DANNY LENNON: Hello, and welcome to another episode of Sigma Nutrition Radio. This is episode 418 of the podcast. My name is Danny Lennon and with me is Alan Flanagan. Alan, how are you sir?

ALAN FLANAGAN: I'm good. I'm trying to figure out how it's December 2021 already, which freaks me out a little bit because the last time I blinked it was April. So yeah, here we are. I have my first mince pie. I waited till December 1.

DANNY LENNON: No, there will be no Christmas talk today. I refuse to participate in any talk of Christmas. So we've got a lot to discuss in this particular episode, I'm looking forward to this one. And it's a topic that often brings up quite interesting debate, I think. And there's some really interesting points to dive through. We're essentially going to be looking at this idea of whether we should be consuming a direct dietary source of DHA, long chain omega-3 fatty acid. And there's a number of reasons why I think this is a particularly interesting issue. So of course, with the omega-3 fatty acid, and we'll get into some of our definitions, and so in a moment, but we know that we can get that from marine sources of foods. So things like fatty fish, or then things like

algae or seaweed, maybe to a lesser extent, but one of the reasons why we tend to see benefits to consumption of those types of foods centers around its content of EPA and DHA, these two long chain omega-3 fatty acids. And then we have the relatively clear data, I would say both from nutritional epidemiology and with randomized control trials of a suggestive benefit for consumption of those. Now today, we're going to be focusing on DHA. But given that we tend to see this data showing health benefit, then the question arises, well, what about people who are not consuming these foods that contain DHA. So A, someone who doesn't consume any fish or someone on a vegetarian or a vegan diet is not going to consume these sources directly. And then that gets us to well, they can consume omega-3 fatty acids in the form of alpha linolenic acid ALA and through conversion when once that is consumed, that ultimately can get down to EPA and then eventually down to DHA. And therefore there may not be a need for a direct source of DHA. And that's kind of one thing we will look up. And then we have to think about the conversion rate which is where the debate kind of, I suppose skews in two different directions based on how someone views the conversion of ALA into ultimately EPA and DHA. But it seems that the conversion is relatively low for EPA, and probably a lot worse for DHA to the point where at least in some populations, it's basically negligible. But we will dive through that. And then we have a series of questions that come off the back of it, which we're going to explore. So I think maybe a good way to frame this and I'll ask you then to kind of fill in some of the gaps after that, Alan, I think is if we were to take a position of making a initial case for a position of what we don't need a direct source of DHA, there are various arguments that I've seen made. Some are pretty strong, some are weaker, and some are more or less common, but they tend to send around a few questions I'll put out here and maybe we can work our way through this later in the episode. So there are questions around well, do we know that the level of conversion from ALA to DHA ultimately, is sub optimal for human health or it's going to be problematic? Is there any evidence that adults

need DHA in the diet due to this poor conversion rate from ALA and then do we have any reason to believe that the DHA that we have endogenously or through this kind of small level of conversion is insufficient for people to have normal health? Do we need a much higher level? And I think there's a number of different arguments which we can probably dive into, some of which relate to if we take the potential roles of DHA as being beneficial for health that are brought up. One relates to cardiovascular disease for example. People might point and say, well, look, we have data on diets that typically don't have a direct DHA source like a vegan or vegetarian diet. And generally compared to a standard diet, we see risk reduction in terms of cardiovascular disease, or at least no increased risk when we compare it to other healthful dietary patterns. So that might be a reason to suggest, well, we don't need this direct DHA source. Another claim might be around, I think one of the most common ones I see is, well, we have no evidence of such a thing as a DHA deficiency. So why do we need to start ensuring we have this direct source of DHA? And then if there are problems with having too low of a DHA intake, what health outcomes, does that lead to that are problematic and what evidence do we have that occurs in populations who don't consume fish or these other marine sources of omega-3? And I think there's various other variations of those types of positions that people may put forth and we'll certainly get into them. But I think that's a kind of general summary of a position that someone may put forth and say, well, this should make us pause and say, maybe we actually don't need this direct source of DHA.

Now, I think, obviously has a lot to explore within that. But as a kind of opening framing of what we wanted to discuss, and some of the kind of claims and some of the background information do you think there's anything that you would add to kind of set things up for people here?

ALAN FLANAGAN: No, I think that sums up the kind of the trying to steal man case as much as possible, particularly because we don't have, you know, set for example, recommended daily intakes. We have an adequate intake threshold, it's recommended. It's

often recommended on the basis of some kind of wider epidemiological findings. And those suggested adequate intakes and recommendations do differ depending on the regulatory body or the kind of country in question. But I think just to frame those questions, overall, a lot of them have a degree of interrelation. So if we're thinking about, well, if we know a level or do we know a level, if this level of conversion is not optimal for human health, there's the level of conversion per se. And then there's the question of, well, if we have no evidence necessarily of a deficiency state, well what happens if we're comparing more versus less or higher versus lower, for example. And so this gets, I think, at the start important to clarify that a lot of the research is not necessarily always in fully people who are following a fully vegan diet or vegetarian diet that a lot of the evidence for benefit is in the general population. And so it may be important to distinguish as we go through, you know, whether we're talking about research looking specifically at people following vegan or vegetarian diets, compared, for example, to omnivores. But yeah, I think overall, that is the kind of the best steel man going forward with the kind of main point of emphasis tends to be well look EPA and DHA are not technically essential fatty acids in the way that ALA is because ALA can technically convert through but again, we'll work our way through all of those as we go.

DANNY LENNON: Yeah. And something that we'll probably revisit, but I want to kind of put out there to start with is what claim we're actually going to investigate or how we should frame this question. Because often online, one of the problems of people talking past each other is how this issue gets framed. I think something you and I have just discussed before we were recording here is that we have a situation where someone may say that well, what we want to ask is, is there such thing as a DHA deficiency? And if you can't provide evidence for that, then what are we talking about here? Whereas that's probably not the right question to ask. That seems like an unbelievably high threshold for requirement for evidence. And probably what the better question is, is there a health benefit to consuming direct source of DHA or

not? So in other words, sure, you can benefit your health through a dietary pattern, maybe that does not consume fish, let's say vegetarian, vegan or otherwise type of diet. But would you have an additional benefit from having a direct source of DHA leading to higher DHA status and that's something we want to probably define. And so that's the kind of question we're getting, is there an additional benefit to health through doing that. So that leads on naturally to the question of, well, when we say a higher DHA status, which is ultimately what we're maybe trying to do what do we mean by this, how are we going to define what an adequate level of DHA in the body is, where that's going to be found, how we're going to measure that and so on. So how would you go about discussing the issue of of DHA status?

ALAN FLANAGAN: Yeah, it's difficult because we don't have you know, reference ranges, for example that you can easily operate off. There's a kind of an evolutionary perspective on this, which I think should be part of the discussion even though, you know, it kind of doesn't lead us necessarily to any conclusion on what an optimal intake would be. But the human brain is by dry weight 60% fat, of which half of that is polyunsaturated fatty acids, essential polyunsaturated fatty acids. But of those essential polyunsaturated fatty acids, DHA comprises over 90% of omega-3 fatty acids in the human brain. Both EPA and ALA are low in brain tissue, they're less than 1% of total brain fatty acid composition. And there are some researchers in this area who have put forward some interesting theories about the role of this nutrient in the process of encephalization, or rapid brain growth and there are a number of kind of anthropological lines of evidence and otherwise that that do support a particular role for the polyunsaturated fats generally, in terms of human brain growth. So one example of that would be other mammals that have high levels of other polyunsaturated fats in their membrane, cell membranes, but that don't have a direct source of preformed DHA, don't have did not develop large brains. And then there's another which is particularly important for when we come to the conversation about conversion, which is that at some point, humans lost the full

activity of what is called a The delta-6 desaturase enzyme. And that's the enzyme that's responsible for converting ALA to EPA and then ultimately to DHA. And, of note, there is the word full activity, which is not semantic. It's possible that we do convert this and we will discuss the levels of conversion. But ultimately, we don't have that full activity such that ALA can completely translation to, you know, higher levels of EPA and DHA. So we have these kind of lines of evidence that very much point to quite an important role in terms of the content and the composition, and even mechanistic understanding of a number of the roles for DHA and central nervous system, cell membranes and that's a kind of, I guess, somewhat of a historical perspective. And then the question then becomes, okay, so this fatty acid appears to be important for the human brain and central nervous system, you know, what are sufficient levels of intake, and that's where things become slightly more complicated. And, generally speaking, there's a cross if we were to look at either the institutions of medicine, for example, or some of the European regulatory bodies, there's a general consistency of an adequate intake recommendation for combined EPA and DHA of around 250 milligrams a day. But there's a real lack of standardized definitions for this. So if we were to look at recommendations from these different, you know, kind of bodies, national or health regulatory bodies, we would see varied recommendations that could be represented in that milligram amount, or, for example, recommendations for two portions of oily fish per week or, for example, a range maybe up to 500 milligrams per day, as a recommendation. There in terms of we, you know, we can kind of get into the research for this in more detail in a while, but I'll just mention it now for pregnancy and lactation, the evidence for the need for direct DHA is quite overwhelming. And so there's very little debate, but in that life stage, it's a critical fatty acid for which a direct sources is required in terms of our current evidence. So there are some more specific recommendations for pregnancy and lactation. But overall, we don't have, you know, broad based recommendations, or certainly anything related to overseeing deficiency states,

because we don't have that evidence. And so if you look at, say, the National Institutes of Health in the States, they have a good kind of summary of this position that we'll elaborate on as we go through, which is that deficiency of essential fatty acids, which in this case is ALA or linoleic acid Omega-6 linoleic acid, we know causes deficiency states, and particularly related to skin. But we also know that, you know, plasma levels of DHA do decrease when an overt omega-3 ALA deficiency can be present, but there's no identified levels at which EPA or DHA and adequacy starts to impair some of these endpoints. Now, there's actually a point in there if we look at some of the early developmental research that's arguable in relation to that, but this definition is really quite important because what it highlights is the difference between defining sufficiency or defining status for a nutrient by reference to, you know, having just enough endogenous levels to prevent an overt deficiency manifesting in terms of visible signs and symptoms and impairing physiological function versus higher levels, compared to lower levels, improving outcomes or more of a given nutrients or increased status in the body being preferable to less. And those are the more both directly testable hypotheses versus as you mentioned earlier, just stating show me evidence for a DHA deficiency is not really a testable concept. It's not particularly falsifiable by reference to current evidence. Whereas if we think about this, as far as do higher levels, improve outcomes compared to lower or is more preferable to less, then we can start to actually piece together more of a picture. And as far as global prevalence if we just take our 250 milligram recommendation a day, give or take adequate intake, which is both EPA and DHA to clarify again, then, when we look at population wide biomarker studies, really less than 20% of the global population actually meet that need. So if we look at indicators of omega-3 status, the highest levels tend to consistently be shown in Scandinavia and Japan, Greenland, for example. But Europe and North America tend to have lower levels, on average, and some countries just are completely absent. And again, we can talk about the correlations with actual health outcomes. So what

is sufficient? As a sum we don't necessarily know for sure. But there's a general kind of recommended dietary intake of 250 milligrams per day, that's relatively consistent from one regulatory body to another. Is that optimal? Well, that's where we get into the question then of, you know, more being more preferable to less, potentially, and how we might go about thinking about that in terms of markers of intake or markers of levels in the body, you know, and then we get to the question, then of, you know, what is this process of conversion and can we actually just meet our needs with relatively exclusive ALA intake?

DANNY LENNON: Yeah, so we've quite a lot to work through there. There's two things that might be worth recapping for people, because I think they're particularly important for the rest of this discussion. But also, to recap, things you just said. One was, you mentioned around this. So uncertainty in terms of sufficiency of a dietary intake. We have recommendations from various organizations, that tend to be relatively consistent in terms of at least when it's given us food based terms of maybe a couple of servings of fish per week, or that could be this combined EPA plus DHA of 250 milligrams per day, as a figure that's given. Notably that says an adequate intake on AI. So again, showing this kind of, I suppose, lack of certainty we might have. And then beyond that, when you look a lot of those recommendations for people who are not consuming fish, or other marine sources of omega-3, that is something that's acknowledged, but there's not really much else that can be recommended, because we don't really know with any degree of certainty what to do. And so the second point that you also made, I think, is particularly important, and why we're addressing the question or framing the question, the way we are, is that again, this idea of looking for evidence of a DHA deficiency is probably not the right question. Because what we actually care about as well, for people who are not consuming direct source of DHA, if they did so and their DHA status was higher, would that confer a health benefit or not and that's probably the real kind of question we want to explore. And I think that sets us up nicely for looking at some ways to then investigate DHA

status within different compartments of the body if we're moving beyond say, dietary intake and one, I suppose marker that's important to spend some time on because this often will get brought up in the debate is around the omega-3 index. And I think there's maybe some, again, talking past one another or misinterpreting some of the uses of this particular marker. Do you want to maybe lay out some of the basics of what omega-3 index is for people who maybe haven't came across that? And then we can maybe from there start jumping into how this relates to our kind of broader question.

ALAN FLANAGAN: Yeah, so the omega-3 index was first proposed around 2004. And what it's characterizing and representing is the sum of DHA and EPA fatty acids that are present in red blood cell membranes, membrane phospholipids. So what's being measured is red blood cells, membrane phospholipid content of EPA and DHA and the omega-3 indexes expressed as a percentage of the total combination of those two fatty acids, relative to other fatty acids present. So you measure a sample, you've got 100, say percent of fatty acids in your sample. And so the omega-3 index will be represented as a percentage of that overall sample. And it's important to kind of clarify, and I know we kind of touched on this in a recording a recent episode with Dr. Austin Baraki in terms of markers, but you know, nutritional biomarkers are important to you know, have valid measure. Red blood cells are quite useful because they actually represent more stable and slightly longer term intake then measuring serum levels, for example. And, you know, for something like DHA, the turnover time in serum is two minutes. So red blood cells provides a reflection of dietary intake because red blood cells turn over every three months give or take red blood cell biomarkers are taken to represent give or take about that three month period of dietary intake. But they're fairly red blood cell content of EPA and DHA fairly stable to, you know, changes, small changes in kind of diet day to day. So they're a good representation of stable intake of EPA and DHA. And these are both very good biomarkers, because although technically, we can synthesize them endogenously,

we know that the conversion is relatively low. And we can use more sophisticated analytical techniques like stable isotope tracers to actually trace that effect. So people could say, oh, well, it's potentially confounded by ALA and take but actually, because of the metabolism that happens for those respective fatty acids, for DHA, it's not actually confounded to the level that people would argue in relation to that because the conversion is so low in the first instance. And because of the metabolism of ALA and EPA slightly different to DHA. And that latter point is quite important, because when it comes to the omega-3 index, DHA is the predominant omega-3 fatty acid that's being represented. Anytime you see a percentage score for the omega-3 index, it's primarily a reflection of the DHA content. It makes up the majority of the composite score in the omega-3 index. Now, again, that's not to say EPA doesn't have its own beneficial effects and important roles, which it does. But because we're focused on DHA today, it's important to note that EPA really is just a small component of the omega-3 index. And we don't really have data that seems to show that the protective effect related or associated with the omega-3 index is driven by the small fraction of EPA that's present. So it does point more to DHA for a number of reasons overall. And the omega-3 index is attractive because the method of the analytical procedure for determining has been standardized. So it's reproducible across studies in different populations. And in terms of those studies, we tend to consistently see that populations with less than about 4% of EPA and DHA as a percentage of total fatty acids present in red blood cell membrane phospholipids have worse outcomes if we compare them to populations with say over 8%. There is was a particularly large study that looked at overall omega-3 index across a range of populations. And again, you could see that this threshold of over 8%, was what was observed in populations in Scandinavia and Japan which as we mentioned earlier, have also the highest levels of dietary intake in relation to when we discuss, like, say, the adequate intake thresholds earlier. And the omega-3 index itself has been shown to be quite a robust predictor of

cardiovascular disease, myocardial infarction in particular. And it's not something like I said earlier, because this is important for its status as a biomarker. It's not something that's just easily altered by general habitual diet. And they've done studies for example, where they've looked at people over like a three month period, and they've looked at their, you know, the stability of their omega-3 index over time within that period and shown it to be quite constant. You can improve and increase the omega-3 index and that it can increase in a dose dependent manner with high dose direct sources of EPA and DHA. But what's interesting, and this again, points to some of the functional relevance of the balance of these fatty acids is studies that have looked at varying combinations of EPA and DHA, say 50%, 52%, EPA, 48%, DHA, this kind of thing, versus studies that have looked at maybe kind of 75% EPA and you know, 25% DHA these kinds of higher EPA doses and lower DHA formulations. Those higher EPA contents don't increase the omega-3 index to the same magnitude as one with the higher DHA content. And part of this is because omega-3 EPA has a much of kind of faster turnover time in red blood cells membranes, whereas DHA has a much slower turnover time overall. And so again when you look at, you know, what is actually driving more significant increases in the percentage, represented by the omega-3 index of red blood cell fatty acids, it's the higher DHA content in mixed formulation, supplemental formulations. And we know that interventions using alpha-linoleic acids, so ALA omega-3 rich supplements, for example, like flaxseed oil, don't increase the omega-3 index. Whereas if you use an algal, a micro algal or an algal oil based direct preformed source, you can increase the omega-3 levels, index levels and and that's been shown in any study that's used one of those kind of vegan vegetarian friendly so to speak, formulations of direct EPA and DHA. And again, it's really pointing at DHA being the primary driver of that increased index.

DANNY LENNON: Yeah, so we have a number of important things that are worth mentioning there. First, we have to acknowledge that this is a pretty good marker and we can use that in for

example, you reference with cardiovascular disease and we can say this is a good verified marker of that, that is mainly driven by the DHA content rather than EPA. And it's a really stable marker of DHA status, given that there's a slow turn over time of DHA. So it's quite reflective of kind of longer term, rather than just an acute change in intake due to the diet over a day or two. And so because of that, we have kind of more faith in this as a marker. And then in terms of actual levels, we can see that where we see differences may depend on what study we're looking at. But generally, if we're looking at let's say, cut offs that are well below 4%, versus ones that are well above 4%, that might be a nice way to kind of compare having higher or lower omega-3 index status. And so that then teases up for kind of a few follow on questions from that. First of all, the important question to ask as well, in people who are not consuming direct sources of DHA, do they actually have a significantly lower omega-3 index? If so, how much lower? Does that tend to be? Does that put them into these types of ranges that we would tend to correlate with poor health outcomes? And then if so, what do we maybe do about that? So if we're looking at the data in reference to omega-3 index that we're kind of using here as a way to assess DHA, but if we look at omega-3 index specifically and then some of the populations that don't consume that directly what do we know about where their levels end up being?

ALAN FLANAGAN: That's fairly consistent, irrespective of the populations studied thus and there is data from different populations that in the absence of direct sources of intake, or in the context of limited dietary sources of direct intake, then you do see lower overall levels of certainly bloods concentrations of both EPA and DHA, but also of the omega-3 index. And so we've seen that in vegetarians and vegans in continental Europe. We've seen it replicated in the UK, and we've seen it in U.S. research as well. So you tend to see yes, either just lower levels of EPA and DHA. And that's really also irrespective I mentioned blood EPA and DHA levels, but it's also kind of almost irrespective of the tissue compartments itself that is measured. Now, in relation to use of the omega-

3 fatty acids index itself, you know that there's been research, for example, a US study Sartor and colleagues, which looked at the omega-3 index status of people following a vegan diet, specifically a vegan diet, and, you know, looked at their baseline levels, and then also then did an intervention to see if they would respond to a supplemental form of them, of EPA and DHA direct source. And if the baseline omega-3 index status was 3.7, the average was 3.7. Interestingly, this was also consistent. This was around the same threshold as omnivores. So it's not that there's some source of unique added, you know, shall we say risk, for want of a better term of low omega-3 index or just low EPA and DHA level.? It's entirely possible that someone on an omnivorous diet consumes a diet without any direct sources of these fatty acids as well. And again, like we said, when we were discussing the omega-3 index that is very common in populations in North America, and in Western Europe, versus Scandinavia, where people might have omega-3 levels index levels of less than 4% or 5%. So it's not necessarily just exclusive to vegans, vegetarians is a consideration. But lacking a direct dietary source independent of the wider diet composition would obviously be associated with these lower levels. But as an overall summation of this evidence, then where the question is, you know, what is the DHA status of people not consuming fish or following vegan or vegetarian diet a vegetarian diet that excludes fish are they lower in DHA? And the answer is, unequivocally yes. And so that obviously leads us on then to well, is that low DHA potentially associated with an adverse kind of risk over the long term? Or is it something that they even need to worry about in the first place, because they consume in a healthy plant based diet, a lot of direct alpha linoleic acid intake or omega-3 ALA intake. So the question then is, is that just sufficient?

DANNY LENNON: Yeah, and so we could certainly investigate that one initial layer of investigating that, and you actually touched on it previously, was when you mentioned that we have some of these intervention trials that have used say flaxseed oil and you actually don't see any change in omega-3 index with that

supplementation whereas we have other trials that when you give people who don't typically consume fish, I believe in like vegan populations, you give them a direct DHA supplement, you tend to see significant increase in omega-3 index. So there's one particular study where I think it was a gram a day for eight weeks, and you tend to see, like the majority, I think 70% plus get an omega-3 index above 8%, which is very high relative to what we're talking about here. So I think we see differences first of all, when you have this direct supplementation versus maybe flax seed supplementation, but then that does indeed doesn't cover everything in relation to ALA sources. And I think this is where a lot of the conversation hinges as you outline of, can an appropriate intake of ALA from various foods, whether that's chia or flax, or walnuts, etc, be sufficient to give an appropriate amount of DHA within the body after conversion within the body? And is that possible to support it? And this also ties in one of the initial issues that you raised at the very start around conversion. So there's a lot to kind of work through on this question of, can we have an ALA intake that is sufficient that we don't need to worry about DHA directly at all. So to start working through this, I suppose the natural point is to look at these conversion rates, because as we said, quite commonly, people will point out well, there's quite a poor conversion of ALA down into these other long chain omega-3 fatty acids. With something like EPA, there's varying figures that we might go through, but it's kind of relatively low, probably 10% or less. And then with DHA, the picture looks even more bleak. So before we get into that, is there anything else we need to frame before we start working through the ALA literature, do you think?

ALAN FLANAGAN: Not generally speaking, I think we you know, we've highlighted that kind of average conversion is minimal, and also potentially important. There's sex differences in conversion as well. Women do appear to convert significantly more ALA to EPA and more DHA, but in men, that conversion to DHA is less than 1%. So that, you know, these are important, potentially important sex differences in regard to that. But ultimately, the overall net conversion to

DHA specifically is in that range of kind of, you know, 1-ish percent.

DANNY LENNON: Yeah, and those figures like you would already mentioned, we have kind of stable isotope tracers that would kind of support those as well. And that we see, if we're looking at the high range like this 9% conversion to DHA would be occurring in female populations. And then for men in some of these studies is basically non existent. So with that, if we are getting this question of, okay, we're not getting really in some people at least any real conversion to DHA, then one of the counter points might be, well, how do we know this is even problematic? How do we know that what is currently there is just not enough for us to deal with. And one particular point that I've seen brought up is, we know that there might actually be a better conversion rate in infants, for example. And so you can maybe make a kind of a hypothetical reasoning there for that, well, we actually have this ability to convert more DHA when we need it in that stage of life but maybe we just don't need it as an adult. And so that's why the conversion is pretty poor. How do we start kind of piecing through that what lines of evidence might be useful in uncovering some of this?

ALAN FLANAGAN: Yeah, I do think that is an interesting point. And there's also this suggestion of one reason we may not see necessarily a benefit to because there is evidence that if you have low baseline levels, that there can be an enhanced conversion, you get greater conversion, and people that have low baseline levels, and one of Penny Kris-Etherton's [ph] group studies had showed that in relation to dose responses, and now that was using direct kind of EPA, DHA, in response to or on the omega-3 index, looking at omega-3 index responses, and yet people that low baseline levels have had a kind of greater magnitude of response. So there is that argument plays into it, do we just have sufficient levels, and is a reason that you don't see a benefit in conversion in some of these trials that actually, once people have sufficient levels of EPA and DHA, there's this concept of reverse inhibition. So you just don't see the conversion of Ala. So that there's a couple of studies

that can kind of illustrate this. The first is, as we've said, if you look at interventions that feed flax or another ALA rich omega-3 plant source, you tend to see significant increases in the conversion of ALA to EPA, and you do see increases in EPA levels from that ALA intake, but you don't see that in relation to DHA. And there's a 2018 intervention that kind of more directly took on this idea of potentially reverse inhibition, i.e. if people just already have adequate levels of EPA and DHA, then it's going to be difficult to see an effect of Ala. So this intervention took people with as a deliberate kind of inclusion criteria low EPA and DHA status, gave them 14 grams of supplemental linseed oil, and was looking at conversion of ALA to EPA and DHA. And while the concentrations of both ALA and EPA increased significantly in red blood cell phospholipids, that was over 12 weeks. But what was really interesting about this study was that the concentration of DHA decreased significantly in response to the high ALA intake. And this has also been shown previously in a range of kind of up to 1.5 grams a day of ALA that DHA declines in plasma and red blood cell membrane phospholipids by around 7%. So the magnitude of decrease in this 2018 intervention was greater, and it was Groupner and colleagues. And this is potentially important when we consider that the omega-3 index itself is looking at red blood cell fatty acid composition, when we consider that the primary kind of reflection of an omega-3 index is reflecting DHA status of those cell membranes. And that, you know, compared to higher versus lower levels of the omega-3 index we tend to see better outcomes with higher levels. So this decrease could potentially be interesting in terms of what's going on now. It's important to clarify that the majority of studies don't necessarily show a decrease in red blood cell DHA status from high levels of ALA intake, but the overall data clearly shows that neither ALA and/or EPA supplementation directly. Neither ALA or EPA is effective at increasing specifically DHA levels. So this is important because it's not just that we're saying ALA doesn't really convert, we're saying direct supplementation of EPA also doesn't really have any appreciable effect of increasing DHA

levels notwithstanding, it's closer to DHA in the kind of steps of conversion and there was also, you know, the the Philip Calder review, which basically looked at DPA levels as well, which is an intermediate between EPA and DHA. And again, we see no real increase from these various supplemental interventions in terms of DHA content. So really the total body of research that we have from various food based interventions at varying doses of direct sources of alpha-linoleic acid, so omega-3, ALA and also of EPA directly, don't appear to have any effect on DHA levels in a range of for ALA to up to 15 grams a day. So DHA levels in the body appear really to be only responsive to direct pre-forms, exogenous sources of DHA, whether diet or supplements.

DANNY LENNON: Yeah. And that literature is extremely consistent. I think even that review paper from Calder's group that mentioned, and for people who may be may or may not have heard that name before one of the kingpins of omega-3 research, generally, his group in Southampton and that paper, which will link to Ella Baker, I think was the lead author on that, that summed up over 50 studies, and basically, the exact same pattern is playing out of, you don't get any real appreciable change in DHA. And so now that we're at that point, we've kind of gone through a chain of things of looking at okay, DHA and omega-3 index may be important here, that there seems to be this really poor ability for us to be able to increase that with any real meaningful effect from supplementation or dietary sources of Ala, or even EPA and then the question becomes, okay, well, what about actual health outcomes when we're looking at endpoints of does this actually matter for health because that's the kind of next objection that would make sense of, okay this all sounds good. But where do we have evidence that this is actually causing health issues and this is quite a tricky question that takes a bit to work through and I think one of the things that you've made clear on a number of occasions so far is that we probably need to consider the kind of risk profile here maybe differently across different stages of life and there's different considerations, but there's also different bodies of literature, which may be relevant. One, that's probably the easiest entry

into this, because I think this is where you get most agreement is in, say, pregnancy, or the early kind of life stage where, unless someone is at a very extreme position, I think nearly everyone that's kind of discussing this issue is relatively on the same board in terms of a direct DHA source is probably a good idea and should be recommended, say during pregnancy. So if we take that area, first of all, what are the kind of main things that we need to note from the literature in that kind of developmental period and early life stage?

ALAN FLANAGAN: Yeah, I mean, it's, it's it's very kind of unequivocal in this in this life stage. So from about 20 to 24 weeks gestation, when we get into the third trimester, there's this period that kind of extends to the first two years of infancy known as the kind of the infant brain growth spurt. And what that's describing, obviously, is a crucial developmental period. But it's from the perspective of these fatty acids characterized by the rapid incorporation of both DHA and arachidonic acids, AA into brain and central nervous system membranes. Now, it appears when you look at this research that arachidonic acid levels in the body are maintained relatively constant, and they don't change too much in response to dietary intake and breast milk holds a content again, fairly constant. But in fact, variations in dietary DHA intake as we might expect from what we've just talked about, in terms of responsiveness of DHA in the body to external intake of other fatty acids or indeed to direct sources is observed in breast milk, for example. So we know that can be responsive to diet as well. Preformed DHA is preferentially incorporated with greater efficiency, and it's quite rapid in this period. There's evidence from a number of different kind of lines in this life stage. There is evidence in preterm infants, for example, actually the kind of the benefits to these fatty acids and it's important to stress that arachidonic acid gets a bit of a bad rep because it's an Omega-6 and all of that kind of jazz is crucial in this life stage as well. And indeed, the ratio of DHA to a in this life stage appears to be particularly important and a kind of one to one ratio appears to be optimal for these cognitive outcomes. But like I said, the difference here is that AA is

maintained relatively constant endogenously, whereas DHA levels are going to be responsive to exogenous dietary intake whether from diet itself or from supplementation. So in preterm infants, it's crucial that they have both adequate events of DHA and AA, particularly to attain full kind of consistency with growth curve trajectories again, because preterm infants are like underweight so to like meet those targets, this is quite important that they have the requisite intake of DHA and AA. Visual acuity appears to be one outcome in particular that is enhanced in terms of preterm infants with DHA and AA supplementation. And then there's evidence of benefit to omega-3 supplementation, both maternally and then in terms of fish consumption, and child's cognitive developmental outcomes whether that's examined at a one year, or even at five years of age. There is a kind of potential chicken and egg scenario when it comes to omega-3 fatty acids and pregnancy, which is that the higher omega-3 levels are associated and actually, indeed, more than associated, there are interventions, confirming this with gestational age. And so they prevent preterm delivery in and of themselves having higher levels of omega-3 fatty acids. And of course, gestational age is possibly the strongest predictor of kind of good developmental outcomes in offspring. But what's interesting is this is and studies that have looked at umbilical cord DHA stores, rather than breast milk DHA, have shown that that was associated with increased cognition when measured at 11 months, and that was in full term infants. So they're possibly getting the benefit of higher levels of DHA associated with greater gestational age in the first place, that's just a benefit. And then there's also the potential for a kind of additive effects of you know, the higher levels of DHA in that life stage because of the central role for it in the developmental nervous system and brain. This has been caught up with over time for quite a while infant formulas, for example, were not always supplemented with direct forms of DHA. So this kind of life stages is an area where you know, the data is quite unequivocal for the importance of a direct source of DHA for

pregnancy related health outcomes and particularly for infants cognitive development.

DANNY LENNON: Yeah, and I suppose the only other thing is something we touched on a moment ago is that we have at least some trials that people may come across where you have this kind of increased ALA intake usually through some type of formula, where you see actual, at least appreciable increases in DHA, but this tends to be in infants. So I think most of the studies would have young infants of maybe less than 12 months. And then you have other studies in children, adolescents, so from 6 to 17. And again, with a kind of a stepwise increase in Ala, you don't really see any change in DHA. So maybe there's some sort of kind of crucial time window early on where we've some better ability to do that. But again, that might be just suggestive at the moment or something to kind of ponder. I don't know if it really tells us much else.

ALAN FLANAGAN: Well, that's the thing because even if there is some enhanced ability in infants, in that, you know, less than one year olds age, to convert Ala, for example, or to increase DHA in response to ALA consumption, the total body of evidence still clearly shows that either higher levels of maternal DHA status and/or with infants through after term, like through the first six months of lactation in particular, still associated with better outcomes, compared to lower. So the question then would be well, is that small increase in the concentration sufficient? And again, pretty much the entire body of evidence would say that more is better than less in this life stage rather than just saying that, oh, well, we have this increase conversion, and that would probably cover needs, because we don't really have that outcome based evidence. Just the evidence really of the small increase in plasma DHA that would occur with some ALA in kids that are, you know, less than 12 months old.

DANNY LENNON: Yeah. And with that population, you've obviously mentioned neurocognitive development as being one of those kind of key areas, we look up because of DHA's role in the brain. And then that also kind of maps onto when we start looking at

populations at the other end of the spectrum when we look at in later in life, and in older adults. This is, of course, a big area of research as well of looking at some of these long chain omega-3 fatty acids and DHA in particular of its potential role there in cognition and there's a variety of different markers we can maybe look at, and different outcomes. So overall, do we see a relatively similar picture in terms of consistency across this type of population? What would you say is the the main kind of themes we tend to see from the work done in older adults?

ALAN FLANAGAN: Yeah, older adults is definitely more challenging to tease out. And again, it might relate to a number of factors that we've discussed before, particularly when it relates to intervention studies. Factors like the baseline nutritional status of participants, diet leading up to that point, the life stage, or sorry, the natural history, the stage and the natural history of the disease in terms of when an intervention is started, particularly as it relates to neurocognitive outcomes. And there's kind of maybe two levels to think about. This as always, we could think of the epidemiology in terms of diet and neuro cognitive outcomes and Dementia and Alzheimer's disease specifically. And that is consistent in terms of both analysis of dietary intake, and then analysis that may look at some biomarkers in terms of generally what we see is an association between these fatty acids, and lower risk of, for example, Dementia and Alzheimer's disease. And interestingly, in these analyses, you see those associations when the analysis is examining and kind of honing in on fatty acids, you see it strongest for DHA, and you don't tend to see associations for Ala. Now when we kind of step out of that research and get into more of the intervention studies, that's where it becomes a lot less consistent, so to speak, than some of what we were just talking about in relation to kind of child cognitive developmental outcomes. And this is where we see interventions that have used both EPA and DHA, some of them have used just DHA. And one of the challenges here is because we're talking about the brain, essentially as an outcome, it can be again difficult to measure or difficult to get like what exactly is being measured and

what are we reflecting as far as long term intake and one of the one of the key aspects of the DHA interventions is that many of them are less than two years. And the reason that might have an interaction with the dose that's used, so we could be talking about a dose by duration of exposure being relevant for the outcomes is because the DHA turnover time in the brain is two and a half years. So brain, daily turnover of DHA is about four milligrams a day. And so that's a long turnover time, compared to as we said earlier, plasma DHA turns over in a matter of minutes. So it may be that actually what's required for more optimal or better outcomes from a neurocognitive perspective over the lifespan is long term and consistent intake. There was a kind of intervention a few years ago that looked at the combination of 500 milligrams DHA and 200 milligrams EPA, and that did run over two years, and it was an otherwise healthy adults Dangar and Alan Dangar [ph] was the lead author on that paper, and, but didn't find an effect on cognitive function. And then a number of more recent studies found that 800 milligrams, and 900 milligrams respectively there's two different studies that looked at those two respective doses did improve outcomes like verbal fluency, for example. One was in that 800 milligram DHA dose Johnson and colleagues was in otherwise healthy older women, and also had a combination with lutein, which is a carotenoid, which was associated with improved learning and memory. And then older adults with age related cognitive impairments. So mild cognitive impairment, MCI but not with Dementia 900 milligrams a day did benefit over a 24 week intervention. So some of the inconsistencies may relate to DHA itself being under-dosed, and they may also relate to the duration of exposure if we're using lower doses, these interventions that have used higher doses have typically been shorter. So again suggests that if there is an effect, that it may be present at these higher doses. But the other point to clarify that's quite important is the interventions that have looked specifically at participants already with dementia and Alzheimer's disease don't really show that the progression of the disease will be attenuated by DHA supplementation. But I don't think that's necessarily

an argument against DHA, because there isn't a drug that's going to prevent that either. We know that, you know, 99%, there hasn't been a pharmaceutical agent approved for Dementia and Alzheimer's since 2004. And none of them are really effective at preventing decline. So from a neurocognitive perspective, whether we're talking about nutrients or drugs, the body of evidence seems to suggest that once at the stage of Dementia and Alzheimer's, there's no real road back. So we're interested in obviously prevention, particularly at the stage of mild cognitive impairment, or early age related cognitive decline. And some of the more recent evidence do suggest a benefit at higher doses. But there is more of an inconsistency in the evidence base for the later life stage and cognitive function in older adults, but does leave us you know, with a couple of questions that would relate to how we might think about otherwise healthy, say, middle aged adults, and particularly as it relates to this conversation of whether someone not consuming oily fish or a direct source of DHA, you know, would they be served actually doing so well before, you know, age related cognitive decline sets in.

DANNY LENNON: Yeah, and I suppose that kind of brings us to trying to pull all this together into some degree of coherent conclusion based on that original question that we framed, and particularly in the context of people that are, let's say, adults who are currently healthy and would it be benefiting to their health to consume a direct source of DHA if they currently don't do so. And we've looked at how that can impact things like the omega-3 index, I think, for example, you already referenced the Sarter paper where they essentially showed that within that you have vegans that they looked at had an omega-3 index below 4%, that was 64% of the vegans they looked at and then 27%, they looked at had one less than 3%. And then we've already tried to get a gauge of well, what would be a “optimal” or at least a better omega-3 index in terms of outcomes. But there's a real difficulty in trying to translate some of this into health outcomes, which I think is where much of the debate kind of is still up in the air and why there is a difference of opinions when people are trying to interpret

this because we're trying to translate this into changes in health outcomes in the end in adults. And so, with that, and kind of everything we've said, if we start trying to wrap this up, how do we go about answering that question of for people who do not currently consume a direct source of DHA, and again, this could be across a number of populations, it often gets discussed in terms of vegans and vegetarians. But as you mentioned, this could be someone eating a typical diet, they just don't consume the recommended intakes of these sources, which is a significant percent of the population which is why if you were to look at the omega-3 index of those two groups would probably be very similar. For anyone in that situation, is there a health benefit to getting a direct DHA source and then obviously, for a population like vegetarian or vegan that would mean supplementing with something like an algae supplement. So if we haven't kind of covered off any areas of those three things we need to, we can maybe do that now or fill in the gaps. But otherwise, we can kind of maybe start pushing this in towards what are the main key take home points that you see are most befitting for people?

ALAN FLANAGAN: Yeah, so in relation certainly to kind of vegan or vegetarian populations as far as interventions go it's important to state that most of the evidence to-date has looked at changes in DHA status rather than health outcomes. Right. So we don't have good even prospective data because the cohorts that contain vegan and vegetarian or certainly vegan populations within the cohorts, the Adventist Health Study too possibly has the longest has been people who have identified as following a vegan diet for the longest period, I think 21 years is the longest in that. But it for interventions, again, it's usually changes in DHA status that are an outcome rather than health outcomes specifically. So when we're trying to parse this together, a lot of what we're saying as far as evidence for benefit is not necessarily in a vegan population for example or a vegetarian population. We're talking about people just with low levels of these fatty acids, which, as you mentioned correctly, is possible in any sort of dietary pattern if you're just not consuming direct preformed sources

through either diet or supplements. I think that's important because there's a burden of proof issue in a way almost so to speak, because to kind of argue that there would be no reason why a direct source would be required even kind of in a prophylactic sense, is to say that there is some reason why all of that literature would not apply in this context. And so, like you said, we have evidence that while direct sources of ALA are good. Generally, absolutely. There's the evidence on ALA at a population level, food rich sources of Ala, we talk about oils and nuts in there, you know, yes, they are rich and ALA but they have a range of other compounds that are also beneficial polyphenols, fiber, other unsaturated fat subtypes and all of this kind of stuff, other beneficial fatty acids like Omega-9 oleic acid. So they're really, you know, this is not a knock on any sort of ALA rich foods at all, as part of really, you know, a healthy dietary pattern. But what we're talking about is, are they sufficient for increasing DHA levels? We categorically know that. So it appears that increasing DHA levels in the body are only really achieved by direct preformed sources of DHA. The second question then is, well, if they don't increase DHA levels, do we need to bother increasing DHA levels. This is kind of range of health outcomes. And then that would lead us to the evidence for well, if we look at populations, and indeed interventions, does it suggest that more or less is preferable or is it equivocal, and whether we're using the omega-3 index, or other tissue biomarker studies, multiple lines of evidence would point to some DHA being preferable to none, and certainly more being preferable to less, particularly for the omega-3 index, which is, like we said before, largely driven by omega-3 status, that increase, you know, of the percentage comparing to low percentages. When we see that prospectively, although that is in the general population, not necessarily people consuming a specific diet, well then what someone would have to argue and provide evidence for is, there's an exception here being made such that these people with an omega-3 index, for example, of less than 4%, or 3%, that that research is not applicable to them. And I, in kind of, you know, the wider reading, you know, preparing for this

can't really find anything that would suggest why that would be the case over the long term.

DANNY LENNON: Yeah. And I suppose that kind of brings into more meta level of when we're trying to make evidence based decisions when we have a clear case here, where yeah, there are some interesting questions or some gray areas or some answers we would ideally like to have. But in lieu of those, we still have to kind of make some type of recommendation here, or make even personal decisions. And in that, I don't think it, I think it's a mistake to think being evidence based is requiring a absurd level of evidence, which seems to be the case sometimes. So this idea of I demand proof that there is evidence for DHA deficiency, if that is the request that seems not only unreasonable, but it seems to be one that is probably not really driven by direct interest in a scientific question, but more by an actual bias or something that can't be met. So I think when we do have this, in lieu of better evidence, we can then make a decision based on what what do we know and then hopefully, the kind of case that has been laid out here would say, well, we do have some things that would probably lead us towards this being a good idea, or at least, it shouldn't be something dismissed because there's not this mythical level of evidence that has not been met. So at least that's what it seems to me like it's sometimes it can be a strange request for evidence that's being asked for.

ALAN FLANAGAN: Right, which is, I think a lot of that comes from a kind of a motivated reasoning standpoints to come to a conclusion that there are open questions here. Absolutely. One study and I thought this was quite a bold claim. It was a small study in Dutch vegans and they were looking at supplemental gamma linoleic acid or ALA itself, alone or in combination looking at EPA and DHA in multiple tissue compartments, and there was again, there was no change but the author's conclusion and in their discussion, what they basically went on to claim was that, well, we saw no change in DHA status. But actually that probably means any additional DHA is what they called 'a functionally irrelevant

surplus.' That's, well that's again, relative to the wider evidence, that's a pretty wild claim. Because this wasn't a long term study looking at health outcomes. It was looking at, you know, responsiveness to DHA. So to claim on the basis of we don't really see this conversion from Ala. So actually, whatever DHA is here is sufficient in anything more as a functionally irrelevant surplus is a bold claim to make. And so this comes back to, well let's kind of extrapolate all of this research out maybe over a lifespan. We know that there is a particular role for DHA in the developmental period from the third trimester through the first kind of certainly two years of life. We know that higher versus lower, more versus less in that life stage both maternal intake, either through diet or supplement, and then through early infancy, is preferable, the evidence pointing to a benefit, and more being preferable to us. And then we get to the later life stage, like we've just discussed and you know, although the evidence has been inconsistent, potentially reflects either under dosing or or if it's a lower dose, not a sufficient duration, certainly to have cognitive benefits, given the two and a half year turnover time of DHA in the brain. But we could see more evidence for benefit in recent interventions, particularly in older adults, with some evidence of either age related early cognitive decline, or even just otherwise healthy, but older adults in their kind of 70s. So then the question becomes, well, what happens between these two life stages where DHA appears to be important, and I see people making an argument that well, and this this comes up a lot in nutrition, well show me evidence that this benefits healthy people. Well, again, that's not the right question to ask in relation to nutrient exposures because the question, nutrients exist on a bell curve of action from insufficiency to adequacy to access, like we've discussed before. So the question is, would deliberate exclusion of any nutrients add up over time to worse health outcomes compared to someone with adequate levels of that intake. We see that more clearly with water soluble vitamins because deficiencies for those appear much more rapidly. For fatty acids and fats, generally, it's an even fat soluble vitamins, it's

a little more with the exception of vitamin D, it's a little harder sometimes to see these because they're tightly correlated to total energy intake. And, you know, really, for someone consuming over about 7% of their calories from fat, they'll have absorption of fat soluble vitamins. So those types of deficiencies tend to only manifest really with severe malnutrition that you'd see in the developing world. So I don't think that's the right question to ask as we've kind of repeated over the course of this episode. And I don't think the right question to ask is, well there's no evidence of benefit and otherwise healthy people because, again, when you're looking at otherwise healthy people, they do tend to have sufficient levels as far as we know what sufficiency is as a minimum with diet. When we do look, and try and stratify people by levels of intake, whether using biomarker compartments or the omega-3 index itself, then in populations without disease, where we're investigating the exposure before disease, then it also quite kind of clearly shows that again, more preferable to less some preferable to none. So I think that question can be an obfuscation. And when we weave in what limited evidence we have to date of the omega-3 status of people not consuming direct sources of DHA, the most kind of prudence, conclusion, and again, kind of, you know, bearing in mind that when the evidence for any question is incomplete certainly from a public health perspective I think the precautionary principle has to apply to a degree. The question then is, why would these populations be exempt from this wider research? Why would people with low levels of omega-3, low levels of DHA specifically low levels of an omega-3 index, why would this research not apply to them. And I think that weighing all of this up again, a direct source would arguably be beneficial compared to none. And so just as a hypothesis, if we took two people following a vegan diet at the age of 30, and they're both following relatively the same healthy dietary pattern, one consumes the direct source of DHA one doesn't who would have better outcomes, you know, 20 years later. Right now, I would be willing to direct my hypothesis towards the person consuming that direct source willing to

be proven wrong on that point. But that's where I would and we don't have that evidence right now.

DANNY LENNON: Right. I think that's the crux of it. Right? It's saying that, okay, we can't say that someone 100% has a need to consume direct source of DHA that we can be 100% certain about, that's not necessarily the claim being made. Like you said, it's in terms of giving pragmatic recommendations what is an appropriate conclusion, given the evidence we do have and even as you frame it, I think that's the way we have to look at it is most probable, to say it's a prudent idea to consume a direct source of DHA based on what we know, that's not saying, we definitely know the answers question. And everyone 100% needs to consume a direct source of DHA. But it's also saying it's probably misguided to look at the shortcomings in the current evidence and say, well, that means I don't need to worry about this at all. This is not of concern. That's probably not the right conclusion to draw from the lack of the level of evidence we would like. Probably the better way to go is well, for now, based on that precaution principle, it's probably prudent to get a direct source of DHA, if that means your food choices don't allow it, then getting some supplemental form is probably a good idea. But if we work out later, that's not necessarily fine. But it seems just like an unnecessary risk to go the complete opposite and say, well, because I don't have the level of evidence I'm looking for that means it is of no concern to me. It just seems like you're towing a line of a risk based on some of the data we have in other areas. Right?

ALAN FLANAGAN: Yeah, a way of framing this would be okay, so we have all of this, these various strands of evidence, different life stages, and otherwise for a benefit to DHA. We know the ALA does not cover bases, so to speak for DHA in terms of either increasing levels. The question then is, are those levels if they're low, and ALA isn't appreciably increasing DHA is that level of DHA as it is fine as it is and the wider evidence just again, would point to, well, if we compare that low level, versus a higher level, or the higher level has more favorable outcomes. So until someone is able, it's, someone can't ask

for evidence of benefit to you know, for, like, you know, that kind of prove the negative please, without also being in a position to show strongly that low level is sufficient, and we equally don't know that. So you know, on the balance of those two competing, you know, we can't really say for certain that this is absolutely required, you know, maybe after infancy if you've got enough, you kind of outlast you for your life, so to speak. And then you need more when you're older and kind of getting starting to forget words. But you if you're going to hold that line that oh, because of the absence of evidence, overall, we don't need it, then you equally have to be able to hopefully show that whatever levels exist in the absence of any direct source of intake are fine and that can't be shown either. So those cancel each other, those kinds of please prove a negative both cancel each other out.

DANNY LENNON: Yeah, I think that kind of rounds us out unless we've forgotten to mention anything. But I think that's a pretty good way to kind of conclude some of these points unless there's something we have missed and you would like to get in before the end.

ALAN FLANAGAN: One thing that has come up, and I've had this conversation with people following fully plant based diets and is well, you know, it's a bit there's a kind of privileged aspect to this because we're saying that people have to supplement but being vegan is a privilege. So I don't see how that's like a push back on the need to cover this basis. Like you know, there's no one in poverty is vegan. That's not being snide at all. You know, it's like the demographics of you know, vegan diets are generally speaking, people who are of means. So I don't know that the economic consideration applies here in the first place because most people are able to cover that base.

DANNY LENNON: Yeah. And even physiologically, it's kind of irrelevant. Right? That would be a separate issue that we could then tackle. Tight? If we did workout that it was a problem. But we couldn't then deny a physiological fact, well, then we could say, well, something needs to be done here on some sort of

public health level to allow those people to get access to it, but doesn't change the physiological fact.

ALAN FLANAGAN: Yeah food fortification or otherwise yeah.

DANNY LENNON: I don't think that's a basis for saying yeah, we can't put forth those ideas around DHA. And this coincides perfectly with the new release of the Sigma Nutrition Microalgal oil that we're rolling out this week. So joke if anyone's thinking this is not the shill for new, no, that was a joke.

ALAN FLANAGAN: Yeah, we we put together a machine learning algorithm which points this app.

DANNY LENNON: We're just going to talk about things. We want to sell from now on.

ALAN FLANAGAN: Yeah, through this app, you can buy our micro-algal vegan DHA. Yeah, yeah. Cashing in. But overall, I just think for now, leaning towards direct source being better than no direct source.

DANNY LENNON: Great. Thank you everyone for listening. We're going to put the show notes this episode up at sigmanutrition.com/episode418, I believe. And so there, I will link up to as many of the things that we've mentioned throughout this episode as possible, as well as. So maybe additional notes might put some definitions in there might be useful to go through as you are replaying this episode or maybe going back over and revising some of the materials. So that will be at sigmanutrition.com/episode418. As usual, if you liked this episode, then please share it with someone else you think might also like if this is the type of topic or conversation that would like then send that across to them. Hopefully they will appreciate it. And I know we will as well. And as well with any questions or comments or shares on social media or any that type of stuff we are of course, very grateful. And I think that pretty much does us. Right?

ALAN FLANAGAN: That is it.

DANNY LENNON: Right. That is us for this week. We will be back in another e p i s o d