>> Jenny, thank you for that outstanding overview. I think it’s important that we be on the same page, that we understand the nomenclature that’s being used in the policy landscape governing the use of cannabis. And with that I’ll move on to our next session. This session will cover non-medical cannabis use and cancer epidemiology, and it will also focus on the co‑use of cannabis with tobacco and potentially harmful exposure, including biomarkers of exposure. I want to acknowledge Neal Freedman from our Division of Cancer Epidemiology and Genetics and Rachel Grana Mayne from our Division of Cancer Control and Population Sciences for their contributions to this session. And I want to note that all of the speakers in this session will discuss challenges and opportunities for research. And with that, our first speaker is Mia Hashibe. She’s from the Huntsman Cancer Institute. Her talk will cover Cannabis and Cancer Risk: Current Evidence and Methodological Considerations. Followed by Mia would be Dr. Amy Cohn, and she’s from the Stephenson Cancer Center, and her talk is focusing on Cannabis and Tobacco Co-use: Patterns, Correlates, and Implications for Reducing Cancer Risk. And then Dr. Benjamin Blount from the Centers for Disease Control and Prevention, who will discuss Potentially Harmful Inhalation Exposure Resulting from Smoked and Vaped Cannabis. Dr. Hashibe is one of the co-chairs of this session, and I want to note that we’ve invited Dr. Gillian Schauer to join us in the panel discussion afterwards. Dr. Hashibe.

>> Thank you for inviting me to talk. Cannabis and Cancer Risk: Current Evidence and Methodological Considerations. I do not have any conflicts of interest. Here’s a review of the talk. Review studies on upper aerodigestive tract cancers, lung cancer, testicular cancer, and several other cancers. I will talk about the methodologic issues from these previous studies and then move on to gaps in previous research. The smoke from cannabis contains several of the same carcinogens and co-carcinogens as tar from tobacco. This raises concerns that cannabis smoking may be a risk factor for cancer. The are results from almost 40 epidemiologic studies on cannabis smoking and the risk of cancer. We’ll apply the criteria for causation based on Hill’s criteria for epidemiologic studies. We’ll look at the strength of association, which we will focus on the risk estimate and the magnitude of risk and also the statistical significance. Second, we’ll look at consistency, looking at repeated observation of an association in different populations under different circumstances. And third, temporality to assure that the cause precedes effect in time. This is an issue for case‑control studies since cancer patients who are already diagnosed are recalling cannabis exposures. Recall bias is an important issue to address in case‑control studies. And fourth, for the biologic gradient, we’ll look at whether the studies assess dose‑response or exposure‑response curves. The first cancer we’ll review are upper aerodigestive tract cancers. In terms of the different subsites included, when we talk about head and neck cancers, this includes oral cavity, oropharynx, hypopharynx, and larynx. When we add esophageal cancer on top of those, we will call this the upper aerodigestive tract cancers. We’ll see that the studies that have been conducted included different combinations of these subsites. There are 10 case‑control studies on cannabis use and UADT cancer risk. Five of these are hospital-based and five are population-based. There are also two pooled data analyses. These are the five UADT cancer studies that are hospital based. The first study was based in New York and included 173 cases and 176 controls. They reported an odds ratio of 2.6, which was statistically significant and a dose response for both frequency and duration with P values that are statistically significant. All of the results that are statistically significant will be shown in bold, and any odds ratios that are reported are adjusted for smoking unless noted otherwise. The two next studies were conducted in the UK, focusing on oral cavity and oropharyngeal cancers for young patients 45 and younger. These studies did not report any association with cannabis use. The fourth study was from Baltimore and included 240 cases and 322 controls. This study stratified on HPV status. So the HPV16 positive patients had an increased risk of head and neck cancer for current cannabis use at 4.7‑fold. However, for the HPV16 negative patients, there was no clear association between cannabis use and head and neck cancer. For the HPV16 positive patients, there were statistically significant dose‑response trends for both frequency and duration. The last study focused on nasopharyngeal cancer in North Africa, with 636 cases and 615 controls, and there was no association reported overall, though there was a suggestion of a dose response with cumulative use with a key value of 0.02. These are the five population‑based case‑control studies. They were conducted in the U.S. as a multicenter study and in other locations such as Washington, Los Angeles, and Boston and also in New Zealand. The study sample size ranges from 70 sinonasal cases, all the way to 434 head and neck cancer cases from the Boston study. And the odds ratio reported, we see no associations across most of these studies. The protected odds ratio reported for the nasopharyngeal cancer study was not adjusted for tobacco, and dose-response relations were not assessed. For the pooled data studies, there are two. This was based in the International Head and Neck Cancer Consortium, and there were studies from Berthiller, et al and Marks, et al. They pooled studies from Seattle, Tampa, Los Angeles, Houston, and Latin America. There were about 4,000 head and neck cancer cases and 5,000 controls, showing the power of the pooling analysis method to create very large sample sizes. So, overall cannabis smoking odds ratio was 0.88, and this was not statistically significant, suggesting no association. The dose-response relation investigated also suggested no association for frequency and duration or cumulative exposure. This study was able to focus on never tobacco users, and no association was reported as shown with the odds ration of .93. The Marks, et al pooled analysis was an update of the previous pooled analysis and included more studies. This study focused on 1,900 oropharyngeal cancer cases and 356 oral tongue cancer cases. The overall cannabis smoking odds ratio was 1.24 for oropharyngeal cancer, and this was statistically significant. Dose-response trends were observed for both frequency and duration. The study focused also on never-tobacco smokers and never-alcohol drinkers in a separate analysis. The odds ratio was 2.11, but the confidence interval overlapped when suggesting no clear association, and no dose response relations were observed for the never-tobacco smokers and never‑alcohol drinkers. For tongue cancer we saw a decreased risk of 0.47, which was statistically significant. And dose-response relations were identified for both frequency and duration for this inverse association between cannabis use and tongue cancer risks. The pooled analyses included studies that had not been published. Berthiller, et al included three studies that were not published out of the five that were included, and Marks, et al included six unpublished studies out of the nine studied pooled. This shows that the strength of the pooled analysis is to include studies that may not necessarily have been published because they had no clear association. The three studies that investigated HPV, whether by assay or by focusing on HPV‑related subsites in the head and neck, are suggesting that HPV may be a modifying factor between cannabis use and head and neck cancer risk. Thus, in summary for UADT cancers, the case-control studies identified both increased and decreased risks, and this might be due to the fact that there’s no association or because risks differ by HPV status, head and neck cancer subsite, or geographic location. For lung cancer, there are four case-control studies. The first two were conducted in Tunisia and reported very strong odds ratios of 8.2 and 2.4. The first study did not report on dose-response associations. The second study investigated dose response, but did not report any. The third study we conducted in Los Angeles with 611 lung cancer cases and a thousand controls. This was a population-based case-control study, and we observed no association between cannabis joint-years and lung cancer risk. We also did not identify any dose‑response relations. The fourth study was from New Zealand, and they reported a very modest increase in risk of 1.08 that was statistically significant. The dose response for frequency was indicated, but the dose response for duration was not assessed. There were also two cohorts and one pooled data study for lung cancer and cannabis use. The first cohort was from Sweden and included 49,000 young men from the military and 179 lung cancer cases. There was no clear association with cannabis use. The second study by Sidney from California also reported no association for cannabis use and lung cancer risk for both men and women. The third study was a pooled analysis, which included almost 2,200 lung cancer cases and three thousand controls. And overall cannabis use was not associated with lung cancer. And this estimate was specifically for never-tobacco smokers to try to rule out confounding by tobacco, and dose response was also assessed, but none were observed. So, for lung cancer, the North African studies reported increased risk. However, tobacco is mixed with cannabis in the region; thus, it’s difficult to rule out residual confounding by tobacco smoking. For these studies, the highest exposure categories ranged from over 50 lifetime frequency, which could be an equivalent of one joint per week for one year or more than one or two joint‑years. So, this could be an equivalent of one to two joints per day for a year and more than 10 joint‑years. So, even the 10 joint-years of cumulative lifetime use of cannabis would translate only to about 0.5 pack-years of cigarette smoking, assuming similar carcinogenic potency and a similar amount of tobacco used in joints and cigarettes. Thus, in most studies on tobacco smoking and lung cancer, the cumulative exposure would be classified as a never smoker. Thus, these studies may not have had enough people who used the cannabis at high frequency or high duration. So, for lung cancer, the results largely appear to not support an association with cannabis use, possibly because of the smaller amounts of cannabis regularly smoked by the study participants. Next, for testicular cancer, there are three case-control studies and one cohort study. These studies were conducted in the U.S. for the case control, and they were a mix of population-based studies and hospital-based studies. They show the odds ratios for frequency and duration. So, the first study is showing a twofold increase in risk for daily or more than one day per week of cannabis use; however, the higher frequency category did not show an increased risk, and the duration category both showed increased risk, but we don’t see higher risk for the 10 or more years of cannabis use. The second study showed a protective effect for using cannabis less than one per day, less than one time per day, and an increased risk for daily or more use of cannabis. There were no associations in terms of the duration of cannabis use. And the third study in Los Angeles reported a twofold increase risk for the lower frequency category but no association for the higher frequency category and also a twofold increase in risk for smoking less than 10 years but no clear association for smoking more than 10 or more years. The cohort study was conducted in Sweden and included 119 testicular cancer cases, starting with a cohort of 49,000 men. There was no overall association with cannabis use, but for the highest frequency use of more than 50 times, the increase in risk was 2.57‑fold. The more-than-50-time use was assessed at age 18 to 20 for men so we don’t know if they had more use after that age. So, for testicular cancer there are three case-control studies that assessed both frequency and duration ,but none showed strong dose‑response relations. Two of the case-control studies adjusted on tobacco use. However, tobacco smoking is not an established risk factor for testicular cancer; thus, it doesn’t meet the first property of confounders. This is not clear that smoking needed to be adjusted on; however, for the studies it is useful to show it as a sensitivity analysis in case the tobacco smoking is associated with other potential compounders. So, for testicular cancer, there were four studies that reported increased risk, but dose-response trends are not established. For childhood leukemia we have three case‑control studies. The first include multicenter studies and included 200 cases and 200 controls and reported an odds ratio of 11, which is very high for maternal use of mind-altering drugs. This was not specific to cannabis, but 9 of the 11 subjects who reported the drug use were using cannabis. For paternal use there was no association from this study. For the second study, this was a much larger study with 1,800 acute lymphoblastic leukemia cases and also 528 acute myeloid leukemia cases and 2,700 controls. This study reported a 1.5‑fold increase in risk that was statistically significant for ever cannabis use by the father. The third study included 638 childhood acute myeloid leukemia cases and 610 matched controls, and maternal use of cannabis was not associated with childhood cancer risk. The paternal ever use was associated with a 1.37‑fold increase in risk. There are three case-control studies for other childhood cancers. For astrocytoma there was no association with cannabis use during the gestational period. For rhabdomyosarcoma we saw an increased risk of 3‑fold for maternal use, which was statistically significant and a 2-fold increase for paternal use. For neuroblastoma there was no association with general maternal use of cannabis, but the frequency of use in the first trimester was associated with a 4‑fold increase in risk. For the childhood cancer studies, they share limitations such as the small numbers of exposed cases, possible exposure misclassification due to potential recall bias. The parents of the children were asked to recall their exposure after the patient was diagnosed; thus, recall bias remains an issue. And also, there were no dose-response assessments. The strengths of the studies include very large sample sizes and information on use of specific drugs within very specific time periods relative to pregnancy and birth. For other cancers, the Kaiser Permanente cohort covered multiple cancers and reported an increased risk of prostate cancer and cervical cancer for cannabis use, but there was no association with colorectal cancer, melanoma, or breast cancer. There were also other studies that reported no association for anal cancer, penile cancer, and non-Hodgkin’s lymphoma. Other studies reported decreased cancer risks associated with cannabis smoking, and this was for non-Hodgkin’s lymphoma. There were two studies for non-Hodgkin’s lymphoma and one study for bladder cancer suggesting a decreased cancer risk. Thus, for childhood cancers and other cancers, there’s still insufficient data to make conclusions on an association with cannabis smoking, though a few studies have reported potential protective effects. So, some methodologic issues across the studies are underreporting. Most of these previous studies were conducted in locations where cannabis smoking was illegal and also during time periods in which cannabis smoking was illegal. Thus, the study participants may not have been honest in reporting their cannabis smoking, even if they were reassured about confidentiality. Thus, this could have led to misclassification of cannabis smokers being classified as non-cannabis smokers. There were also small sample sizes of cancer cases in some of the studies, and if the possible association between cannabis smoking and cancer risk is moderate, as an example risk ration less than two, a large sample size of cancer patients would be needed to detect the association. And the third issue was that too few heavy cannabis users were identified. So, the previous studies did not have study subjects who reported high frequency of cannabis use. However, the patterns of use may be changing with the legalization that’s occurring across the U.S. So, confounding by tobacco smoking is a major issue in these studies. So, tobacco and cannabis co-use makes the effect of cannabis very difficult to disentangle from the effect of tobacco. So, possible solutions are to restrict the study to non-smokers or to adjust for tobacco smoking statistically. So, we saw some of the pooled analysis and some of the larger population-based case controls’ restriction on smokers. There is a possibility that the cannabis users who don’t use tobacco may be a unique population, and this might the generalizability of any results that we see for cannabis users who are non-smokers or non-tobacco smokers. And the adjusting for tobacco smoking requires a lot of variables to reflect the tobacco risk (unint.) and so these are the four that are required. So, the first variable would be never, current, and past use; and then we need to address frequency of tobacco smoking, so it could be cigarettes per day; and also the duration and years of smoking. The first variable is the years since quitting tobacco smoking. And across these four variables we need it for all different types of the smoking. So we would need these four variables for cigarette smoking, cigar, pipes, and vaping, and other methods, but most studies don’t collect this level of detail. Thus, it is difficult to adjust for tobacco smoking appropriately. So, moving on to the gaps in previous research. The exposure assessment has been focused on smoked cannabis, and there is a complete lack of data on other types of cannabis use. There are no studies on vaping or cannabis in edible forms. So, these would need to be studied for cancer risks. The second gap is that there are few cohort studies that are prospective in design. The prospective study design would really help to minimize the possibility of recall bias, which we saw is a limitation for case‑control studies. The third gap is using biological markers in combination with self-reported measures of cannabis use. Other previous studies used biological markers, and there’s an opportunity to incorporate markers with development of very interesting markers for cannabis. And the fourth gap is to fully leverage pooled data in epidemiologic consortia. We saw that the pooled data allows for much larger sample sizes and incorporation of studies that may not have shown any association on their own, which may have remained unpublished, and also it allows for focusing on specific subgroups, such as the non‑tobacco smokers. So, in conclusion, new well‑designed epidemiologic studies on cannabis use and the risk of cancer are needed. I’d like to thank the NCI and NIDCR for their support of reviews of the cancer and cannabis-use studies and for supporting some of the studies, especially the Los Angeles study and the pooled data analysis studies. And I’d also like to thank my co-investigators and co-authors, who helped me to think through the methodologic issues and to carry out some of the studies and pooled data analysis. Thank you.

>> Good morning and thank you for the opportunity to present on cannabis and tobacco co-use today. I want to acknowledge my funding through NIH and NIDA, the FDA Center for Tobacco Products. I have no conflicts of interest to report. When I initially set out to do this presentation, I admit I was a bit overwhelmed at covering an entire field of cannabis and tobacco co‑use in just 25 minutes. So, to set the tone, I want to provide some key takeaway points for you. First, cannabis use alone has some noted health benefits, but it is the co-use of cannabis with tobacco that’s associated with a variety of health problems. And what you’ll see is that co-users have higher rates of tobacco use, which we know is the leading cause of cancer. Second, not all co-use is the same. There are a variety of tobacco and cannabis products that can be used in many different ways. Poly-tobacco use is also quite common and increases the health consequences associated with co-use, and we’ll only be able to scratch the surface today. Third, my goal is to present the broad strokes and foundational information about co-use. I think more work is needed among specific sub-groups with high rates of cancer to understand the co-use correlates and cancer-related consequences. Most studies, understandably, have focused on younger ages groups, who are less likely to show acute cancer risk. Finally, cannabis and big tobacco industries outpace our public health efforts in terms of spending. Dedicated time and funds are needed to counteract industry spending and reach. First, I want to talk about what is co-use and provide some definitions. There are several different types of products and ways that co-use can occur. A joint refers to wrapping cannabis in rolling paper, not tobacco, and a joint does not contain any tobacco. A spliff is similar to a joint, except tobacco is not added. Some users state the benefits of spliff smoking include it’s easier to roll a spliff than a joint because the tobacco provides structure; the tobacco in the spliff masks potentially strong odor of combusted cannabis; and the product burns more smoothly. Blunt smoking refers to removing all or part of the tobacco from a cigar and replacing it with cannabis. Noted benefits among blunt users are that blunts are large so they can be used in a group, and they can also increase one’s high; blunts come in flavors, unlike smoking a joint; and the thick tobacco paper of the cigar allows for a slower burn. Vaping cannabis refers to vaping or heating flower or THC concentrates, oils, or wax in a variety of vaping devices. And smoking cannabis through a hookah device refers to combining the flower or loose leaf cannabis or, again, THC oils, extracts, or concentrates with shisha, which can also be flavored or unflavored. The use of multiple hoses in a shisha, hookah, or waterpipe allows for sharing and a more social experience. There are also several different types of co-use. Combined use describes the use of cannabis and tobacco within the same product, such as a blunt or a spliff. Simultaneous use is the co‑use in the same episode, but not necessarily combined; for example, chasing, which refers to smoking tobacco after using cannabis. Lastly, concurrent use refers to the use of cannabis and tobacco on separate occasions but within the same time period, such as in the past 30 days or the past year. So why focus on cannabis and tobacco co-use? First, tobacco use is quite high among co-users, as you will see form this data from the National Survey of Drug Use and Health. Sixty-eight percent of past-month cannabis users report past-month tobacco use, compared to just (inaud.) percent non-cannabis users; and 77 percent of past-month cannabis users report any past‑month combustible tobacco use, compared to just 23 percent. These numbers are staggeringly high and concerning, given the known links between combustible tobacco use and cancer. Beyond tobacco use, there are a variety of health and psychological consequences associated with co-use. Co-use is associated with greater cannabis and nicotine dependence; poor tobacco and cannabis cessation outcomes; mental health problems like alcohol, drug use, depression, and anxiety; and increased cancer risk or behaviors related to cancer risk, including respiratory problems. Finally, there are health disparities and hidden risks associated with co-use that are important to consider with respect to cancer risk. As you will see in this presentation later, the demographics of co‑users are similar to those who show cancer-related health disparities. There are also several hidden risks associated with co-use that the general public may not be aware of or think about, including firsthand and secondhand smoke exposure. Many of the same constituents in tobacco smoke are found in cannabis smoke. One recent study by our keynote speaker found that almost 27 percent of U.S. adults report exposure to cannabis secondhand smoke. Second, co‑users misperceive harm associated with their use. For example, even though the tobacco is removed from a blunt, blunts still contain nicotine on the cigar wrapper, furthering the cycle of tobacco use and perhaps dependence. Finally, there’s a double whammy, as I’m calling it, of smoked or combusted tobacco with combusted cannabis. Ingesting these together may increase exposure to cancer-causing carcinogens. However, there’s only (unint.) work in this area with humans. Now I want to present what we know about current patterns of co-use. So, as many of us in this audience know, we have seen tremendous declines in cigarette use for decades now, but this isn’t the entire picture. We’re seeing the use of other tobacco products increasing, and most of these products are co‑used with cannabis. We’ll see on the left a figure of increasing emerging tobacco use among adults and on the right, increasing emerging tobacco use among youth. The prevalence of cannabis and tobacco co‑use have also increased significantly. I want to point out that while this figure estimates co-use up to 2012, the rates may likely be higher now due to increasing use of blunts, vaping cannabis, and smoking cannabis with hookah. I’ll show some current rates of past‑30‑day co-use of those in some future slides. Now, what products are most popular among co-users? The next few slides are just showing recent data from wave four of the Population Assessment of Tobacco and Health Study or the PATH Study. These were collected in 2017 and ’18. The slides highlight the relative popularity of different tobacco products across youth, young adult and adult co-users, and tobacco-only users. This table shows the prevalence and popularity of past-30-day use of 10 different tobacco products among youth, past-30-day cannabis and tobacco co-users and past-30-day tobacco-only users. Unfortunately, given the low prevalence, we were not able to include past‑30-day blunt use in this table. Past-30-day blunt use was not asked among all users in the PATH dataset. First you’ll see that 8.26 percent of youth who report past-30-day tobacco use engage in co-use behavior. Second, in terms of product popularity, we can see that cigarettes and e-cigarettes are the two most popular products used across both co-users and tobacco‑only users, followed by cigarillos, likely because they come in flavors and they’re relatively inexpensive. I finally want to point out a significantly greater percentage of co-users report past-30-day e-cigarette use compared to tobacco-only users. It’s possible this could be due to cannabis vaping, but more work needs to be done. This table shows the prevalence and popularity of past-30-day tobacco product use among the young adult co-users and tobacco-only users. What’s different here is that nearly half of young adult past-30-day tobacco users report co-use, which is nearly five times higher than among the youth. Cigarettes emerged as the most popular product used equally between co-users and tobacco‑only users, and blunts were the second most popular product used in the past 30 days among co‑users, endorsed by 42 percent of them, but they were much less popular among tobacco-only users, ranked as the eighth most popular product. I want to note that a small percent of past-30-day tobacco‑only users reported past-30-day blunt user, highlighting that there is misclassification, that blunts are sometimes not considered a tobacco product or a cigar. Finally, co-users reported significantly higher prevalence of cigarillo or filtered cigar smoking in the past 30 days, relative to the tobacco-only users and a lower prevalence of smokeless tobacco use. The high prevalence of little cigar use is concerning, as smoking cigars conferred similar cancer-related risk compared to cigarette smoking and in some cases, greater ingestion of toxins and cancer-causing carcinogens. Finally, this table shows that almost a third of adults age 25 and older report past-30-day co-use. Cigarettes, again, remain the most popular product regardless of co-use status, followed by e‑cigarettes and cigarillos or filtered cigars. Blunts were the fourth most popular product among co-users. And then finally, with the exception of cigarettes, co‑users (inaud.) a higher prevalence of all combustible tobacco products assessed here, compared to the tobacco-only users. Thus, adult co-users may be exposing themselves to more cancer-causing carcinogens and toxicants compared to tobacco-only users. What are the basic demographics of those who co-use? First, co‑users are more likely to be black compared to tobacco‑only users, and co-use has increased by 23 percent among black and 21.9 percent among Hispanic individuals, a faster rate than among white. In terms of gender, the majority of co-users are males, as you can see here. Co-users are more likely to be male also compared to cannabis-only and tobacco-only users, and co-use has increased at a faster rate among males than females, by about 13 percent. We also see high proportions of co-users report low income and lower educational attainment. In terms of cancer disparities, the mean cancer death rate is higher in the lowest income counties in the U.S. Finally, only a small proportion of co-users report poor health status, but co-users are more likely to report poor health status compared to non-users of cannabis and tobacco. What do we know about links between cannabis and tobacco initiation? There are several theories to explain co-use, and it’s likely not just one theory explains every instance of co-use. The gateway hypothesis suggests that substance use follows a sequence, starting with lower hanging fruit like alcohol and tobacco and moving to harder drugs like cannabis. The reverse gateway hypothesis states the opposite where harder drugs like cannabis precedes softer drug use perhaps as individuals mature out of harder drug use. The vulnerability hypothesis suggests that co-use occurs as a symptom or expression of an underlying vulnerability or predisposition to engage in a variety of health risk behaviors. Theories of reinforcement would suggest that cannabis use is used to enhance the high of inhaled nicotine, such as in the case of blunt smoking, or nicotine is used to counteract the depressive effects of cannabis. Finally, peer norms would suggest that leaving home and going to college influence the co-use of a variety of substances that had previously been off limits. And we see this in literature that shows a high increase in substance use behavior during the transition from high school to college. The association of tobacco and cannabis use and their initiation is most likely reciprocal, and the literature remains pretty unclear as to which comes first. In some studies tobacco use precedes onset of cannabis use. For example, one study found that e-cigarette use predicts subsequent cannabis use among youth and young adult adolescents. Another study found that youth and young adults who report a more pleasant first cigarette smoking experience are more likely to report subsequent cannabis use, and in contrast, those who report a negative or unpleasant first smoking experience are less likely to report subsequent cannabis use. In other studies cannabis use predicts onset of tobacco. For example, in a national study of young adults, ever marijuana use predicts the onset of little cigar or cigarillo use but not traditional cigar use. This, again, highlights that not all co-use is the same. Someday/everyday cannabis use among young adults has also been shown to predict hookah trial six months later, and in one study 22 percent of young adults who reported hookah trial engaged in pre-trial everyday/someday cannabis use. To examine which product comes first, this table shows the prevalence and sequence of alcohol, tobacco, and cannabis initiation among youth and young adults from the PATH Study. This table is broken down by the number of substances first tried at the age of initiation. For example, if Joe reported trying alcohol at age 15 and tobacco at age 15, he reported multiple substance trials. If he reported only trying alcohol at age 15 and nothing else, he reported single substance trial. And what we find from this data among single substance triers, not surprisingly, is that alcohol is overwhelmingly tried first, followed by tobacco use. Over half of youth and almost a third of young adults report using alcohol before anything else. It’s also important to point out that only three percent of youth and two percent of young adults tried cannabis before they tried anything else. This may also allay some concerns that the increase in legal cannabis policies has had an impact on onset of cannabis initiation relative to other substances. Among those who tried multiple substances for the first time at the same age, we also see that trying alcohol and tobacco at the same age is much more common, while trying cannabis and tobacco for the first time at the same age is less common, only among three to four percent of the young adult and youth population. Thus, co-use of cannabis and tobacco at initiation seems to be less common. Now I’m going to provide some more detail about individual tobacco product co-use with cannabis. In terms of the co-use of cannabis with cigarettes, cigarettes are the most popular products used among co-users, as we saw before. Sixty percent of past-month cannabis users report cigarette smoking. Thirty percent of current cigarette smokers report past‑year cannabis use. Daily cannabis use has increased among cigarette smokers in the past decade. In fact, the most rapid increase is among former smokers, and this suggests some possible compensatory effects of perhaps withdrawal attenuation of cannabis use on nicotine withdrawal symptoms. Cannabis use disorder is two to four times more common among smokers than non-smokers. And with respect to cannabis chasing with tobacco, it’s been uniquely associated with certain dependence symptoms separate from blunt smoking, again, highlighting that not every tobacco product is co-used the same with cannabis. One study found that those who report chasing cannabis more frequently have three to five times higher odds of reporting cannabis dependence symptoms. Cannabis and cigar co-use has also become increasingly more popular. Twenty-six percent of cannabis users currently use cigars; 42 percent use blunts. Correlates of cannabis and cigar co-use include being male, being African American, being young adult or older young adult, and having higher rates of cigarette, alcohol, and illicit drug use. Cigar use is associated with the same negative health outcomes as cigarette smoking, including increased cancer risk, coronary heart disease, and COPD. This figure shows the prevalence of past-30-day cigar-only, blunt-only, non-blunt cannabis use, and dual use of cigars and blunts in the past 30 days among U.S. adults from the National Survey of Drug Use and Health. What I want to point out here is that blunt use and dual use of blunts with cigars in the past 30 days are overwhelmingly reported by young adults. Forty-seven percent of blunt smokers and 49 percent of dual cigar and blunt users are young adults. With respect to blunts, several studies have found that blunts and cigars are perceived as less harmful and addictive than other tobacco products. Misclassification of blunts is also a concern, where some users either do not consider a blunt a cigar, or a tobacco product, leading to underestimates in surveillance surveys. Some do not know their blunt-smoking product is actually a cigar. They only know the product by the brand name that they purchase, but they did not know that it was a cigar in some research studies. It’s important to note again that even though the tobacco may be fully removed from the blunt, the wrapper still contains nicotine, increasing addiction potential of these products. Blunt smoking has also been associated with greater cannabis dependence problems, including tolerance. This figure shows perception of risk of smoking cannabis one to two times a week among the same group of adult cigar and blunt smokers that I had presented before. As you can see, the dual blunt and cigar smokers also had the lowest perceived risk of smoking cannabis compared to other groups, and remember, these groups were overwhelmingly young adults. The prevalence of past-year cannabis vaping has also increased significantly among all younger age groups just in the past few years. These data from the Monitoring the Future Study show that in 2019 about 21 percent of young adults and twelfth-graders reported past-year cannabis vaping, and 7 percent of eighth‑graders. There was a six percent increase in cannabis vaping among young adults; a seven percent increase among twelfth-graders; and the small but still significant 2.6 percent increase among eighth‑graders. This may also be one reason behind the public health epidemic called EVALI, also referred to as e-cigarette and vaping-related lung injury, which was largely driven by vitamin E acetate found in THC oils being used in e-devices. Less is know about cannabis co-use with hookah. Most large population‑based studies are just now starting to ask about it. According to PATH data, 51.7 percent of adults past-year hookah users report past-year cannabis use, compared to only 10 percent of non‑hookah users reporting past-year cannabis use. And 65 percent of youth ever-hookah users report ever‑use of cannabis, compared to just 9.5 percent of never‑hookah users. Tobacco and cannabis industry practices may also play a key factor in shaping co‑use. You’ll see in this pyramid at the bottom the tobacco industry spends about $24 million a day, which is just over $9 billion a year. The tobacco industry historically targets low-income neighborhoods and specific vulnerable demographics. These individuals also have high rates of cancer risk. The cannabis industry in the next rung of this pyramid was estimated to have spent about $6 million a day in 2019 on marketing, which is about $2.26 billion that year. And at the very top is the daily and annual spend of the combined NCI grant portfolio that has focused specifically on tobacco use. This equates to approximately $180,000 a day or $65 million a year. Sixty-five million dollars a year may likely sound like a lot, but putting this in perspective, it would only be enough money to counteract approximately 4 days of tobacco marketing spend and 11 days of cannabis marketing spend. Increasing co-use rates have not operated in a vacuum, however. Not surprisingly, co-use has increased among young adults, the age group for whom the tobacco companies have had a long history of targeting through marketing. Further, certain product features have been developed to facilitate cannabis use. Note here the image of splitarillos. These are little cigars that are prepackaged with a perforated strip down the middle to allow for easy removal of the tobacco for blunt smoking. Many young people know about this product and specifically buy it for that reason. These are images of dry cannabis vaporizers and THC oil cartridges. They look very similar to e-cigarettes or electronic nicotine devices. Finally, because cannabis is a Schedule I drug, no print ads or marketing materials may be sent through the mail; however, the workaround to this is the use of social media platforms, some of which allow for CBD marketing with restrictions. Celebrity endorsements, such as the images you see here, are also free advertising and legal in some cases for those industries. I posted a meme here of the rapper Wiz Khalifa smoking a blunt, seemingly touting the use of a blunt as a form of celebrating for getting into college. Research shows that exposure to celebrity endorsements of tobacco products is associated with susceptibility and intentions to use those products. Less is known about the impact on intentions to use cannabis and tobacco together. I’d like to close with a few recommendations. I’ve identified several research, clinical, and policy priorities for reducing cancer risk associated with co-use. First, given the high co-occurrence between cigarette smoking and cannabis use, one approach would be to study the impact of lower nicotine cigarettes on the market as a means of reducing uptake and initiation of cannabis. The Food and Drug Administration has proposed to introduce low-nicotine cigarettes on the market, and this may be one pathway to reducing co-use. Second, we need prevention campaigns that correct myth perceptions about the harms associated with co-use. The compendium of research shows that blunt smokers though to likely expose themselves to the greatest amount of cancer-causing carcinogens, have the lowest perceptions of harm of both cannabis and blunt smoking. Third, reducing access to tobacco products may have downstream effects on cannabis use. With the recent increase in the legal purchase age of tobacco products to 21, it will be important to study the impacts of this new policy on delayed onset of ad uptick of cannabis use, particularly among those age 18 to 20 who no longer have easy access to these products. Fourth, we need research funding to evaluate the etiology, development, and offset of co-use and links of cancer and cancer-related behaviors. For example, with more and more states allowing for some sort of legal cannabis, policymakers should consider how local cannabis laws may reduce or promote tobacco use such as limiting dispensaries within a certain distance of tobacco retail outlets. I am encouraged by NCI’s growing interest in this topic. Finally, we need to work within our communities, particularly dispensaries and the cannabis industry, to promote and deliver tobacco cessation programs within the context of dispensaries. Thank you again for the opportunity to participate.

>> All right. So, this is Ben Blount from the CDC’s Division of Laboratory Sciences. Today I’ll be talking about Potentially Harmful Inhalational Exposures Resulting from Smoked and Vaped Cannabis. The work I’ll be presenting today results from a number of CDC and outside of CDC collaborators that I’ll acknowledge at the end of my presentation. Next slide please. So I have no conflicts of interest to declare, and the views that I’ll articulate in the presentation today are mine and do not necessarily represent the official position of the U.S. CDC. Next. So, an overview for my presentation. As you can tell from my title, I’m the chief of the Tobacco and Volatiles Branch, and so I’ll be drawing parallels between tobacco products and cannabis products to connect the dots between emissions and exposures to users and secondhand exposures to people adjacent to users as well as potential harm caused by those exposures. I’ll have some case studies about potentially harmful chemicals in cannabis smoke in particular. And lastly, we’ll have a number of different case studies looking at biomarkers of smoke exposure. So, once the chemicals get into people’s bodies, being able to measure and assess the exposure, confirm the exposure by measuring those chemicals and their breakdown products in biological fluids. Lastly, Dr. Sharpless (ph.) and Dr. Cohn mentioned the e-cigarettes or vaping product associated lung injury outbreak earlier about a year ago. So I’ll be talking about that and how laboratory analyses helped us to characterize the harmful exposures related to those products. Next. So, to connect the dots, I wanted to draw some parallels from the current work that my group is doing related to tobacco products. So, you can see in the upper left‑hand corner graphic our work with product where we’re characterizing the chemical constituents of a product, looking at active ingredients, contaminants, potential modifications, helping to clarify counterfeit products. Secondly, and a more complicated analytical challenge, looking at the emissions of those products. So, for a smoke product, using a smoking machine, looking at smoke constituents such as polycyclic aromatic hydrocarbons or volatile organic compounds, aromatic amines, heterocyclic amines, carbon monoxide, tar, metals, other chemicals that are transmitted through the smoke and sometimes formed in the smoke and then lead to exposure to the person using the product. So, our focus in I think broad areas where we need to understand human exposure and potential health consequences of these products by understanding the topography, how the products are being used, confirming that exposure has happened by measuring selective and sensitive biomarkers of exposure in biological fluids and then finally developing assays for biomarkers of potential harm to connect the dots further to potential pathologies. Next slide. So, at CDC our first smoking machine is shown in the panel at the upper right-hand corner. We developed this a couple decades back when I first joined CDC in the laboratory that David Ashley was leading at the time. Subsequently, CDC and other laboratories have used different smoking machines to characterize emissions from tobacco cigarettes, including a linear smoking machine where one can look at cigarette emissions individually, as well as a rotary smoking machine shown on the right for pulling signal from multiple cigarettes for a single more robust measurement. Next slide please. So, on the next slide you see results from a case study, this being the Health Canada funded (unint.) of mainstream and sidestream smoke from both tobacco and cannabis rolled into cigarettes and smoked using standardized smoking protocols. Of course, the link between marijuana smoking and lung cancer has not yet been demonstrated, as Dr. Hashibe pointed out in her presentation earlier this session, but some of these exposures will increase risk potentially to adverse health outcomes, especially as the prevalence and intensity of use increases. So, the case study that I’ll be citing here is the Moir, et al study looking at that chemical composition of mainstream and sidestream smoke, using those standardized protocols. Next slide. So in these tables you can see the results that Moir, et al presented, following a low-intensity and high-intensity smoking regime. In these tables next you can see benzene, for example, benzene levels from a smoked tobacco cigarette – next – as it compares to a smoked marijuana joint. Really comparable levels of benzene forming in that smoke when smoked the same way and the same volume of or the same mass of leaf product being smoked that way. Next on table seven, and here you can see the respiratory irritant acrolein at 437 micrograms per gram tobacco smoked. Next. For comparison 300 micrograms of acrolein per gram of marijuana smoked. So, these levels of respiratory carcinogens and irritants are a similar magnitude between tobacco and cannabis when smoked in the same way. Next slide. So, a further case study, I guess in summary of this case study, cannabis and tobacco smoke toxicants exhibit a similar pattern and ballpark amount with, of course, notable exceptions for active ingredients, specifically thinking about nicotine and nicotine-derived toxicants such as tobacco-specific nitrosamines in tobacco and then for cannabis the cannabinoids and the terpenes that Dr. Schauer was describing in her presentation. So, I think a key component is understanding how people use the different products and using biomonitoring to assess the internal dose of these products as they’re being used. To do that, I’d like the next slide and to talk about some actual exposure studies. Next slide. So, in this first exposure study, this was led by a collaboration led by David Ashley, together with Marilyn Huestis when she was at NIDA and CDS, and this study was just published a few months back. The study design is shown in the lower left-hand corner. It involves a combination of daily smokers of cannabis and non-daily smokers of cannabis coming in to a clinic for a washout overnight, followed by a cannabis exposure event that was either eat, vape, or smoked, and then collection of all subsequent urinary voids for the next 72 hours, followed by a washout period of one week and then the design was repeated with the next exposure round. Next slide. And here you can see the results from one study participant where in the top panel after the individual smoked a joint, the level of the smoke exposure biomarker cyanoethyl mercapturic acid, which is a metabolite of the probably human carcinogen acrylonitrile, that measurably increased and then decreased over the next few hours after that smoking event. We did not see a similar increase following vaping or eating a cannabis product. Next slide. Also from this study, we were able to achieve very nice exposure to K curves and to derive a half-life. Half-life for this selective smoke exposure biomarker 2CYEMA varied from two‑and‑a-half hours to 10 hours with a median of around four hours. So, this exposure biomarker is quite useful. And in the next slide I’d like to talk about applying these measures to population data as opposed to the individualized data that I presented earlier. So this study was one that was published a couple years back, and it posed the question are smoke exposure biomarkers higher in urine collected from people who self-describe as recent cannabis users. Next slide. And in this presentation, you can see that with NHANES, it’s an ongoing CDC survey that’s designed to collect data on the health and nutritional status of the U.S. population. It’s designed to be representative of the U.S. population based on age, sex, race/ethnicity, and income. And NHANES has been an ongoing survey for the last few decades. As part of the survey, many interview questions are asked, including some questions about cannabis use, and blood and urine specimens are also collected. Those specimens are used for measuring biomarkers of exposure to environmental chemicals. Next. Some of the biomarkers of exposure include smoke exposure biomarkers, volatile organic compounds, aldehydes, aromatic amines, heterocyclic aromatic amines, and polycyclic aromatic hydrocarbons, also other toxicants that are smoke biproducts, metals, tobacco-specific nitrosamine, and for cannabis products for measuring terpenes. We are able to look at nicotine and nicotine metabolized both in serum and urine. And unfortunately, this is a typo on this slide in that we are not measuring cannabinoids. We apply to that, but on this national survey we’re not able to measure cannabinoids in these urine samples, but that would be very useful if we could. Next slide. When we look at this data, let me explain these nine panels. Each panel is for an individual PAH in this case. The first column is recent cannabis use. The next column is cannabis use five days or greater ago; and the third column, non-users; the final column, tobacco cigarette users. And the pattern you can see in this data is the recent cannabis smokers have higher levels of these PAH exposures than do the non-users. Sometimes this is statistically significant; sometimes it’s not, and consistently lower levels in the cigarette smokers. Next slide. In tabular view, if you could highlight the next two boxes for me, you can see acrylonitrile biomarker cyanoethyl mercapturic acid is actually 20‑fold higher in recent cannabis smokers compared to non-users. Next. But in cigarette smokers, it’s still about four-fold higher than found in the recent cannabis users. Next please. And so as Dr. Cohn mentioned in her presentation, dual and co-use of tobacco and cannabis are quite common. I’d also like to talk a bit about data from the FDA’s Population Assessment of Tobacco and Health Study or PATH Study. Of course, this study is focused on tobacco but also includes those cannabis-use questions. And CDC is measuring biomarkers of exposure to both nicotine and also to combustion products and other emissions that would be common to both tobacco and smoked cannabis products. Next slide. So in this slide from a really nice study done by Danielle Smith and Maciej Goniewicz and co-workers at Roswell Park, you can see higher smoke exposures in dual users of cannabis plus single tobacco products. And for these four panels, the no cannabis use, single-use of that product is shown with a gray bar, a lightly shaded bar. The darkly shaded bar is dual use of that product plus cannabis use. And you can see consistently across these four (unint.) from fluorine, pyrene, acrylonitrile, and acrylamide, the dual users of cannabis plus that single tobacco product have higher exposures to those smoke toxicants. Next slide. So, hopefully I’ve convinced you of the increased exposure to these potentially harmful smoked toxicants from smoked product. I’d like to spend the rest of my time talking about the 2019 outbreak of lung injury associated with e-cigarette or vaping product use next. So, the EVALI outbreak was just in its wrap-up phase a year ago. It seems so long ago, but just a year ago we were at the tail end of this outbreak curve. Overall, 2,807 lung injury cases were associated with the use of e-cigarette or vaping products in all 50 states, the District of Columbia, and two territories. Overall 69 deaths in 29 states and the District of Columbia attributed to EVALI. Next slide. The patient characteristics were striking in that before onset these were generally healthy young adult males. E-cigarette and vape product use was highly prevalent. Eighty-nine percent reported using THC vape products, 73 percent reported using nicotine products, and 60 percent reported using both types of products. Next. The clinical course involved hospitalization. Fully three-quarters required supplemental oxygen and a third active intubation and mechanical ventilation. So very serious respiratory endpoints. Next. And early in this study were difficulties associating specific products or causal agents with injury because case-associated vaping cartridges were not always available for testing or when submitted by the study participant, they contained little product for analysis. Also, case patients used many different types of products in different ways and weren’t always able or willing to answer interview questions about these potentially illicit products. Next slide. So, we set our primary strategy on analyzing bronchoalveolar lavage fluid. As shown in this cartoon, the bronchoscope is inserted deep into the lung. Sterile saline is deployed from the end of the bronchoscope that washes the epithelial lining fluid away from that surface, and that fluid is then retracted as a lavage fluid retracted back in the bronchoscope and can be used to characterize lipid‑laden macrophage, as well as to serve as a matrix within which to look for potential chemical toxicants that could be accumulating at that target tissue. Next. So, with our BAL fluid samples that we were able to obtain 54 different study participants, we tested a number of different potential toxicants, ranging from plant oils to petroleum distillates and mineral oil; medium chain triglyceride oils; terpenes, both terpenes that are small and can be used for solvents, things such a limonene and pinene, but also larger terpenes such as squalene; and lastly, we also measured vitamin E acetate. Next. So, very importantly, of our 51 EVALI case patients, we needed to have some healthy comparators. We were able to obtain those from a collaborative engagement with Peter Shields at the Ohio State University and get some healthy comparators, non-users, some e-cigarette users, and some cigarette smokers. Next. And when we applied our analytical methodologies, we subsequently were able to find that vitamin E acetate was present in 94 percent of the BAL fluid samples obtained from EVALI case patients. Next. And next and next. And you can see that this compares to only a couple singletons of the other toxicants for which we tested. And on the rest of the table to the right, you can see that none of the healthy comparators had vitamin E acetate or any of the other potential toxicants and diluents in their bronchoalveolar lavage fluids. Next slide. So, what is vitamin E acetate? It’s the form of vitamin E commonly found as a food additive and dietary supplement as well as an additive to cosmetic products. It’s generally recognized that it’s safe when ingested or applied dermally, but the inhalational toxicity is not well characterized. Next slide. So, why was vitamin E acetate being added to certain vape products? And here you can see in this graph some of the products that we received from EVALI case patients. Well, the vitamin E acetate can be used as a thickener to cut or dilute illicit THC vape cartridges, and it actually looks like a THC oil. Next slide. In this slide on the left panel you can see actually a video, but just one of which is an almost exclusively pure vitamin E acetate. The other is a THC oil that contains very little vitamin E acetate. These look fairly similar. Also, on the right you see a photograph that compares these two cartridges that have been stored at an angle and then inverted immediately before the photograph, and you can see a similar viscosity. So, the take-home message here is that a consumer would not be able to distinguish between these two cartridges. Next slide. And on the next slide you can see that we have coherent data on vitamin E acetate in case-associated products initially from the New York State (unint.) lab, subsequently from the Utah Public Health Laboratory and FDA, finding vitamin E acetate closely associated in cartridges linked to most EVALI cases. Subsequently, Melissa Arons and colleagues at Utah have identified a close correlation between the presence of vitamin E acetate in confiscated product seizures in Utah and national case counts. Next slide. So, as I wrap things up, just to mention a couple of biological plausible pathways here where vitamin E acetate could cause lung injury. The simplest one is just a direct disruption of surfactant function where vitamin E acetate accumulates in lung, and at a critical concentration it disrupts the ability of the phosphatidylcholine gel to maintain the rigid surface tension and the rigid structure of the alveolus. That causes collapse and then the lung is no longer to support respiration. Next slide. Alternatively, vitamin E acetate, the structure that’s shown here, next, can/might be thermally decomposed during the vaping product to form a reactive ketene such as ethenone as shown in this diagram. That is a highly reactive electrophile that could react with lung tissue to cause acute pulmonary toxicity. Next slide. By one or both of these procedures, we now know that vaping vitamin E acetate alone does cause lung injury. So, thanks to Yasmin Thanavala and Maciej Goniewicz at Roswell Park for setting up this experiment where mice were exposed to vaped vitamin E acetate for a heavy exposure protocol for a relatively short period of time. CDC subsequently showed that vitamin E acetate accumulated in the lung epithelial lining fluid of these mice, and lipid laden macrophage formed as well as inflammation and injury. So, this connected the dots between vaped vitamin E acetate and lung injury. Next. So, in conclusion, smoking a single cannabis joint can measurably increase exposure to a harmful smoke chemical, specifically the probably human carcinogen acrylonitrile. Self-described recent marijuana users have higher smoke exposure than non‑users, and dual users of cannabis and tobacco products tend to have higher smoke exposure than exclusive users of those same products. And lastly, vaping liquid constituents, even those on the generally recognized as safe list can cause harm when inhaled, and the notable example here is vaped vitamin E acetate in the EVALI outbreak. Next slide. Lastly, I just want to acknowledge the many people who contributed to this, especially Matt Karwowski, my laboratory task force co-lead. The laboratorians listed under Matt’s name for about four months worked through weekends and holidays extreme hours to get that outbreak solved. Also, the Emergency Operation Center, Brian King, Peter Briss, Gillian Schauer. Excellent teamwork to solve the outbreak. Lastly, we could not have done it without the help from external partners Peter Shields at Ohio State, Doug Heitkemper at FDA, the Association of Public Health Laboratories, as well as David Ashley, Maciej Goniewicz and Binnian Wei involved with the other collaborative studies that I described. Next. And just a shoutout to the many state health departments that assisted with EVALI, and finally to thank you in the final slide for your attention.

>> Thank you, everyone. And we’ll begin a panel discussion. Mia and I will lead the discussion. And by what I’m seeing in the chat feature, you guys were highly engaged, and we appreciate that. So that should allow for a robust discussion during this panel. So, I’m going to start with the first question, and I’ll ask Dr. Hashibe. So, one question was around pesticides, heavy metals, mold, and cannabis, and I don’t think that any of the epidemiologic studies really addressed that, right. So, what do you think about that, and should we, you know, be considering that or adjusting for that? Would you comment on that?

>> Yeah. None of the epi studies have addressed anything like that. I’m not aware of any studies that looked at cannabis separately and pesticides as well. Perhaps Dr. Blount’s analysis with biomarkers could give some light to that in future studies, but unfortunately, I don’t think there’s anything right now that we could speak to.

>> Karen (ph.), I think this is a, you know, we definitely need to engage Dr. Blount with the epidemiologists who are doing this work and collecting the data. Ben, you wanted to comment?

>> I’ll just add that biomonitoring indeed can be a useful tool for assessing inhaled exposures. It’s also important to do some studies in the laboratory to characterize what happens to that pesticide during the smoking or vaping process. Sometimes there could be decomposition to a more reactive form, and in screening that’s needed to understand that potentially harmful exposure as well.

>> And Dr. Ellision, I was just going to chime in from a policy perspective to note that there are not many states that are testing for the breadth of heavy metals. In particular, developing those test methods across the range of these products has been challenging. And so in practice, you know, we don’t necessarily even have information about heavy metals or pesticides to be advocating consumers with, and I think that’s another important step.

>> Yeah. Yeah. It’s a big gap. Mia?

>> Great. Dr. Schauer, you mentioned that the public health hasn’t had a really big role in regulatory issues for cannabis. What do you think could be improved and what are ways that public health could be more involved?

>> Yeah. Thanks. I’ll try not to give a whole separate presentation on that (inaud.). [Laughter] I think in terms of actually setting the regulations, while for medical cannabis we see that public health agencies are often the regulator, it can be a check the box. You know, it’s an unusual function for a public health agency to regulate something. And so when adult use comes along, public health has not, until Arizona just legalized, been named the primary regulator. So Arizona I think will be an interesting case to watch. Their public health department will be regulating adult‑use products. But I think there are a host of opportunities for public health and research, even if public health is not at the (inaud.) of regulation. So data monitoring and collection is critically important (inaud.) really late to the gate on that. That should be happening in states before policies change, and we have work as a community to do to improve our data collection systems. I think there’s also a critical role in terms of public education, which again, should be starting before policies change so that the public’s aware of what are the products, what is the science, you know, how are the policies impacting use, et cetera, and then I think engagement with community members. You know, everybody brings a certain perspective about cannabis to the table, and I think the challenge is to sort of check your own perspective at the door and be able to hear from all sides and figure out how to bring the community together to make a safe environment.

>> And I think there’s a question around some of the data that were presented, and I don’t know if this question could be answered, but someone asked so, basically, legalization of cannabis led to the reduction in overall population use. And I think this is a question for Dr. Cohn. Can you address that?

>> What’s the question exactly?

>> The question is asking whether the legalization of cannabis led to the reduction in overall population use.

>> And that’s a question for me? Because I don’t –

>> Yes.

>> Yeah, I don’t believe I presented that data necessarily in the –

>> Yes, I didn’t think so.

>> I did present data showing that the age of onset or the onset of cannabis use relative to alcohol and tobacco hasn’t seemed to increase. So, you know, my take from that is that, you know, there definitely has been concern that if we increase cannabis legalization, we increase availability, we increase access, and maybe younger people are, you know, using it more often as the first product that they use or they’re initiating at an earlier age. But from the data that I’ve looked at from PATH, it doesn’t really seem to bear that. So cannabis still really isn’t the first product that people are using. Young people are still going with alcohol and tobacco. So I hope that answers that question.

>> And in terms of the broader epidemiology around cannabis, we have seen in adult-use states that there’s been an increase among young adults in terms of their use as well as in their daily or (inaud.) daily use.

>> Right.

>> And then as was mentioned in the chat, we kind of clump other adults in one category, but if you stratify that, you do see that there’s been an increase. Particularly among older adults the prevalence is still very low, but as policies have liberalized, we’ve (inaud.) where adults begin to use or use again. And then there’s that flatline trend in youth, which I mentioned is seen in states that have adult-use policies as well. Some of them have actually seen a decline in youth, slight decline. But as I mentioned, I think it’s really early and there are some limiting factors in terms of interpreting those data.

>> Right.

>> And one thing I would add to that is just to say that as non-medical use increases, especially we are seeing additional secondhand exposure, especially in children, and from a public health standpoint, that’s an important factor to consider as well.

>> I just want to – I don’t know if I can add to the question we had earlier about kind of what role does public health play in this, and this kind of relates to Ben’s presentation. I’ve worked with the PATH data as well and some of that biomarker data, and what is not available is that there are no biomarkers related to, you know, THC. And that’s partly because, you know, cannabis is still a Schedule I drug and so there were concerns about assessing that. And so I think, you know, and this has been brought up in everyone’s presentation, this dichotomy between, you know, we need to know more and we need to be assessing and yet at the same time because of the limitations because it’s a Schedule I drug, you know, there’s a lot we can’t look at. And I think if we had large national datasets like PATH or other datasets where we have, you know, thousands of biomarker data and we can look at biomarker exposure, that will certainly help us answer some questions, but right now, you know, we’re really limited in our ability to do that because of the laws.

>> Great. There’s a question for Dr. Blount. What is vitamin E acetate? What are the properties and effects on the body? I think this was covered in your slides, but I think it’s a really important question so –

>> Yeah. And just to highlight that, vitamin E acetate is used as a vitamin for oral consumption, but when it’s inhaled, that is when lung injury is associated with it. So there appears to be a consequence of inhalation of vitamin E acetate where it either breaks down and forms a reactive byproduct when it’s vaped and reactive byproduct damages the lung or vitamin E acetate itself accumulates in the epithelial lining of the lung and the body is not able to clear it and that causes the alveolar sacs to collapse and, therefore, to create lung injury. So, those are the two leading hypotheses about how vaped vitamin E acetate could damage the lung.

>> Thank you. So, there’s a question regarding exposure to carcinogens and increasing use of, you know, cannabis, which has some of the same carcinogens as tobacco smoke, and given the increased use of that, why aren’t we seeing a higher incidence of, for example, lung cancer? So that’s one of the questions that came. Can one of you speak to that please?

>> I’ll just comment from an exposure standpoint. I think as Paracelsus said it, the dose makes the poison, and there could be something with the, you know, as Dr. Hashibe mentioned in her presentation, when we talk about cigarette smokers, we talk about cigarette pack years for the number of years they smoked a pack of 20 cigarettes a day. With marijuana, it tends to be more one to two joints per day. And so the higher potency perhaps leads to lower smoke exposure because – or at least traditional and, therefore, fewer joint years. But with non-medical use increasing, perhaps that intensity will lead to more adverse health effects. So, I don’t know. That’s my two cents’ worth from an exposure standpoint.

>> Yeah. From the epi studies, they are from a decade or more ago so it does not reflect any of the vaping or other types of use, and it was largely in a period and in locations where cannabis use was illegal. So we’re very concerned about the underreporting that could be happening in those studies. So I think we need more studies, modern studies with the new types of use.

>> And I want to underscore something that Dr. Blount said, which was that we are seeing patterns of use change, and cannabis has not traditionally been used like tobacco. We haven’t traditionally seen, you know, a pack-a-day cannabis users, but that is something that I think we will begin to see in (inaud.). So it’s not represented in the studies that we have at this point, but that may change our calculus on health effects.

>> Right. So, there was a comment about educating people and starting slow, going slow with THC to prevent acute adverse effects. And Dr. Schauer mentioned that people have a different interpretation of what low is and perhaps some harm reduction messages are important to communicate. So, Dr. Schauer, maybe you could expand on that a little bit more.

>> Yeah. I mean I think that’s something that a number of state marketplaces are seeing is the tagline that came from the industry that I think is the harm reduction message, start low, go slow. We’ve also seen policies follow that whereby, you know, edible dosing, for example, that I talked about is meant to be a lower dose and individually packaged to avoid, you know, overconsumption. So I think harm reduction messages like that are things that we should be looking for in the science and maybe are not the traditional area that public health has gone to here, but, you know, this is now legal in a majority of states and people are using it, and not everyone’s using it medically. And so we need to be thinking about what sorts of messages can help promote safe, responsible use among legal adults, and I think the start low, go slow is probably a wise one. We just need to be careful about how we define low and not allow our definition of low to set a standard of what is expected in a dose. So I think there’s some caution needed, but certainly there’s promise in those sorts of messages.

>> Yeah. I just want to add to that I mean I think the public in general is not fully educated in terms of the difference between CBD and THC and I mean, you know, we as researchers, we have these catchphrases and we generally understand, but I think, you know, we need to educate the public about the differences between both. I think, you know, if somebody does have, let’s say, a legal medical (unint.) or they live in a legalized region, they still may not understand what it means when they’re buying a product that says how much CBD and THC is in that product. And I know in the state where I happen to live in Oklahoma, you know, the poison control department worked really hard to get warning labels on, you know, edible cannabis because people would misperceive that they could eat four gummies and, you know, you can’t take the same dose as an edible. And they were really just providing the number of the poison control center so then they could kind of log that information and talk people through what to do next. So I think more (unint.) needs to be done like we did in the tobacco field with warning labels and educating people about what is in these products. I think people have the general sense that there are a variety of things in tobacco products. I think the public is less clear about what happens to be in a variety of different cannabis products that are out there.

>> Yeah. There’s a question regarding the Drug Enforcement Administration policy regarding CBD, and I think this is for you, Dr. Schauer. Is it still Schedule I? And if that’s the case, only if it is plant derived? It’s hard to get a clear answer. So what do you say about that?

>> I think that’s an emerging area of discussion. So, the Farm Bill unscheduled CBD as defined, you know, as having less than or equal to .3 percent Delta 9 THC, and it also unscheduled the constituents of that plant. The issue is that THC has a number of isomers. Delta 9 is one of them, but there are a number of other isomers that also have psychoactive properties, Delta 8 for example, Delta 10. These were not clearly defined in the policies that were set forward. And so I think there’s a lot of discussion in states. I’m less aware of the federal discussion that’s happening on this, although I am sure there is some, but there’s certainly discussion in states about exactly what is legal. The other thing that we’re starting to see is you can take CBD that’s extracted from the hemp plant and you can create conditions to turn that CBD into Delta 8 or Delta 9 THC, and that allows for a much more concentrated derivation of, say, Delta 8, which is not found in big proportion in the plant itself. And so there are questions about whether that extraction process from CBS is legal, is plant based, is synthetic, et cetera. So I think this is really an open area, and different states are interpreting it differently, and I would hope that in the coming months we’ll see more clarity because there’s a lot of confusion. And we talk about consumer awareness. It’s possible states are setting their edible doses largely based on Delta 9 THC. Delta 8 THC, according to the WHO is about 50 to 75 percent as potent but still psychoactive. And so it’s possible that you may be seeing, if regulation doesn’t catch up, products on the CBD marketplace that may be more psychoactive than products on the regulated adult-use marketplace. So again, lots of need for quick science, for quick policymaking, and I think most importantly for consumer education.

>> Thank you for that. I just want to do a quick follow-up on that question. There is a question that just recently came through the chat feature that asks about the potency of some of these products and implications for their dependence and perhaps other health implications. Can you comment on that please?

>> Yeah. I think there’s going to be a recurring theme through this conference, which is that we don’t have sufficient science. So, as has been mentioned, most of our research has been conducted with plant-based, you know, smoked cannabis and doesn’t reflect the more potent products and the different modes of use that we’re seeing. So it’s really difficult at this point to say what the gamut of health effects may be. I think the least that we should expect is some increase in dependence because these are much more potent products that are being consumed, you know, daily or near daily, and we know that the more you consume, the higher the association with potential abuse or dependence or use disorder. So I think that’s the least of what we should expect to see. I’ll also say though that just in manufacturing many of these concentrates, there are other public health issues. In Oregon, for example, it’s a felony to manufacture a cannabis concentrate at your home because of the solvents that you use in the manufacturing process and it can create explosions. So, you know, there are some public health consequences that we haven’t even touched on yet that also exist with some of these concentrates. So, lots more research is needed to get a good answer on that.

>> Thank you.

>> Okay. I think we need to probably wrap up in about two minutes, but we can go over a few more questions. There’s one question that came up. Is the NIH and NCI urging lawmakers to change the scheduling of cannabis to make it easier to study? How can we help?

>> Yeah. That sounds like a question for me, given that I’m the only one on the panel who is with NCI. Well, as federal employees, we don’t lobby Congress. We are a research institution and so we make sure that the research is getting done to understand the health implications of using the products. There are occasions through which we are called to deliver testimony to Congress based on a science of a particular substance, and we have been called upon to do that, but in terms of lobbying Congress, that is outside the scope of our position. And, you know, that’s something that we wouldn’t, you know, for folks on the call who are advocates or who are, you know, not affiliated with the federal government in any way, that’s something that you’re free to do.

>> Do we have time for one more question or do we need to wrap up?

>> Yeah, let’s do one more question.

>> Okay. There’s a lot of questions coming in, so sorry that we can’t cover everything. Please feel free to contact the speakers if you have some really urgent questions.

>> Oh, (inaud.)

>> (inaud.) time to say.

>> Yeah. So, this is an easy one. Someone asked for childhood leukemia how is age defined. They wanted some clarity on that.

>> Oh, yeah. That’s for –

>> (inaud.) Hashibe.

>> Yeah, cancers that are diagnosed up to 18 years of age.

>> Okay. Thank you. Well, I’m sorry that we’re out of time. We have so many questions that we didn’t get to. And as you can tell from the research that was presented today and from the panel discussion, that there is a great deal of research that still needs to be done in the area of cannabis and cancer. I want to thank all of our panelists and our keynote speakers for participating today. And as Dr. Hashibe mentioned, if you have any additional questions, please feel free to reach out to the speakers directly. Thank you very much for your time.

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