DANNY LENNON: Let's talk about artificial sweeteners. So really, there's probably a large number of terms that those of you listening will have heard in relation to this, whether that's artificial sweeteners, noncaloric sweeteners, etc. There's a number of different ways we could maybe start defining this. Probably the way that is easiest to separate this first, I'm guessing, is the difference between nutritive and nonnutritive sweeteners. And so, as that name suggests, nutritive having some degree of nutritive value, typically, these are going to be sweeteners that have a caloric and/or kind of carbohydrate content that is going to be in excess of these nonnutritive sweeteners. And as that name suggests, typically you're going to be having zero or close to zero calorie or carbohydrate content, although it kind of depends on which ones we're talking about. But we can get into some of the nuances there, so maybe I'm going to start with you Niamh, and let us get into some definitions around artificial sweeteners. What's the easiest way to think of these different groups of them, what do we exactly mean by an artificial sweetener, and how should we kind of delineate between those from the get go?

NIAMH ASPELL: Yeah, so as you've kind of mentioned, there's lots of different terms that have been used, if you're looking at the literature, they'd describe them in lots of different ways. But as you mentioned, those two kind of overarching categories of nutritive or nonnutritive sweeteners is probably the easiest way to distinguish between them. So for nutritive sweeteners that you mentioned, they do have calorie content, some of them extremely low, but then you also have things like just your natural sugars and your table sugar. We'd also include sugar alcohols in that, so things like sorbitol and mannitol; and they occur naturally in plant foods, so things like berries and fruits, so they're natural sweeteners, but they do have a small bit of calories in them or energy in them. So they're deemed as sugars or nutritive sweeteners. And then, we have natural caloric sweeteners, so they also contain small bit of calories as well. An example of that would be plant based sweeteners, so things like stevia, and stevia has been around for a long time, but it's only been approved quite recently for kind of more widespread use. And then, you've got nonnutritive sweeteners and that's kind of what we're focusing a little bit more on, and the literature focuses on these types of sweeteners, and those would be the kind of artificial sweeteners, so they're kind of naturally noncaloric sweeteners, so they provide little or no calories whatsoever. I think the most common ones would be kind of aspartame, sucralose, or saccharin.

In terms of, kind of, identifying them in foods, they can either be labeled on food packaging, with their common name, as I've described there, or they can be commonly labeled as E numbers. So E numbers are typically seen as kind of unhealthier, kind of, harmful by consumers, and I think that's what links the association a small, but with artificial sweeteners. E numbers being kind of considered as being kind of harmful in some capacity, but really, E numbers, they are just additives, and they provide kind of limited or

no nutritional value. But it doesn't necessarily mean that they're bad. E just stands for them having received their quality approval or safety approval from the European Union. So a lot of them are beneficial as well. I think about people who have this association with E numbers being quite bad, I think around kind of food colorings and some adverse effects. But typically, they are beneficial, and kind of the rules were kind of developed to regulate so that dangerous substances wouldn't be included in food, so artificial sweeteners kind of falls within this.

When we think of artificial sweeteners or sweeteners, they all fall into these categories, but they're all a little bit different structurally, so they all have very different responses in terms of absorption, digestion, excretion, and then, there's some unique attributes to them as well. So how sweet they are, the aftertaste, and how long the sweetness is there. There's varying kind of scales of sweetness, most of them are intensely sweet, but there's varying scales of sweetness. And I think that's why they've become such an important kind of strategy or tool for their kind of main purpose in removing sugars from certain foods and replacing them with low calorie or no calorie sweeteners, so that they kind of sustain or maintain that level of sweetness, but we're removing some of the calorie contribution that would typically be there with sugars.

DANNY LENNON: Yeah, and so, I think probably their use or why they're maybe added to certain products or used in certain products is probably relatively clear or logical at the get go that if we have something here that can obtain a certain level of sweetness in a product, but at the same time, not having the same degree of calories or added sugar, at least, it is plausible that that could have some benefit for either weight loss, weight loss maintenance, diabetes, blood sugar control, etc., and we'll certainly investigate whether that plays out in some of the outcome data later on. You just mentioned that we have

these nonnutritive sweeteners that we're going to focus in on today, those main ones being sucralose, aspartame, saccharin, and maybe Ace-K. One of the interesting things then to get into is, well, if we're investigating the levels that these are going to be used, you've noted that there are multiple fold, hundreds of times fold more sweet than, say, sugar. And so, therefore, the question becomes, well, how much of these are getting added to foods, and how do we work out what a safe level is. And so, if we start looking at some of this determination of safe levels, as with any of these food additives, they're going to have an acceptable daily intake set, and this will be different depending on what jurisdiction we're in, but they tend to be relatively similar. But I think sometimes there might be some confusion around what it means to have an acceptable daily intake or a certain limit that we're placing on a food additive, and, in this case, artificial sweeteners. So maybe with that, and I'll turn to you here, Alan, around the regulation and the kind of process of getting a safe level attributed to something like a nonnutritive sweetener, what are some of the important things to know about that, because I think that helps clear up some of these confusions of what we mean by something being safe.

ALAN FLANAGAN: Yeah, and it's a really important clarification for consumers or for people that are otherwise confused by potentially some of the misinformation about the use of nonnutritive sweeteners is they're not independent of regulatory oversight. They are a compound in the food supply and as such are subject to regulatory oversight and safety evaluation. The bodies responsible for that regulatory oversight will differ by jurisdiction, so in the US, it would be the Food and Drug Administration or the FDA; in Europe, it would be EFSA or the European Food Safety Authority; and previous to that, in the EU, there was the SCF, which was the Scientific Committee on Food. There is an international one as well, which is like

JECFA, and that's basically a joint food additives and World Health Organization Expert Committee on Food Additives. And what they are undertaking essentially is a hazard assessment to determine levels of intake that would be acceptable in the population. With any hazard assessment, we're talking about an equation that is trying to identify risk. It's risk assessment, and risk we can kind of quantify as the hazards multiplied by the exposure. So the hazard, of course, is the agent with a potential to cause harm, which in this case, is anything that's being added, nonnutritive sweeteners. And then we have to question the exposure to that potential hazard or agent in the food supply, and what might habitual levels of consumption be. And because artificial sweeteners have a designation, and any compound being added to the food supply will have the designation of what's called a concern level, and the concern level isn't necessarily a reflection of their potential for harm, it's also reflecting how common the exposure in the population would be, i.e., are these compounds likely to be consumed by a lot of the population in certain amounts, and a combination of that potential exposure, and the potential toxicity will give rise to a concern level.

And so, nonnutritive sweeteners are considered a high concern level, and this means that certain levels of evidence are required in order to satisfy the regulatory bodies that these compounds are acceptable and safe for human consumption. There's two types, broadly speaking, kind of, two strands of evidence that we could just think of, one is called the technical data, and that relates to a lot of the factors that Niamh just mentioned, like, the chemical composition of a compound, what's its sensory properties in terms of, say, mouthfeel sweetness level; its stability in foods, if you're going to be replacing sugar in a baked goods, for example, is the nonnutritive sweetener compound going to have the same kind of stability within a food matrix. And then,

of course, the anticipated intake in the population, and we use population derived food intake data to then estimate if we're replacing sugar in these foods with a nonnutritive sweetener, if we're placing sugar in these beverages with this nonnutritive sweetener, what are the actual intakes of these foods and beverages in the population so we can anticipate what the potential level of exposure in the population is. So that's the technical data, and then, you've got the safety data. And because of the concern level, because nonnutritive sweeteners are deemed high concern, this means that a full range of safety studies must be included, and this is based on animal toxicology studies, which look at both short term, and then lifetime toxicity potential in species that have to have metabolic pathways of disease that would be applicable or equivalent to what we would see in humans. And they look at genetic toxicity, genetic mutations, they look at intergenerational effects, because it's in an animal model, is there adverse effects on reproduction, are there adverse effects during pregnancy, or on birth in the offspring and development in the offspring, and other kinds of toxicity related outcomes, and they also look at the absorption, metabolism, distribution, and excretion of the compounds.

And from all of this data, there are two important thresholds that are then identified. One is called the NOEL which is no observed adverse effect over lifetime, which is this measure of hazard, but the NOEL itself, is the level at which there was no observed adverse effect. So although we can kind of quantify it, people will often say, well, it's the lowest level that safe, but actually a better way for people to think about it, is the highest dose at which no adverse effect was observed. And then, the LOEL, which is the lowest observed adverse effect level, tends to be higher, but that tends to be the lowest level at which certain adverse effects were. So the NOEL, which is a more conservative threshold, is the one that is then

taken to then start to calculate the process of an acceptable daily intake in the population. And that's by multiplying the no observed adverse effect level by what they call an uncertainty factor, and that's typically of a 100. And so, from that, we then get the acceptable daily intake, and then, of course, we can compare that acceptable daily intake, once the compound is in the circulation of the food supply, to what habitual levels of consumption are. And that allows us to start to put things in context. So a good example is always a aspartame, the ADI for that is 40 milligrams per kilogram of bodyweight in the EU, and 50 milligrams per kilogram of bodyweight in the US. But that dose, were someone to even get near the ADI or at the ADI would be one-thousandth of the actual no observed adverse effect level, in terms of what the habitual population levels of intake are, which are currently four milligrams. So that's even one-tenth the acceptable daily intake and one-thousandth the NOEL. Even if you were to consume the full ADI itself, that would still be a fraction of the no observed adverse effect level. So there's a strong regulatory framework in place, it's an ongoing safety assessment by EFSA and the FDA, a huge amount of scientific data, both technical and safety has to be provided. And from these very conservative estimates are used, and then worked backwards from to calculate an acceptable daily intake for the population.

DANNY LENNON: So let me just recap really quickly on three of those terms in particular that I think were really important that you highlighted. First, you mentioned this concern level, and importantly, for people to note there is that this is not only relating to the toxicity potential of whatever compound we're discussing, but also relates to the exposure in the population. So when we're talking about certain nonnutritive sweeteners being designated as high concern level, that relates also, presumably then to how widespread they are within products and consumption within the population at large, in

addition to their potential mechanistically. And then of those two other numbers where we get to like a daily intake level, the first one at no observable adverse effect level, this is, of all that animal data we have, what is the highest possible dose that we've seen that can be continually consumed without any adverse effects. And then, using the uncertainty factor, we can divide that by a 100, and this gives us an ADI, and this is, again, a 100-fold less than the level at which we've never seen any adverse effects. And then we can start to use that as an acceptable data intake figure as a starting place. With all that, is there anything in that regulatory process, Niamh, that you would add there, or think are particularly important to emphasize?

NIAMH ASPELL: Not too much, I think it's, yeah, the main point really is that the ADI gives such a large margin of safety for even the most sensitive consumer of nonnutritive sweeteners. The only other thing would be I know that they're reviewing or going to change that calculation for the ADI, and they would use a benchmark dose level instead, and that will overcome some of the challenges that they have during their risk assessments at the moment, just given the variability in the data that's available at the safety reporting and technical reporting. The BMD or BMDL which will be the new kind of calculation for threshold levels of artificial sweeteners will kind of overcome some of those issues around dose selection, so we'll see all of these types of studies, you'll find that most of the literature applies different doses, it will also overcome some sample sizing, so I think that will improve it or maybe increase the specificity of it, but I think it shouldn't really highlight that there's any concern, because we're so kind of far away from that at the highest level that we should be – that we can't be kind of consuming. But I think it will become a little bit more accurate, and will help us to interpret some of the findings that are currently presented around safety concerns around artificial sweeteners.

So it will kind of just maybe create a little bit more accuracy around interpreting some of those findings, but, at the moment, the regulatory bodies still haven't decided the best kind of model design for the BMD or the kind of application of use as well. And, of course, then if they bring in any modeling assessment, they'll have to redo their risk assessments again, and then, that will complicate, you know, that will just take a long time. I think you've already touched on the point that it's a continuous process for every, since kind of the 80s, it's almost every three to five years where they've reviewed all of the new evidence available for artificial sweeteners and EFSA have published their most kind of comprehensive risk assessment for aspartame in 2013. And again, with aspartame, because it's been most widely used and used for the longest period of time, they've got more data in different populations within the community, and they've got more assessments done on the byproducts of aspartame as well, which haven't been done with other sweeteners. So they've got a lot better knowledge on that. And again, the jury was out, and that was deemed safe and deemed safe for various groups, except for people with PKU, I should just throw that in. But for general population, we'd probably get into a bit later on, but for the general population, it's still, they're still very much so deemed as being safe. I know I've started reviewing, currently re-reviewing all of the agents that have an E number, and essentially, they've pushed artificial sweeteners right down to the end of that priority list because they've done such extensive evaluation on its safety. So in that regard, I think there's a lot of evidence to show that it's been documented, it's been safe, and it's quite – it's a very, very rigorous evaluation. But for some reason, there's still a lot of concern around their use, so I think there's still a lot being published there.

DANNY LENNON: Yeah, so let's get into that, because, as we've noted, that there's not only this large safety

factor that we've taken into account when these daily intakes are suggested, but if you compare that then to how much people are actually consuming regularly, it's even well below those limits typically as well. But despite that, we still have a continued, I suppose, negative reputation that these nonnutritive sweeteners have for a variety of reasons, particularly in certain maybe circles around the internet, whether it's wellness or, are these health gurus, there's a particular fervor of how detrimental nonnutritive sweeteners are, and we can maybe explore why that might be the case a bit later on. But for now, maybe let's get into some of the particular claims we hear come up over and over again, one of the most common, if not the most common, is probably related to cancer risk, and this is rooted, I suppose, in a combination of both observational and animal trials, and again, is one where a lot of time people point to this is a real pause for concern. So maybe I can ask you, Alan, to walk us through some of the history here, because, where did some of the original fears about cancer risk originally emerge, and what do we make of that?

ALAN FLANAGAN: I think there's actually two slightly different examples in Europe, and then, in the US, I think before we actually kind of launch into it, there's a point that people should bear in mind while we're working through the discussion about carcinogenicity, or potential carcinogenicity, which is, these safety animal toxicology studies that we were talking about are designed to elicit an effect, like, this is their intended purpose is to pump the little rat full of as much of this stuff as possible, until they get cancer or some form of reproductive act. This is the whole purpose of that model, is to actually try and elicit adverse effects by continually increasing doses that are administered until adverse effects emerge or are shown. So not great for the little rat, but good for human health, potentially. So it's just an important point to bear in mind that were there to be a study that someone can pull out of the far

corner of the internet to say, aha, look, this study found an adverse effect, if it's an animal toxicology study, it was likely supposed to find an adverse effect. With that, there are kind of in the US, in particular, there was a controversy in relation to acesulfame K, and in the EU, there's also been some controversy in relation to a aspartame. So starting with the EU kind of controversy first, that really all stemmed from three studies by the same group, Soffritti was the lead author in relation to these studies, and each of these studies purported to find a carcinogenic effect of aspartame in rats.

And there was then a 2015 meta-analysis of a carcinogenic bioassay animal studies. Now, this 2015 meta-analysis concluded no significant relationship, and ultimately that 2015 meta-analysis even included these Soffritti studies, and still came to the overall conclusion of no association between aspartame at various experimental doses and occurrence of cancerous tumors. So that shows that the weight of evidence is still in favor of no carcinogenic effect of aspartame, but then, EFSA, the European Food Standards Agency, did their own kind of further digging into these particular studies, ultimately, resulting in a kind of a rejection of their conclusions on the basis of their actual model. They used not only kind of like much older animals, but they also misdiagnosed malignant tumors, in what was actually just hyperplasia.

So there was methodological issues with their conduct of the study, and the EFSA also found various other kinds of violations of OECD testing protocols for animal models, animal toxicology models. So despite the controversy from these studies, the kind of methodological approach of the authors has been quite rigorously rebutted by EFSA as the regulatory body, but they've also still been included in an overall synthesis of all animal toxicology studies of aspartame, which still, despite their inclusion found no significant effect. So I think that that's an important kind of finding,

because even with the inclusion of these studies, the weight of evidence still favors no effect. And then with Ace-K, that was slightly different because there's kind of first and second generation nonnutritive sweeteners, and some of the nonnutritive sweeteners that were approved in the late 80s, that there was kind of a lack of available certainly observational human data that you would like to combine with your animal toxicology studies to form an overall conclusion at the time. And so, Ace-K was also approved by the FDA in America prior to the standardization of the animal carcinogenic bioassays that are required, so that led to some criticism that, well, hang on, the actual assessment of carcinogenic potential of Ace-K is really incomplete or inadequate. But then the National Toxicology Program in the United States also then came up and did more recent reviews of Ace-K, and cancer in the animal toxicology studies and found no effect of Ace-K on carcinogenicity in those models. And then, if we come over to the EU then, as far as kind of reconciling the whole Ace-K potential debate goes, in 2009, when the Scientific Committee on Food was superseded by EFSA itself, EFSA mandated that all nonnutritive sweeteners currently in use in the EU have to be reevaluated, which included updated technical and toxicology data, and Ace-K was concluded to be safe in that assessment, which included an extension of permitted use even to children.

So I think as far as the kind of carcinogenic potential of certain of these compounds goes, yes, it is likely, unfortunately, to be the case that a quack or otherwise would certainly be able to find some form of toxicology study showing an effect. The question is, is that toxicology study truly consistent with the totality of evidence that we have on a given compound; and certainly the other compounds that have, the first generation compounds like saccharin, for example, which certain studies suggested in association with bladder cancer, but those mechanisms weren't applicable in

humans. And again, saccharin, with such a body of evidence being around for so long, is considered, along with sucralose, to be one of the safest and most reviewed nonnutritive sweeteners in the circulation. So between human epidemiology and the weight of data from animal toxicology studies, there's very little evidence that these are any carcinogenic concern in humans.

DANNY LENNON: Niamh, would you add anything to that in relation to the cancer that we have today, or any points that you'd want to make before we move on from that?

NIAMH ASPELL: No, I think the main point is, it's probably unfortunate that so much kind of time is still being spent on doing meta-analysis, and into the studies, there's still meta-analysis coming out on very similar, where they're trying to determine very similar things on very similar studies. And again, there's one published last year, and it was the same conclusion, that there was no kind of relationship between artificial sweeteners and cancer outcomes. And then again, just to point of this Soffritti group, and a lot of the limitations around their study design, and I think it was pointed by EFSA as well is that they've used a breed of mice that were known to have a high incidence of spontaneous tumors. So I think it's probably just a massive frustration that these types of studies are still being conducted, and still being published, and then taking the attention of food bodies like, or EFSA who then have to go and reevaluate all this data and make sense of it again. But yeah- no, I think and I hope maybe that some of this is kind of put to bed in terms of the association between cancer and artificial sweeteners. At the moment, I just think there’s no strong evidence there whatsoever.

DANNY LENNON: One thing I do want to ask you about that you highlighted to me, Niamh was that we see this associational data from both European and US cohorts that suggests an association between nonnutritive sweetener consumption and

mortality. What should we make of this data – can you maybe walk us through what some of that associational data is shown, and how we should interpret that accurately?

NIAMH ASPELL: Yeah, I think it's really hard to interpret it in any meaningful way, really, but when it comes, I suppose, to determining dietary behaviors, is if you're looking at single dietary behaviors and trying to link that to premature death or cause of mortality, I think we're really, really pushing the boat out on that idea, I think attributing a single behavior, or a single ingredient that is deemed safe for consumption levels that are much lower than those safety cutoffs you mentioned, is a bit of a stretch, but there's a lot of publications, and there's been a lot of work done in this area. And I think one of the publications that kind of got most attention was published in 2019, and this was in the papers entitled Association with Soft Drink Consumption and Mortality in 10 European Countries. This is quite a big investigation, they used some of the EPIC study data. I think that the lead author was associated with UCD, Mullee, et al, and it was published in JAMA in 2019. But essentially, what they had reported, and it's quite misleading, but they got a lot of attention because they suggested that sugar drinks, so drinks that are sweetened with sugar, high energy kind of drinks, there's about an 8% risk of premature death compared to a 20-26% increased risk from people who take artificial sweeteners. So the kind of conclusion here is that actually artificial sweeteners are more harmful or worse for you in terms of life expectancy or health outcomes than their original sugar drink. So this kind of got quite a lot of attention.

The one kind of big, I suppose, positive of this study, I say, it's a positive, they had about half a million participants or data points, I suppose, in this study, they followed them up for 16 years. So it was quite a long follow up. They waited to see who passed away. About 40,000 people had passed away over that time period.

Now, to be fair, they did exclude people based on who had like cancer, heart disease, and history of stroke, history of diabetes, and they removed people who were outliers in terms of their energy intake, where they kind of deemed that to be unreliable kind of reporting unreliable data. But I think this really, really feeds into kind of consumer and public mistrust in nutrition science, so it's taken a single observational finding, communicating it or translating it in quite a poor way, saying I think there's been a lot of cases in the past, particularly in nutrition science, where there's one thing that we're told is better for you, and then a while later, we're told it's bad for you, and this is what I think this publication is communicated to a certain extent. But in no way has it kind of answered the question of whether artificial sweeteners harm health. We understand that, it might just be that people who regularly drink large amounts of diet drinks, typically, lead more unhealthy lifestyles in general. The kind of idea that we couldn't kind of rationalize those unhealthy behaviors by choosing kind of better options, so if you take a diet drink, you're like, okay, well, I'll have the double burger, whatever it might be, because I'm going to offset that with having a diet drink, and that kind of mentality. And then also, people who typically use diet drinks are probably looking after – are more conscious of their weight, and potentially, are more focused on kind of weight management, and I've been off till one of the solutions is to displace their normal drinks or their sugary drinks or their diet drink. A lot of these studies don't account for a displacement of those calories, so they just say, well, they're having artificial sweeteners, but are they substituting their diet with increased amount of calories from somewhere else as well. So we still don't really understand what this means, we just know that the people in this particular study were more likely to be drinking the sweetened drinks, which I think is a bit of a challenge. And then also, in this study, it's a 16-year follow-up, which is great, but they only measured or

assessed people's consumption of artificially sweetened drinks at baseline. So if you're currently drinking artificially sweetened drinks, we don't know that you've continued to drink those through the 16 years. And the whole point of the ADI as well is its long term chronic consumption is if you go above and beyond that, that might be harmful. But we're not really testing that. We're not really observing that in any of these particular studies.

DANNY LENNON: I mean, the question of what confounders to look for is probably one that people listening right now are thinking of that we could theorize, at least, or speculate on different things that could be attributed to why people with higher intakes of artificially sweetened beverages may see these associations. But I wonder, like, do we actually have any of this well characterized of the demographics of those with highest consumption, is that even plausible to be able to try and work out and does it really add anything to what we're thinking about.

ALAN FLANAGAN: Yeah, I think one of the issues...

NIAMH ASPELL: I'm just thinking of this particular study, they're fairly well balanced between the two groups, the group that were drinking artificial sweeteners had a slightly higher BMI. So I think the group that were more likely to consume sugar drinks had a BMI on average of 24, and those who drank artificial sweeteners more frequently had a slightly higher BMI on average of 26. So they were slightly more overweight, and they might potentially had more unhealthy and dietary kind of patterns, but they also didn't – this is one problem with these studies as well, they review people's consumptions of artificially sweetened beverages, but artificial sweeteners are in such a wide variety of foods, whereas they don't assess the other, you know, the group who don't drink artificial sweetened beverages drink normal beverages or just drink water, could

still be consuming quite a lot of artificial sweeteners through consumptions of other confectionery or baked goods or cakes or they're being, you know, a lot of products are being reformulated to be low sugar foods. So most of the studies that I've come across are just specifically looking at soft drink consumers, as opposed to artificially sweetened high diets.

ALAN FLANAGAN: Yeah. If we were talking about a food related exposure, I don't know, red meat, for example, we'd have enough understanding of the wider literature in relation to kind of food specific effects on intermediate risk factors, and we'd also have an understanding of the kind of effects of substitution and replacement. For me, I think, and Niamh, you've already mentioned this, the biggest limitation of the study, or, I guess, there's two. I mean, on the one level, yes, they did adjust for a lot of factors that we might particularly think may associate with healthy behaviors such as BMI, smoking, alcohol, which are non-dietary potential confounders, but their dietary kind of adjustments were really confined to total energy, red meat, and vegetables, and vegetable juices, fruit and vegetable, and vegetable juices. So there are obviously a lot of other potential factors that could have been included, depending on the – and the EPIC data tends to be fairly robust, but the question then comes back to the biggest issue with any of these papers would be the substitution effects. Right? And, one, there is no substitution analysis, they did mutually adjust for artificial sweetened soft drinks, and sugar sweetened soft drinks. But actually, and Niamh, you've mentioned this, like, what's the substitution taking place? In relation to the artificial soft drinks across the different levels of consumption, there were no significant associations with mortality until you got to the very highest comparison group compared to the reference group.

So it was only in people consuming over 500 mil per day that an association with mortality

emerged compared to the reference group. And so, the question then is, well, what is it that artificially sweetened soft drinks may be replacing or displacing in the diet, and we don't know that. So I think this is a methodological challenge that needs to be teased out, like, if we're going back to the red meat example, we can model the substitution effects of replacing red meat with white meat, or red meat with fish, or red meat with dairy, for example. And this is a no known in the literature, and you can seek out to deliberately look at these mutually substitution amounts of isocaloric intakes of a food, but we have no idea what 500 mil plus of an artificially sweetened drink is replacing or displacing in a diet, even if other factors like smoking and alcohol and BMI and education status, and these important potential non-dietary confounders are being adjusted for. So I would be very, very cautious about any sort of interpretation from this particular study.

DANNY LENNON: Yeah, and some of those methodological issues we'll get into again, when we look at some of these other outcomes. To move on past some of that mortality data, I think, probably one of the areas where there's most of this discussion, at least, in various places online that you'll see is how does consumption of nonnutritive sweeteners impact bodyweight. And typically, there's actually two diverging ways to think about this, and both we need to kind of scrutinize, on one side, mechanistically, it seems logical to some degree that if you swap in a nonnutritive sweetener, as opposed to sugar sweetened products, that means less calories ingested and thus a reduction in bodyweight, but, of course, is a very simplistic line of thinking. On the other end, we can then have claims around, actually, no, these nonnutritive sweeteners are doing things that are problematic for the body, and that will actually drive us to consume more calories overall, even though that actual beverages have less calories, whether it plays a role in our preferences and liking and some other behavioral things we can maybe get to in a

moment. But if we start with that first claim, around this line of thinking, well, surely we're going to see this reduction in bodyweight, and it can be useful as an intervention for bodyweight reduction. When it comes to some of the human outcome data, what we actually see, so maybe I'll start here with you here, Alan, what is your take on the research looking at bodyweight as one of the outcomes in some of the human trials?

ALAN FLANAGAN: Yeah, I think with the epidemiology, we have some of these potential associations with higher bodyweight similar. A lot of the limitations that we've just been discussing would apply to that body of research, and, specifically, reverse causality is not usually well dealt with in those observational associations. So, thankfully, in this sense, we do have a number of human intervention studies, I mean, ultimately, we're coming from the perspective of, if these are nonnutritive, these are noncaloric containing, or if they do have calories, they're minuscule in their contribution, we would expect that were these drinks or sweeteners to substitute for actual sugar and calorie intake, were that to facilitate a reduction in energy, that would be the intended direction of effects that we would expect would be a reduction in bodyweight, or at least, certainly, no bodyweight gained if it was just an isocaloric kind of substitution. We have a number of synthesis, evidential syntheses, and a systematic review and meta-analysis, 15 human randomized control trials where nonnutritive sweeteners are being used as an intervention to reduce calorie intake. And again, the intended direction of effect was a lower bodyweight and BMI, and waist circumference in these interventions, and this was, you know, 15 trials is a good sample size, but some of them were particularly big studies as well for them were studies in children. And ultimately, this is a fairly consistent direction of effect that we see in human interventions where nonnutritive sweeteners are used to displace actual calories and energy, well, then

the outcome is, is what we would expect where a reduction in overall energy is facilitated by the swapping of noncaloric sweeteners or nonnutritive sweeteners for actual energy and calories.

DANNY LENNON: One of the aspects related to this, and I think we actually touched on this in the food environment episode, Niamh, was around if we think about preferences and liking, and particularly how strong that plays a role in childhood for developing preferences for food later on, this is one of the areas where people will point to and say, well, actually, this is a concern for artificial sweeteners that whilst in this meal, they might be reducing calorie intake, they're having this high degree of sweetness, and so, particularly with children, and maybe even for people older, that it's essentially giving this learned preference for sweetness, and so then, in the grand scheme of things, maybe this leads to overconsumption. Do we have any evidence that even looks at that question, how would we piece apart some of these behavioral impacts or preference, liking, all that type of stuff, as it might relate to consumption of calories for the inclusion of these types of sweeteners?

NIAMH ASPELL: Yeah, I think that's a really common kind of thought that people have of artificial sweeteners that because they're so sweet, and you're not getting the energy following afterwards that you're going to start craving it or that your taste perceptions will slightly change if you get used to these really intensely sweet food products. And I think there is good evidence in terms of early exposure to intensely sweet foods that will kind of encourage the likingness, and behavior, and desire for them. There was a really good paper published last year, by Yunker et al, in the Journal of Medicine, and they looked at obesity and sex differences in terms of the effect of sucralose sweetener versus a natural kind of table sugar on appetite and reward processing. And this was a – it was quite a well-designed study.

There's a couple of limitations I'll mention, but it was a randomized crossover trial, and they had a good sample size. So they wanted to explore in a little bit more detail this idea that once you kind of taste that sweetness of your sweet receptors, that are kind of awoken to a sense that you will then desire sweeter food. So they examined true fMRI neural reactivity to different types of high calorie food cues, and metabolic responses, and again, like we mentioned before, even though there's no calories in any of these sweeteners, or very, very low calories in these sweeteners, they still all work differently metabolically. And so, there is potential there that they will have different metabolic responses, and then also, they assessed eating behaviors following consumption of sucralose, which is a sweetener, nonnutritive sweetener. And this is in a sample of 74 healthy young adults, and because it was crossover, they were all brought back on different occasions to be given the different investigational products, so they were either given a glass of water that was sweetened with the standard sugar, and they were given water that had the sucralose in it, or they were just given unsweetened plain water.

So on the day of assessment, they conducted a couple of different kinds of examinations, so 20 minutes after they consumed the drink, each participant was put into an MRI machine, and then, they were shown lots of different foods. So kind of high calorie, high density, sweet and savory foods, and that was designed essentially to expose participants to images of foods that they might have an increased desire for if they've had the nutritive sweetener. And they focus a little bit on a couple of different areas of the brain to see if there was an increased reaction or an increased response, and there was a response in certain areas of the brain, that's the frontal cortex of the medial or the orbital frontal cortex, and there are two regions of the brain that we know have the kind of highest baseline metabolic rate or activity at rest. So when you're in this form of situation in

an MRI kind of scan, and in other studies have been shown to be related to kind of different goals or goal directed behaviors in humans. So these are – they assessed meaningful areas of the brain activity. And they did show that those increased activity and those areas following the consumption of artificial sweeteners in participants who were obese. They also took blood samples, so they did oral glucose tolerance tests, and they wanted to measure their glucose response, and they also measured hormonal response to different sweeteners, but they detected no difference. And in people's and glucose response, if they had a nonnutritive sweetener, it was the same as if they were to drink the water, but then if they had the glucose, obviously, they had a glucose response or a response in their blood glucose, you could see a change in the curve.

So the first part of the study, they just wanted to assess these behavioral changes, and were consuming the sweetener, and then a couple of hours later, they released all of the participants into their room with a buffet and just said go for it, and see what they eat, and then measured how much they eat. And they found that females who were more likely to consume more calories, if they had drank an artificially sweetened drink, they didn't see the same effect in meals, and they also showed that it was more likely to be females who were obese as well. So it was obese females were more likely to go towards eating more after they had an artificially sweetened drink. There is a couple of limitations in the study, I think it is quite interesting, it's a well-powered study, and I think they had it really well designed. The only thing I think is a little bit hard to interpret is they gave them this dose of artificial sweetener, but then they did the oral glucose tolerance test for a couple hours and the fMRI in that period of time as well. And then they allowed them to go to the buffet and eat the food, so I don't know, in terms of the impact of artificial sweeteners a couple of hours later, or whether these people were just hungry, because the

other group had about 500 calories of glucose at the start of their test.

So potentially, they didn't have as much hunger as maybe the group who received the artificial sweetener who were still fasting because they'd been previously fasting the night beforehand as well. And also, just for being – this is just anecdotal, but being involved in a lot of these oral glucose type studies, typically people who don't regulate, so all of these people weren't regular consumers of sugar sweetened beverages or artificially sweetened beverages. If you were to drink that 75 grams standard oral glucose tolerance test drink, it can definitely be a little bit, I don't know, I think it can decrease your appetite a small bit, if you're not – it's quite a large volume of sugar, and it can maybe change your appetite a small bit. So I think that was maybe a slight a slight limitation of the study as well, because they contained, I think it's about 300 calories in one of those oral glucose drinks as well. So in comparison to that, I'm not sure how great a comparison it is. But I think it is quite interesting in terms of the MRI data. I'm not sure if the MRI data completely correlates then with the amount they actually afterwards, in my opinion, but I think it's interesting that there was a response there in those areas of the brain associated with a desire to eat more calorie dense or eat more foods if you've consumed an artificial sweetener afterwards. There was a couple of other oral CTs that looked at this as well, and there's one in 2020 by Ebbeling, and they looked at the effect of artificial sweeteners on sweet taste preferences. Theirs is quite good because they used one of the – they used three different groups, so they basically had people who received either a sugar sweetened beverage or an artificially sweetened beverage, or then just plain or sparkling water, and they followed – this is a much longer period, so they were given these different drinks, and they were followed up over a year. But the researchers didn't find any kind of overall differences in weight gain, or change in dietary

habits in between the three groups, until they looked at a sub sample, until they looked at a group of participants who had a lot of abdominal adiposity. So they had more weight or more fat around their midsection, and that, obviously, is a risk factor for other metabolic kind of consequences. These groups are all balanced at baseline in terms of their BMI, it was just that this group, their fat distribution was slightly different, but it showed that there was no, very little weight loss or gain in any of the groups, except for when people were consuming the sugary drinks, they gained a lot more, and it's those people who had more weight around their center.

So I think there is evidence there. There is a small bit of evidence in terms of weight management, but not an awful lot, and I think that's then confirmed in terms of health claims that we have artificial sweeteners. I know we've talked a lot about the kind of safety claims and the safety assessments from EFSA, but in terms of EFSA actually delivering a health claim on nutritive sweeteners, there's nowhere near enough evidence to do that for weight management or the people's ability to kind of control or restrict their diets. I think EFSA included in one of their reports in the last, I think was 2011, that there is no clear cause and effect relationship to substantiate the claim within, like with intense artificial sweeteners, replacing them for sugars, and achieving a normal bodyweight. So there's still a lot to be understood, and I think the reason why those health claims aren't kind of in places, the evaluation process to receive a health claim in Europe against a product requires an extremely large amount of data, right back to that technical and safety data, but on top of that then the tolerability data, the dose response data, the feasibility in humans, and then large interventions in various groups, because health claims in Europe have to be generalizable, they have to be applicable and tested in all groups of society. And what I have seen through a lot of these studies, and in the studies that I had

mentioned previously when we're looking at associations with mortality, they're already using these – we've got the EPIC study, or the Nurses' Health Study, or there's a professional study, and they've all shown the same thing, but they're all also studies in middle class white males and females. So I think they're very limited in that sense. We're kind of nowhere close to having a real definitive answer, I don't think, on a strong answer around a health claim on bodyweight management.

DANNY LENNON: Right, yeah, and that's worth noting that that's a very different claim, and also different level of evidence versus what someone might be thinking of, in their individual experience or as a practitioner of, if you're working with someone who drinks two liters of Coca-Cola a day, would it be beneficial for them to swap all of that to a Coke Zero, that's probably going to make a fair dent in their caloric intake, presuming the rest of their diet stays the same. But that's not what we're talking about here in relation to this data on a more population wide level of use of these various nonnutritive sweetener products and weight management, so just as a clarifying point there. With that, I am keen to get into some of the data around glycaemia, because I think this is kind of where a lot of the interesting stuff does come up, and is, again, another area where you see claims on both ends. So if we're looking at, in a long term, I suppose, glucose tolerance, or then we can look at some of the stuff on a more short term acute basis of the glycemic response immediately to ingestion, again, we see two kind of different claims here that we should probably investigate, one being, do these artificial sweeteners actually impair glucose tolerance, or cause abnormal glucose and insulin responses, which is something that is often claimed; and then second, on the other end of the spectrum of, if these sweeteners are replacing sugar, could that then be of benefit to glucose control in a long term, or in a population of people with diabetes, for example. So if we're to look at this area, where

does some of this discussion around sweeteners impairing glucose tolerance come from, where are some of the studies? I know there's a couple, Niamh, that you highlighted as well, but at a general overview level, where are these kind of claims are emerging from do you think?

NIAMH ASPELL: Yeah, there's a lot of weak evidence, I think for this. So I'll go back maybe to when a paper for I know you have previously discussed in a podcast, a couple of years ago, and that was published in Nature, and that got a lot of attention. So there's two kind of components to this study, it was published – it was conducted by the Weizmann Institute in Israel. And I think a lot of their work is really, really extensive and done in a great lot of detail. But that particular publication, I won't go into much detail because there's been some newer ones since then. So I think if people are interested, I think you've gone into in quite a bit of detail, I think it was Episode 184. But this was a, essentially, their researchers hypothesize that chronic, which I think is a stretch, the term chronic, but chronic artificial sweeteners can disrupt gut microbiome, which then can, in turn, have a negative impact on glucose tolerance.

So a lot of the other studies where we look at, or glucose tolerance tests and taking an artificial sweetener, we've shown that the curves aren't the same as if you were to take an actual sugar containing calories or containing glucose. So with this particular study, it was done in two different streams, the first part they looked at giving mice a really, really high dose of sweetener. So there's different formulations, there was saccharin, sucralose and aspartame, and they gave this to mice over a 10-week period; and they showed in mice that those who consumed water glucose and sucrose, there was obviously differences in their tolerance curves. They also showed that this may be related to the bacteria and the gut as well. So they wanted to kind of extrapolate

these findings, these earlier findings to humans, and they did a really, really brief short intervention – not intervention, they did an assessment with seven participants, so basically, they, for a week, they gave this very small number of seven people and the FDA's maximal acceptable daily intake of saccharin, so it's five milligrams per kilogram bodyweight, and they showed that some of them, so four of them developed poor glycemic response after that kind of weak intervention. And this then generated this idea that there's responders and non-responders to artificial sweeteners, and what they show then when they went on to look at their microbiota was that this particular group had a lot more of one particular bacteria in their microbiome, and they thought that potentially that this bacteria had something to do with a change in their glucose response. And this paper got a lot of attention, I think at the time. There was a lot of limitations around it but it was the first paper that, or the first study that really kind of highlighted it.

Last year, I think there was probably a better designed study based off this 2014 study that is published by Serrano et al in microbiome, and what they wanted to do was see if high dose saccharin supplementation induced gut microbiota changes, and then influenced glucose response, or it contributed to glucose intolerance in healthy humans. They also did a similar kind of side study in mice as well, and this study was a lot larger, so they had a double blind or a CT. Again, the other study didn't have a control group, but this particular study, they investigated saccharin and different outcomes, and they had it broken into four different arms. So they gave the study participants either saccharin, lactisole which is like a molecule for sweet taste receptors. So back again to see if there's going further into this biological activity around the different artificial sweeteners again, and seeing if that that has an influencer effect. So these sweet taste receptors, we know there's particular ones, in the mouth, so oral sweet taste

receptors, but then there's other ones that have been found in the gut as well. Obviously, they don't respond to taste, but they have other kinds of reactions of detecting that they have induced a sweetness, a sweet kind of beverage or sweet food, essentially. And so, they gave that, and then they gave saccharin with this sweet taste receptor, and this is in a capsule format as well, so the participants were all kind of blind to what they were receiving, which a lot of the other studies previously hadn't done.

So they wanted to kind of achieve the maximum ADI, and this is only a two-week study, but they conducted a parallel study in mice in a very, very similar kind of format, but in total they have sample of 54 at baseline, and the baseline – the participants characters because they're baseline were really quite well balanced in terms of anthropometrics and metabolic markers, so they did a lot of triglyceride and other blood markers for lipids, and their insulin and their glucose, and everything was very well balanced at baseline. They did state in the paper though that the participants, and this is one thing that I always find funny with these kind of trials is, a two-week period where people are set off into the wild of going back home and told, you know, don't have anything else with artificial sweetener, or don't drink this, or don't do that, and maintain certain physical activity guidelines and manage your dietary requirements. So I was very interested in how they did this for this particular population, because they state that all of the participants complied with these requirements, and they said that the requirements are detailed in the methods, but there's no mention of them in the method. So I'd love to know a little bit more, and what that compliance was, I think it's really difficult when it comes to artificial sweeteners to exclude them entirely if you're not in the artificial sweetener kind of group. But apart from that, they've other really good methods, they did kind of gold standard methods for analyzing fecal samples for gut

microbiota, and then, it was also a really well powered study as well. But they did lots of multi-group comparisons beyond kind of post hoc to reduce these multi group effects.

So they required explicit and open in terms of how they analyzed the study, but the majority of interventions in this area so far have shown that there's no association between artificial sweeteners and glycemic control, and the study has shown the exact same. So it wasn't, it didn't match, I suppose, in terms of what the previous authors had shown in the Suez paper. And in contrast, there was a large number of positive associations or positive effects observed in their mice study, in their animal study, which is typically what we see in a lot of the literature. So they found all of the significant findings in their animal models, but in the human participants, the effects weren't noticed. And I think there's a couple of different things, but my main, I suppose, consideration there is how long is long enough to be able to induce a glycemic dysregulation in a population of healthy subjects. I think two weeks is a bit of a stretch, I'm not sure what you're going to find in that situation. So I think, yeah, there's other meta-analysis, there's one published in 2019, and again, they found their peeled effects show that there's no mean difference in postprandial. So a lot of these studies are looking at post meal response for artificial sweeteners and postprandial insulin response, and again, in that meta-analysis in 2019, they found that there was there's no significant mean difference, definitely not one that is clinically meaningful, and I think that's what these papers are lacking as well. If there is an association, I think there's four out of 18 studies that showed an association, but the difference or the change was very, very minimal, and it wasn't meaningful in a clinical context, some of them also just reported changes in insulin response, but without glucose response and I think, again, that means clinically, that's not particularly meaningful again.

DANNY LENNON: Yeah, this seems like one of those areas, as it was with some of the others that we mentioned, where there's this disconnect between some of the animal data and then the human outcome data. One of the interesting things that you had highlighted, Alan, I think, in relation to some of the appraisal of some of these studies in relation to glucose metabolism, and nonnutritive sweeteners was in particular in relation to the placebo that's used. Can you maybe just speak to that and outline that for people, because I think that's an interesting point?

ALAN FLANAGAN: Yeah, well, these compounds, and their proportionate benefit for the food supply in the population is in replacing sugar and displacing the presence of sugar in foods and beverages. And so, in reality, that's possibly the most appropriate comparison, and we've seen this play out, for example, with some of the ad libitum energy intake studies that Niamh was talking about. You can see a difference in the amount of energy consumed between whether the placebo is water where you don't tend to see that much of a difference, and if you do see a difference between artificial sweeteners and water, it's fairly small, and then, comparing nonnutritive sweeteners to actual sugar, and then you see a big difference. So it does matter, but it's particularly important for the glycemic control studies and the postprandial metabolism studies because, in effect, what you end up seeing, there's two kinds of considerations when it's a comparison to water is we know that these compounds are not biologically inert, so there is a metabolic activity to them. And often, as Niamh said, what you basically see in these studies is these kinds of findings that are purported to be a difference, usually in something like the peak glucose level, or potentially, some degree of the insulin response, and these are kind of offered as, oh, there's a potential negative to these, but then you actually look at the ranges within which they're compared to, and none of them

are outside the range of a normal response for a glucose tolerance test, for an oral glucose tolerance test. The differences are generally nominal, but there are differences. Now, if we were to compare the postprandial glucose response to an OGTT, for example, or even to a food based test, then we could, for example, expect that, actually, the effect of artificial or nonnutritive sweeteners would be what we would predict, it would be significantly lower compared to a sugar control, and potentially, the oral glucose tolerance test on top of that. And, of course, that's the kind of intended purpose of these compounds in the food supply. So these nominal non-significant, although there are differences, we are comparing then in this context a compound that is not completely benign, is not biologically inert versus water, which practically is.

So I think that is an important factor to then say, well, actually, there's really no overall difference, there's no adverse effect on oral glucose tolerance. And even if there were to be a glycemic response of some sort, let's just hypothetically say that there is some degree of responsive GLP-1 or glucose, well, if you've consumed – if the test is, for example, a nonnutritive sweetener or diet soda, well, there's no other sugar within that, there's no additional glucose absorption. So whatever activation is there, is occurring in the absence of any additional glucose contents that are there to be absorbed, which is another factor. And again, potentially, that explains why you get these tiny little effects on some markers, but not others. So an outcome that's been shown in some of these studies is, well, there was a little bit in the longer term studies, there was a little bit of an effect on HbA1c, but in the absence of any effect on glucose and insulin. So again, it's going back to that point Niamh made about the biological plausibility and relevance of these findings is questionable to know, and a lot of this stems – a lot of the, quote-unquote, difference that people will have up and say,

look, a nonnutritive sweetener had this effect. In reality, that effect is compared to water, and even at that, it's nominal to the point of nothing of any sort of clinical or biological significance.

DANNY LENNON: So before we then get to some conclusions, and wrap this up, I want to just return to maybe one of the philosophical or speculative things that we can maybe talk about here, that's not necessarily concrete, but our own speculation on given all that we've discussed today, and seeing this, I suppose, distinct lack of evidence in human outcome data, at least, that nonnutritive sweeteners definitely cause various harms that they're often charged with causing, but at the same time, we know that they still have this really bad reputation. I'm just wondering, can we maybe speculate on why that is the case, is this simply down to the fact that they are something that is not natural, and so, it's like a naturalistic fallacy that they must inherently be bad, and that's why there's such an aversion to them, or are they just an easy target, or is there something deeper going on, is there maybe a way people tend to look at data that is different, at least, these different conclusions? So I don't know if either of you want to jump in on that to start, but I'm just interested in that thought of like, why do we have something where we continue to see such strong aversion to, despite this disconnect with actually concrete outcomes.

NIAMH ASPELL: Yeah, I think there's a number of reasons why we're so suspicious. I think to offer consumers something that's really intensely sweet tasting, and then there's no negative, there's a bit of a, well, there must be, there has to be, is this too good to be true kind of thing. But I think one of the big things is, and it's been done a lot more in other areas, but if you think of consumer behaviors, there's a lot of evidence that consumers typically perceive foods that are associated or that have words associated with them that they would determine as being good or healthy. So linking food healthiness or

words like organic or natural, they don't – we don't typically link the word artificial to health and wellness. So I think in terms of that word in itself, people don't like when things aren't natural or organic, and even though there's lots of things that are organic and natural, that aren't good for you, but people still perceive I think there's a word association there as well. And even when you think within artificial sweeteners themselves, when you put artificial sweeteners in particular, foods, so if you put it into a soft drink which people typically box into that category of being a bad food, if you put artificial sweeteners in it, then you're, I don't want that, soft drinks aren't good for you, so I don't want that artificially sweetened one. Whereas a protein shake is determined to be a health food or healthy food, but protein shakes are also very much formulated with a lot of artificial sweeteners as well. So it depends on the food that you're putting it into and what we associate I think that with being, whether it's a healthier and unhealthy food, and then how it's branded. So if it's artificially sweetened, or if it's branded as this is a low sugar food, people are usually very suspicious and go, well, if it's low sugar, what else have you done to it, there must be something bad in it to make it taste good again. So I think there's a lot of that kind of skepticism, I think, even though we have all the safety data, and then, again, the fact that they're labeled as E numbers, and people have this kind of negative connotation around E numbers, because certain blue colored foods made children get a little bit excited. And then, they associate then that particular E number with all being bad, but actually E numbers have made a lot of our foods very, very good. So I think that's a big part of it, and then, I don't think it helped that for the last 30 years, every couple of years there's a publication saying that they're causing cancer, even though that's been constantly refuted and kind of pushed to the side. That's my opinion.

ALAN FLANAGAN: Yeah, I think there's the kind of skepticism as well, that we've seen a lot during COVID of who

are the regulators, and this kind of them, which goes hand in hand with the wider, obviously, conspiratorial kind of thinking movements, which the wellness community has kind of, has very much, almost merged into. And so, you now get this conflation between conspiratorial thinking, wellness, and this real rejection of structures of authority. So we spent a lot of time discussing various regulatory bodies, well, to a certain strain of person, that's exactly the kind of thing that they don't trust, notwithstanding, just, for example, that the EU has banned over 1300 compounds for use in personal care products, so cosmetic ingredient products, on the basis of even just preliminary evidence from toxicology studies. So the regulatory framework works as far as protecting consumer on public health. But the fact that these compounds, I think, go through a process of approval and regulation by essentially kind of various, either governments or kind of, in the case of the EU, kind of supranational regulatory bodies is likely to feed into the kind of suspicion that certainly a lot of the wellness crowd would have for the ascertainment of their safety. So it would be that, well, I don't trust – we saw it with the vaccines as well – I don't trust the vaccines. So I think that feeds into, I think that feeds into a lot of it. And then also, the fact that with the one study or the study that comes out every couple of years that's associated with cancer, it's like, the problem there is probably that we're expecting people to give a shit about what science says, again, for the most part, if people have a certain belief or worldview, that one study is all they're ever going to hold on to, it's they're not interested in the scientific process or method, they're interested in a piece of information that allows them to uphold their worldview. So yeah, so you'll get the likes of Mark Hyman that are still churning out the same toxicology studies to support a claim for cancer in the absence of any evidence.

DANNY LENNON: Yeah, and I think on the other side of it, there's a risk that people can run of actually giving fuel

to those type of arguments when they go so far in the other direction as to say, oh, any of this stuff to do with artificial sweeteners is nonsense or completely safe, in all cases for all people at whatever doses, whereas really, that's not what we have evidence for right now. We have a certain amount that says, look, it seems pretty safe, we have no real negatives on these various human outcomes in these trials that we have today; but to try and say that there's absolutely nothing, then all it takes is for one kind of quack to show them one of these animal trials, or one of these non-randomized trials with a couple of humans where we're showing this disturbance in glucose tolerance. And then, some of those, oh, but someone told me there's this doesn't exist, so they must have been lying. Whereas the more kind of accurate and nuanced position is, look, there's still a lot of kind of gray area here, and there's a difficulty in meeting the level, the threshold of evidence for a number of these things we're trying to determine, but based on everything we have right now, it seems that the normal doses that someone would be consuming aren't going to cause any health problems in humans, and that's a different position as to dismissing any possible mechanism of there ever being a problem, which is the other thing.

ALAN FLANAGAN: Yeah, I do think that is important for people, it's just the acknowledgement that these are not biologically inert compounds. And so, that there is an effect, this comes back to this thinking we've talked about before about the difference between mechanisms versus effect. Right? If there is an activation in some brain region, does that necessarily imply or mean certain outcomes. If there is this transient little bump in GLP-1, does that actually mean adverse effects on postprandial glycaemia, or normal carbohydrate food metabolism? So I think acknowledging that there's biological activity to these compounds, they have a pharmacokinetic profile and pharmacodynamic profile, and largely, we do understand what that is. But yeah, we can acknowledge that

there may be an effect, but that effect may be utterly meaningless in the kind of the big picture of actual outcomes or dietary intake or metabolic effects.

NIAMH ASPELL: I think so there's a paper published a couple of years ago, and it kind of feeds into all of that as well that the majority of papers on artificial sweeteners have been funded by industry, but I think it's very clear in EFSA and the FDA that they clearly state, if you want to use an ingredient to reformulate your product, you need to pay to do those studies, and you need to provide the evidence to us. So I don't think – I think, because I sometimes jump to the conclusion that if it's funded by certain companies or organizations that we can't trust the evidence that they provide, but because the EFSA claims or making EFSA statements is such a rigorous process, they have to, if they don't do it by the book, in terms of providing that data, and the protocols and the study of design that EFSA wanted to see, then it's not going to be considered. So I don't think that that should describe what evidence we have as well, at the moment, so I think people are maybe a bit – have reservations around that. But I think if there's a sweetener, and you want to reformulate your product, EFSA is not going to go off and do the tests for you, you're going to have to try and prove that yourself as well. So as long as it's done in an open and transparent way and followed by the way EFSA want their dossiers to be put together and submitted, then I think we can kind of rest assured that they're going to be to a certain standard.

ALAN FLANAGAN: I think we could almost apply that thinking to a lot of different areas within nutrition. I mean people with dairy, people will say, oh well, this is an industry funded study, and it's like, yeah, well, and nutrition science is a poverty stricken area of science that doesn't get half the funding of major, other biological sciences. And so, funding has to come from somewhere, and it's not the funding, that's the problem. It's

whether the funder has an undue influence on the design and analysis and presentation of the study, and that's where we get into the actual critical appraisal of the research and the study itself. And where a study stands up to the scrutiny of that appraisal, then the funding becomes less relevant, so I always do think that it's important to acknowledge a funding source, and then, critically appraise the paper on its merits; and if it stands up to that scrutiny, then for me, the emphasis then on the funder becomes undue if it's not warranted in terms of the critical appraisal and the methodological quality of the particular study, and then, of course, a wider body of evidence.

DANNY LENNON: So in terms of a conclusion, are we in agreement that based on the human outcome data today, and the body of evidence more generally, and looking at these typical intakes that we see in the general population, that by and large at normal levels of intake, or average levels of intake, that there is no undue risk to these various health outcomes that we've discussed, at least, today, based on current data with that kind of notable exception that I think Niamh you alluded to earlier of PKU, this genetic disorder where people can process phenylalanine appropriately, and so, they need to avoid aspartame, in particular. But beyond that, for any of these other issues that we've discussed today in relation to glucose tolerance, cancer, etc., it doesn't seem that there's any major risk to human health from these normal levels of intake, is that a relatively fair conclusion that we can leave people with?

NIAMH ASPELL: Yeah.

ALAN FLANAGAN: Yeah.

NIAMH ASPELL: I think weight management is such a complex, it's a very complex thing to understand, and I think artificial sweeteners and artificially sweetened drinks aren't the only factor there. I think if people want to use artificially sweetened drinks in place of a sugar drink, I

think that's maybe probably a better option, and I think a lot of the advice would be to kind of move from sugar drinks to artificially sweetened drinks, drink less of them until you then start to maybe drinking water or naturally sweetened kind of juices and stuff. But yeah, I think they serve their purpose, I don't think that we can attribute their consumption to any kind of safety concerns at the moment, or poor health outcomes, I think what's been presented so far is much more complex than the Diet Cokes.

ALAN FLANAGAN: Yeah, I think having regard to current population levels of consumption for each, I know, we've kind of tended to hone in on the discussion with some of the evidence on things like aspartame or sucralose or Ace-K, but on the whole, all of the nonnutritive sweeteners currently approved for use in the EU and in the US are consumed at habitual levels in the population that are so far below any sort of concern for safety or toxicology or any sort of adverse health outcomes, and then, indeed, whatever inconsistencies may be in the research, some of which we've tried to parse today, the reality is that the weight of evidence doesn't support any particular adverse effect. And as Niamh said, with weight management, you're into such a complexity of behavioral factors, and so, yeah, that potentially, you could get some people for whom the substitution for energy is a positive step and allows them to facilitate a reduction in total energy, and perhaps you get people who, in consuming diet sodas, kind of, suddenly have a different behavioral effect, and maybe, oh, I've got free energy to use up now or something like that. And so, I just think with that outcome, it's very difficult to kind of say one way or the other, but, I mean, ultimately, artificial sweeteners or nonnutritive sweeteners aren't necessarily even any requirement for weight management. So it’s not something that we need to get necessarily bogged down in, and the major outcomes that people have tended to be really concerned about like cancer and

mortality and otherwise, I think we can really at this point say, there would be very little evidence based reason to have those concerns.

DANNY LENNON: Excellent. And I think that rounds us out.