Algae-Based Astaxanthin is Far Superior to Synthetic and *Phaffia* Yeast Astaxanthin

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Introduction

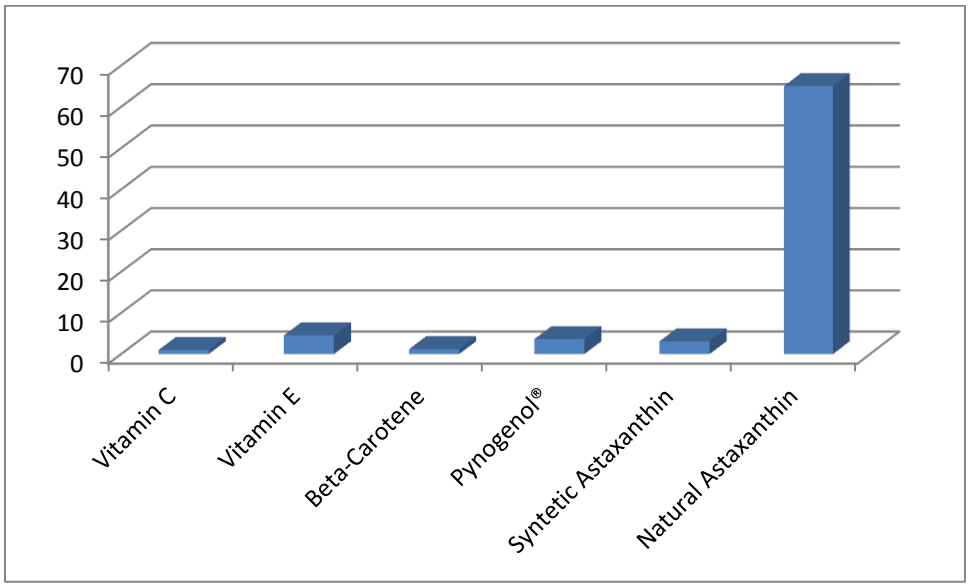
It is extremely important to understand the vast differences between Natural Astaxanthin from microalgae and its distant cousins which are produced from genetically mutated *Phaffia* yeast or from petrochemicals. This is becoming a critical topic for people in the supplement industry as well as consumers since synthetically-produced Astaxanthin is now being promoted as "Nature Identical." Synthetic Astaxanthin (which is synthesized from petrochemicals in an elaborate process) has been used for over thirty years in the animal feed industry, primarily to pigment the flesh of farm-raised salmon. Yet it was only introduced as a human nutritional supplement in 2013 after several famous doctors and opinion leaders started publicizing what an excellent supplement Natural Astaxanthin is and its popularity quickly escalated.

Phaffia-derived Astaxanthin (whose official nomenclature was changed recently to *Xanthophyllomyces dendrorhous* but is still commonly referred to as "*Phaffia*") is a species of yeast which in nature produces small amounts of Astaxanthin. Companies involved in the commercial production of *Phaffia* have genetically manipulated this species to produce exponentially more Astaxanthin. While a full review of the vast differences between these molecules would be too comprehensive for this paper, it is important that our Readers understand that these are three completely distinct molecules. In fact, other than sharing the same chemical formula, all three are almost exact opposites in all other respects.

The regulatory status of both *Phaffia*-derived and Synthetic Astaxanthin is in question in many countries. For example, in the USA, Synthetic Astaxanthin has never undergone a New Dietary Ingredient petition with the US Food and Drug Administration, while algae-based Astaxanthin has been allowed by FDA at ongoing doses of 12mg per day and at 24mg per day for thirty day periods. Astaxanthin from *Phaffia* is allowed by the US FDA, but with restrictions against long term use; against the use in children; and perhaps most significantly, at dosage levels of only 2 mg per day. Generally, a 2 mg dosage of algae-based Astaxanthin has only been shown sufficient in human clinical research in the area of immunomodulation (Park, et al, 2010), one of many potential physiological benefits of Astaxanthin. For other health benefits, dosages from 4mg up to 16mg are indicated (Capelli, et al, 2014). Incredibly, for products that are being offered as health supplements, the published literature does not contain human clinical research on safety or any health benefits from either Synthetic or *Phaffia*-derived Astaxanthin.

Natural Astaxanthin from Algae is 20 to 90 Times Stronger as an Antioxidant than Synthetic Astaxanthin

Of paramount importance, a critical finding of a landmark series of head-to-head antioxidant experiments is the clear superiority of Natural Astaxanthin to Synthetic Astaxanthin in antioxidant strength. In both university research at Creighton University under the auspices of acclaimed antioxidant researcher Debasis Bagchi, PhD as well as in independent laboratory testing at Brunswick Laboratories, Natural Astaxanthin extracted from microalgae was found to be a minimum of 20X stronger in antioxidant activity than Synthetic Astaxanthin produced from petrochemicals. The research is represented in the graph below; Natural Astaxanthin was tested for free radical elimination against Synthetic Astaxanthin as well as several other commonly used supplemental antioxidants. In each case, Natural Astaxanthin came out the undisputed champion with antioxidant strength ranging from 14X greater than Vitamin E to 65X greater than Vitamin C (Capelli, et al, 2013).



Free Radical Elimination (Capelli, Bagchi, Cysewski, 2013)

Further corroborating this landmark research, a study published by French university professors in conjunction with a leading medical doctor in 2015 again showed how much stronger Natural Astaxanthin from *Haematococcus* microalgae is than Synthetic Astaxanthin. They tested two forms of Natural Astaxanthin against Synthetic in two different models, the Trolox equivalent antioxidant capacity assay and an evaluation on HUVEC (human umbilical vein endothelial cells). The two natural forms tested were algae extracts produced by supercritical CO2 extraction and by solvent extraction, both of which are commercially available for use in food supplements. The results for both of the extracts with Natural Astaxanthin were outstanding—90X stronger than Synthetic Astaxanthin—and with absolutely no sign of toxicity. "The intracellular antioxidant activity in natural extracts was approximately 90 times higher than Synthetic Astaxanthin…Therefore, these results revealed the therapeutic potential of the natural

extracts in vascular human cell protection against oxidative stress without toxicity, which could be exploited in the prevention and/or treatment of cardiovascular diseases" (Regnier, et al, 2015).

Animal Research Shows Huge Differences in Efficacy Between Algae-Based Astaxanthin and *Phaffia*-Derived or Synthetic Astaxanthin

The vast differences in antioxidant activity result in different functionality between Natural and Synthetic Astaxanthin. In addition, functional differences between Natural Astaxanthin and *Phaffia*-derived Astaxanthin are also apparent, although we are still awaiting the first publication of tests of antioxidant strength between the two. Pre-clinical research in this area is beginning to emerge; in fact, five indicative studies have already clearly defined Natural Astaxanthin's functional superiority in animal trials. In the first, Natural Astaxanthin was again shown to have superior antioxidant activity as compared to Synthetic Astaxanthin when fed to rats. Rats were given either Natural Astaxanthin from *Haematococcus* microalgae or Synthetic Astaxanthin for fourteen days, and then enzymes indicative of liver protection were measured along with the antioxidant enzymes catalase, superoxide dismutase and glutathione. Natural Astaxanthin showed "better hepatoprotection and antioxidant activity, therefore it can be used in pharmaceutical and nutraceutical applications" (Rao, et al, 2013).

The second study was even more interesting because it tested all three forms in an animal trial—algae-based, *Phaffia*-derived, and Synthetic Astaxanthin. This study was published as a joint project between the Department of Food Science at University of Massachusetts and the Department of Food Science at South China Agricultural University. The authors had no conflicts of interest (meaning that they were not employed or associated with any company involved in the Astaxanthin business, making them completely independent and unbiased). They experimented with a worm that is commonly used as a model organism for longevity and antioxidant testing called *Caenorhabditis elegans*. This worm is very appropriate to use in this type of experiment for two key reasons: First of all, it has 60% to 80% of the human gene homologues making experiments with this worm representative of potential results in humans (Kaletta and Hengartner, 2006). Secondly, this worm has a three week lifespan, allowing for rapid testing and results.

The worms were separated into four groups: A control group, a group treated with Natural Astaxanthin from *Haematococcus* microalgae, a group treated with Astaxanthin from the mutated yeast *Phaffia*, and finally, a group treated with Synthetic Astaxanthin made from petrochemicals. Each of these distant Astaxanthin cousins has different stereoisomeric forms (which in plain English means that they are shaped differently): The form in Natural Astaxanthin from microalgae is 3S, 3'S; the form in mutated *Phaffia* yeast is 3R, 3'R; and finally, the form in Synthetic Astaxanthin is a statistical mixture of 25% each of the forms in microalgae and *Phaffia* yeast along with the predominant form 3R,3'S (which is called "meso" and accounts for 50% of the total). The authors of this study stated, "Astaxanthin is a potent antioxidant with different stereoisomers in nature. However, there have been no reports about the functional activities of different stereoisomers so far. Our present finding shows there is a significant difference between Astaxanthin stereoisomers against oxidative damage, which is useful for rational utilization of Astaxanthin in functional food."

The worms underwent oxidative stress for 24 hours. The way that the scientists created oxidative stress was by introducing paraquat (a toxic, fast-acting herbicide) to the worms. The worms were tracked for five days after exposure to paraquat; amazingly, by the fifth day, Natural Astaxanthin had kept approximately 50% more of the worms alive versus control. In fact, all forms of Astaxanthin made the worms live significantly longer, with Natural Astaxanthin from *Haematococcus* microalgae-treated worms living the longest of all four groups. Additional tests were done on different oxidative parameters with all Astaxanthin groups showing improvements. Results indicated:

- Antioxidant enzyme superoxide dismutase (SOD) in the Natural Astaxanthin group was approximately 50% higher than control.
- Catalase in the Natural Astaxanthin group was approximately 90% higher than control.
- The Natural Astaxanthin group was higher than the *Phaffia* Astaxanthin and Synthetic Astaxanthin groups in both SOD and Catalase.
- Relative fluorescence intensity (which indicates the accumulation of reactive oxygen species) was much lower in all Astaxanthin groups, again with N-AX being the best performer.
    - The change versus control for Natural Astaxanthin was approximately 33% more than Phaffia.
    - The change versus control for Natural Astaxanthin was almost double Synthetic Astaxanthin.
- Green-fluorescent protein (GFP) production is induced by oxidative stress and is used to measure SOD-3 production levels. SOD-3 can convert the major isoform of mitochondrial SOD, an important antioxidant enzyme (Libina, et al, 2003). "We found that SOD-3 GFP expression among Astaxanthin treatment groups was markedly higher than that of the control, and the SOD-3 GFP expression in the Natural Astaxanthin-treated group was significantly higher than the *Phaffia* and Synthetic Astaxanthin-treated groups during the first to third day period ($P < 0.05$). This result was consistent with the effects of Astaxanthin stereoisomers on the reactive oxygen species level where Natural Astaxanthin exhibited higher antioxidative activity than the other two stereoisomers."

"In conclusion, our results demonstrated that Astaxanthin could increase oxidative resistance, decrease levels of reactive oxygen species, increase enzyme activity of SOD and Catalase, and enhance expression of SOD-3 in *C. elegans*. These effects may contribute to the observed survival increase in the worms under oxidative stress" (Liu, et al, 2016).

This study is excellent proof-in-action of how different Synthetic and *Phaffia*-derived Astaxanthin are from Natural Astaxanthin from microalgae. Coupled with the rodent study we cited above where Natural Astaxanthin was superior to Synthetic in protecting the liver, we're starting to see conclusive evidence in animals of how the vast differences between these disparate forms of Astaxanthin can affect the health that the animals experience.

There is one additional animal trial that tested Astaxanthin from algae against both Astaxanthin from *Phaffia* and Astaxanthin from petrochemicals. This study was done in 2005 at a university in Japan on the effects of Astaxanthin on gastric ulcers in rats. The results of this study showed

that algae-based Astaxanthin may protect rats from ulcers. This is not particularly earth-shattering news, as it's been known for years that Astaxanthin has potential to prevent ulcers, particularly ulcers caused by the bacterium *H. plyori* (Bennedsen, et al, 1999; Wang, et al, 2000; Akyon, et al 2002) and ulcers caused by damaging substances such as alcohol (Kim, et al, 2005a; Kamath, et al, 2008), naproxen (Kim, et al, 2005b) and acetic acid (Yang, et al, 2009).

What is of top interest here is that this publication showed significantly better potential for Astaxanthin from algae to prevent gastric ulcers than Astaxanthin from the mutated yeast *Phaffia Rhodozyma* and Astaxanthin synthesized from petrochemicals. Rats were stressed by putting them into chest-level water for 24 hours after having fasted for 24 hours. This study tested the three forms of Astaxanthin as well as beta-carotene and Vitamin C. All the rats given carotenoids including all three forms of Astaxanthin as well as beta-carotene before being stressed were appreciably protected against the formation of gastric ulcers as compared to rats in the control group and the group given Vitamin C. But the rats given algae-based Astaxanthin did the best of all: "Ulcer indexes in particular were smaller with the rat group fed Astaxanthin extracted from *Haematococcus* than the other groups" (Nishikawa, et al, 2005).

In 2008, a similar study was done on the effects of Astaxanthin on ulcers in rats. This study tested Synthetic against algae-based Astaxanthin, but did not include *Phaffia*-derived Astaxanthin. They used ethanol to induce ulcers and found that pre-treatment with Natural Astaxanthin outperformed Synthetic Astaxanthin in inhibiting the formation of ulcers. Synthetic Astaxanthin did not show any inhibition all, while amazingly, Natural Astaxanthin showed inhibition of ulcers at a level that is better than the ulcer drug omeprazole (which is sold under the brand name Prilosec®). Natural Astaxanthin showed a "dose-dependent gastroprotective effect on acute, ethanol-induced gastric lesions in rats…Presence of Astaxanthin esters in *Haematococcus pluvialis* has an added advantage that, generally carotenoids, although potential antioxidants, may lack such properties in vivo because of the pro-oxidant effect. Esterified Astaxanthin shows comparatively better stability than free Astaxanthin, and hence it may exhibit more health beneficial effects than free Astaxanthin" (Kamath, et al, 2008).

The very first study of health differences in animals between different forms of Astaxanthin was done back in 1998. This study focused on a species of shrimp called *Penaeus monodon* which is known as the "giant tiger prawn." This study was done at a university in Thailand in support of the large shrimp-farming industry in that country. They did a series of tests on three different larval and post-larval stages during the shrimp's life cycle. They separated the shrimp into four different groups:

- One treatment group was fed a commercial diet augmented with algae-based Astaxanthin.
- The second treatment group was fed a commercial diet augmented with Synthetic Astaxanthin.
- One control group was fed the same commercial diet without any addition of Astaxanthin
- A different control group was fed a natural diet that the shrimp would normally eat in the wild.

Believe it or not, in all three larval stages, shrimp fed algae-based Astaxanthin survived at higher rates than shrimp fed Synthetic Astaxanthin. Fifteen days after the post larval stage, shrimp fed

algae-based Astaxanthin were showing better survival rates than all three other groups (amazingly, even better than the shrimp fed the natural diet). In addition, tests of low water salinity were done to examine the different groups' tolerance levels, and the shrimp fed the algae-based Astaxanthin diet again outperformed all others. Shrimp from all three other groups died faster than the algae-Astaxanthin fed shrimp when subjected to low salinity. Similarly, there were statistically significant differences in growth rates as well; shrimp fed the algae-based Astaxanthin and the natural diet grew faster than shrimp fed Synthetic Astaxanthin or the commercial diet without Astaxanthin.

It's very interesting to note that the shrimp fed Synthetic Astaxanthin were the lowest performers. For example, in one larval stage, all three other groups outlived the shrimp fed Synthetic Astaxanthin. This shows that Synthetic Astaxanthin is certainly not "Nature Identical." Not only couldn't Synthetic perform as well as Natural Astaxanthin in this study, it didn't even do as well as shrimp fed a diet without any Astaxanthin!

> "From our results, the highest survival rate of zoea and mysis [two larval stages] was obtained with shrimp fed algae-based Astaxanthin, followed by the natural diet, the commercial diet without Astaxanthin and the Synthetic Astaxanthin diet in descending order. This indicated that shrimp larvae accept Natural better than Synthetic Astaxanthin…The postlarva after fifteen days fed natural diets containing Natural Astaxanthin were larger than those fed diets containing Synthetic Astaxanthin or no Astaxanthin. The best postlarval growth was in the group fed algae-based Astaxanthin and was significantly better than that for the groups fed Synthetic Astaxanthin. This indicated that Astaxanthin from *Haematococcus pluvialis* (mostly in esterified form) performs significantly better than free, Synthetic Astaxanthin…Determination of 50% cumulative mortality upon low salinity challenge showed that larvae fed algae-based Astaxanthin endured better than larvae fed the natural diet, the Synthetic Astaxanthin diet and the commercial diet without Astaxanthin."

Among many fascinating aspects of this study, one of the most is that they examined shrimp in both a healthy environment, plus shrimp subjected to stress by being put in a low salinity environment. In both cases, Natural Astaxanthin helped the shrimp survive much better when compared to Synthetic Astaxanthin. This is a powerful first study on this topic, and the fact that no other animal research like this was done until many years later is troubling; if there had been multiple studies done over the years, perhaps the obviously inferior synthetically-produced Astaxanthin would not have been launched for human use.

The final statement of this study really sums it up nicely: "Although the mechanism by which Astaxanthin improved the response to stress cannot be explained, the information that Natural Astaxanthin (from *Haematococcus pluvialis*) is more efficacious than Synthetic Astaxanthin for growth, survival and stress resistance of shrimp larvae should be useful for further research on shrimp larval nutrition" (Darachai, et al, 1998). We might add that, while the authors of this study were focused on shrimp in support of the Thai shrimp farming industry, the implications of this study and the four more recent studies showing the clear superiority of Natural Astaxanthin from microalgae over other forms should be strongly considered for all living organisms (including humans), not just shrimp.

Survival rates, resistance to stress, protection of the liver, prevention of gastric ulcers, even growth rates and longevity—all of these health concerns show better results when animals are fed Natural Astaxanthin from *Haematococcus* microalgae than when animals are fed Astaxanthin from other forms or control diets without Astaxanthin. After examining these five comparative animal studies, a key question remains: Does this research relate to the use of Astaxanthin in humans? We don't know, as we're not aware of a single clinical trial showing any health benefit in humans for Astaxanthin from mutated *Phaffia* yeast or Synthetic Astaxanthin from petrochemicals. And even more frightening, there aren't any safety studies in humans for *Phaffia* or Synthetic Astaxanthin. Without clinical trials showing health benefits and extensive safety research in humans for these other forms, we highly recommend that consumers avoid being the guinea pigs on these questionable products. In fact, it's hard to imagine why anyone would experiment on themselves by taking these untested forms since Astaxanthin from microalgae (which has approximately 100 clinical trials showing various health benefits and extensive safety data) is widely available.

Safety of *Phaffia*-Derived and Synthetic Astaxanthin is a Troubling Question Mark

It's particularly important to understand the safety concerns with Synthetic and *Phaffia*-derived Astaxanthin. As discussed above, the US FDA is so concerned with the mutated yeast form that they do not recommend it for long-term use or for children, and only allow it to be used at a level of 2mg per day. The safety concerns with Synthetic Astaxanthin are even more severe. Astaxanthin is not the only nutrient that comes in both synthetic and natural forms where there are serious safety concerns with the synthetic form. In fact, even with molecules in the carotenoid family that are closely related to Astaxanthin, synthetic forms have been found to be a grave concern. The reason that synthetic nutrients may have compromised safety is not yet understood by scientists. One theory is that a molecule that has been synthesized may not contain all physiologically active components that nature created in the natural version. A good example of this is with Vitamin E; the synthetic version is solely dl-alpha tocopherol. But in nature, the Vitamin E complex contains several different tocopherols and tocotrienols; and in fact, the tocotrienol constituents yield outstanding health benefits while the tocopherol constituents are not nearly as active. For example, tocotrienols have been shown active in preventing neurodegeneration (Sen, et al, 2006), protecting the liver (Magosso, et al, 2013) and kidneys (Haghighat, et al, 2014), and even in preventing hair loss (Beoy, et al 2010).

Now let's look at two carotenoids closely related to Astaxanthin that are available synthetically. We'll start with the most famous member of the carotenoid family which is also the most researched: Beta-carotene. There are hundreds of published studies showing potential benefits for beta-carotene for conditions including immunity as well as prevention of cancer (Moorhead, et al, 2005). But it appears that synthetic beta-carotene does not absorb well; in fact, one study indicated that natural beta-carotene absorbs ten times better than its synthetic cousin in rats and chickens (Ben-Amotz, et al, 1989). And absorption is only one of the concerns with synthetic beta-carotene; even more importantly, there are valid concerns with both its safety and efficacy. With regards to antioxidant potential, synthetic versus natural beta-carotene mimics the results with Astaxanthin. Synthetic beta-carotene is primarily the trans-form, while natural beta-carotene contains large amounts of the cis-form. The 9-cis beta-carotene form, which is found in high amounts in natural beta-carotene, is a more efficient lipophilic antioxidant than the synthetic trans-form. The stereochemistry of this carotenoid (similar to the situation with Astaxanthin) is important in antioxidant potential as well as absorption and transport (Ben-Amotz, et al, 1996).

Now for the top issue: Safety. A famous study done in Finland in the 1990's tested synthetic beta-carotene on heavy tobacco smokers. The results of this study contradicted dozens of pre-clinical trials and epidemiological studies that indicate natural beta-carotene has cancer-preventative properties (Moorhead, et al, 2005). The results of this large-scale study showed a slight increase in cancer among the subjects supplementing long-range with synthetic beta-carotene (Heinonen and Albanes, 1994). Imagine how shocked people were who were taking beta-carotene as a cancer-preventative supplement when the newspaper headlines read "Beta-carotene increases the risk of cancer." However, subsequent research that compared natural beta-carotene extracted from *Dunaliella salina* microalgae with synthetic beta-carotene indicated that it's the synthetic form which may be involved in the formation of cancer. In fact, the study

concluded that natural beta-carotene could be valuable in tumor prevention and supplementary treatment (Xue, et al, 1998). Even though natural and synthetic beta-carotene have the same chemical formula (just like the case with the different forms of Astaxanthin), they are different in every other way. Natural beta-carotene absorbs better, has stronger antioxidant activity and may prevent cancer; meanwhile synthetic beta-carotene may actually cause cancer.

Another synthetic carotenoid was actually taken off the market because of serious health concerns. Similar to Synthetic Astaxanthin, synthetically-produced canthaxanthin has been sold for many years for inclusion in animal feeds. But for a short time in the 1980s, synthetic canthaxanthin was sold for human use as an internal tanning pill; people who took high doses of this product got a tan without going out in the sun. (Sources of natural canthaxanthin are very scarce, so there are no commercially available products featuring the natural form.)

Canthaxanthin is much more closely related to Astaxanthin than beta-carotene since it's in the same subgroup of carotenoids as Astaxanthin called "xanthophylls." Xanthophylls differ structurally from the other carotenoid subgroup called "carotenes" (of which beta-carotene and lycopene are the most famous members) since they have hydroxyl groups attached to the molecules. (A hydroxyl groups is a hydrogen atom covalently bonded with an oxygen atom.)

After consumers started using the synthetic tanning pills with canthaxanthin, an unforeseen side effect appeared: Golden crystals formed in consumers' retinas, and synthetic canthaxanthin was immediately removed from the supplement market. In addition, regulators around the world began limiting or prohibiting the use of synthetic canthaxanthin in animals feeds due to this serous safety concern (European Commission, 2002; Australia New Zealand Food Standards Code, 2011). The crystallization in the retinas eventually disappeared, but it is extremely disconcerting how long it took for complete reversal. Follow up research published in 2011 found that complete disappearance of the golden crystals took approximately twenty years (Hueber, et al, 2011).

With other synthetic carotenoids increasing the incidence of cancer and causing crystallization in the retina, we were very surprised to see Synthetic Astaxanthin introduced to the human supplement market without doing long-range safety studies in humans. In addition, questions about efficacy of Synthetic Astaxanthin remain unanswered despite multiple antioxidant tests showing 20X to 90X inferior antioxidant activity and multiple animal trials showing poor performance as compared to Natural Astaxanthin. Despite these profound differences, Synthetic Astaxanthin is being marketed as "Nature Identical," which couldn't be further from the truth. The conclusion of the Creighton University study testing Synthetic versus Natural Astaxanthin clearly summarizes the case against Synthetic:

> "For these reasons, the authors recommend against the use of Synthetic Astaxanthin in human nutraceutical supplements until extensive, long-range safety parameters are established and human clinical trials showing health benefits are conducted. In the event that Synthetic Astaxanthin attains these two milestones, due to the extensive differences between the two molecules, it should be distinctly labeled as "Synthetic Astaxanthin" on consumer product labels, and dosage levels should be approximately 20X to 30X higher than those of Natural Astaxanthin in order to obtain similar antioxidant activity" (Capelli,

et al, 2013).

List of the Vast Differences Between Algae-Based Astaxanthin and Other Forms

It's not only differences in antioxidant potential and real-world health benefits that we described in the chapters above that separate these distant cousins; as we mentioned in the beginning of this discussion, in every way other than the chemical formula they share, Natural Astaxanthin from algae is as different as night and day from the two other forms of Astaxanthin. Briefly, the primary differences between the forms of Astaxanthin are:

- **Shape**: As we pointed out above, the Natural Astaxanthin molecule's stereochemistry is unique (it is shaped differently than the Synthetic and the *Phaffia* Astaxanthin molecules).
- **Esterification**: Natural Astaxanthin is 95% esterified (it has a fatty acid molecule attached to either one or both ends of the Astaxanthin molecule). Synthetic and *Phaffia* Astaxanthin are exclusively "free" Astaxanthin and do not have fatty acid molecules attached.
- **Synergy**: Natural Astaxanthin from *Haematococcus pluvialis* microalgae comes complexed in nature with supporting carotenoids: There are consistently small amounts of other antioxidant carotenoids such as lutein, beta-carotene and canthaxanthin ranging from 3% - 15% of the total carotenoid fraction which work in unison with Astaxanthin to provide a synergistic effect when ingested. Synthetic and *Phaffia* Astaxanthin do not contain supporting carotenoids.
- **Source**: Synthetic Astaxanthin is synthesized from petrochemicals in an elaborate process. *Phaffia* Astaxanthin is produced from genetically-manipulated yeast. Natural Astaxanthin is extracted from natural *Haematococcus pluvialis* microalgae.
- **Safety**: Natural Astaxanthin has an extensive portfolio of human safety studies and a history of close to twenty years of safe use as a commercially-sold nutritional supplement. Synthetic Astaxanthin has never been directly tested in humans for safety. (This is an overriding concern due to serious safety issues with related synthetic carotenoids beta-carotene and canthaxanthin.) Meanwhile, the US FDA is so concerned with *Phaffia* Astaxanthin from mutated yeast that they do not recommend it for long-term use or for children, and they only allow it to be used at a level of 2mg per day.
- **Efficacy**: Amazingly and perhaps most importantly, Synthetic and *Phaffia* Astaxanthin have <u>never</u> been shown to have any health benefit in human clinical research. They are completely untested and there is a possibility that they do not have any health benefit at all, even at high doses. Meanwhile, Natural Astaxanthin has been shown to have diverse health benefits in approximately 100 different positive human clinical trials.
- **Antioxidant Strength**: Natural Astaxanthin is at minimum 20X to as much as 90X stronger than Synthetic Astaxanthin as an antioxidant. There have not yet been head-to-head antioxidant comparisons between Natural and *Phaffia* Astaxanthin; however, we expect vast differences in antioxidant disparity between these molecules as well due to *Phaffia's* chemical similarities to Synthetic Astaxanthin.
- **Dosage**: In the event that Synthetic Astaxanthin is ultimately proven safe for long-range human consumption, dosages would logically be a minimum of 20 times greater than corresponding dosages of Natural Astaxanthin due to its vastly inferior antioxidant

profile. This high dosage requirement would most likely put Synthetic Astaxanthin out of reach economically for most consumers (Capelli, et al, 2013). And while the difference in antioxidant strength between *Phaffia* and Natural Astaxanthin remains unproven to date, due to safety concerns, *Phaffia* Astaxanthin is only allowed at 2mg per day dosage in USA rendering it virtually useless for many of the indicated health benefits in humans.

Summary

With this brief analysis of these three distant Astaxanthin cousins, we quickly see that Synthetic and *Phaffia*–derived Astaxanthin are entirely different from and far inferior to Natural Astaxanthin from algae:

- Chemically they are completely different in every way except for sharing the same chemical formula.
- Both *Phaffia* and Synthetic Astaxanthin have been shown to be substandard in pre-clinical animal studies.
- Synthetic Astaxanthin is comparatively very weak as an antioxidant.
- Neither *Phaffia* nor Synthetic Astaxanthin has ever been clinically validated to have any health benefit in humans.
- And most frightening of all: Neither *Phaffia* nor Synthetic Astaxanthin has ever been tested for safety in humans.
- Regardless of how Synthetic and *Phaffia* Astaxanthin are marketed, it is clear that they are not "Nature Identical."

For all of these reasons, we highly recommend that consumers ensure that their Astaxanthin is the natural form extracted from *Haematococcus pluvialis* microalgae.

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