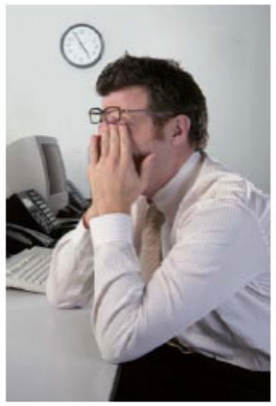
# Astaxanthin and Eye Fatigue

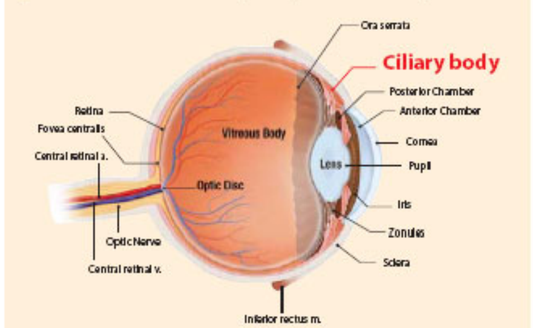
## Astaxanthin for Eye Health



The advances of information technology, software and electronics have led to the widespread use of screen based equipment or visual display terminals (VDT) especially at work or leisure. VDT's are important because it forms the essential interface between an operator and computer to perform specific tasks. The problem acknowledged by the ophthalmic community is that habitual users of VDTs often lead to higher visual fatigue complaints. This phenomenon known as asthenopia prompted a large number of occupational safety studies. For example, epidemiological studies over the last decade revealed significant factors that contribute to eye fatigue. These studies, sometimes involving up to 6,000 sufferers identified the following causes: insufficient lighting, poor ergonomics and uncorrected vision. Despite the new information, follow-up studies later showed that the implemented improvements were only effective in 50% of sufferers. The possible explanations for this observation could be that other factors remained undiscovered, poor implementation of improvements, or visual work had become even more visually demanding. It is likely to be a combination of these factors so that current solutions are insufficient to reduce asthenopia.

The symptoms of asthenopia include sensitivity to glare, headaches, sore eyes, and blurred vision. Standardized questionnaires that assessed subjective eye fatigue symptoms are in most cases mild, but symptoms get progressively worse if the causes are not rectified. Furthermore, certain ophthalmological tests can also detect eye problems, for example accommodation amplitudes, rate of accommodative reaction (positive and negative directions), critical flicker fusion (CFF) and pattern visual evoked potential (PVEP). So far, nine Japanese clinical studies conducted by six independent ophthalmological establishments were able to conclude the efficacy of astaxanthin to alleviate visual asthenopia by observed improvements in the accommodation function and recovery of the ciliary body (Figure 1); retinal blood flow and inflammation markers.

Figure 1. Location of the ciliary body in the human eye




Some might argue that asthenopia is non-life threatening or not disabling compared to age-related macular degeneration, and there is no conclusive evidence suggesting that VDT work damages the eye e.g., advancing myopia; nevertheless this phenomenon contributes to the functional discomfort that greatly affects the quality and performance at work and leisure.

### VDT Definition

VDT comprises of a keyboard for data input and a display screen for graphics, text, numbers and for control of the input.

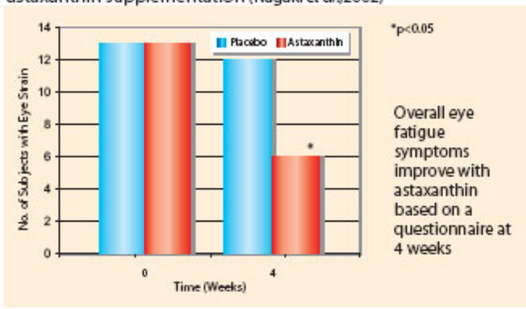
### Accommodation Definition

The change in refractive power of the eye to focus objects at different distances.

## Asthenopia (Eye Fatigue)

Asthenopia otherwise called eye fatigue occurs on a daily cycle, in that the visual performance generally decreases naturally from morning until night. This problem exacerbates with a daily VDT load that lasts between 4 to 7 hours by affecting the accommodation performance of the ciliary body, which controls lens refraction. A couple of randomized double blind placebo controlled pilot studies demonstrated the positive effects of astaxanthin supplementation on visual function. For example, a study by Nagaki *et al.*, (2002), demonstrated that subjects (n=13) who received 5 mg astaxanthin per day for one month showed a 54% reduction of eye fatigue complaints (Figure 2). In a sports vision study led by Sawaki *et al.*, they demonstrated that depth perception and critical flicker fusion had improved by 46% and 5% respectively on a daily dose of 6 mg (n=9). The effect of astaxanthin on visual performance prompted a number of other clinical studies to evaluate the optimum dose and identify the mechanism of action.

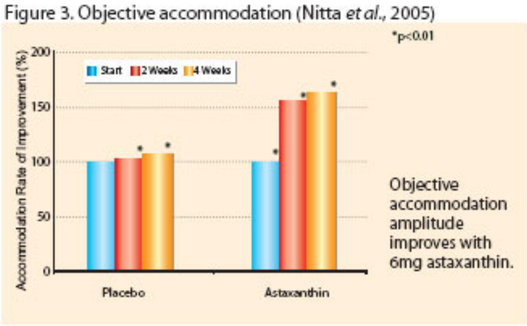
Figure 2. VDT Subjects with Eye Strain Symptoms before and after astaxanthin supplementation (Nagaki *et al.*,2002)




## Reducing Asthenopia

A study by Nakamura (2004), demonstrated significant improvements in reducing asthenopia and positive accommodation for the 4 mg ($p<0.05$) and 12 mg ($p<0.01$) groups. However, it was not until Nitta *et al.*, (2005), who established the optimum daily dose at 6 mg (n=10) for a period of 4 weeks by comparing eye fatigue using a visual analogue scale (VAS) based questionnaire and accommodation values. Overall, the 6 mg group improved significantly better at week 2 and 4 of the test period. Furthermore, questionnaire results obtained by Shiratori *et al.*, (2005) and Nagaki *et al.*, (2006), also confirmed the previous findings that astaxanthin supplementation at 6 mg for 4 weeks improved symptoms associated with tiredness, soreness, dryness and blurry vision. Another study by Takahashi & Kajita (2005), also demonstrated that astaxanthin attenuates induced-eye fatigue, as opposed to treating eye fatigue, which suggests prevention rather than treatment. Astaxanthin treated groups (asthenopia negative) were able to recover quicker than the control group after heavy visual stimulus. Later, Iwasaki & Tawara (2006) also confirmed the same tendencies of subjective eye fatigue complaints in a randomized double-blind placebo controlled double-crossover study.

Figure 3. Objective accommodation (Nitta *et al.*, 2005)




Since the questionnaires may be subjectively limited, the direct measurements of parameters associated with asthenopia are better indicators. These include accommodation amplitude (Figure 3); rate of accommodation reaction (positive and negative directions); CFF (critical flicker fusion) and PVEP (pattern visual evoked potential). Based on the quantitative information, the accommodation related measurements consistently improved after the treatment period (Nagaki *et al.*, 2002, 2006; Nakamura *et al.*, 2004; Takahashi & Kajita, 2005; Shiratori *et al.*, 2005; Nitta *et al.*, 2005; Iwasaki & Tawara, 2006) whereas the CFF and PVEP remained inconclusive (Sawaki *et al.*, 2002; Nagaki *et al.*, 2002; Nakamura *et al.*, 2004). Therefore, the mechanism by which astaxanthin improved eye fatigue strongly indicates accommodation.

## Mechanism of Action: Improved Accommodation, Increased Blood-flow and Anti-inflammation

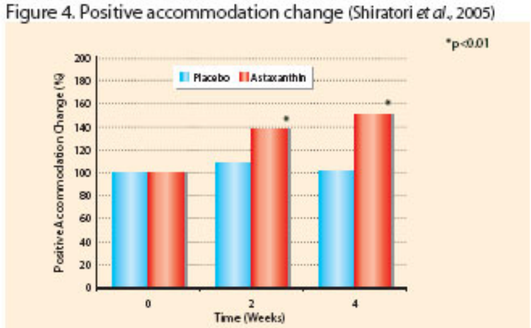
Accommodation measures the lens refractive property and it corresponds to the ciliary body function. This small ocular muscle controls the lens thickness in order to focus the light on the retina. In heavy visual workloads, the eye is focused on a fixed object distance for extended periods that will cause muscle spasms or develop fatigue detectable by accommodation tests. These tests are interrelated and include the following: accommodation amplitude; accommodation reaction (positive or negative) and high frequency component (HFC). Each clinical study used a combination of accommodation tests to indicate the amount of fatigue present. For example, increased accommodation amplitude in all treated subjects indicated improved reaction on near and far objects (Nagaki *et al.*, 2002, 2006; Nakamura *et al.*, 2004). Figure 4, Figure 5 and Table 1 reveal the higher rate of accommodation reactions measured in astaxanthin treated groups. These indicate the speed at which the ciliary body reacted to the direction change of focus (negative accommodation means from a near object at 35 centimeters to distant object at 5 meters or vice versa); (Nitta *et al.*, 2005; Shiratori *et al.*, 2005; Nakamura *et al.*, 2005; Iwasaki & Tawara, 2006).

The effects of astaxanthin are significant from 2 weeks.

Another technique called HFC directly measured the microfluctuations in the lens during the accommodation response and typical values exist between 50 and 60 for normal eyes. Asthenopia sufferers (values greater than 60) experienced faster rates of recovery (Figure 6) in that their HFC results decrease towards normal values in less time compared to control groups (Takahashi & Kajita, 2005).

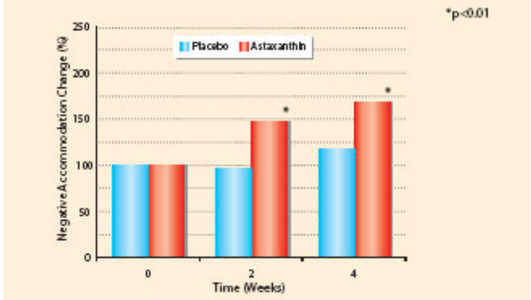
Another randomized placebo controlled study by Nagaki *et al.*, (2005) detected the increase of retinal blood flow in the astaxanthin treated group that received 6 mg for 4 weeks (n=14, $p<0.01$). Even though the precise reason for accommodation

Figure 4. Positive accommodation change (Shiratori *et al.*, 2005)




Rate of positive accommodation improves with 6 mg astaxanthin

Figure 5. Negative accommodation (Shiratori *et al.*, 2005)




Rate of negative accommodation improves with 6 mg astaxanthin

Table 1. Improvement of negative accommodation time with astaxanthin (Iwasaki & Tawara, 2006)

| Ingestion Group | Negative accommodation time (s) | | |
|---|---|---|---|
| | Pre | Post | Rest |
| Astaxanthin | 1.05 ± 0.07 | 1.23 ± 0.09 | 1.06 ± 0.07 |
| | NS | *1 | *2 |
| Placebo | 1.03 ± 0.07 | 1.35 ± 0.08 | 1.27 ± 0.08 |

Mean value ± standard error: n=10 (both groups, idnentical cases), *1p=0.0429, *2p=0.0004, NA:not significant

improvement seen with astaxanthin is not yet clear, the author postulated that based on the rheological improvement measured in the retinal capillary vessels, most likely means more blood also reaches the ciliary body and provides more nourishment to the ciliary muscles. Furthermore, the rheological improvement agreed with Nagaki *et al.*, (2005) who studied ten healthy subjects treated with 6 mg astaxanthin for ten days (Figure 7). The blood exhibited significantly higher flow rates (*ex-vivo*) compared to the control group ($p<0.05$) utilizing the micro-array channel flow analyzer (MC-FAN).

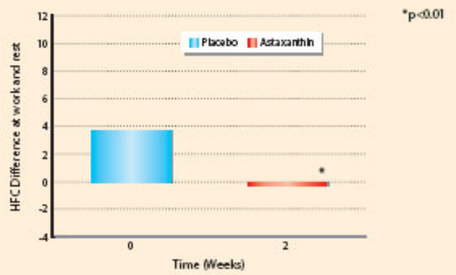
Lastly, a top Japanese ophthalmology research collaboration between Hokkaido, Yokohama and Tokyo concluded anti-inflammatory properties of astaxanthin in endotoxin-induced uveitis (EIU or eye inflammation) both in vivo and in vitro models. Ohgami *et al.*, (2003) observed in a dose dependant fashion that astaxanthin doses of 1, 10 or

100mg/kg dose in rats had the same anti-inflammatory action as 10 mg/kg prednisolone (n=8, $p<0.01$). Inflammation markers such as nitric oxide synthase (NOS), prostaglandin E2 (PGE2) and tumor necrosis factor (TNF)-α were all significantly reduced. In human terms, 4 mg astaxanthin per day may deliver the same benefits as 4 mg prednisolone without the side effects of intraocular pressure build-up. Other reduced biomarkers were cellular infiltration and protein build up in the aqueous humor.

In another study, Suzuki *et al.*, (2006) confirmed the same effects while they carefully studied the anti-inflammatory effect of astaxanthin in the iris-ciliary body of rat eyes. This was also the first study to prove that astaxanthin suppressed NF-kB activation by free radicals in the EIU rat model (Figure 8). The result is a lower pro-inflammatory response that would otherwise perpetuate local sites of inflammation that may also help explain why astaxanthin worked to alleviate eye fatigue in numerous clinical trials.

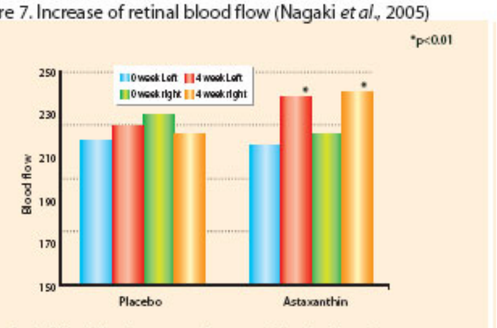
For astaxanthin to work, it has to pass through the human blood-retinal barrier (BRB) for which there is no direct evidence because a non-invasive specific quantification method is not available. However, the BRB is a selective barrier similar to the blood-brain barrier (BBB) which is better understood, so astaxanthin is expected to pass through because of the molecular size is less than 600 Daltons. Furthermore, astaxanthin belongs to the same carotenoid xanthophyll group as lutein and zeaxanthin, both of which are concentrated in the macular region of the eye. Unlike, beta-carotene or lycopene (carotenes), xanthophylls are the only carotenoids detected in the eye so far.

Figure 6. Accommodative Recovery observing difference of HFC (Takahashi and Kajita, 2005)



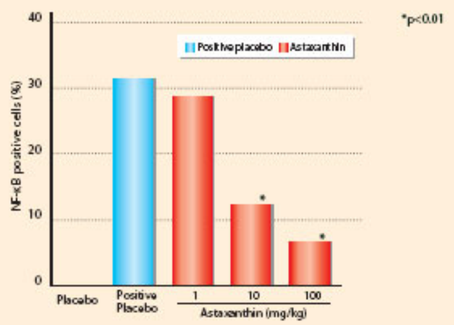

Astaxanthin improves HFC accommodation recovery during rest periods after visual work.

Figure 7. Increase of retinal blood flow (Nagaki *et al.*, 2005)




Retinal blood flow increases with astaxanthin after 4 weeks.

Figure 8. Number of NF-κB positive cells in eye ciliary body during inflammation (Suzuki *et al.*, 2006)




Astaxanthin reduced the number of inflamed cells in the ciliary body.

## Outlook

Eye fatigue or asthenopia is a common problem that occurs with the regular use of VDTs and may be resolved with findings from many worldwide epidemiological studies. However, if current improvements tend to be only 50% successful and other factors are likely to be involved, therefore, based on the current clinical evidence, astaxanthin offers a complementary alternative by reducing inflammation, improving accommodation and increasing blood flow.

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## Patent

Medicament for improving the Failure of Accomodation, US 2005/0171214