AstaREAL® Astaxanthin and Safety

Fuji's Commitment to Safety

Astaxanthin, either as a purified Haematococcus pluvialis extract or in algal biomass, has been evaluated in multiple studies to determine its potential for adverse effects and genotoxicity. The study type, study design, test material and findings are summarized in the following tables.

AstaREAL® and Clinical Studies

The clinical database for AstaREAL® includes 25 human studies (15 double-blind, placebo-controlled trials) with more than 840 subjects undergoing treatments lasting from 2 weeks to 6 months. The doses used in these trials ranged from 2 to 45 mg/person/day. The trials were designed to investigate the safety and tolerance for AstaREAL® astaxanthin using different doses, treatment periods, research design and demographic variables including age, gender and ethnicity. All studies revealed No Observed Adverse Effect Level (NOAEL) based on hematological, serum chemistry, urinal analysis and self-report questionnaires. A summary of clinical trial designs, doses and adverse effects noted in these investigations is presented in Table 3-4.

A double-blind controlled study conducted in Japan in 2010, 15 healthy adults' subjects ingested 45mg/daily of AstaREAL® Astaxanthin for 4 weeks - 7 times higher than the suggested dose of 6mg/daily. The study revealed NOAEL on all standard examination parameters including eye intraocular pressure (review on Kajita et al, 2010).

AstaREAL® and Acute/Subchronic Test

The animal toxicological studies database for AstaREAL includes 11 trials ranging from single dose to 90-day subchronic test. The doses used in these trials ranged from 400mg to 2000mg/kg. All studies revealed NOAEL. A summary of clinical trial designs, doses and adverse effects noted in these investigations is presented in Table 1-2.

In vivo micronucleus test was conducted on mice after ingesting 2000 mg/kg of AstaREAL® in a single dosage (Takahashi et al. 2009). The study revealed NOAEL on food consumption, body weight, hematology, clotting, or detailed pathology and clinical observations. When tested for genotoxicity, there was no evidence for mutagenicity in Ames/Salmonella assays. Furthermore, subsequent in vitro study showed no induction of chromosome aberration and no mutagenicity effects. In a teratology study, rabbits, after ingesting 400mg/kg, revealed no maternal embryo-toxic or teratogenic effects over the gestational period.

AstaREAL® Safety Conclusion

A comprehensive set of studies in both animals and humans clearly constitute a sufficient database to evaluate the potential toxicity of astaxanthin in extracts or algal biomass. The lack of any toxicological findings from any study on astaxanthin is supportive of a reasonable expectation of safety from its recommended use. Furthermore, an independent expert, Harry G. Preuss M.D. of Georgetown University Medical Center, has reviewed the available literature through 2001 on the safety of astaxanthin. In his report, Dr. Preuss evaluated dietary, animal toxicity and human studies. His report concludes that astaxanthin, when used in proper doses, is safe and deserves no more safety concerns than the use of other carotenoids.

Table 1. Animal Toxicological Studies Conducted Using Astaxanthin Biomass

Study Type	Dose of Astaxanthin Extract/ Duration	Species/ Assay Cells	Results	References
Acute and Subchronic toxicity	10,000 ppm; 50,000 ppm; 200,000 ppmm OECD-GLP Compliant	Rats Wistar rats (10 sex/group) 4 groups	NOAEL of the astaxanthin-rich biomass for male and female rats were determined as 14, 161 and 17,076 mg/kg body weight/day or 465 and 557 mg astaxanthin/kg/day, respectively	2008. Stewart et al., Food and Chemical Toxicology. Vol.46 (9); pp.3030–3036
Oral LD 50 dose study	12g/kg body weight single dose observed for 14 days OECD-GLP Compliant	Rats 5/sex		
Short-term repeat dose toxicity study	6g/kg for 14 days OECD-GLP Compliant	Rats 6/sex		
Ames Mutagenicity	Up to 5000 µg/ml in plate assay OECD-GLP Compliant	Salmonella with 4 standard test strains ± S9	No increase in revertants	1998 Report # 28708 Fuji Commissioned Study
E. coli Mutagenicity	Up to 5000 µg/ml in plate assay OECD-GLP Compliant	E. coli WP2 uvr A ± S9	No increase in revertants	1998 Report # 28708 Fuji Commissioned Study
Micronucleus Induction in Vivo	2000 mg/kg in single dose OECD-GLP Compliant	Mice 5/sex	No increase in micronuclei	1998 Report # 26832 Fuji Commissioned Study
Mammalian Cell	Up to 5000 µ/ml	Mouse lymphoma	No increase in mutation	1998 Report # 28709 Fuji Commissioned Study
Mutagenicity	OECD-GLP Compliant	L5178Y cells	Frequency	

NOAEL: No Observed Adverse Effect Level

Table 2. Animal Toxicological Studies Conducted Using Astaxanthin Extract

Study Type	Dose of Astaxanthin Extract/ Duration	Species/ Assay Cells	Results	References
Micronucleus Test and Chromosome Aberration Test Toxicity Study	2000 mg/kg in single dosage	25	NOAEL on food consumption, body weight, hematology, clotting, or detailed pathology, and clinical observations. No inductivity of chromosome aberration, no mutagenicity	2009. Takahashi et al. Journal of Clinical Therapeutics and Medicines Vol.20 (6); pp.79-87. Fuji Commissioned Study
90-Day Subchronic Oral Toxicity	37-925.9 mg/kg/day	100 Rats	NOAEL on food consumption, body weight, hematology, clotting, or detailed pathology, and clinical observations.	2004. Takahashi et al., Journal. Clinical Therapeutics and. Medicines Vol. 20(8); pp.867-881. Fuji Commissioned Study
Acute Oral Toxicity	2000 mg/kg in single dose	Rats 5/sex	NOAEL on food consumption, body weight, hematology, clotting, or detailed pathology, and clinical observations. Loose stools noted.	2004. Takahashi et al., Journal of. Clinical Therapeutics and. Medicines. Vol.20(8); pp.867-881. Fuji Commissioned Study
Ames Mutagenicity	Up to 5000 µg/ml in plate assay	Salmonella with 4 standard test strains ± S9	No increase in revertants	2004. Takahashi et al., Journal of. Clinical Therapeutics and. Medicines. Vol. 20(8); pp.867-881. Fuji Commissioned Study
13-Week Subchronic Toxicity	0.025, 0.075 and 0.25% of diet	Rats 10/sex/dose level	NOAEL on food consumption, body weight, hematology, organ weights or gross or microscopic pathology exams. Increase in cholesterol at high dose level only noted serum chemistry change. NOAEL-0.25%	1999. Ono et al., Bulletin of Natural Health Science Vol. 117. pp.91-98
41-Day Repeat Dose Toxicity and Fertility Study	400 mg/kg in diet or 0.04%	Rats 8 males in toxicological study 15/sex in breeding	NOAEL on growth, clinical observations, organ weights and plasma levels of liver enzymes. No effect on fertility, litter or pup size or any gross abnormalities in offspring.	1997. Nishikawa et al., Translated from Proceedings of Department of Nutrition of Koshien University, Vol. 25(A); pp.19-25

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Table 3. Human Studies Astaxanthin Biomass

Study Type	Dose of Astaxanthin Extract/ Duration	Species/ Assay Cells	Results	References
Muscle Endurance/Safety Observation	4 mg/day for 6 months Double-Blind-Placebo-Controlled	40	NOAEL reported in treated groups. Increased muscle endurance.	2008. Malmsten et al., Carotenoid Science, Vol.13. pp. 20-22
Dyspepsia/Safety Observation	16mg/day or 40 mg/day for 4 weeks Double Blind Placebo Controlled	132	NOAEL reported in treated groups. Significantly reduced dyspeptic symptoms.	2008. Kupcinskas et al., Phytomedicine. 2008 Jun Vol.15 (6-7); pp.391-399.
Dyspepsia/Safety Observation	40mg/day for 8 weeks Placebo Controlled	21	NOEAL in treated groups.	2007. Andersen et al., FEM Immunology and Medical Microbiology Vol. 50 pp.244-248
Plasma Lipids & Peroxidation/Safety Observation	8 mg/day for 3 months Double Blind Placebo Controlled	20	NOAEL reported in plasma vitamin A or C equivalents, lycopene or other carotenoids, no change in interleukin markers; no change in serum lipids or fatty acid profile; significant decrease in fatty acid peroxidation.	2007. Karppi et al., International Journal for Vitamins and Nutritional Research Vol. 77(1); pp.3-11
Sperm Quality/Safety Observation	16 mg/day for 3 months Double Blind Placebo Controlled	30	NOAEL reported. Increased quality of sperm.	2005 Comhaire et al., Asian Journal of. Andrology. Vol. 7(3); pp.257-262.
Helicobacter Pylori/Safety Observation	40 mg/day for 3 weeks Open Label	10	NOAEL reported in treated group. Significantly reduced dyspeptic clinical symptoms.	1998. Lignell Report GS98/01 12th International Carotenoid Symposium Fuji Internal Report

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Table 4. Human Studies with Astaxanthin Extracts

Study Type	Dose of Astaxanthin Extract/ Duration	Species/ Assay Cells	Results	References
High-Dose Safety Assessment	45mg/day for 4 weeks	22	NOAEL reported based on hematological, serum chemistry and urinalysis parameters.	2010. Kajita et al., Journal Review of Clinical Ophtalomogica Japonica Vol. 3(4); pp.365-382
Long-Term Consumption Safety Assessment	9mg/day for 12 weeks Open-label	15	NOAEL reported based on hematological examination, biochemical testing, urinalysis and interview with physician before and after 4, 8 and 12 weeks of treatment	2010. Matsuyama et al., Japanese Journal of Complementary and Alternative Medicine Vol. 7(1); pp.43-50
Efficacy and Safety	12mg/day for 8 weeks Open Label	35	NOAEL. Enhance antioxidant capacity/reduce lower limb vascular resistance, decrease blood pressure	2009. Iwabayashi et al., Anti Aging Medicine 6 (4); pp.15-21
Intraocular Pressure Safety Assessment	30mg/day for 4 weeks Double Blind Placebo Controlled	25	NOAEL reported based on hematological and biochemical blood tests, ophthalmological examinations including intraocular tension and questions by doctors	2009. Kajita et al., Journal of Clinical. Therapeutics Medicines. Vol.25 (8); pp.37-49
Blood Flow Safety	6mg/day for 4 weeks Open Label	15	NOAEL reported in treated groups	2008. Tsukahara et al., Journal of Nutritional Food. Vol 8(1); pp. 27-37
Eye Function/ Safety Assessment	6 mg/day for 4 weeks Double Blind Placebo Controlled	59	NOAEL on biochemical & hematological examination and questionnaire. Reduced eye fatigue.	2006. Nagaki et al., Journal of Clinical Therapeutics and Medicines. Vol.22 (1); pp.41-54
Exercise Tolerance/ Safety Observation	5 mg/day for 2 weeks Double Blind Placebo Controlled	19	NOAEL reported in treated groups	2006. Nagata et al., Carotenoid Science Vol. 10; pp.102-106
Blood Rheology/ Safety Assessment	6 mg/day for 10 days Single Blind Placebo Controlled	20	NOAEL reported on subject questionnaire, blood rheology, and serum biochemistry.	2005. Miyawaki et al., J. Clinical Therapeutics and. Medicines. Vol. 21 (4); pp.421-426
High Oral Dose/ Safety Assessment	30 mg/day for 4 weeks Open Label	10	NOAEL reported on full blood tests.	2005. Ohgami et al., Journal of. Clinical. Therapeutics and Medicines. Vol. 21 (8); pp.79-87.
Long Term Oral/ Safety Assessment	6 mg/day for 12 weeks Open Label	15	NOAEL reported on full blood tests.	2005. Tsukahara et al., Journal of Nutritional Food. Vol. 8 (1); pp.27-37
Eye Function/ Safety Assessment	6mg/day for 2 weeks Open Label	10	NOAEL reported in treated groups	2005. Takahashi and Fajita. Journal of Clinical Therapeutics and Medicines Vol. 21(4); pp. 431-436
Eye Function/ Safety Assessment	6 mg/day for 4 weeks Double Blind Placebo Controlled	20	NOAEL reported in subject questionnaire, biochemical & hematological examination.	2005. Shiratori et al., Journal of. Clinical Therapeutics. Medicines. Vol. 21(5); pp.543-556
Eye Function/ Safety Assessment	6 mg/day for 4 weeks Double Blind Placebo Controlled	36	NOAEL reported in subject questionnaire, biochemical & haematological examination.	2005. Nagaki et al., Journal of. Clinical. Therapeutics and. Medicines. Vol.21(5); pp.537-542.
Eye Function/ Safety Assessment	6 or 12 mg/day for 4 weeks Double Blind Placebo Controlled	40	NOAEL reported based on subject questionnaire, reduced eye fatigue.	2005. Nitta et al., Journal of. Clinical. Therapeutics and Medicines Vol.21(6); pp.637-650.
Eye Function/ Safety Assessment	2, 4, 12 mg/day for 4 weeks Double Blind Placebo Controlled	49	NOAEL reported in treated groups	2004. Nakamura et al., Journal of Clinical Ophthalmology. Vol. 58(6); pp.1051-1054
Eye & Muscle/ Safety Observation	6 mg/day for 4 weeks Double Blind, Placebo Controlled	34	NOAEL reported on full hematological analysis. Increased eye function. Reduced lactic acid.	2002. Sawaki et al., Journal of Clinical Medicine 18(9); pp.1085-1100
Eye Function/ Safety Observation	5 mg/day for 4 weeks Double blind, placebo controlled	26	NOAEL reported in treatment groups. Reduced eye fatigue.	2002. Nagaki et al., Journal of Traditional Medicines Vol. 19(5); pp. 170-173

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Table 4. Human Studies with Astaxanthin Extracts (cont'd)

Study Type	Dose of Astaxanthin Extract/ Duration	Species/Assay Cells	Results	References
Safety Assessment	2, 4 or 12 mg/day for 4 weeks Open Label	17	NOAEL reported on blood rheology, serum biochemistry.	2002. Fuji Internal Report
Bioavailability/Safety	40mg/day, Single dose	32	NOAEL reported in treated groups.	2003. Odeberg et al., Eur J Pharm Sci. Vol. 19(4); pp.299-304
Safety Assessment Eye Fatigue Accommodative Function	9mg/day for 4 weeks Double Blind Placebo Controlled	84	NOAEL on biochemical and hematological examination and questionnaire. Reduced eye fatigue and improved eye accomodative function	2010. Nagaki et al. Journal Review of Clinical Ophtalomogica Japonica Vol 3(5); pp.461-468.

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AstaReal
Be you, Just healthier

3 Terri Lane, Unit 12
Burlington, NJ 08016
Tel: 609-386-3030 ax: 609-386-3033

www.astarealusa.com contact@astarealusa.com