DANNY LENNON: With that, let's get into our main topic for today, and we're going to be talking about dietary nitrates and nitrites. So really, we're going to be focusing in on this nitrate-nitrite-NO pathway, and how this can potentially influence various aspects of health. We're going to look at where we get those various sources of nitrates and then nitrates in the diet, and there's probably two elements of that where we see actually conflicting discussions about the healthfulness or potentially the health detriment depending on what we're talking about. And there's many layers to this, and so, we're going to probably focus in on a few. Within this general topic of dietary nitrates and nitrites, what is the most interesting aspect of it to you that you think we should focus today's conversation on?

ALAN FLANAGAN: I mean, there's generally, I think, for most people listening in their heads, their nutrition hat on, they're probably thinking, red meat and processed meat consumption as the constituents of those foods that may respectively increase or explain to some degree, some of the associations with increased risk that are observed prospectively in cohort studies, and then also in terms of mechanistic evidence that many people I think misconceive

as only confines to animal models, but we have human studies on this as well. So I think there's that, and then, I think, perhaps, as well, then in more recent years, maybe people have become aware that actually we also find nitrates primarily in terms of diet, in vegetables, and obviously, vegetables and fruits are strongly inversely associated with risk. And so, it's probably that, as you highlighted, this kind of oppositional direction of effect, related to what people may perceive as the exact same exposure. So how is it potentially explaining a risk in one context and potentially a factor that is explaining a reduction in risk in another context, and I think that's probably where the crux of the interest comes, in terms of the related directions of effect that we see for kind of vegetable and fruit consumption, where it's pretty consistently lower risk. And we know that it's probably the only very uncontroversial facts that we could all establish and agree on with nutrition. And then the more controversial one would be unprocessed meats in particular, I think that that's something that is more kind of nuanced, and can be difficult to tease out, while I think processed meat consumption, unless it's a very extreme keto carnivore camp, I think there would also be fairly broad consensus that that would be a risk, and a risk that holds true kind of in different populations, particularly for colorectal cancer.

And one of the explanations that sometimes might be offered for the difference between red and processed meat is people will say, well, processed meat has nitrates added as food additives. And so potentially it's that, whereas unprocessed fresh red meat would not and would have lower levels of preformed nitrates in it. So that's often offered as an explanation for, well, unprocessed meat's not likely to be a risk, but maybe if we accept processed meat, this could explain the difference. So I think they're the kind of high level points that are mostly interesting, I think, with this topic.

DANNY LENNON: Sure. And we'll definitely get into the topic of processed meats, because when we're talking about that, within the processing of those, and the curing of meats is where we have this nitrites added, and there's certainly a lot to discuss there. I think probably from the health aspect, it might be useful for us to outline, well, why are we thinking about this nitrite or this nitrate-nitrate-NO pathway, NO being nitric oxide; and here this may have potential effects when we're looking at blood flow and vasodilation, and hence why it's been looked at in areas of atherosclerosis. And I think, kind of an interesting side note, when I was looking at some of the history of some of this research, when it started being noticed that there may be conversion within the body where we're getting movement from, say NO to NO2 minus, which is nitrite, and NO3 minus, which is nitrate, one of the early studies that was done was by Green et al, 1981, where they showed that this nitrate excretion seemed to be four times the intake that someone would have of dietary nitrates. So hence, like where is that coming from, and started this work to work that out. And given about what you said about the sources of nitrate being particularly good sources, green leafy vegetables, that paper by Green et al, 1981, was followed up by one of his colleagues, almost unbelievably, Leaf et al, 1989, which showed this nice kind of lineage of one of the precursors L-arginine I think, then conversion into NO, and then NO2 minus, and then NO3 minus. And so, we're starting to see that there's conversion between these and it can go up and down this pathway, which we'll probably discuss at a later point, but hence why we're trying to work out, well, what is having these various impacts on health, because it seems at least on the dietary nitrates, which, again, we're mainly getting from green leafy vegetables, spinach, rocket, beetroot and so on, seems to correlate with positive health outcomes which we'll discuss including blood pressure. But I thought that was just an interesting aside, when looking at some of the evolution of this.

ALAN FLANAGAN: Yeah, and coming across there was a nice paper, just a review which had laid out some of the, in relation to cardiovascular diseases, ischemic heart disease, in particular, that for treatment of hypertension and angina, both nitrates and nitrate esters were used kind of as early as the 1930s for those indications, so there is a history of use of these compounds in a clinical context. And, of course, there are these inverse associations epidemiologically with vegetable sources of nitrites and reduced incidence of cardiovascular disease. And then intervention studies using nitrate rich beetroot juice in particular has been a popular intervention supplement, I guess, would be the right word, where you do see a reduction in blood pressure that is observed in people even with kind of what would be normal, high normal blood pressure and also hypertensive. So, I think this is where, where people probably get confused is because we're using the same term, nitrate-nitrite, but we have to be very specific with the source of that. And then also, as you highlighted, there's this cycle in the body, where, for example, nitrates can be reduced to nitrites, even in the oral cavity – in the mouth, when people are chewing food with a salivary enzyme reaction. And then, there are potential interactions that might explain why the food source of nitrates is particularly relevant for associated kind of health effects. But it's not to say that these are compounds that are only – they have certainly, I think, come into people's consciousness, because of the provision of an explanation for red meat and processed meat consumption, potential explanation for the associations with their risk related, but that's not the exclusive use of these compounds. And there is a kind of long history of interest in them for their ability to influence vascular function, endothelial function, blood pressure, and related heart disease and cardiovascular health.

DANNY LENNON: Yeah, and I think on that topic, probably some of the work we may reference later, I guess, is probably out of Nathan Bryan's lab, who seems

to have focused a lot on these positive health effects of nitrates, and how that influences hypertension, and then also atherosclerosis risk. And I know his work kind of shows that this loss of nitric oxide or NO is associated with atherosclerosis, and essentially, you can use that as a marker of arterial health to some degree. And if you look at people who are in an older adult population, 65 plus versus people who are young adults, you see massive discrepancies in the amount of nitric oxide that they're producing there – so giving rise to this idea, well, this is going to have some benefits for arterial health, endothelial function that you just mentioned. And one of the interesting things actually noted on some of the work that that his lab has done was that, given that nitrate itself is relatively inert, and as you mentioned, has to be converted that into nitrite within the body by bacteria, much of that goes on within the mouth, as you just noted, his group did some work actually looking at mouthwash, and when you provide that to people over the course of this study, and they saw increases in blood pressure, on average, in a number of these participants. And in some people, it really jumped up on some of these outliers, and they were kind of putting it down to this potential mechanism by using that mouthwash, you're not getting this conversion to nitrite, and potentially, then could have this downstream effect on blood pressure or so it goes.

ALAN FLANAGAN: Yeah, so the mouthwash eradicates the bacteria required for that activation, and, as a result, then you essentially get the parent compound, which is not reduced, and then has an opposite effect?

DANNY LENNON: Yeah. So yeah, the benefit of having those extra nitrites was basically cancelled out because they're not being produced. So that was just kind of interesting, but at least, fits in with what one might kind of hypothesize mechanistically if nitrites are indeed having that effect. And so, maybe we can talk a bit

about that of, like, what do we actually know in terms of nitrite, in terms of, is it beneficial, perhaps, and in what context might it be beneficial, what does it actually do in terms of influencing blood vessels and so on, and then maybe talk about some of these aspects on blood pressure, before we turn our attention later to kind of meet.

ALAN FLANAGAN: I think that's, yeah, a helpful point of departure. So basically there's two primary sources in humans, in mammals generally. We have the endogenous metabolism of nitric oxides to form nitrates, and then we also have direct intake through diet. The biggest source is vegetable consumption, but there's a kind of hierarchy with vegetables in terms of their nitrate content. So very high nitrate content vegetables would be watercress, spinach, rocket, celery, and red beetroot, very low nitrate vegetables would have – and so by very high, that's over 2500 milligrams, 2.5 grams per 100 gram of fresh weight, very low, less than 20 milligrams per 100 gram of fresh weight would be vegetables like garlic or onion, potatoes, squash, artichoke, asparagus, and then you've got these kind of midrange vegetables between 50 and 250 milligrams which would be like cabbage, leek, fennel, celeriac, these kind of vegetables. So quite ubiquitous, but existing in different ranges. In a typical diet with anything over 200 grams of vegetables, dietary intake of vegetables will be the main source of nitrate in the body. That sounds like a fairly low threshold, I'm sure, to most Sigma listeners, but in the general population, it's really not much higher than that in the UK, I think the vegetable average is like 260 grams a day. Nonetheless, it's in a range when vegetable intake would form the major source of nitrates.

And then we have – so nitric oxide in the body is basically generated by all cells through the action of these enzymes known as nitric oxide synthases, and that's dependent on availability of the amino acid arginine, and it's quite a

reactive – nitric oxide is quite reactive in terms of redox biology. And so, it's quickly metabolized in the body to form nitrates and nitrites which are more stable. With nitrates, obviously, like we said, there's the kind of synthesis in plants and vegetables that we ultimately eat; with nitrites, they can be food additives, and there's two major types, sodium nitrite, which has an E number E250, and potassium nitrate which is E249. And they're typically added to cured meats to inhibit the growth of bacteria, and they kind of add color and a degree of flavoring to it as well. You can have certain preformed, amounts of preformed nitrites in vegetables and foods. But it's not – it's present in quite small amounts. So nitrite intake from the diet can be taken in primarily through as food additives, particularly in processed meats, and then it can also be nitrites in the body that are endogenously synthesized from nitrate intake would be the kind of, the major source of nitrites that are synthesized in the body.

DANNY LENNON: Fantastic, yeah. And I think one reference just for people listening that they might want to check out and probably refer to later of, if we're looking at sources of dietary nitrate, there is a quite a useful nitrate veg table that was developed by Satnam Lidder and Andrew Webb – I think that was for the British Heart Foundation, originally, I believe, and kind of just showing different foods that are a source of those, but quantifying them in units of nitrate. And so, people can just refer back to that, to kind of get a gauge of how much of these different foods would confer various units. But we'll probably talk about that a bit later on. I think probably based on where we're starting with first, if we look at some of those potential beneficial impacts, and we're looking at really here if we keep our focus to impact on hypertension, or just for people who are normotensive what the impacts on blood vessels and their overall risk then of things like atherosclerosis, we will leave to them aside for the moment maybe exercise performance,

which is a separate conversation which nitrates can be quite big in. But for the moment in relation to health, there does seem to be – initially, there was evidence looking at how nitrites in the body can then have potential beneficial impacts in certain circumstances. So I think some of the earlier work was on like acute myocardial infarction. You also then started to see potential for it to have an impact on blood pressure, and it certainly seems that most of the intervention trials are looking at adding in nitrates, whether via dietary means or supplementally seems to have impacts on blood pressure as well. Is that a relatively consistent finding in your mind when it comes to some of these impacts on blood pressure?

ALAN FLANAGAN: Yeah, it seems to me to be fairly consistent in terms of – and there's the understanding of the effects of endothelial nitric oxide synthase on these various regulatory processes that influence vasodilation and constriction, but vasodilation in a beneficial sense, consequently, obviously, blood pressure, but there's also benefits on inflammatory responses, and platelet aggregation that may be relevant as well to beneficial effects on atherosclerosis progression and related cardiovascular processes. So this is where we get – there's two kind of members of this family that are important. So there's eNOS, which is endothelial nitric oxide synthase, which are a family of enzymes on the vascular endothelium, the kind of activation of which is associated with those beneficial processes that I just mentioned; and then there's lowercase iNOS, which is inducible nitric oxide synthase; and these kind of other members of the family can actually generate inflammatory and immune responses that can be a promotion of carcinogenesis by kind of inhibiting cell death apoptosis. So I think maybe, although it's a very crude dichotomy that I'm about to kind of state for listeners, I think it might just be helpful to think of kind of eNOS, endothelial nitric oxide synthase on the one hand being this kind of these members of this group of

enzymes that have beneficial effects on vascular function that relate to vasodilation, blood pressure, inflammatory processes, etc.; and then inducible nitric oxide synthase or iNOS, on the other hand, which may be more associated with some adverse effects on inflammatory and immune processes.

And so, for nitric oxides, the kind of vast majority of nitric oxides in circulation is from these endothelial nitric oxide synthase family of enzymes. And this is where, obviously, there's a potential interest then in nitrates, the biggest concentration in circulation, like I think we've mentioned already, is in saliva. And then we have this addition of exogenous intake through diet, and we have this reduction to nitrites, and that's supplied to the gastrointestinal tract, absorbs, and potentially then has these impacts eNOS, which is endothelial nitric oxide synthase family of enzymes that have the beneficial kind of mechanistic regulatory processes that we just described.

DANNY LENNON: I suppose we're looking at this as a collective pathway, given that nitric oxide has this half-life of I think like less than a second or something like that in the body. And so, we're looking at this of dietary nitrate, and then that in turn in the body can be converted to nitrite, and then into nitric oxide. And then we can also have the supply of nitrates specifically. So we kind of got to that point now, and it seems that through a number of interventions, for example, if you look at all the beetroot juice trials, they tend to have these changes in blood pressure through some of the impacts we're having. And so, overall, particularly when you look at the dietary patterns with a lot of vegetables that would be high in dietary nitrate, so green leafy vegetables across the board, are always, for numerous reasons, beyond just the effects we're discussing, have positive health effects, but this may be one due to their nitrate content. But given all that, as we've outlined at the very start of this episode, we're then saying,

well, where does all this stuff emerge about there being potential problems, because so far, it seems to be a picture of more dietary nitrate and even nitrite is a positive thing for all these impacts. And so, if we get into some of the discussion around potential issues, and a lot of this does circulate on the processed meat discussion that you outlined, I guess, one of the key distinctions that might be the reason why we see something different in this context is that it's often nitrosamines that people are referring to that are in cured meats. And this is where we have this interaction between those nitrates and other compounds that are found specifically in red meat I know, but before you've mentioned, heme iron or hemins and so on. So can you maybe just talk through that, first of all, of did the nitrosamines potentially being this issue, and how does that relate to nitrates per se?

ALAN FLANAGAN: Yeah, and this is such a crucial distinction, because it gets us kind of more towards the actual what is in the research that would explain mechanistically why there might be significant associations with particularly processed meat consumption and adverse health outcomes. We tend to say, processed meat nitrites, for example, and we've said that, yes, they are used as additives and they're... and that implies that, again, it's the nitrite itself that is almost maybe directly having some sort of effect. What, in fact, are the compounds that are exposures of interests, in relation to the associations between red meat and processed meat consumption are actually these different carcinogenic compounds, heterocyclic amines, polycyclic aromatic hydrocarbons which we're not going to touch on today, but there are compounds, for example, that can be created from charring, cooking methods, barbecuing, and that kind of thing. What we're talking about in relation to nitrates and nitrites is what are known as N-Nitroso compounds, and these are different, they're produced by a reaction of nitrates and nitrogen oxides, with these kind of alkyl amide compounds. And these compounds

can react with DNA, which could be again, in terms of having a negative effect on DNA, damaging DNA could be a potential explanation for why there may be, again, some adverse effects. But it's nitrosamines, and nitrosamides and other N-Nitroso compounds. So when I say NOCs, that's a kind of a family of compounds that have been shown to be carcinogenic, certainly in mechanistic animal models. And so, it's the generation of these N-Nitroso compounds that is likely to be more of where we get this potential explanation associated with nitrates and nitrites. And it is quite strong, I mean, as an example, there's a mediation analysis from the National Institutes of Health retired persons study the, NIH-AARP cohort, where you had this quite wide contrast in red meat intakes from quite low levels of 20 grams a day up to about 160, give or take. And a mediation analysis looked at the contributions of processed meat nitrates and nitrites, to what extent the relationship of cardiovascular disease and cancer was mediated by those compounds by heme iron. And heme iron accounted for about a quarter of the relationship of processed meat nitrates, accounted for up to 70%.

So you do get this strong mediating effect of these compounds, however, it's likely to be the exposure to these interaction compounds that are formed from the reaction of nitrites with these other nitrogen oxides to form these N-Nitroso compounds, this family of compounds, nitrosamines, and nitrosamides, like I said, that have been shown to be carcinogenic. And so, you can get that from processed meats, the process of adding these nitrites increases the concentration of these compounds, and therefore, the kind of interaction or reaction potential with these foods. And there are N-Nitroso compounds that have been looked at specifically in relation to colorectal cancer for example, and the relative risk which is rare for nutrition is over to, when looking at some of these N-Nitroso compounds formed from nitrates. And interestingly, there was a finished

cohort that found, when it looked at the N-Nitroso compounds, that relative risk was significantly like two-fold increase in risk, but not nitrite intake alone. So, and that's speaking to the fact that it may be this reaction of nitrite.

So yes, processed meats are high in preformed nitrites, but it's perhaps the high concentration of them providing more of a substrate essentially for this reaction, generating these carcinogenic N-Nitroso compounds. And while a lot of people will be quick to say aha, but animal models, which is always valid to bring up, there is human data on this as well, which is often just kind of not really looked at or discussed and Sheila and Bingham's research and the group that produced a lot of these human studies, elegant, tightly controls, metabolic ward studies, looking at the generation of these compounds in humans consuming various levels of red meat in the diet from 60 grams a day up to 600 grams a day, and essentially, you see linear increases in the creation of these N-Nitroso compounds with greater levels of red meat. And this applies to unprocessed red meat consumption as well, and interestingly, where we might start to get an explanation with unprocessed meat and epidemiology, there seems to be a certain dose threshold, there doesn't seem to be much risk at levels of less than 100 grams a day. But if you find cohorts, well conducted cohorts with large sample sizes, where there are groups within the cohort consuming over say 150, 60, 70, 80, you start to see a more consistent association with risk.

And interestingly, the formation of N-Nitroso compounds from heme iron is strongly implicated and may explain this, and Bingham's research produced a number of studies where they demonstrated pretty profound increases in N-Nitroso compound formation from heme from red meat. And what was interesting with some of their research was they also compared it to say, ferrous iron that you might supplement with. And so, they were

getting comparisons with the iron form administered, and they didn't see any increase in N-Nitroso compounds associated with ferrous iron, they didn't see any increase associated with white meat or fish. But they did see this significant increase in NOC formation, and it wasn't simply the nitrate components of foods, which has been shown elsewhere, but particularly related to the heme form of iron that will be found in red meat. So I think that starts to, in terms of human research, bring us into a realm of more plausibility for why certain higher thresholds even of unprocessed meat consumption, particularly in the context of low fruit and vegetables and fiber, might be something that increases risk for, particularly colorectal cancer.

DANNY LENNON: So our carnivore friends shouldn't be using the benefits of a high nitrate, vegetable rich diet as a reason that we can eat more bacon.

ALAN FLANAGAN: Yeah, wouldn't really appear to be a smart play. But I wouldn't associate smart plays with that crowd. So...

DANNY LENNON: No, that makes a lot of sense. And so yeah, to recap for people where we are, we're looking at these dietary nitrates and then there that we say get from green leafy vegetables can then get converted within the body into nitrates, and then along this pathway, then can have these various beneficial health impacts. But in relation to meat consumption, not only are they sources of nitrate, but they also then that nitrate can interact with other components within red meat like heme iron and these amines and amides, that Alan's mentioned, which produce these N-Nitroso compounds, which they may carry more of the risk rather than saying it an isolated thing down to nitrite. And that might account for why we're seeing such differences, and certainly, I think, as we've discussed on the podcast before, and I think as you've outlined in one of our statements on red meat, this can be a highly controversial issue, not even from people that

are necessarily pro all red meat or pro carnivore or anything, but a lot of the time there can be a bias towards not trying to acknowledge there is any risk of meat consumption, and that may not be necessarily accurate or in line with most of the data we have.

ALAN FLANAGAN: Yeah, and when you look at these human studies, so let's even just kind of "steelman" this for a second, forget all of the animal mechanistic work, because people will just throw that out. Even if we're confining it to the human experimental research that has looked at various levels of red meat, unprocessed and processed, various forms of iron, the formation of these compounds, and comparing, for example, white meat or fish, well then, we start to have a fairly consistent plausibility from those human studies. That explains the epidemiology findings where we see associations with red meat but not white wheat, and we see associations with red meat but not fish. And we seem to see somewhat of a threshold of risk with higher intakes for unprocessed red meat, and there, the human studies would very much – I mean, one study, for example, which was looking at 240 grams a day of fresh meat, red meat, unprocessed red meat or processed meat, the same dose, and you saw a fourfold increase in the formation of N-Nitroso compounds in the unprocessed fresh red meats, and you also saw a 6.5 fold increase from the processed meat. So the idea that any of these potential mechanistic explanations only apply to processed meat, may not necessarily be the case, it just may be that the magnitudes of the endogenous N-Nitroso compound formation is much greater with processed meats because of the preformed nitrite levels in it. But to say that potential explanations that explain processed meat associations don't apply to unprocessed meat associations, I think that's largely difficult to substantiate based on human data, and it would appear that certainly higher levels of to Bingham's research, they looked at 400 and

600 grams a day as well. You see quite profound increases in the formation of these carcinogenic compounds, and sometimes, as they have shown, that is not necessarily attenuated with the addition of non-starch polysaccharides or fiber types that you might expect to be protected. I think in one study, they added 20 grams a day of a type of fiber, and it didn't kind of really attenuate to any great degree the formation of these compounds with higher levels of red meat.

DANNY LENNON: So maybe just to round that off, and maybe to round this whole discussion when we talk about practically what that means maybe for most people's dietary intake, first, if we look at the meat intake side of this, and, again, we've discussed this before, but maybe as a kind of recap on that, pragmatically, based on the best evidence we have to hand right now, with the caveat that there's probably more to unearth, and there's a lot of caveats to what an individual may consume at a broad level, what would be a fair conclusion for people to take away about levels of meat intake that would correlate with positive health?

ALAN FLANAGAN: This is one of those shocking conclusions that actually the guidelines that have been set by scientists and experts working in this area are actually sensible. I know it's a lot to take in listeners, but there are some people who actually know what they're talking about, have sat down and come up with some recommendations, and they happen to be quite pragmatic. So yeah, I'm being a bit facetious, but if you look at the recommendations for processed meat consumption, less than 50 grams a day, that that seems to be quite pragmatic. I don't think I would be looking to eat processed meat every day, but I think that is something that is worth relatively minimizing, acknowledging that a bacon sandwich every now and then is wonderful. Secondly, in relation to unprocessed red meat, the threshold of 500 grams a week, I also think is quite pragmatic. When we think of the dose

thresholds as it relates to daily intake that you might see an observational epidemiology, when you think that that tends to be nonexistent or certainly difficult to detect at less than a 100 grams a day, 500 grams a week – sounds like a lot when you say 500 grams out loud, but you're talking about maybe an average of 65, 60 to 70 grams a day, it's not a huge amount. And I think that's a pragmatic suggestion, if that was two servings of 200 grams at different times a week in the context of high fiber, vegetable, and all that good stuff, then I happen to think that the World Cancer Research Fund guidelines are a fairly pragmatic reflection of what we know at this particular time. So I'm kind of inclined to hold up those recommendations for listeners.

DANNY LENNON: If we then think about what might be a good intake of dietary nitrate, this becomes a bit of a one where there's maybe a bit more of a gray area, and certainly you'll see different recommendations from different research groups, at least, relevant to what is out there, and I've certainly seen discussions about how the ADI for dietary nitrates is relatively low somewhat I think, and they have some issues that the data that that may be based off of, I think data from maybe the 60s in animal models. But in terms of actual intake, some of the studies that I saw were pointing to while we have an average intake in US populations about 150 milligrams per day, that's over the course of the whole day, so over multiple meals, rather than a bolus dose. The studies where we're seeing changes in actual blood pressure seemed to be intakes around 3 to 400 milligrams, and so, that might not be appropriate.

ALAN FLANAGAN: Yeah, it seems like the limits WHO and the FAO ADI limits are quite low, 3.7 milligrams per kilo of body waste, and for nitrates, and for nitrites, 0.06 milligrams per kilo of body weight, for an average kind of 70 kilo person, you're not talking about much more than 250 milligrams a day or something like that for nitrates and nitrites. And even if you were to

just – the five servings of fruit and veg a day, the five a day kind of target roughly in actual weight of food is about 400 grams of fruits and vegetables per day, that's kind of the lower target. But that would be kind of daily nitrate intake of about 157 milligrams a day. There was this interesting comparison with the DASH diet in particular, where they've got this emphasis on certain amount of servings of vegetables and fruit every day, and if I remember, it was like a 500% the amount of nitrates in the DASH diet would be about 1.2 grams a day, and would exceed the WHO limits by about 500%. So there is at least I think sufficient evidence from what we would see with kind of dietary patterns and interventions under the epidemiology to suggest that, at the very least, there is little to no observed adverse effect of intakes that far, by orders of magnitude, exceeds the current limits that have been set.

DANNY LENNON: Yeah. So we're seeing this kind of discrepancy, but probably more work to be done to give some of those recommendations, because I can't remember who was talking about it, it might have been in one of Andrew Webb's paper, but talking about the origin of that ADI was kind of based on this 60s data from animal models, possibly dogs, I think, where they use the upper level given in some of those dose response studies. But they hadn't seen negative impacts, but they just got up to these really high levels, but obviously, when you translate that into a human ADI, you have to have this hundredfold margin of safety, as we've discussed before. But yet, now you're ending up with these probably relatively low upper level targets. Yeah, so what we can do in the show notes for people is we will link to some of those places where you can check various sources of nitrate in different foods. So we've mentioned some of the best sources of dietary nitrates. We can look at the nitrate veg table by Lidder and Webb, which is quite useful. There's also probably the caveat here to put in that, interestingly, you see quite a lot of variants geographically in the amount of nitrate within

food. There's one of the studies from the states that I remember looking at where they looked at vegetable produce in I think a few different cities, I think it was like New York, LA, Raleigh, North Carolina and Dallas maybe. And so they went to the same grocery store chain, and bought produce, and then came and tested nitrate levels, and you saw huge differences. I think there might have been like a 10 or 15 fold difference in nitrate between Dallas and New York for something like celery or something like that. So it was interesting, but obviously just the caveat here with people is that based on growing conditions and geography and that type of stuff, that can change nitrates within foods and interesting, again, organic food tends to sometimes have a bit less because they can't use some of these fertilizers that will be a source of this. So yeah, I think that kind of rounds up some of the pragmatic stuff unless there's anything that we didn't get to that you think would be interesting to add or that we want to add in for people?

ALAN FLANAGAN: Not really. I mean, yeah, we kind of did spend a lot of time on the potential negatives with red and processed meat, but explaining that that's not more likely related to these reaction compounds formed. But yeah, I think for dietary nitrate intake that we primarily derive through vegetables and fruit, even without a specific kind of supplemental form with a concentrated beetroot juice, but actually just from diet alone, you do see some quite significant and meaningful reductions in blood pressure in individuals in food based interventions as well. So there are some importance benefits to consuming these, and obviously as well, the caveat that without being overly reductionist, there are likely multiple benefits to consuming these food sources in terms of micronutrients and other bioactive food components as well.

DANNY LENNON: Yeah, and of course, anyone who has an interest in sports nutrition knows that this is quite a hot topic era as well, specifically with

most of that research looking at beetroot concentrate supplementation. So here you're looking at change in vasodilation, muscle contraction, mitochondrial function, which seems to have a positive impact on performance, particularly in endurance sport. But that is a topic for another day. The only other thing that I'd made a note of that is it kind of just an interesting aside on this topic that I had never came across or heard of, before starting to read up more for this particular episode was in reference to breast milk. And early on for the first number of days, after a newborn is born, that breast milk tends to be high in nitrites, and the idea being that, at that time point, obviously a newborn's gut is sterile, so it hasn't been inoculated with gut bacteria. So breast milk actually corresponds to this and has those nitrates or nitrites, because the newborn would be unable to convert nitrates into them. And then, after a few days, as the gut starts to be inoculated with bacteria, breast milk starts to change in that same time course, and naturally becomes more of a source of nitrate, as opposed to nitrite, because now the baby can actually start to convert those nitrates, and I just found that fascinating from an evolutionary perspective.

ALAN FLANAGAN: Wow. Yeah. That's really fascinating. So kind of speaking to some need, recognition of need.

DANNY LENNON: So yeah, that was kind of cool. But yeah, other than that, I think, yeah, we will round up our topic on that for the moment.

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