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Discussion

J. Keeton: I noticed that some of these omega three's will present fishy flavors in meat products. Do you know what levels actually cause the fishy flavors that sometimes develop?

P. Addis: That's a very good question and unfortunately the answer to that is an extremely small amount of omega-3 oxidation will produce off-flavors or odors. Work done at the University of Massachusetts by Herb Hultin presented at last fall's American Chemical Society meeting indicated that fish will develop a fishy flavor due to rancidity of these fats, even in extremely small quantities — that is, not enough to see a decline in nutritional value. You cannot measure a loss in omega-3 content. It's just that there is enough hydroperoxide formed that it smells and tastes fishy. It's a really difficult technical accomplishment to prevent the rancidity but not an impossible one.

Keeton: So is it the hydroperoxide?

Addis: In this type of fishiness, yes. There's another type of fishiness that is related to trimethylamine oxide conversion into trimethylamine. That's not really related to this at all because trimethylamine production results from bacterial reduction of trimethylamine oxide.

F. McKeith: Paul, is there any advantage to using alternate sources of omega threes? Are you looking at full fat soybeans? You're going to have omega sixes as well as omega threes. Will that have a negative effect when people consume pork or other meat products as well?

Addis: You mean in terms of platelet function?

McKeith: If you wanted to boost the level of omega threes in meat products, could one use something like a full fat soybean where you will get some elevation?

Addis: You would get some. There is already so much omega six there and any omega three that you put in the product will materially alter that ratio. But whether or not the person would get the health benefits, that's something that still needs to be figured out. John, you've done some work with some flaxseed, which is probably the best of all the oils for linolenic acid content. That's another oil where you have a

much better ratio of omega three to omega six.

Mustafa: You mentioned that the structure is very important in omega three. I would like to know if it would be possible to synthesize omega 3 by encouraging bond migration to get a double bond between the carbon atoms. Would that be physiologically important? For instance, catalysts are used to hydrogenate oils and these also encourage bond migration. I was thinking you can use soybean oils which have a little bit of linoleic acid or some other form of vegetable oils, you can encourage the bond migration and you can probably by manipulation get some of bonds up to that level.

Addis: If you can reproduce the same structure, I'm sure it would be useful. I would say more power to you; I'm not a hydrogenation chemist. I know of no such method currently available.

R. Benedict: You've mentioned that you have a decrease in thromboxanes and leukotrienes. Is this due to inhibition of specific enzymes and has anyone done any enzyme inhibition studies with it?

I have a second question: On fish, would the normal practice of washing with lemon juice decrease the extent of oxidation because of citric acid and ascorbic acid that you might have?

Addis: I'll take them in reverse order. It could be. Certainly we have shown in the herring, although I didn't present the data, that chelating iron does help to retard rancidity. The herring actually has a fairly high iron content. Now a lot of fish are a lot lower in iron so this may not be as effective.

With respect to how decreases in thromboxane and leukotrienes occur, it is partly because omega-6 and omega-3 fatty acids compete for the same elongase and desaturate enzymes; EPA and arachidonate compete for the same cyclooxygenase so that less thromboxane A_2 is formed. By having a high omega-3/omega-6 ratio, you favor the formation of the three series which are either more active in terms of prostacyclins or less active in terms of thromboxane activities or a combination of those. I didn't go into all the details but my manuscript will include some key references. It is a highly complicated biochemical sequence but I think the net effects are very well established.

W. Means: The omega-3s and some of these other fish oils, as you mentioned, are pretty subject to oxidation and if oxidation of fatty acids and cholesterol products are indeed causing initial injury, is it kind of a trade-off? And is there a difference between the fish we consume here in U.S. vs some of the other populations that maybe contain fresher fish that maybe aren't oxidized as much?

Addis: I think nowadays there's so much fish traded all around the world that rancidity differences probably won't be necessarily very large. As far as your first question, you're certainly correct. I have real concerns about that because we have analyzed in our lab a few of the fish oil preparations when they were first commercially available on a large scale and they had very high levels of lipid oxidation products. You can imagine what happens to the long chain omega-3 fatty acids: they are the most susceptible to oxidation. Some problems are: A reduction in the levels of EPA and DHA because they're the first two to oxidize; formation of peroxides which have all of the detrimental effects on atherosclerosis summarized earlier; and you also have the flavor problem. A lot of people who took these capsules complained of regurgitation of some unusual flavor and odors. And so those were all valid problems. I think with good quality control and manufacturing methods, there are some good quality oils now available. Another important factor is that a person should consume much higher levels of vitamin E in their diet because in the body in-vivo oxidation can be accelerated by polyunsaturates.

R. Miles: Do we know exactly what causes the fish to produce the omega-3 fatty acids? Is it genetic? Is it the diet you mentioned? The algae? Has anybody isolated a gene?

Addis: Well, basically, all fish concentrate the omega-3 from the algae. They're probably not any more effective than we are at actually making EPA and DHA out of linolenate. Plants, including algae (phytoplankton) make the omega-3 fatty acids; some zooplankton may eat the phytoplankton in water and then a small fish eats zooplankton and a big fish eats the small fish and it goes right up the chain. So you have bigger lake trout maybe around for 20 or 30 years and they are very high in fat content. They have consumed a lot of smaller fish and there's just been a concentration of the EPA in their tissue. Some biotechnologists are attempting to synthesize EPA and DHA by gene isolation techniques but I believe the progress is slow, in terms of a commercially viable process.

J. Romans: Do you have any evidence that people might thin their blood too much and bleed excessively?

Addis: It's a good question. I've asked this a number of times to medical doctors and they insist that excessive bleeding is not a problem. I have a hard time believing that if you had advanced atherosclerotic lesions and the doctor had you on very high levels of fish oil and you walked through a glass window/door or were in an automobile accident and got cut up badly, that there isn't going to be a risk of excessive bleeding associated with using the fish oil. But doctors insist that you may bleed more, but it's not going to be a problem.

Romans: Can you comment on the epidemiological studies that have been done vs actual controlled studies as to the many positive effects of fish oil that you have reported?

Addis: Generally, the epidemiological data would put fish oils in a more favorable light. Clinical studies are somewhat mixed although generally quite favorable. When you get into the problem of doing work with clinical studies or even with laboratory animals, there is some disagreement in the literature and the question that I like to raise is: Is the disagreement possibly due to the fact that some of the researchers were unaware of the fact that the oils they were using might have been quite rancid? If you're studying platelet interactions and you have an oil that is rancid, you'll have less omega-3, you'll have more peroxides and both of these effects will work against trying to show an antiaggregatory effect of fish oil.

R. Kauffman: I'd like to have two questions answered. 1) Why again biologically, is the ratio of the 3's to the 6's important? 2) Did you say that this material could actually be synthesized in the laboratory economically?

Addis: The amount is important as well as the ratio. It's just that it seems easier to understand as a ratio. Basically, it's the competition between omega-3 and omega-6 for certain enzymes which makes the ratio important. Regarding synthesis, the organic chemists don't have a very good, cheap way of synthesizing it.

Kauffman: Are there interactions between the two?

Addis: Yes, in that one is more effective than the other in inhibiting the enzymes and prostanoid synthesis. And some are better substrates for certain enzymes. They compete for cyclooxygenase and for the 2-position on physiologically active phospholipids.

Now, I would like to throw out a point for discussion. One way around the rancidity problem, if you're trying to incorporate omega-3 into a tissue might be to use prerigor processing and vacuum packaging. Max Judge and his co-workers at Purdue and researchers at Illinois have shown that two useful factors are that pre-rigor ground meat retains a higher pH and if vacuum packaged quickly enough (while the tissue is metabolizing) oxygen is used up (that is, left behind the tissue after packaging). A very stable product with respect to the development of rancidity will result. For instance, the hot processed pork for breakfast sausage currently marketed has a 70-day shelf life. It would be interesting to determine whether hot processing might be a way to help retard rancidity whether you're feeding the animal omega-3 or incorporating it. Any comments on that?

Benedict: There has been some work in the past at the USDA where they had protected the vegetable oil from oxidation by formaldehyde encapsulation. They found that they could have it go through the ruminants without being oxidized and resulting in polyunsaturated meats or milks. But on some of the meats, like hamburger, it tended during processing to become oxidized more rapidly and if you didn't inactivate it, the milk would become rancid.

If you inhibit some of the prostacyclin synthesis, will you have trouble with some of the beneficial aspects, as in reproduction with people on a high omega-3 level?

Addis: Upsetting the thromboxane/prostacyclin ratio too much could produce reproductive problems and one is well advised to use fish oil with a reasonable amount of prudence. They are very potent and active chemicals. Here is some practical advice; if your arteries are in good shape, I would say eating fish twice a week is probably a good way to go. If you have really bad arteries, then maybe you ought to ask your doctor about looking into using a high-quality fish oil.

Benedict: What about using algae as the initial source?

Addis: Algae have very low concentrations of EPA and DHA. Some work is being attempted in the area of biotechnology and gene splicing to try to change that but it's slow.

M. Stromer: Is there difference in benefits in consuming omega-3 in natural foods products vs dietary supplements?

Addis: Probably only in the concentration of EPA and DHA. These are the active ingredients as far as eicosanoid synthesis is concerned.