable for certain analytes but may require to be combined with other techniques for others.

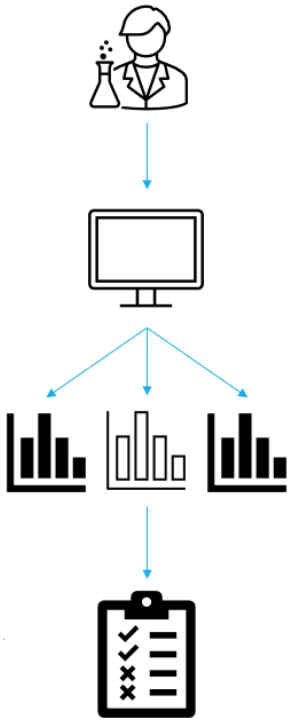
Many laboratories around the world heavily rely on GC-MS mixture separation and compound identification. There are several limitations to such reliance on GC-MS. Examples of such limitations include that some compounds are non-analysable by GC-MS due to their physical/chemical properties; and some laboratories fail to update their reference spectral libraries potentially missing some newer compounds.

3. Databases are not equally curated [1].

An analysis of several free, online databases for metabolites using GC-MS and LC-MS data was undertaken and found that not all databases were to the same standards.

For example, at the time of the study, the data on Mass Bank was sometimes misannotated, poorly extracted and noisy.

Whilst it can be assumed that the quality of the spectra has been improved since 2016 when that review was published, this issue highlights the need for constant improvements and considerations that should be taken into account when uploading and extracting data from free online databases.



4. Whilst the value of free online databases is evident, there is a growing concern about compound misidentification.

The issue lies in bias within the database results. As an example, bias in the databases could mean that one compound is being identified most often rather than it being correctly identified. Simplified, the results may be precise but not accurate.

Wei et al. [8] illustrated this issue on NIST 05 in 2014. NIST 05 is an earlier version of the NIST 20 local database. It has greater than 180,000 mass spectra available.

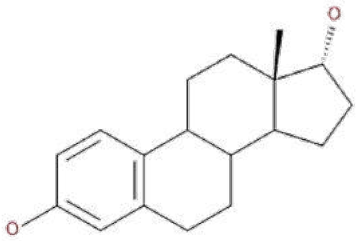


Figure 3: Structure of Beta-Estradiol

Beta-Estradiol (Figure 3) was searched on the database as an unknown. By using a spectrum matching based identification technique, the first compound proposed as a match was 17-alpha-estradiol (Figure 4) whereas beta-estradiol was the second suggested compound.

These two compounds had similarity scores of 0.9564 and 0.9465, respectively using this method of identification.

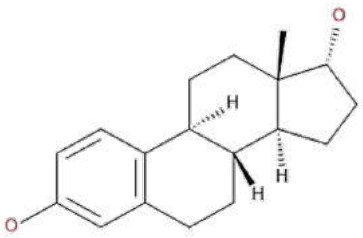


Figure 4: Structure of 17-alpha-estradiol

The risk of misidentification in this case is illustrated as the true value is not deemed the most suitable match.

To address this potential misidentification risk, NIST incorporated into the software a 'Hybrid Similarity Search' which searches all available databases. This utility was first made available with NIST 17 which is the version of NIST MS library between NIST 05 and NIST 20 and offers one solution to the identified issue.

In 2015, Dührkopa, et al.[9] proposed yet another solution that was based on the generation of a 'top 10 hit list' where the reviewing chemist is to determine the appropriate result from a list of proposals using their knowledge and experience.

The generated mass spectral data is uploaded onto their specialized software which performs algorithmic analyses and comparisons to all databases available. A list of the 10 most suitable mass spectra is then generated which then gets reviewed by the reviewing analyst who is responsible in making the final identification. It is up to the discretion of the reviewing analyst to determine the true result which reduces any bias from data presented on online databases but which does not remove the bias associated with the reviewing chemist.

5. Another issue of concern is over saturation which occurs if databases continually accept mass spectra of all drug types.

In such a situation, compounds of similar spectra but with largely different structures could be mistaken for each other as demonstrated by the previous point.

This again could lead to the misidentification of a compound misreporting of that compound's frequency that is in truth not present in the sample [1][2][9][10].

In conclusion, online databases can be useful tools in the provision of accurate and unbiased identification of unknown under certain conditions as demonstrated above and they rely on global collaboration on data that is highly reproducible in the laboratory thousands of kilometres away. Caution, however, should be exercised, particularly as databases begin to grow so that bias does not negatively influence the correct identification of an unknown.

Similarly, the impact that oversaturation of databases could have on the ability to successfully identify an unknown using the free online databases, could diminish the value of those exact databases. This final limitation cannot, at this time, be accurately assessed due to the current lack of data rendering unknown both "if" and to "what extent" oversaturation can truly cause a negative shift in the way online mass spectral databases are used for unknown drug identification.

Acknowledgements

This article was written by an undergraduate student studying for a BSc in Investigation and Analysis at the Atlantic Technological University Sligo (based on two undergraduate module's (Research Thesis and Analytical Toxicology coursework) under the academic supervision of Dr Geraldine Dowling

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Academic Programmes

Bachelor of Science Forensic Investigation and Analysis
Department of Life Sciences
School of Science
Atlantic Technological University Sligo, Ireland

Forensic investigation and analysis encompass the application of a forensic investigative approach using advanced analytical science for the provision of scientific data and evidence. The underlying analytical science combines forensic, biological, chemical, communication and information technology skills. These skills can be applied to the investigation of crime, testing for toxins or illicit drugs, DNA profiling or statistical analysis.

Programme Overview

This 4-year programme gives graduates skills in both forensic and analytical science making them highly employable in a broad range of sectors. Students will study both biology and chemistry through the exciting and stimulating medium of forensic science.

A major focus of the programme is the development of excellent practical analytical science skills which are in great demand by employers and for postgraduate research.

The stimulating programme facilitates engagement with a variety of learning experiences including the following :

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- training in molecular biology techniques for the development of DNA profiles
- collection and chemical analysis of gunshot residue
- learning how to test for toxins and illicit drugs
- engagement in flexible student centred work experience
- expert witness training and activities to enhance communication skills
- projects involving information technology and advanced scientific instrumentation

Year One

Students are provided with a solid foundation in Biology, Chemistry, Physics and Mathematics, as well as introductory modules in Information Technologies, Criminal Justice and Forensic Science.

Year Two & Three

First-year modules are studied more in-depth as the programme progresses with added subjects such as Crime Scene Investigation and Management and Instrumentation used for Forensic Analysis, Genetics, Molecular Biology, Statistics, and Quality Assurance.

Year Four

This final year focuses on high-level investigative, observational, evidence interpretation, research and crime scene management skills. Students will complete their work experience, presentation and forensic based research project in this year.

Graduates from this course will be versatile with key skills in chemical analysis, bio-analysis, information technology and communications, and project management. These will enable them to attain employment in laboratories in a variety of sectors from forensics, environmental, pharmaceutical and food industries as well as engaging in further postgraduate studies.

Professional Accreditation

This programme is accredited by the Chartered Society of Forensic Science in the UK for the component standards Interpretation, Evaluation and Presentation of Evidence(IEPE), Crime Scene Investigation(CSI) and Laboratory Analysis (LA). As the first third-level course on the island of Ireland to achieve this accreditation, it gives graduates the assurance that they have an internationally recognised qualification and are ready to undertake a professional career in forensic science.

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Please see more information https://www.itsligo.ie/courses/bsc-hons-in-forensic-investigation-and-analysis/
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Post Graduate Education in Drug Addiction and Addiction Toxicology

Institute on Drug Abuse, Toxicology and Pharmaceutical Science
Ege University Institute on Drug Abuse, Toxicology and Pharmaceutical Science, Turkey

Ege University Institute on Drug Abuse, Toxicology and Pharmaceutical Science serves in the field of forensic and addiction and is the first institute to be established in this area in Turkey.

Postgraduate education takes a place within the scope of two departments, namely the Drug Addiction Department and Addiction Toxicology Department. Programs accept students from the fields of Health, Science and Social Sciences in accordance with the multidisciplinary approach in the subject of addiction and was the first program opened in this field in Turkey. Some 89 students have completed their master's and doctorate education and 77 students are continuing their education.

The institute on Drug Abuse, Toxicology and Pharmaceutical Science has an Addiction Toxicology and Research Analyses Laboratories. In the Addiction Toxicology Laboratory, drug screening and confirmation analyses are routinely performed on biological materials for the detection of legal and illegal substances. Illegal substance analysis and research studies are carried out within the framework of international standards and guidelines. Addiction toxicology analysis continues in the following areas; Probation cases, Clinical cases and Workplace Drug Testing.

The institute continues its studies with the aim of increasing the qualified manpower in the fields of addiction, addiction-related toxicology and developing science and technology and new methods and techniques. In addition, postgraduate education, research and applications for the benefit of universal science and society are undertaken. The Addiction Toxicology Department carry out training and research activities in the following areas;

- Forensic Science
- Drug Abuse and Addiction Toxicology
- Forensic and Clinical Toxicology

Many projects are undertaken creating new approaches for the detection of substances in forensic toxicological analyses. Research is undertaken focusing not only on classical biological materials but also on new alternative matrices such as dry blood spots, sweat, saliva, surface and wastewater as examples.

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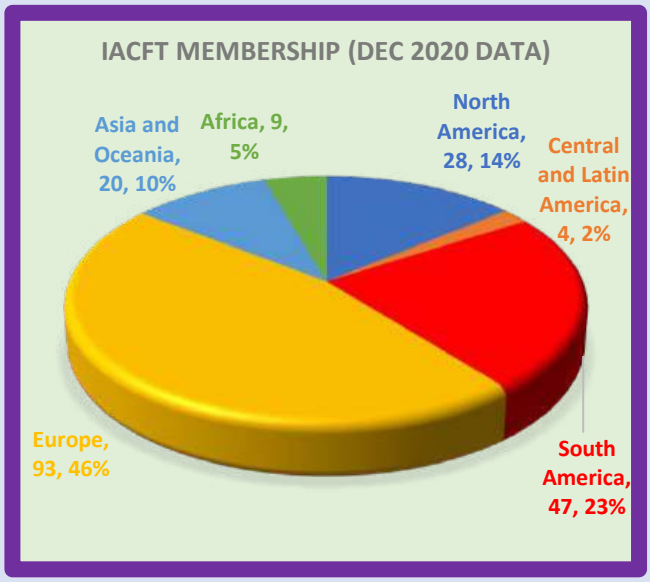

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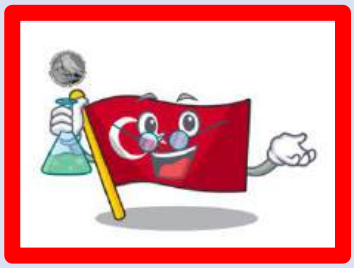

Acknowledgements

IACFT would like to thank all authors for their articles but in addition all editors and founding members who contributed to reviewing articles for the IACFT Gazette


Serap Annette Akgür


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