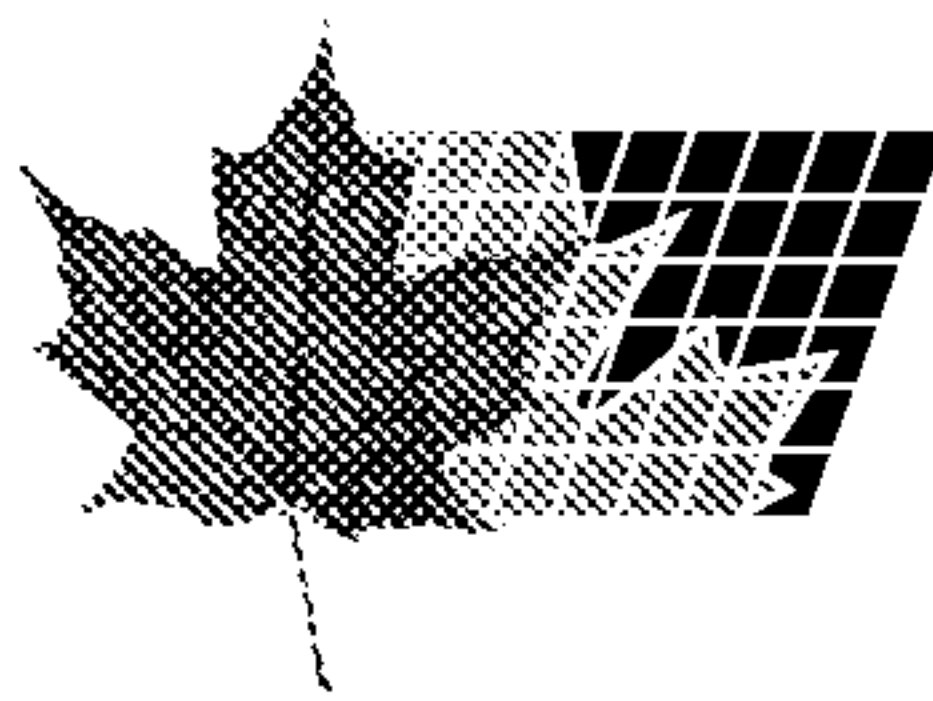




(72) LIGNELL, AKE, SE

(71) ASTACAROTENE AB, SE

(51) Int.Cl.⁷ A61K 31/12, A61K 31/07

(30) 1997/09/04 (9703191-8) SE

(54) **MÉDICAMENT POUR L'AMÉLIORATION DE LA DUREE DE
LA FONCTION MUSCULAIRE OU LE TRAITEMENT DE
TROUBLES OU DE MALADIES MUSCULAIRES**

(54) **MEDICAMENT FOR IMPROVEMENT OF DURATION OF
MUSCLE FUNCTION OR TREATMENT OF MUSCLE
DISORDERS OR DISEASES**

(57) L'invention concerne un médicament pour l'amélioration prophylactique et/ou thérapeutique de la durée de la fonction musculaire chez un mammifère et/ou pour le traitement de troubles ou de maladies musculaires chez un mammifère (par exemple, syndrome du cheval noué), qui comprend au moins un type de xanthophylle (par exemple, astaxanthine). L'invention concerne également l'utilisation de xanthophylles dans la préparation du type de médicament considéré, et un procédé permettant l'amélioration prophylactique et/ou thérapeutique de la durée de la fonction musculaire chez un mammifère et/ou le traitement de troubles ou de maladies musculaires chez un mammifère.

(57) Medicament for the prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, e.g. equine Exertional Rhabdomyolysis, comprising at least one type of xanthophylles, e.g. astaxanthin, is described. Further, the use of xanthophylles in the preparation of such medicaments, and a method of prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, are disclosed.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/12, 31/07	A1	(11) International Publication Number: WO 99/11251 (43) International Publication Date: 11 March 1999 (11.03.99)
(21) International Application Number: PCT/SE98/01526 (22) International Filing Date: 26 August 1998 (26.08.98) (30) Priority Data: 9703191-8 4 September 1997 (04.09.97) SE (71) Applicant (for all designated States except US): ASTAC- AROTENE AB [SE/SE]; Idrottsvägen 4, S-134 40 Gustavs- berg (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): LIGNELL, Åke [SE/SE]; Klippstigen 5, S-139 00 Värmdö (SE). (74) Agents: ONN, Thorsten et al.; AB Stockholms Patentbyrå AB, Zacco & Bruhn (publ), P.O. Box 23101, S-104 35 Stockholm (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: MEDICAMENT FOR IMPROVEMENT OF DURATION OF MUSCLE FUNCTION OR TREATMENT OF MUSCLE DISORDERS OR DISEASES		
(57) Abstract Medicament for the prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, e.g. equine Exertional Rhabdomyolysis, comprising at least one type of xanthophylles, e.g. astaxanthin, is described. Further, the use of xanthophylles in the preparation of such medicaments, and a method of prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, are disclosed.		

5

**MEDICAMENT FOR IMPROVEMENT OF DURATION OF MUSCLE FUNCTION OR
TREATMENT OF MUSCLE DISORDERS OR DISEASES.**

10 The present invention relates to a medicament for the prophylactic and/or therapeutic
improvement of the duration of mammalian muscle function and/or treatment of
mammalian muscle disorders or diseases, comprising at least one type of
xanthophylles, especially astaxanthin. The invention also relates to the use of at
least one type of xanthophylles for the production of such a medicament and to a
15 method of prophylactic and/or therapeutic improvement of the duration of
mammalian muscle function and/or treatment of mammalian muscle disorders or
diseases, e.g. equine Exertional Rhabdomyolysis.

Background of the invention

20

Exertional rhabdomyolysis, also referred to as exertional myopathy, tying-up
syndrome, azoturia, or Monday morning disease, is probably the most common
muscle disorder in horses. Predisposing or associated factors that have been
implicated in the pathogenesis of this condition include electrolyte imbalances,
25 hypothyroidism, and vitamin E-selenium deficiency. Therefore, treatment of horses
affected by exertional rhabdomyolysis have included pain relief, rehydration and
correction of electrolyte abnormalities (See e.g. The Horse: Diseases and Clinical
Management, edited by C. N. Kolbluk, T. R. Ames, R. J. Geor, W.B. Saunders
Company, Philadelphia, 1995, pp. 809-810).

30

Xanthophylles, including astaxanthin, is a large group of carotenoids containing
oxygen in the molecule in addition to carbon and hydrogen. The carotenoids are

produced *de novo* by plants, fungi and some bacteria. Astaxanthin, in the form of naturally produced algal meal of cultured *Haematococcus* sp., has been marketed as antioxidant for mammals, especially humans.

Description of the invention

5

The present invention provides a medicament for the prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, comprising at least one type of xanthophylles.

10

In a preferred embodiment the type of xanthophyll is astaxanthin, particularly in a form esterified with fatty acids.

15

In a most preferred embodiment the astaxanthin in esterified form with fatty acids is algal meal of cultured *Haematococcus* sp.

Examples of mammalian muscle disorders or diseases include human myopathies and connective tissue diseases, as well as equine myopathies and connective tissue diseases.

20

In a particular embodiment of the invention, the mammalian muscle disorder is equine Exertional Rhabdomyolysis.

25

The medicament according to the invention may comprise a mixture of different types of xanthophylles or different forms of the same xanthophyll, such as a mixture of synthetic astaxanthin and naturally produced astaxanthin.

30

The medicament of the invention may comprise additional ingredients which are pharmacologically acceptable inactive or active in prophylactic and/or therapeutic use, such as flavoring agents, excipients, diluents, carriers, etc., and it may be presented in a separate unit dose or in admixture with food or feed. Examples of separate unit doses are tablets, gelatin capsules and predetermined amounts of

solutions, e. g. oil solutions, or emulsions, e.g. water-in- oil or oil-in-water emulsions. Examples of food in which the preparation of the invention may be incorporated is dairy products, such as joughurt, chocolate and cereals. The daily doses of the xanthophyll in the medicament of the invention will normally be in the range of 0.01
5 to 1 mg per kg body weight.

The present invention also comprises the use of at least one type of xanthophylles in the preparation of a medicament for the prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian
10 muscle disorders or diseases. Once again, the preferred type of xanthophyll is astaxanthin, particularly in a form esterified with fatty acids, e.g. in the form of algal meal of cultured *Haematococcus* sp. ; and in a specific embodiment the mammalian muscle disorder is equine Exertional Rhabdomyolysis.

15 Further, the invention comprises a method of prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, e.g. equine Exertional Rhabdomyolysis, comprising administration to said mammal of a prophylactically and/or therapeutically effective dose of a medicament according to the invention.

20

Short description of the drawings

Figure 1 is a diagram showing the up-take of different carotenoids, e.g. astaxanthin, in rat muscle.

25 Figure 2 is a diagram showing the up-take of different carotenoids, e.g. astaxanthin, in rat heart.

Figure 3 is a diagram showing the carotenoid content in different rat organs after feed supplementation with astaxanthin.

Experiments

The medicament used in the experiments is the xanthophyll astaxanthin which was produced via culturing of the algae *Haematococcus* sp. by AstaCarotene AB,
5 Gustavsberg, Sweden.

Astaxanthin from other sources, and other xanthophylls as well, are expected to be similarly useful for the purposes of the invention. An advantage of using astaxanthin from algae is, however, that the astaxanthin exists in a form esterified with fatty acids
10 [Renström B. et al, 1981, *Phytochem* 20(11) :2561-2564], which esterified astaxanthin thereby is more stable during handling and storage than free astaxanthin.

Uptake of astaxanthin in rat

15

The experiment was conducted to establish if astaxanthin in the form of algal meal was taken up by rat and to see in which organs and tissues astaxanthin is accumulated.

Performance

20

A medicament in the form of feed containing 100 mg astaxanthin per kg feed in the form of algal meal was prepared.

Twenty-four male rats were divided into two groups; one group received feed without algal meal, and the other group received the feed containing algal meal.

25 After three weeks 6 rats from each group were sacrificed, and the remaining rats were sacrificed after 6 weeks.

At slaughter organs were excised, i. a. thigh muscle and heart, and they were freezed for later analysis of the content of carotenoids with the aid of HPLC.

Results

Astaxanthin could be demonstrated in both thigh muscle (see Fig. 1) and heart (see Fig. 2) of those rats that had received the feed supplemented with algal meal. In the control group, astaxanthin was not detectable.

- 5 Muscular tissue and particularly heart showed amongst the highest levels of astaxanthin after supplementation compared to the rest of the examined organs (see Fig. 3)

Effect of astaxanthin in horse

10

This preliminary experiment was conducted to establish if astaxanthin is taken up by horses and if supplementation with astaxanthin in the form of algal meal would improve the physical performance of trotting-horses.

Dosage

The horses received 100 mg astaxanthin per horse (approx. 500 kg) per day in the form of algal meal. The meal was supplied to the horses either sprinkled on concentrated feed or in the form of oil suspension.

Uptake

Astaxanthin could be demonstrated in muscles from horses that had received supplementation with the algal meal. The analyses were performed with the aid of HPLC on muscle biopsies. Astaxanthin could also be demonstrated in plasma samples from horses who had received the supplementation.

25

Effects

The most striking effect of the supplementation has been on horses suffering from muscle problems, so-called Exertional Rhabdomyolysis. In some horses this disorder appears when they are trained and raced regularly. It is not known what it is that
30 causes the problems, but it is believed that the muscles are tightened and therefore the circulation is impaired, resulting in degradation of the muscular tissue. Today,

there is no remedy for the problem except rest and increased dosage of vitamin E in the feed.

Problem-horses who have received the astaxanthin-supplementation have been free from the symptom after 2 - 3 weeks, and they have been able to train and race in a normal way. In cases where the supplementation has been stopped or the dosage has been less than 30 mg astaxanthin per day, the symptom has reoccurred after approximately 2 weeks. The algal meal supplement has been given to a total of 8 so-called problem-horses, and they have all responded positively to the supplementation.

10

Effect of astaxanthin on the physical performance of humans

The experiment was conducted so that for a period of 6 months, 20 healthy volunteers received 1 capsule containing 4 mg astaxanthin in the form of algal meal each morning in association with food, and 20 healthy volunteers received 1 capsule containing placebo.

15

Before the experiment was started, reference values were registered for each person with regard to strength/endurance, strength/explosiveness, condition, and weight.

20

Performance

The **strength/endurance** was estimated when a person made a maximum number of knee-bending in a Smith-machine with 40 kg load under standardized conditions.

25 The **strength/explosiveness** was tested under standardized conditions in a Wingate-machine with individually adapted load and registration of maximum effect during 30 seconds. The values were related to effect/ kg of body weight.

30 The **condition** was tested by a step test with 17 kg load and bench height of 32 cm until steady state pulse was reached. (I.e. the pulse did not differ more than three strokes from the measurement of the previous minute).

The **weight difference** between before and after the experiment was checked with a digital scale.

Results

- 5 No significant difference was established between the astaxanthin group and the placebo group in any of the tested parameters due to the small number of test persons.

10 With regard to condition (VO_2 max./kg, minute) there was no significant difference between the groups; a reduction of 1.75% for the astaxanthin group and 1.37% for the placebo group.

A reduction was also seen for both groups in the (strength/explosiveness) Wingate test (W/7 kg); - 4.13% for the astaxanthin group and - 5.81% for the placebo group.

15

Both groups gained weight ; 1.0% for the astaxanthin group and 2.1% for the placebo group. However, the individual differences were quite large, and no tendency could be established.

- 20 However, there was a clear difference between the groups in the strength/endurance test; 61.74% for the astaxanthin group and 23.78% for the placebo group.

25 In summary, the positive performance effect that was attributed to astaxanthin by individual athletes does not seem to be related to an increased condition or explosive strength but to strength/endurance according to this experiment.

CLAIMS

- 5 1. Medicament for the prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, comprising at least one type of xanthophylls.
2. Medicament according to claim 1, wherein the type of xanthophyll is astaxanthin.
- 10 3. Medicament according to claim 2, wherein the astaxanthin is in a form esterified with fatty acids.
4. Medicament according to claim 3, wherein the astaxanthin in esterified form with
- 15 fatty acids is algal meal of cultured *Haematococcus* sp.
5. Medicament according to any one of claims 1 - 4, wherein the mammalian muscle disorder is equine Exertional Rhabdomyolysis.
- 20 6. Use of at least one type of xanthophylls in the preparation of a medicament for the prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases.
7. Use according to claim 6, wherein the type of xanthophyll is astaxanthin.
- 25 8. Use according to claim 7, wherein the astaxanthin is in a form esterified with fatty acids.
9. Use according to claim 8, wherein the astaxanthin in esterified form with fatty
- 30 acids is algal meal of cultured *Haematococcus* sp.

10. Use according to any one of claims 1 - 9 , wherein the mammalian muscle disorder is equine Exertional Rhabdomyolysis.

5 11. Method of prophylactic and/or therapeutic improvement of the duration of mammalian muscle function and/or treatment of mammalian muscle disorders or diseases, comprising administration to said mammal of a prophylactically and/or therapeutically effective dose of a medicament according to any one of claims 1 - 4.

10 12. Method according to claim 9, wherein said mammalian muscle disorder is equine Exertional Rhabdomyolysis.

Muscle

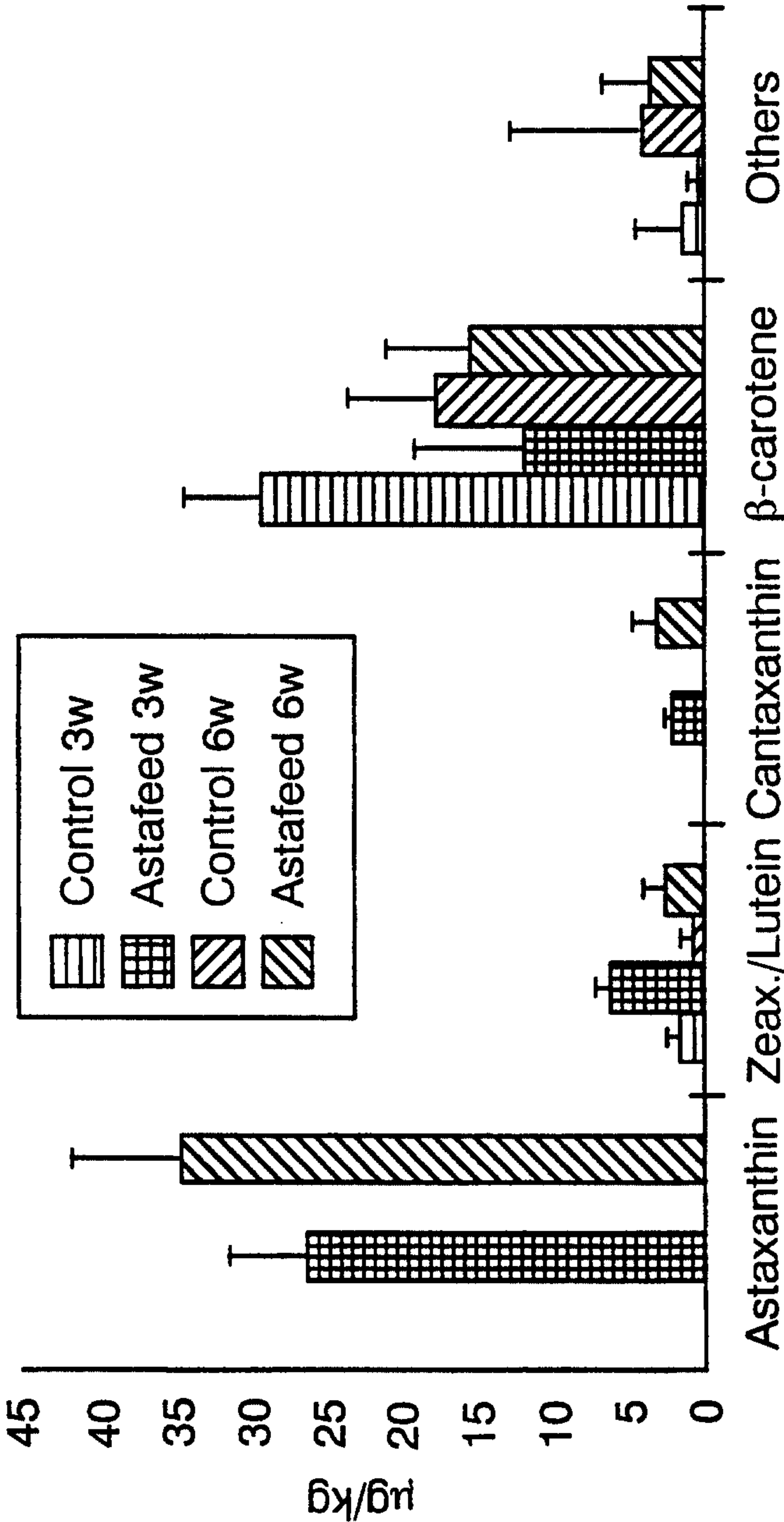


FIG.1

Heart

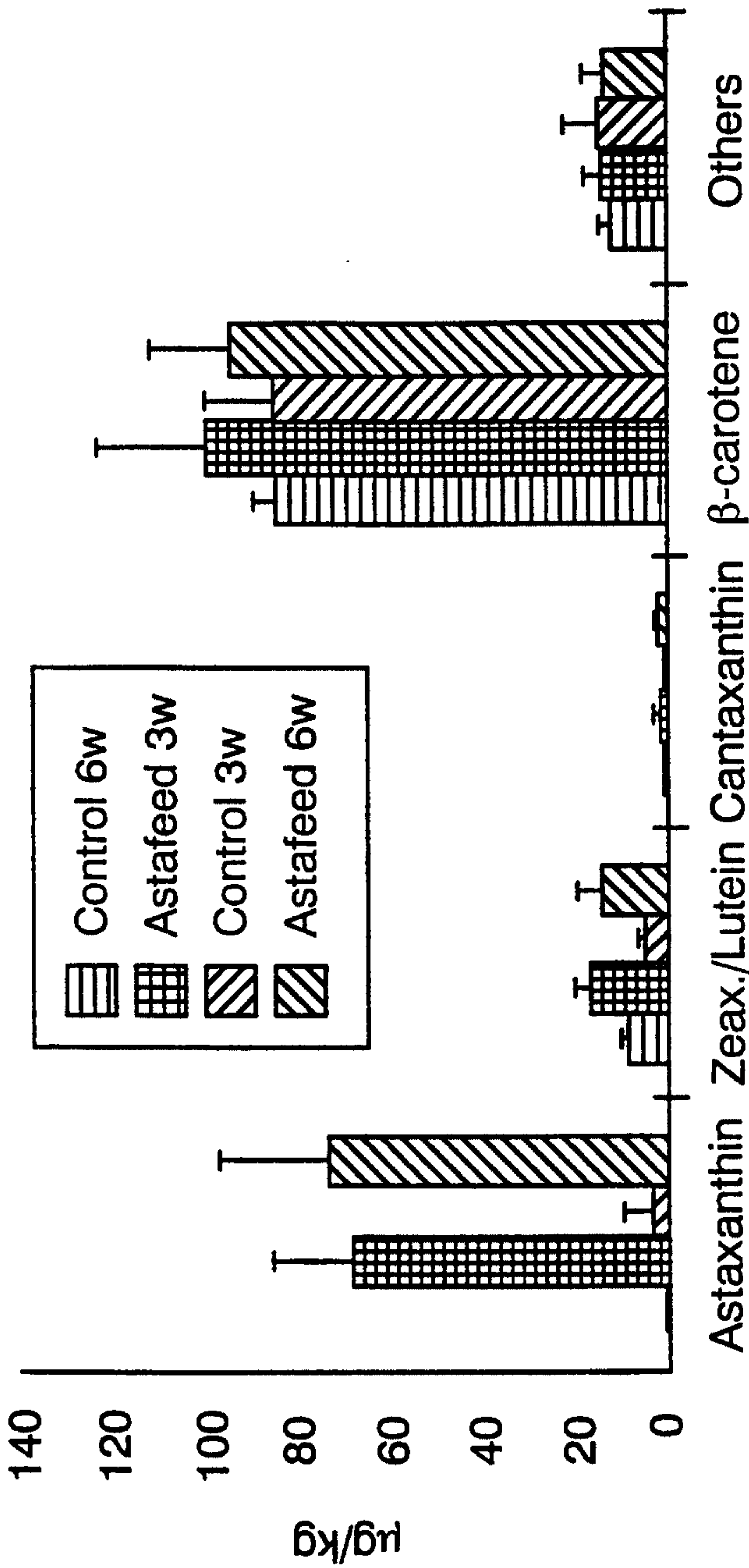


FIG.2

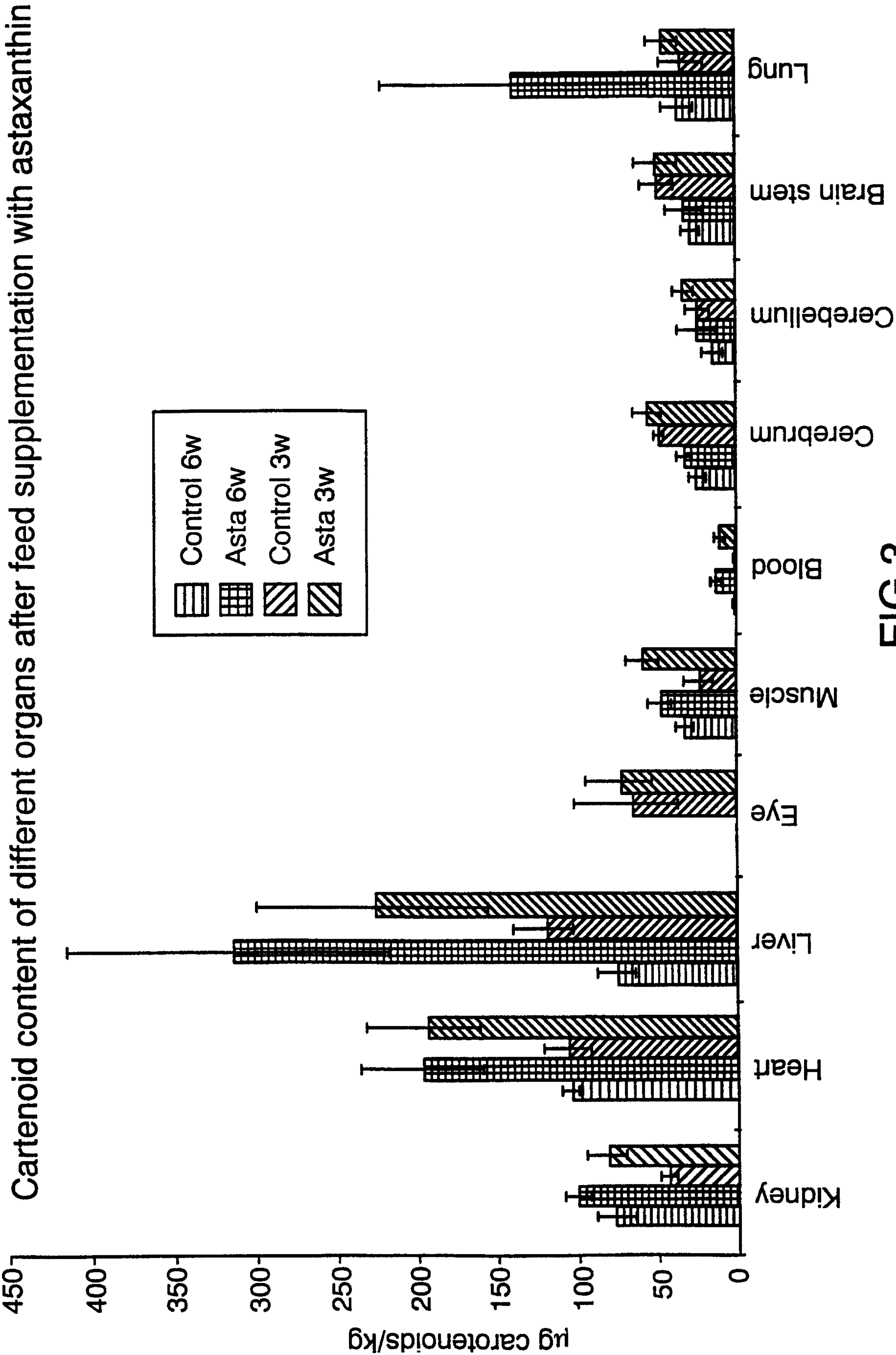


FIG.3