I am Sanela Martic, professor at Trent University in the Department of Forensic Science. I would like to welcome you to the forensic toxicology podcasts. (sirens in the distance). Through the streets of Vancouver, a rush to the scene. Now with a few extra precautions. As one health emergency exacerbates another, that's been unfolding for years. So is he awake and stuff? This is one of the few thousand overdoses BC paramedics had been responding to each month. On the middle of a sidewalk on Vancouver's Downtown Eastside, a man is unconscious and struggling to breathe. Like in so many other cases, fentanyl is the likely culprit. And for those who survive, paramedics say it's now taking longer to revive them. Hey sport. Okay, alright. Can you sit up for us? We want to make sure you're okay. It's the paramedics. Were giving these people high doses of Narcan and they're starting to breathe and they're not waking up.

Is it okay if I take your blood pressure and stuff real quick? Brian Twaits as a paramedic specialist trained to give advanced life support and frequently called upon to help crews respond to overdoses. The program was launched three years ago, not long after the province declared a health emergency because of drug deaths. It was a crisis then, and is worse now. I think what we're finding is it's more widespread. It's in all of the corners of the province. You're getting it in Prince George, you're getting it in Victoria, you're getting it in the interior. It's just picking up everywhere. Between May and the end of July, more than 500 people in BC have died of overdoses. The social implications of COVID-19, are one likely factor. Physical distancing means some safe consumption sites have had to shut down, or reduce their space and more people are using alone. Another cause increasingly toxic drugs. Experts speculate border closures have disrupted the supply, leading some to concoct mixtures with additional chemicals. This one is fentanyl, and we don't need much sample. We need about ten milligrams or the size of a match head. Alan Customs is a spectrometer technician with Get Your Drugs Tested in Vancouver. He tests samples that are dropped off or mailed in from across Canada. Now we get all types. We get people who are dealing, checking their substances, checking what to buy, or people who are cutting their samples and trying to see what percentage that they've cut it at. After the border closed Customs says he started seeing drugs with benzodiazepines cut in, which like fentanyl also depresses the central nervous system. And it's fentanyl, you'll see it just peeking out. Then he started noticing higher amounts of fentanyl. Normally it sits around 5-10%. We were seeing, you know, 15 to 20, 25 to 30, so much stronger. To most people that is enough to overdose, even a seasoned user with a high tolerance. You just heard Fighting an Opioid Overdose Epidemic During a Pandemic by CBC News the National in 2020. Welcome to the forensic toxicology podcasts. This one will be dedicated to opioids, fentanyl, specifically. Fentanyl was first developed in the 60's by Janssen as a potent opioid anesthetic and analgesic, and since the late 70s, fentanyl and it's analogs have been synthesized in labs and sold as heroin substitutes or mixed with other illicitly sourced drugs. Of course, leading to an increase in fentanyl related overdose and deaths. Fentanyl is really a very dangerous drug. It is 100 times stronger than morphine and 20 times stronger than heroin. One of the Canlii cases, fentanyl is stated as a more dangerous drug than either of those chemicals. It is used as a painkiller for chronic severe pain. However, it may also be produced illicitly. It can be made into pills which look like Oxycontin pills or mixed into other drugs, such as cocaine. In those forms, persons may take fentanyl without knowing that they are taking fentanyl. Fentanyl is currently approved and commonly used to treat breakthrough pain in cancer patients and in various other clinical conditions that involve non-cancer pain, such as post-operative pain. Pharmaceutical fentanyl comes in various forms, which may include delivery by a patch, orally, by spray, etc. Let's reflect, is there a difference in peaking or effect of the drug between the administration methods? Indeed, the half-life and duration of fentanyl effects depend on the route of administration. For example, fentanyl elimination half-life is seven hours for buccal and transmucosal routes. It is 219 minutes for intravenous and 2 to 12 hours for transdermal application. Fentanyl has a rapid onset, a few minutes only in a short duration of action around a couple of hours. For transmucosal it is so inflated and buccal routes and longer of course for transdermal ones that they can go for several days. So, with the fentanyl patch, the drug is absorbed through the skin. Fentanyl patches come in different types. Patches hold different amounts of drug ranging from delivery to the patient of around 12 micrograms per hour, up to 100 micrograms per hour. And there's really a lot of fentanyl in the patch. Fentanyl is only available by prescription only to persons who have an existing tolerance for opioids at the time it is prescribed. Of course, there are numerous ways to use fentanyl. Patches can be tampered with or cut into smaller portions as the patches are not designed or intended to be cut. Small portions of patches may contain dangerous or even lethal doses of fentanyl. Even the amount of fentanyl left in a used patch may be enough to cause a drug overdose in some individuals. Let's consider this case: Player v. Janssen-Ortho Inc., 2014 BCSC 1122 from CanLII website. What's the context? So the case before this court concerned a pharmaceutical patch of fentanyl. Fentanyl transdermal patch technology in Canada. Fentanyl is a member of the opioid family, it is a potent drug, along with morphine and many others, it's categorized as a strong opioid. In Canada, it is authorized for use for treatment of moderate to severe pain. It is only available by prescription. Unlike other strong opioids, fentanyl is fat-

soluble, and as a result, can permeate the patient's skin. Hence, using it as a patch is feasible. It can therefore be administered transdermally in the form of a patch. Generally speaking, these transdermal patches are designed to release a constant flow of fentanyl into the patient's bloodstream over a period of several days. Let's reflect what property of fentanyl makes it possible to be administered dermally? Fat solubility. Most opioids are lipophilic, consequently, meaning lipid loving, and consequently fentanyl and it's analogs can pass easily through membranes, including the blood-brain barrier. Fentanyl analogs have closer chemical structures to fentanyl than morphine. So low oral bioavailability is predicted. In the case of intranasal fentanyl, bioavailability is around 90%, while oral transmucosal administration, has a bioavailability of about 50%. The intravenous volume of distribution VD for fentanyl is four liters per kilogram, meaning three to eight liters per kilogram, really, a range. As we know, this compound is very lipophilic, very hydrophobic, and it loves to integrate easily into fats of the tissues and into the cells. Transdermal fentanyl patches have been available in Canada since 1991, when Health Canada granted a company authorization for the sale of specific patches. That patch is a reservoir type of transdermal fentanyl patch. As an innovator drug, this patch was initially protected by a patent so that no other companies were permitted to sell transdermal fentanyl patches prior to 2006. Whilst a drug enter off patent period. A number of other companies applied for authorization to release generic versions of the product. Among the pharmaceutical companies that successfully received Health Canada authorization for sale of generic transdermal fentanyl patches were many other companies. And you can check this case to find the companies' names. One of them, for example, manufacturered the ratio fentanyl patch, the other one manufacturered specific node patches and so on. Health Canada authorized the sale of some of these in 2006, 2008, and more recently 2009. As a result of corporate mergers, some companies actually took over and still make these patches. All the patches manufactured by sub companies currently are matrix drug in adhesive style patches, and will be discussed in more details in the case, but the generic drugs are not required to match the innovator products exactly. They only need to be bioequivalent, so that the same level of active ingredient is released from the generic product at the same rate as it is released from the innovator product. The genetic versions may therefore differ from the innovator product in their delivery mechanisms or other design elements. So what's the premise of this case? Let's reflect. The claimant question involves transdermal fentanyl patches, a form of prescription painkillers for the active opioid Fentanyl that is delivered by a patch apply directly to the patient's skin. The defendants manufacturers market and distribute these patches in Canada. The plaintiffs say that the fentanyl patches are defectively designed such that they cause serious harm in ordinary use and they seek to certify a class action against all of the defendants. So what happened? Wade Robert Player died in August 2007 at the age of 34. Not long before his death, he suffered severe injuries in a motor vehicle accident and as a result, had prescription for pain management via a transdermal fentanyl patch. He was wearing a fentanyl patch at the time of his death. Let's look at the corner and toxicological reports. The coroner's report lists the cause of death as fatal respiratory depression due to a prescription drug interaction. Indeed, the toxicology found the presence of fentanyl, and many other drugs such as Trazodone, Carbamexepine, Gabapentin, Celecoxib, Citalopram, Olanzapine in Mr.

Player's bloodstream. It is important to notice that the biological matrix used for testing on the chemicals was indeed the blood. It is interesting that Mr. Player actually use both ratio fentanyl and Duragesic brand patches during the course of his treatment. The ratio-fentanyl is a matrix drug in adhesive style patch, while Duragesic is a reservoir patch manufactured by the other company. So let's get into more details into more extended coroners and toxicological reports. In this case, the document provides a number of details from Mr.

Player's post-mortem examination. The autopsy report indicates that at the time of death,

Mr. Player was wearing two fentanyl patches, one on each arm. Now, the report does not suggest that the first patch was still active. When Mr. Player put on the second patch. The report does not suggest that the use of two patches resulted in a fentanyl overdose. The toxicology report includes a somewhat cryptic comment, that suggests otherwise, as it says, blood level of fentanyl as found after regular application of patches. So it appears that fentanyl was one of the drugs and Mr. Player's system at the time of death. But there is no expert evidence that would allow to determine the role of that fentanyl played in the death. In addition, the coroner's report cannot prove cause of death. Was it really the interactions of the drugs that results in that outcome. Or was it specifically fentanyl. Evidence from the toxicologist, postmortem examiner, or even an expert interpreting the autopsy at toxicological findings would really be necessary to prove causation. It is interesting that experts in forensic toxicology, and forensic pathology have expressed the opinion that post-mortem Fentanyl levels can be relied upon as an estimate of the fentanyl level in the decedants at the time of death. On cross-examination, for example, there was evidence given by toxicologists in the US Milan proceedings and that was referenced to. In that particular proceeding in that transcript, the toxicologists indicated that post-mortem fentanyl levels

are not reliable indicators of the level of fentanyl in the blood at the time of death or the drug release rate of fentanyl patch in question. So the reliance of post-mortem fentanyl levels in determining cause of death is somewhat controversial, as there are studies that suggest it is reliable and studies that suggest it is not. Sounds to me, we have a quite a lot of work to do in toxicology of fentanyl. We need to understand its elimination rates, we need to understand its presence in biological fluids and ultimately how to use the concentrations of fentanyl and its metabolites in biological fluids to interpret concentrations of active drug at the time of death, for example, and even to link the outcome to the drug. I hope you enjoyed the forensic toxicology podcast on opioids, specifically fentanyl. Thanks for listening.