



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date:

FEB 02 2004

6052 '04 FEB -4 P1:54

From:

Division of Dietary Supplement Programs, Office of
Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject:

75-Day Premarket Notification of New Dietary Ingredients

To:

Dockets Management Branch, HFA-305

Subject of the Notification:

Sutherlandia leaf Powder

Firm:

Green Man International Inc.

Date Received by FDA:

9/11/03

90-Day Date:

12/10/03

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Tanya Jackson

95S-0316

RPT 199



Food and Drug Administration
College Park, Maryland 20740

Mr. Andrew R. Laing
Green Man International, Inc.
245 South Gilpin Street
Denver, Colorado 80209

SEP 11 2003

Dear Mr. Laing:

This is to inform you that the notification, dated June 23, 2003, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on June 30, 2003. Your current notification concerns the substance called Sutherlandia leaf powder, identified as Sutherlandia frutescens (L.) R.Br.Moshe & Van Wyk ined., that you intend to market as a new dietary ingredient.

The description of the dietary supplement in the notification states that 300 mg of dried Sutherlandia leaves and soft green stems will be present in each capsule. The notification recommends that one 300 mg capsule be taken twice daily with food. The dietary supplement label will warn against the use of this product by pregnant and lactating women, and since no formal long-term studies have been conducted, it will also warn that the product should not be taken continuously for a period of three months without consulting a physician. The label will also suggest that the product be kept out of reach of children.

Under 21 U.S.C. 350b(a)(2), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing Sutherlandia leaf powder, identified as Sutherlandia frutescens (L.) R.Br.Moshe & Van Wyk ined., when used under the conditions recommended or suggested, will reasonably be expected to be safe.

According to the notification, a 90-day monkey study resulted in no toxic or adverse effects at doses of 0, 9, 27 and 81 mg/kg bw/d. However, a No Observable Effect Level (NOEL) was not assigned and the relevance of the monkey study to the recommended human dose of 600 mg/person/d for three months was not discussed. The notification mentions a study conducted in mice with Sutherlandia at a single dose of 1500 mg/kg bw/d. However, the notification did not provide any information about the test article used in the study and how it relates to the article intended for commerce. In addition, the notification did not include the age, sex or number of mice or the parameters measured during the study. The information provided in the notification does not provide evidence sufficient to support the safe use of Sutherlandia as a new dietary ingredient.

For the reasons discussed above, the information in your notification does not provide an adequate basis to conclude that a Sutherlandia herbal supplement, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Under 21 U.S.C. 321(g)(1)(B), an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease in man is a drug. The information contained in your submission, namely the inclusion of a list of documents setting forth diseases for which Sutherlandia may be an effective treatment, suggests that it is intended to treat, prevent, or mitigate diseases. See 21 CFR 101.93(g). These representations suggest that this product is intended for use as a drug within the meaning of 21 U.S.C. 321(g)(1)(B), and that it is subject to regulation under the drug provisions of the Act. If you intend to make claims or representations of this nature, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, Montrose Metro II, 11919 Rockville Pike, Rockville, Maryland 20852.

Your notification will be kept confidential for 90 days after the filing date of June 30, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

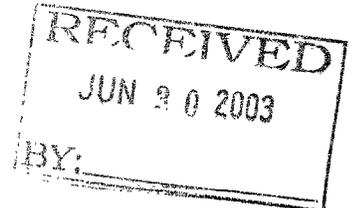
Sincerely yours,

A handwritten signature in black ink, appearing to be 'SJW', with a long horizontal line extending to the right.

Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

COPY

Green Man International, Inc.
245 S. Gilpin St
Denver, CO 80209
Phone: 303-722-5940



June 23, 2003

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Notification of New Dietary Ingredient

Dear Sir or Madam:

This is a 75 day notice pursuant to 21 CFR 190.6, and 21 USC 350b of the Dietary Supplement Health and Education Act of 1994. I wish to notify the FDA that I plan to market **Sutherlandia** as a new dietary ingredient. I am submitting this original and two (2) copies of this notification. I shall not introduce the ingredient or deliver it for introduction into interstate commerce until at least 75 days after the date on which FDA receives this notification.

Distributor

Green Man International, Inc.
245 S. Gilpin Street
Denver, Co 80209

Name of New Dietary Ingredient

Sutherlandia

Latin Binomial Name: *Sutherlandia frutescens* (L.)R.Br.Moshe & Van Wyk ined.
Please note that there exists also *Sutherlandia microphylla* Burchell ex DC. This is a subspecies of *Sutherlandia frutescens*. The names of the two species/subspecies are often used interchangeably and they are considered to be essentially the same plant.

Description of Dietary Supplement

- **Level of New Dietary Ingredient in the Product**
300 mg Sutherlandia per one capsule. Capsules are manufactured from the dried leaves and soft green stems of the plant. No chemical extraction – 100 percent pure plant.
- **Conditions of Use Stated in the Labeling**
Labeling will suggest that one 300 mg capsule be taken twice daily with food. The labeling will warn against the use of this product by pregnant or lactating women. Because no formal long-term studies have been conducted, the label will warn that the product should not be taken continuously for a period of more than three months without consulting a physician. It will also suggest that the product be kept out of reach of children.
The label will further state that the product is free of corn, yeast, wheat, soy, peanuts, salt, dairy product and dairy products and it is formulated without the use of preservatives, artificial colors or flavors.
- **Evidence of safety for the dietary supplement**
Please find attached documentation which establishes that the dietary supplement, when used under the recommended conditions, will reasonably be expected to be safe.

Respectfully Submitted,

Andrew R. Laing (**designated individual**)

Phone: 303-722-5940, mobile: 303-947-0641, e-mail: leapyear96@msn.com

Attachment

Please note: The plant material used in the attached study – “**A Toxicity Study of *Sutherlandia* leaf powder (*Sutherlandia microphylla*) Consumption**” – is identical in form to the new dietary ingredient that I propose to market. The *Sutherlandia* raw material used in the study is the same chemotype raw material as studied by the Medical Research Council (MRC). It was given to the MRC by Dr. Carl Albrecht, a partner at Phyto Nova, the company from which I will be importing the *Sutherlandia* capsules. While the title of the study refers to *Sutherlandia microphylla*, the report itself explains

that “(t)he plant material used in this study... were identified as *Sutherlandia frutescens*, subspecies *microphylla*, by Professor Ben-Erik van Wyk, Head of the Botany Department of the Rand Afrikaans University...Plants were dried at ambient temperature in the shade and leaves and small twigs were utilized” (see 4.2.1. plant material).

The final report on this Toxicity Study was issued in April, 2002. The study was sponsored by the **Medical Research Council of South Africa** and South Africa’s **National Research Foundation**.

The internationally recognized **Medical Research Council of South Africa (MRC)** is one of South Africa’s eight statutory science councils and the country’s premier biomedical science research institution. Some examples of current MRC research include: seeking an effective AIDS vaccine for Africa, effecting changes in mosquito control and malaria drugs and participating in the Global Alliance on Tuberculosis Drug Development (please see <http://www.mrc.ac.za>).

The **National Research Foundation (NRF)** is another of the country’s eight statutory science councils. The NRF is the South African government’s national agency responsible for promoting and supporting basic and applied research, as well as innovation. The NRF provides services and grants vital for supporting research and postgraduate research training (please see <http://www.nrf.ac.za>).

The Indigenous Knowledge Systems Division (IKS Division) of the MRC is dedicated to scientific and clinical validation of promising indigenous medical plants. *Sutherlandia microphylla/frutescens* is a promising indigenous medicinal plant with a history of use going back at least 105 years.

To date, no adverse effects have been reported from this plant. Nevertheless, in order to strengthen the working hypothesis that the plant is indeed safe and efficacious, the MRC decided to use this plant as a test case for safety and efficacy studies on the “clinical platform.” This exhaustive independent safety study was conducted at the MRC Animal Center using 16 vervet monkeys in four groups (control, 1x, 3x and 9x dose of the equivalent recommended daily dose).

Over 50 variables involving involving blood chemistry, haematology, physiology and animal behavior were monitored and evaluated by MRC scientists, statisticians and a medical doctor. No single indication of toxicity was found after feeding the vervet monkeys with dried *Sutherlandia* leaf powder for three months, even at 9x dose. This is the first time that an indigenous South African medicinal plant has been evaluated for safety using vervet monkeys in a controlled environment.

Please note that the contact person for this study is Dr Gilbert Matsabisa of the MRC. He may be contacted at

e-mail: motlalepula.matsabisa@mrc.ac.za

phone: 011-27-21-938-0480

The study follows:

**A Toxicity Study Of *Sutherlandia* Leaf Powder
(*Sutherlandia microphylla*) Consumption**



FINAL REPORT: April 2002

Sponsors:

- 1. Medical Research Council of South Africa**
- 2. National Research Foundation**

Compiled by

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Mr. M. Mdhuli (Scientist)
Dr. M.A. Dhansay (Clinician)
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1. Main objective

The purpose of this study was to investigate the possible toxicity of consumption of *Sutherlandia* leaf powder (*Sutherlandia microphylla*) in vervet monkeys (*Chlorocebus aethiops*), by determining a variety of biochemical, haematological, physiological and physical variables. These variables reflect liver, kidney, muscle, respiratory, intestinal, bone and general biological function.

2. Ethics

The study was approved by the Ethics Committee for Research on Animals (ECRA) of the Medical Research Council (Project No. 110).

3. Abbreviations

AST	Aspartate Transferase
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
Ca	Calcium
CK	Creatinine Kinase
Cl	Chloride
LDH	Lactate Dehydrogenase
GGT	Gamma Glutamyl Transferase
Hb	Haemoglobin
Hct	Haematocrit
HDL-C	High Density Lipoprotein Cholesterol
K	Potassium
LDL-C	Low Density Lipoprotein Cholesterol
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
Mg	Magnesium
Na	Sodium
RBC	Red Blood Cells
RDW	Red Cell Distribution Width
WBC	White Blood Cells

4. Materials and methods

Note: The project protocol was submitted to the sponsors prior to the start of the study, including detailed proposals of all tests to be conducted, and was agreed upon by all parties. The study was designed to evaluate toxicity but not efficacy.

4.1. Nonhuman primates, environment and housing

All vervet monkeys (*Chlorocebus aethiops*) used in the study were maintained in the Primate Unit of the Diabetes Research Group of the MRC under identical housing conditions. The closed indoor environment was maintained at 25 – 27 °C, a humidity of 45%, about 15 air changes/hour and a photoperiod of 12h. All individuals selected for this project were healthy adult males, which were identified with numbers in ink tattoo. Additionally, all cages were marked according to individual, group designation and experiment number. The project was identified and recorded as Experiment 110. The same diet (see 4.3.) was fed throughout the study and water was available *ad lib* via an automatic watering device. All individuals were housed singly during the study but had regular access to exercise cages and environmental enrichment.

4.2. Treatments

4.2.1. Plant material

The plant material used in this study was harvested in the vicinity of Murraysburg, Western Cape Province, South Africa. The plants were identified as *Sutherlandia frutescens*, subspecies *microphylla*, by Professor Ben-Erik van Wyk, Head of the Botany Department of the Rand Afrikaans University (Voucher specimens were dried and stored). Plants were dried at ambient temperature in the shade and leaves and small twigs were utilized. The dried material was powdered using a coffee bean grinder (Robert Bosch Hausgeraete GmbH, E – Nr. MKM 5000) and sterilized with gamma rays at 18.0 kGy (HEPRO, Montague Gardens, Cape Town). Sterilized material was tested for microbial contamination, and no bacterial growth (including *Salmonella* and *Clostridium*), yeasts or moulds were found after 11 hours of incubation (SWIFT Micro Laboratories (Pty) Ltd., Rosebank, Cape Town).

4.2.2. Dose

Adult male vervet monkeys (n=16) were randomly divided into four groups of four individuals each and allocated according to Table 1. The recommended daily dose of *Sutherlandia* leaf powder for humans is 9.0mg/kg bodyweight. This recommended dose is based on the use of two *Sutherlandia* tablets per day, each containing 300mg *Sutherlandia* dried leaf powder.

Table 1. Treatments

Group	<i>Sutherlandia</i> leaf powder concentrations
1	9.0 mg /kg bodyweight (recommended dose)
2	27.0 mg/kg bodyweight (3x recommended dose)
3	81.0 mg/kg bodyweight (9x recommended dose)
4	Control (maize meal)

4.2.3. Duration of treatments

The treatment period was three months.

4.3. Administration of *Sutherlandia* leaf powder

The plant material was mixed into the standard diet, which consisted of 120g of stiff maize porridge, presented as “patties”, containing micro- and macronutrient supplementation. The controls received 120g of standard diet only.

Every individual received an identified amount of food containing the exact dose of *Sutherlandia* leaf powder. Compliance was monitored daily and food consumption/wastage was measured every two weeks.

4.4. Dosing schedule

The diet containing *Sutherlandia* leaf powder was fed every day in the morning throughout the study and the same feeding times were adhered to.

4.5. Clinical monitoring

Blood samples were collected once a month throughout the study. Biochemical variables were determined with a Technicon autoanalyzer and haematological variables with a Coulter STAK S at an accredited laboratory (Pathcare). At the time of blood sampling, body weight, body temperature, respiratory rate, as well as pulse

rate was recorded, and blood pressures were measured using a Dinamap XL vital signs monitor with a neonatal blood pressure cuff #4. For the blood sampling, the vervet monkeys were sedated with Ketamine at 10mg/kg bodyweight intramuscularly and blood was obtained by femoral venipuncture. Urine was collected every two weeks by means of a funnel placed under each cage, and analyzed with urine test strips (UriCheck, RapiMED Diagnostics, South Africa) for leucocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin and glucose.

The following tests were conducted on the blood samples (for definition of abbreviations see section 3):

Haematology: RBC, Hb, MCHC, MCH, MCV, RDW, Hct, platelets, Hb, WBC, basophils, eosinophils, neutrophils, monocytes, lymphocytes.

Clinical Biochemistry: bilirubin (total and unconjugated), AST, ALT, ALP, GGT, LDH, CK, protein, albumin, globulin, cholesterol (total, LDL-C, HDL-C) urea, creatinine, Na, K, Cl, Ca, Mg.

4.6. Observations

All individuals were observed daily and any changes in behaviour (e.g. alert, depressed, fearful, unresponsive, confused, excited, irritable, aggressive) were noted. Apart from clinical signs such as loss of appetite and diarrhea, the following criteria were used to determine wellbeing: coat condition, posture, locomotion, activity, vocalisation and activity in the exercise cage.

4.7. Statistics

All variables were analysed by the MRC Biostatistics Unit utilizing the SAS Version 8 statistical package with the Repeated Measures Analysis of Variance; $P < 0.05$ was considered significant. Statistics were generated for time interactions, time-group interactions and differences between each treatment group and the control group.

5. Results

5.1. Preliminary considerations

- Results and observations are reported and interpreted mainly in terms of possible treatment effects and not biological variation.
- The results in a study such as this do not preclude individual susceptibility and response to the consumption of herbal medicines or any other medicinal compound.
- *Sutherlandia* leaf powder was not tested in pregnant and young animals and the results cannot be extrapolated to these groups.

5.2. Compliance

All individuals consumed their food containing *Sutherlandia* leaf powder bush immediately and no habituation was needed. Food consumption was 100% throughout the study period.

5.3. General observations

The *Sutherlandia* leaf powder had no side effects. There were no signs of discomfort, ill health or abnormal behaviour throughout the study.

5.4. Haematology

The treatment was not associated with statistically or clinically significant changes except for the following:

- A statistically significant difference in red blood cells between group 2 and the controls
- A statistically significant difference in the haemoglobin between group 2 and the controls
- A statistically significant difference in the platelets between Group 1 and the controls

None of the changes was clinically significant and the explanations for this conclusion are provided in Table 2, page 7.

5.5. Biochemistry

The treatment was not associated with statistically or clinically significant changes except for the following:

- Statistically significant differences in the globulins between groups 1, 2 and the controls
- A statistically significant difference in CK between group 1 and the controls
- A statistically significant difference in the ALT of group 2 and the controls
- Statistically significant differences in the ALP between groups 1, 2 and 3 and the controls
- A statistically significant difference in the unconjugated bilirubin between group 1 and the controls
- Statistically significant differences in the urea between groups 1, 2 and 3 and the controls
- Statistically significant differences in the total cholesterol in groups 1, 2 and 3 and the controls.
- Statistically significant difference in the LDL cholesterol between group 2 and the controls

None of the changes was considered clinically significant and the explanations for this conclusion are provided in Table 3, pages 9 and 10.

Table 2: Summary of haematological observations

Variable	<i>P</i> < 0.05	Interpretation	Conclusion
Red Blood Cells	Yes Control vs. Gr. 2	No time-group interaction (<i>P</i> =0.1986), no change in group receiving highest dose (see figure 1)	Not clinically significant
Haematocrit	No		
Haemoglobin	Yes Control vs. Gr. 2	No time-group interaction (<i>P</i> = 0.2151), fluctuation in control group (see Figure 3)	Not clinically significant
Table 2 continued	<i>P</i> < 0.05	Interpretation	Conclusion
MCV	No		
MCH	No		

MCHC	No		
RDW	No		
White blood cells	No		
Neutrophils	No		
Eosinophils	No		
Basophils	No		
Lymphocytes	No		
Monocytes	No		
Platelets	Yes Control vs. Gr. 1	Change in control group (see Figure 14), no changes in other groups on higher doses	Not clinically significant

5.6. Physiological variables

The treatment was not associated with statistically and clinically significant changes except for the following:

- A significant difference in the mean arterial pressure between group 1 and the controls
- An increase in the heart rate in groups 2 and 3.

None of these changes was clinically significant and the explanations for this conclusion are provided in Table 4, page 10.

Note regarding the heart rate: In view of the increase in heart rates in groups 2 and 3, and despite the lack of statistical significance, an extra measurement was obtained for this variable while the monkeys were still being treated (treatment only stopped when all last results were obtained and verified). This extra measurement clearly indicated a decline and return to baseline values in both groups (see [Figure 42](#)). Physiological variables can fluctuate due to exogenous factors.

5.7. Urine analysis

No changes consistent with a treatment effect could be observed in any group.

Table 3: Summary of biochemical observations

Variable	P < 0.05	Interpretation	Conclusion
Ca	No		
Mg	No		
Na	No		
K	No		
Cl	No		
Albumin	No		
Globulin	Yes Control vs. Gr.1 Control vs. Gr.2	Decline in both groups, no change in group receiving highest dose (see Figure 21)	Not clinically significant
Total Protein	No		
CK	Yes Control vs. Gr. 1	Considerable fluctuations in the controls and group 1 (see Figure 23), no changes in both other groups receiving higher dose	Not clinically significant
LDH	No		
GGT	No		
ALT	Yes Control vs. Gr. 2	Group 2 peaks sharply in week 8 only (see Figure 26), no changes in other groups	Not clinically significant
AST	No		
ALP	Yes Control vs. Gr. 1, 2 and 3	Change (decline) in control group (see Figure 28)	Not clinically significant
Total Bilirubin	No		
Table 3 continued	P < 0.05	Interpretation	Conclusion
Unconjugated Bilirubin	Yes Control vs. Gr. 1	Fluctuation in control group – no changes in both other groups receiving a higher dose (see Figure 30)	Not clinically significant

Glucose	No		
Urea	Yes Control vs. Gr. 1, 2 and 3	Considerable fluctuation in control group (see Figure 32)	Not clinically significant
Creatinine	No		
Total Cholesterol	Yes Control vs. Gr. 1, 2 and 3	Fluctuation in control group (see Figure 34)	Not clinically significant
HDL	No		
LDL	Yes Control vs. Gr. 2	Fluctuation in control group (see Figure 36)	Not clinically significant

Table 4: Summary physiological observations

Variable	P < 0.05	Interpretation	Conclusion
Body weight	No		
Body temperature	No		
Systolic Pressure	No		
Diastolic Pressure	No		
Mean Arterial Pressure (MAP)	Yes Control vs. Gr. 1	A steep nadir in group 1 at week 8, recovers at week 12 (see Figure 41)	Not clinically significant
Heart Rate	No	No statistical difference but both groups receiving a high dose increased, a fifth measurement indicates a return to baseline values (see Figure 42)	Not clinically significant

P – values of all variables indicating significant differences are provided in table 5.

Table 5: *P* – values of variables with statistically significant differences/changes

Variable	Time interaction	Time - group interaction	Control versus
----------	------------------	-----------------------------	----------------

Red Blood Cells	0.0541	0.1986	Group 2	0.0410
Haemoglobin	0.1213	0.2151	Group 2	0.0409
Platelets	0.0075	0.2474	Group 1	0.0332
Globulin	0.0013	0.0059	Group 1	0.0011
			Group 2	0.0032
CK	0.8997	0.2333	Group 1	0.0348
ALT	0.0094	0.0355	Group 2	0.0167
ALP	<0.00001	0.0141	Group 1	0.0492
			Group 2	0.0013
			Group 3	0.0103
Unconjugated Bilirubin	0.0739	0.1642	Group 1	0.0165
Urea	0.0787	0.0441	Group 1	0.0145
			Group 2	0.0121
			Group 3	0.0301
Total cholesterol	<0.0001	0.0088	Group 1	0.0356
			Group 2	0.0240
			Group 3	0.0473
LDL cholesterol	0.0020	0.0870	Group 2	0.0315
MAP	0.1413	0.0821	Group 1	0.0423

Note: The statistically significant differences recorded above were all due to fluctuations in the control group or not associated with changes in groups receiving higher doses, as outlined in tables 2,3 and 4, and were not considered clinically significant.

6. Conclusions

Note: These conclusions refer to *Sutherlandia* leaf powder consumption in adult male vervet monkeys for three months.

- At the recommended dose, *Sutherlandia* leaf powder consumption was not associated with toxic or other side effects within the parameters of this study.

Statistically significant differences between this group and the controls were either due to fluctuations in the control group or not associated with changes in both groups receiving a higher dose (see below). The changes were therefore not considered clinically significant.

- At 3x the recommended dose, *Sutherlandia* leaf powder consumption was not associated with any toxic or other side effects within the parameters of this study. Statistically significant differences between this group and the controls were due to fluctuations in the control group or not associated with changes in the group receiving the higher dose (9x). The changes were therefore not considered clinically significant.
- At 9x the recommended dose, *Sutherlandia* leaf powder consumption was not associated with toxic or other side effects within the parameters of this study. Statistically significant differences between this group and the controls were entirely due to fluctuations in the control group and therefore not considered clinically significant.

Unit abbreviations for Appendices I – III

Fl	femtolitre
g/dl	gram/decilitre
g/kg bw	gram/kilogram bodyweight
g/l	gram/litre
iu/l	international units/litre
kg	kilogram
mm/Hg	millimetre Mercury

mmol/l	millimol/litre
pg	picogram
rdw	red cell distribution width
umol/l	micromol/litre

APPENDIX I: Haematology

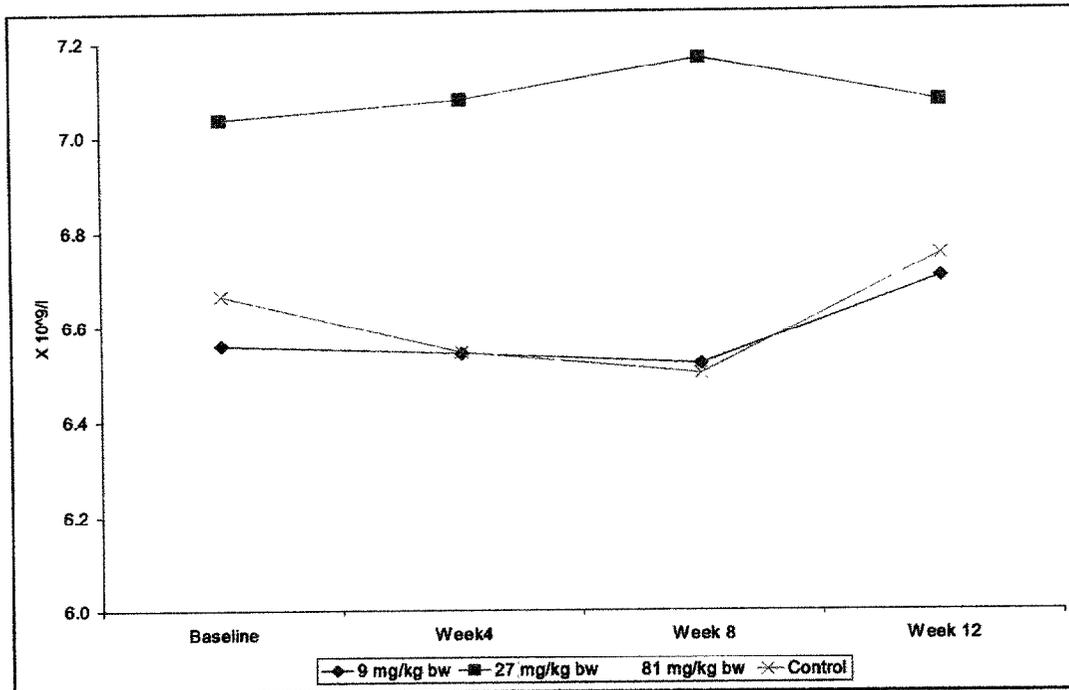


Figure 1. Red blood cells

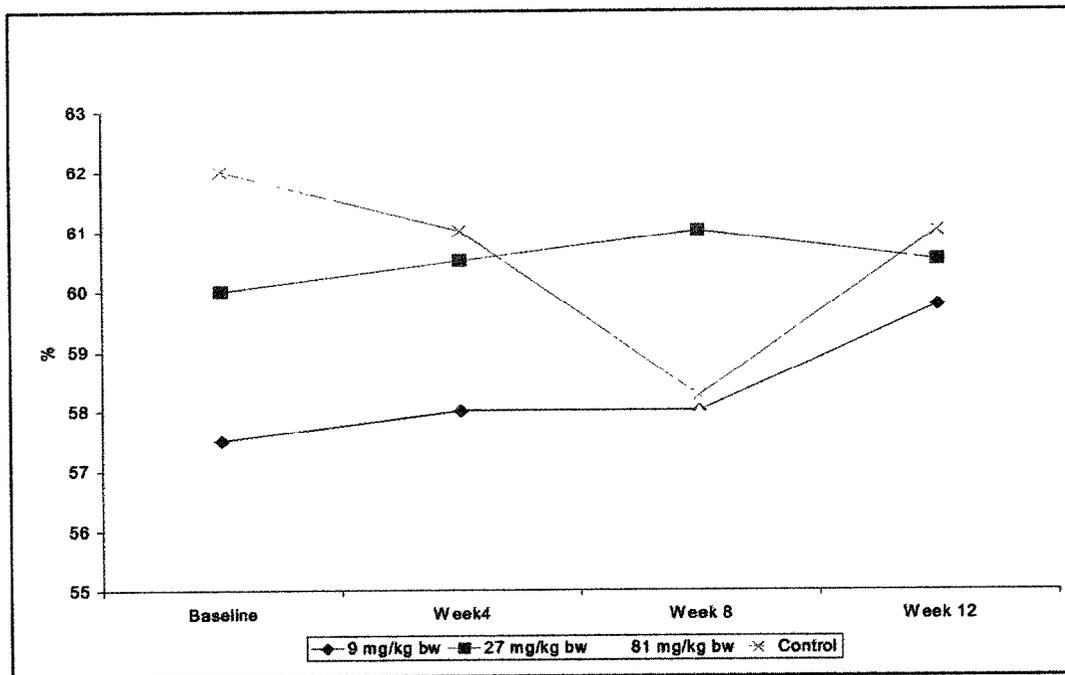


Figure 2. Haematocrit
APPENDIX I: Haematology, continued

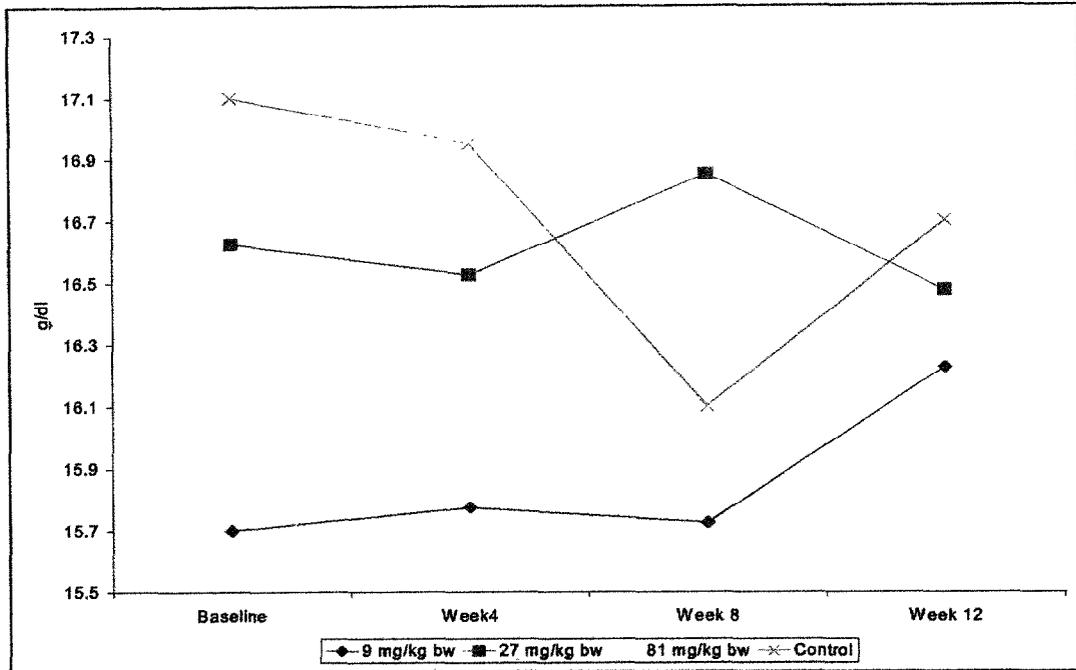


Figure 3. Haemoglobin

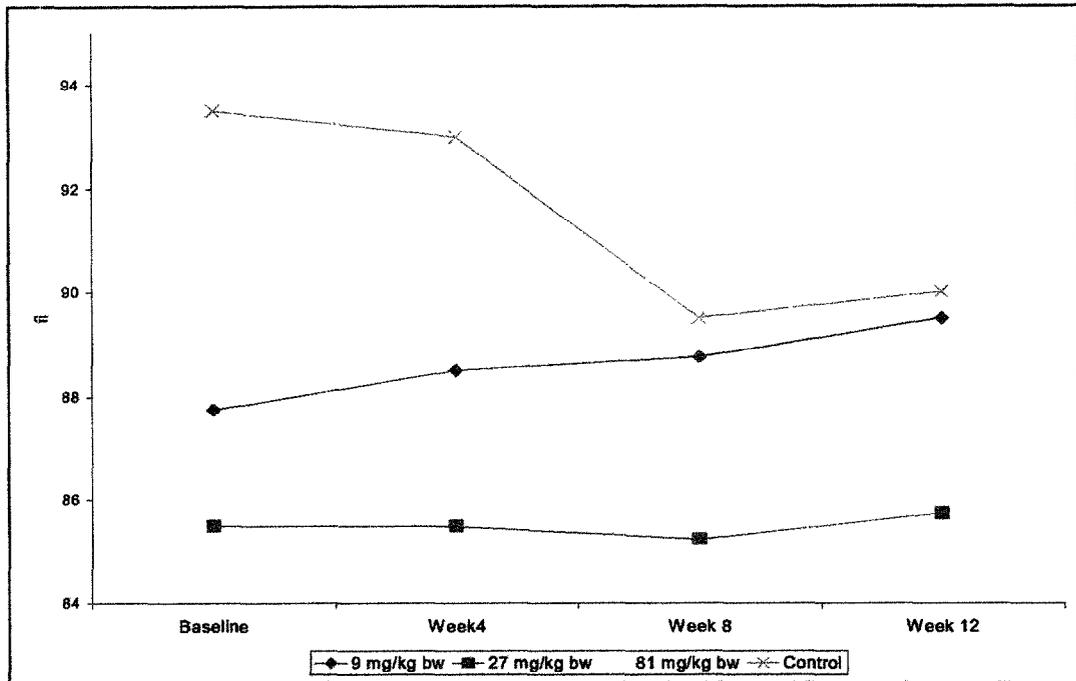


Figure 4. Mean corpuscular volume

APPENDIX I: Haematology, continued

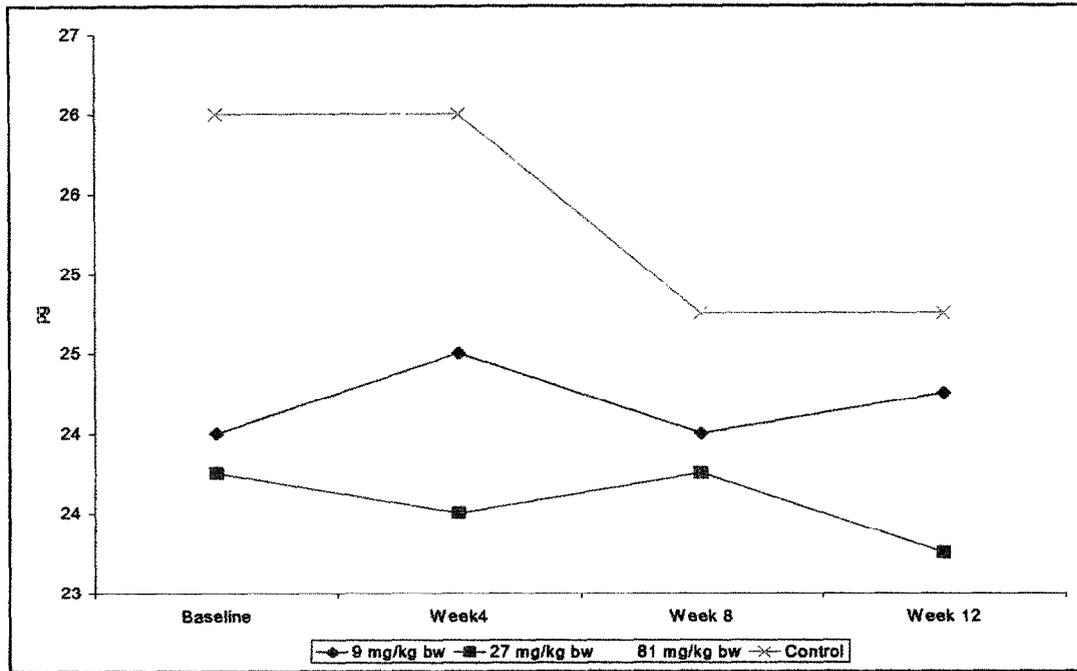


Figure 5. Mean corpuscular haemoglobin

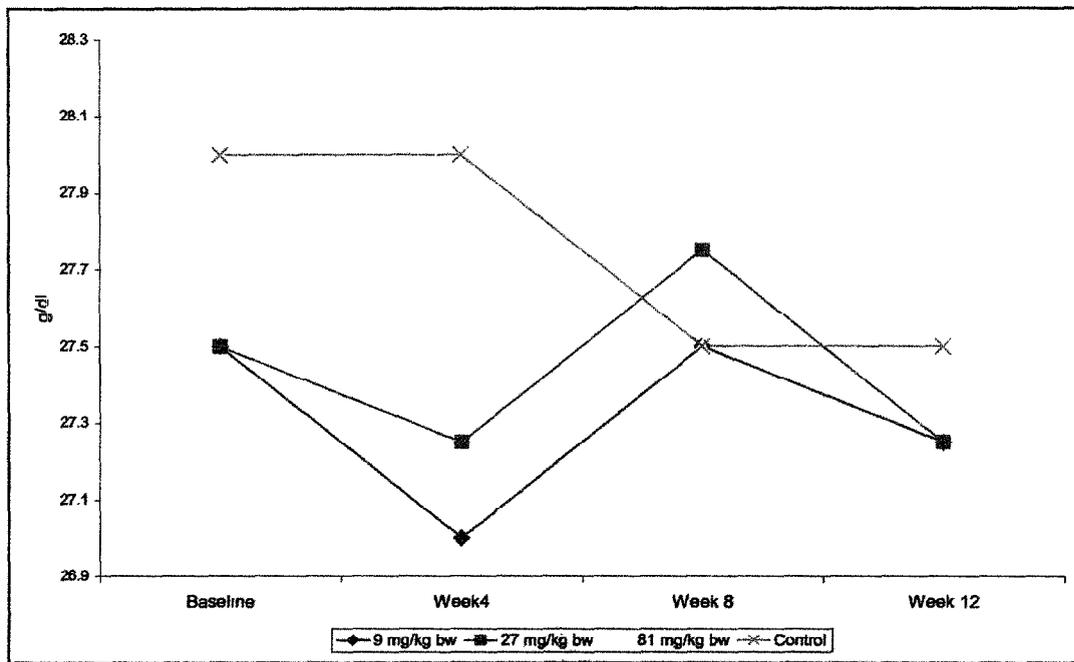


Figure 6. Mean corpuscular haemoglobin concentration
APPENDIX I: Haematology, continued

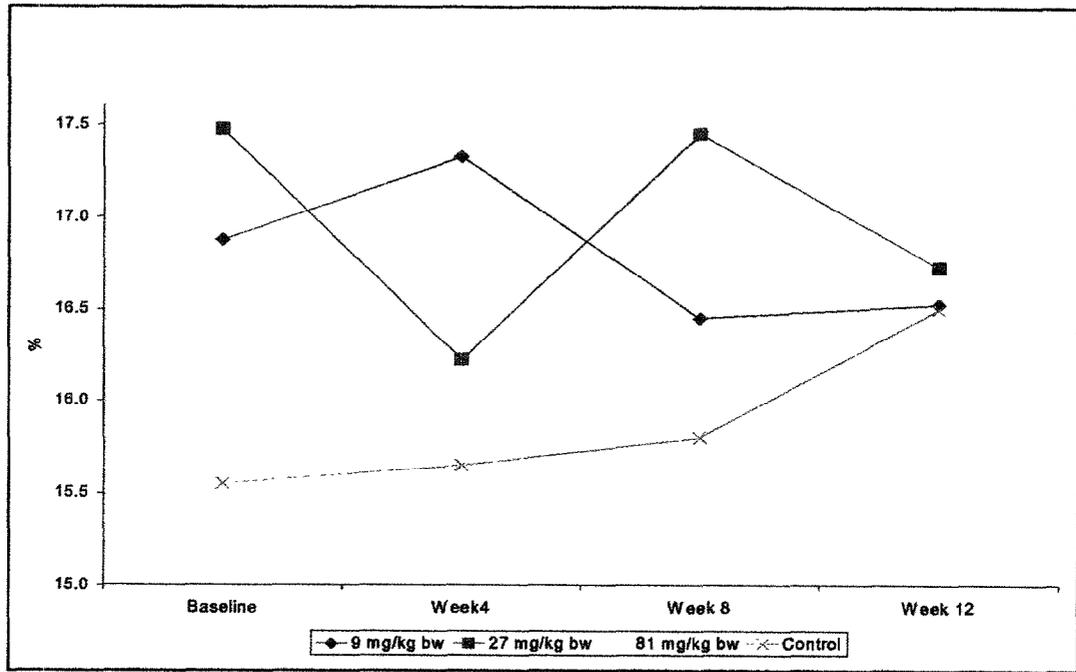


Figure 7. Red cell distribution width

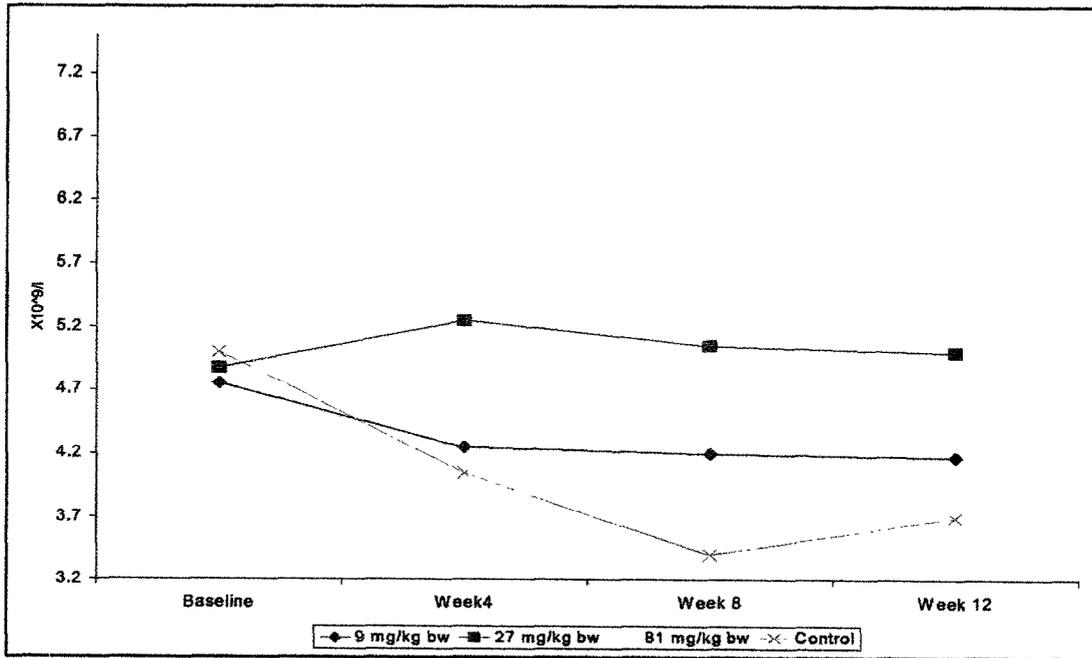


Figure 8. Total white blood cells
APPENDIX I: Haematology, continued

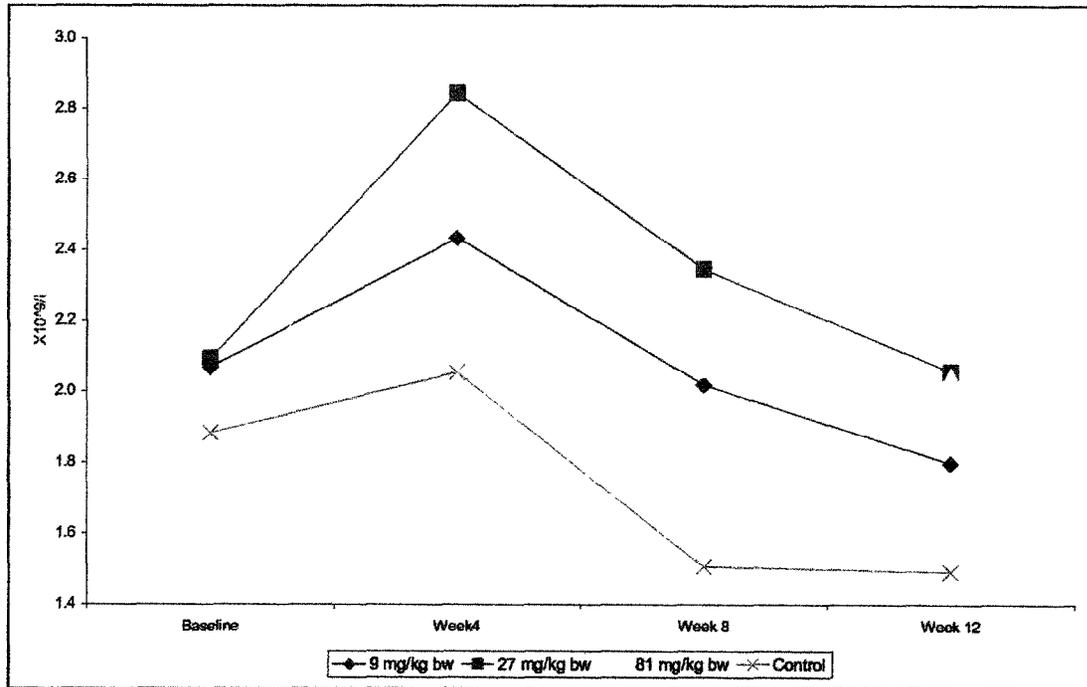


Figure 9. Neutrophils

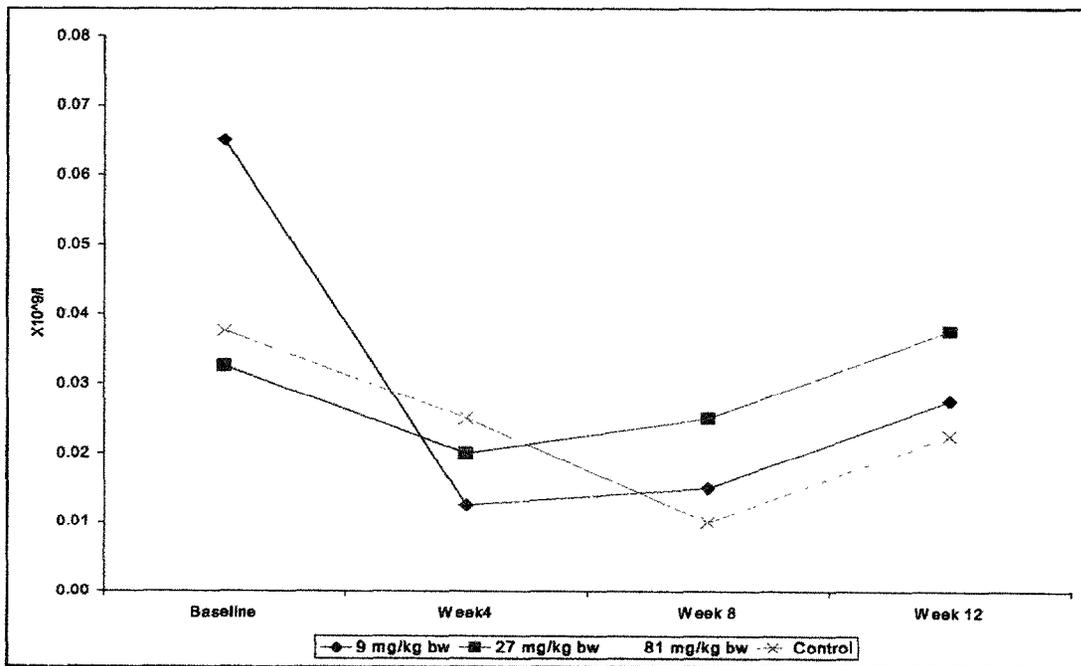


Figure 10. Eosinophils
APPENDIX I: Haematology, continued

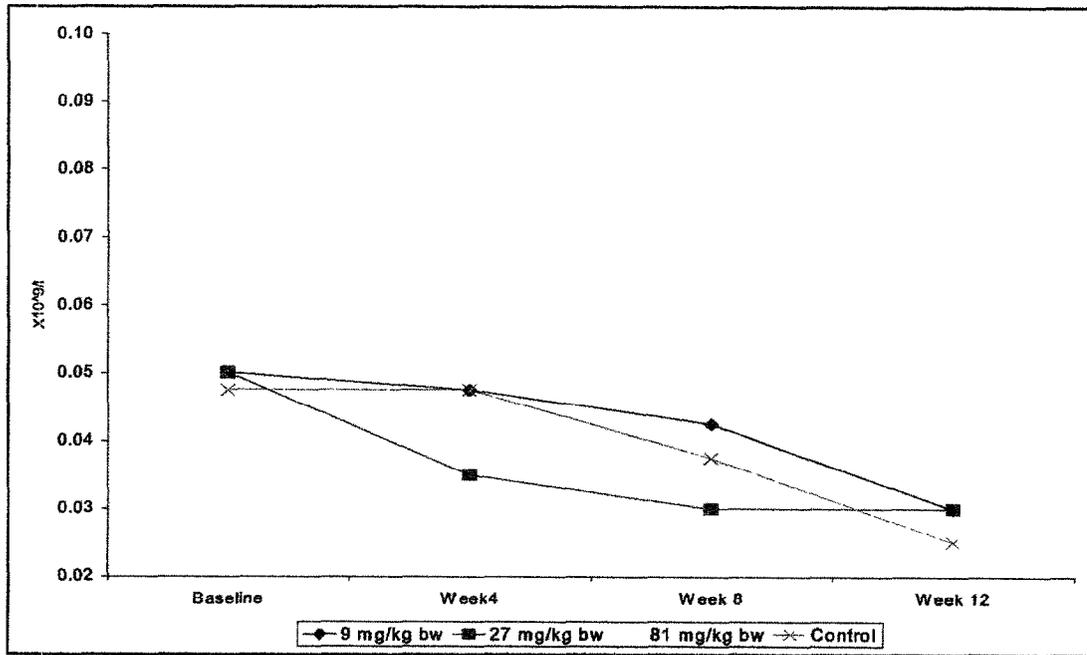


Figure 11. Basophils

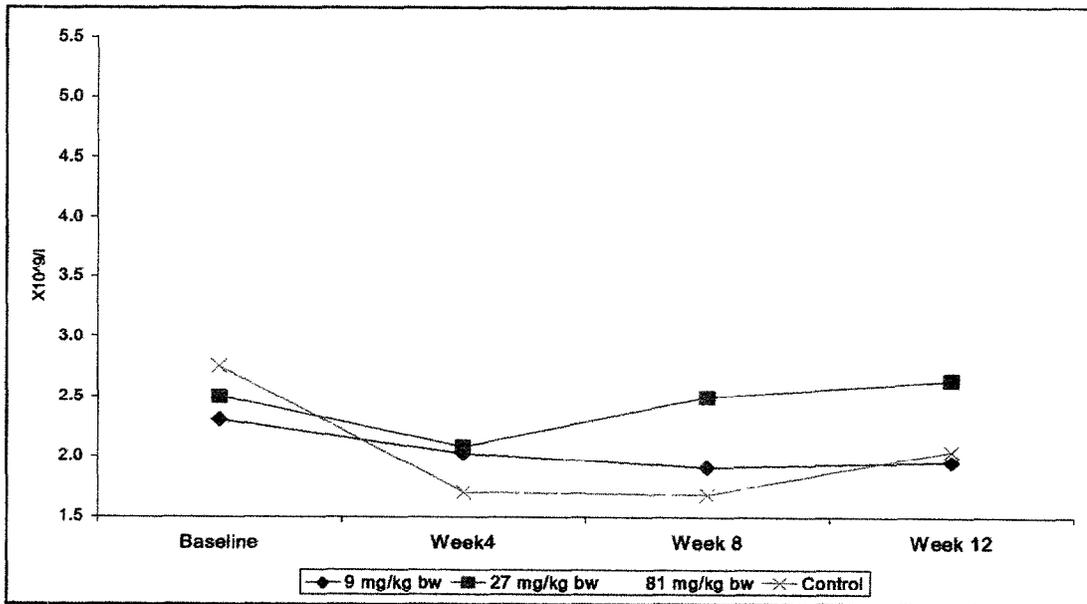


Figure 12. Lymphocytes

APPENDIX I: Haematology, continued

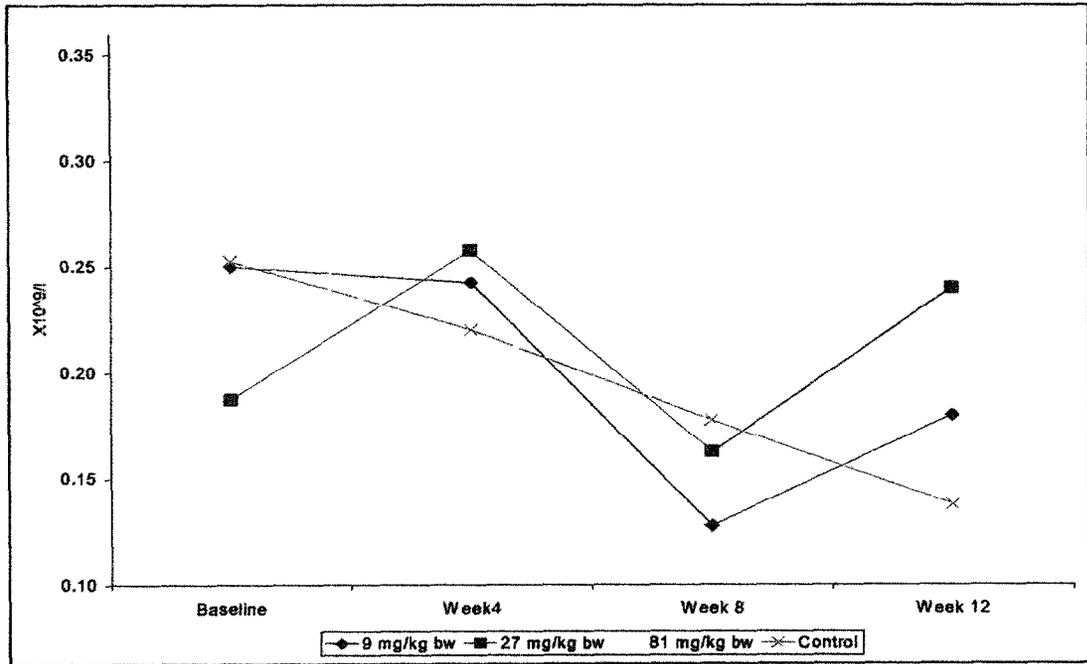


Figure 13. Monocytes

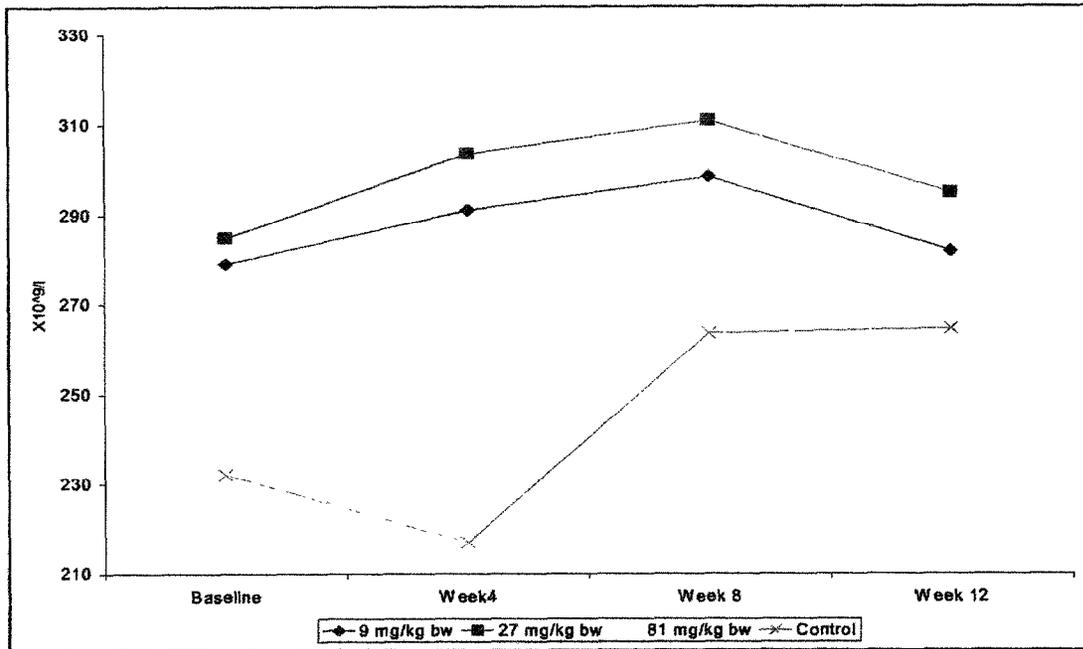


Figure 14. Platelets

APPENDIX II: Biochemistry

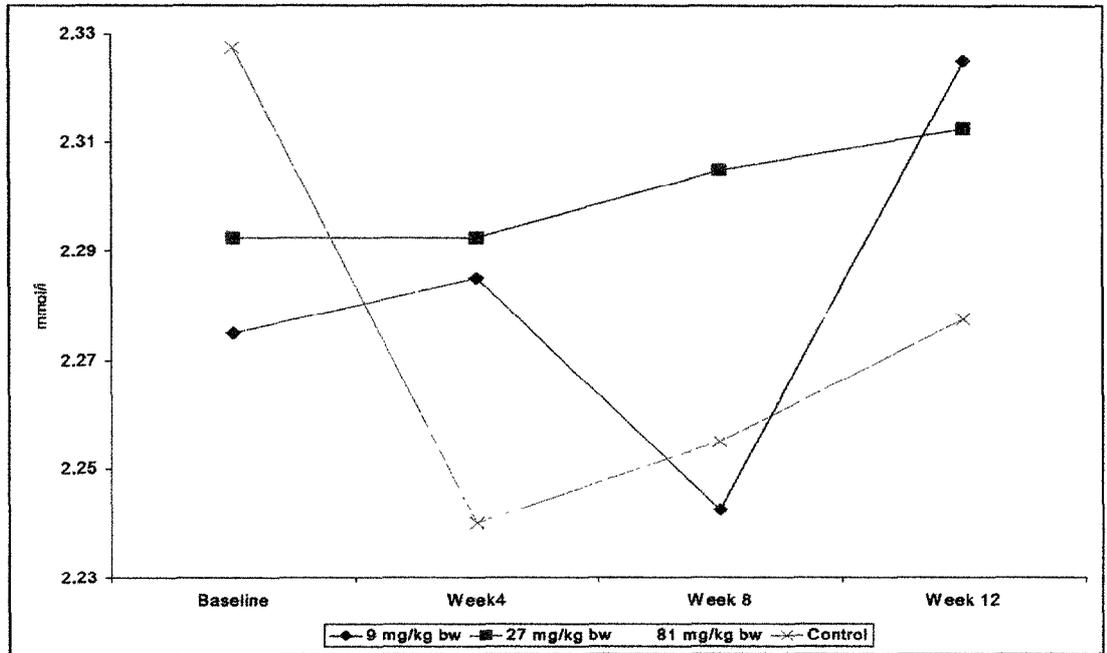


Figure 15. Calcium

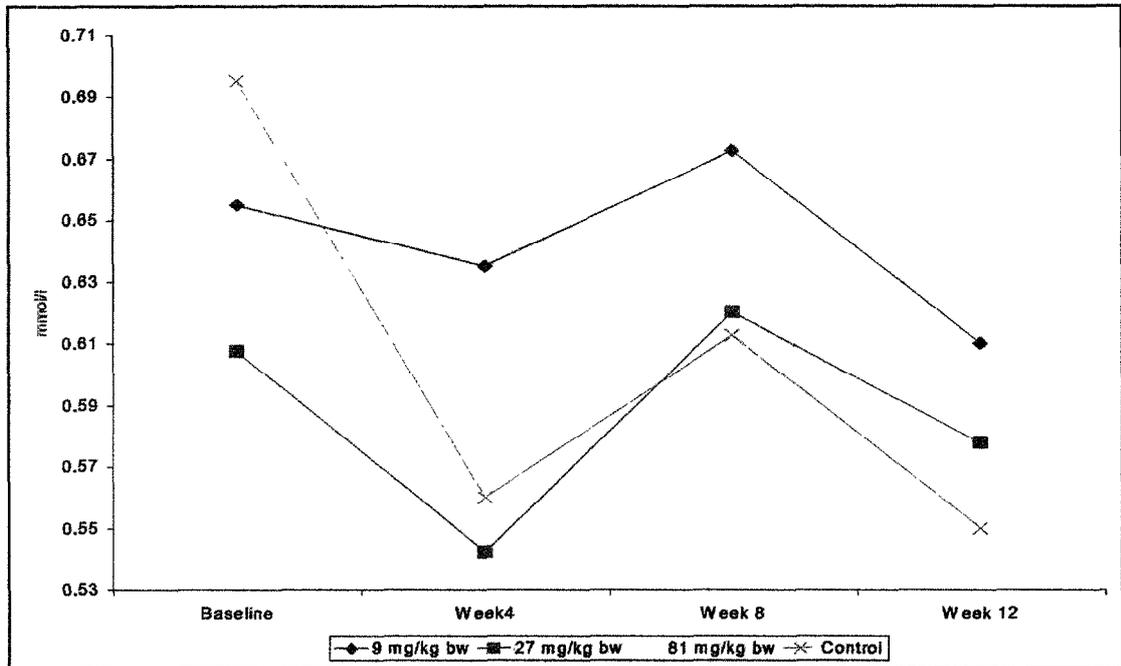


Figure 16. Magnesium

APPENDIX II: Biochemistry, continued

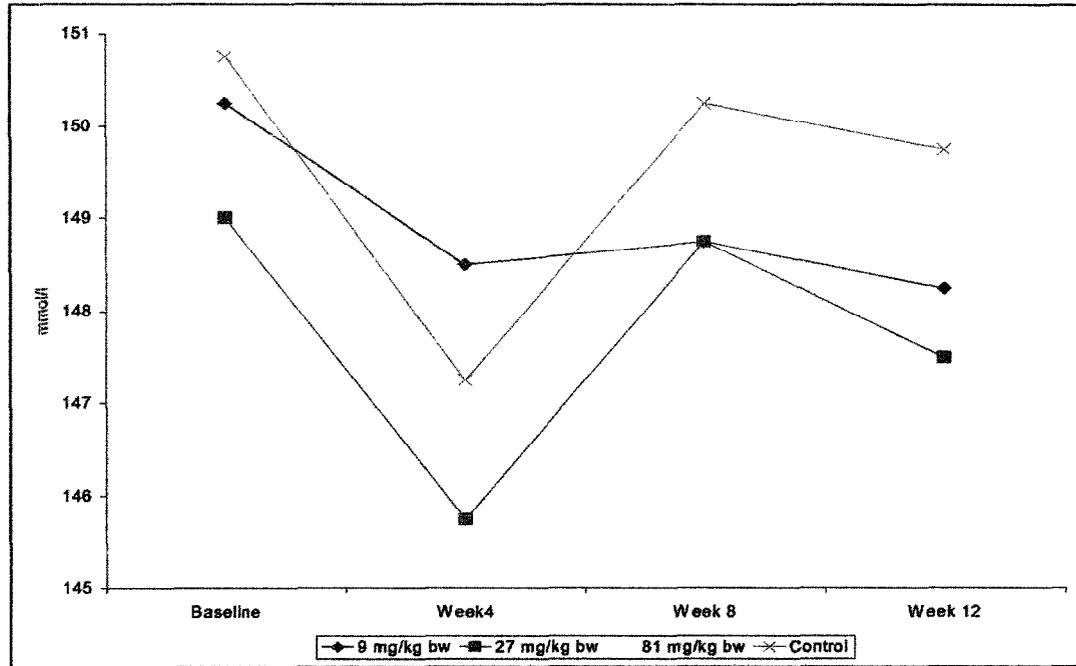


Figure 17. Sodium

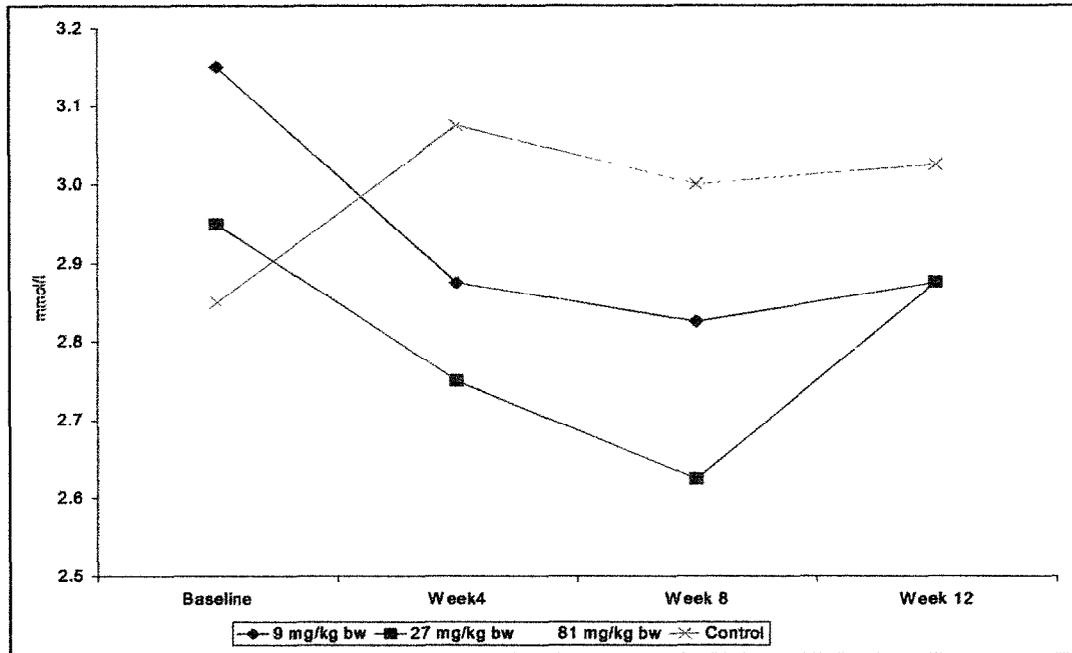


Figure 18. Potassium
APPENDIX II: Biochemistry, continued

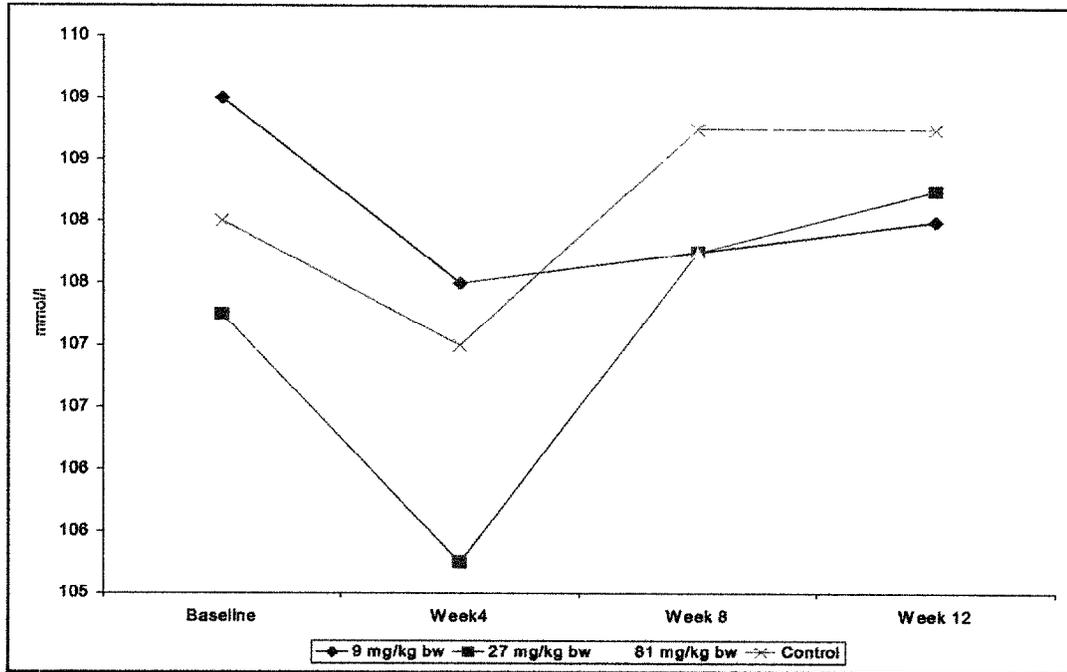


Figure 19. Chloride

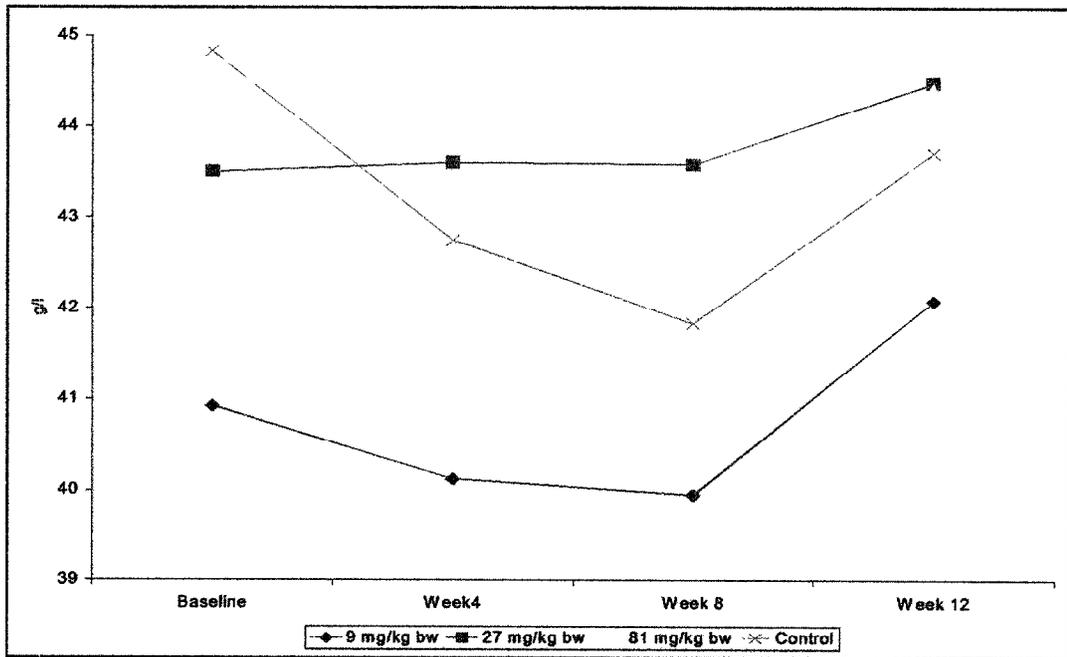


Figure 20. Albumin

APPENDIX II: Biochemistry, continued

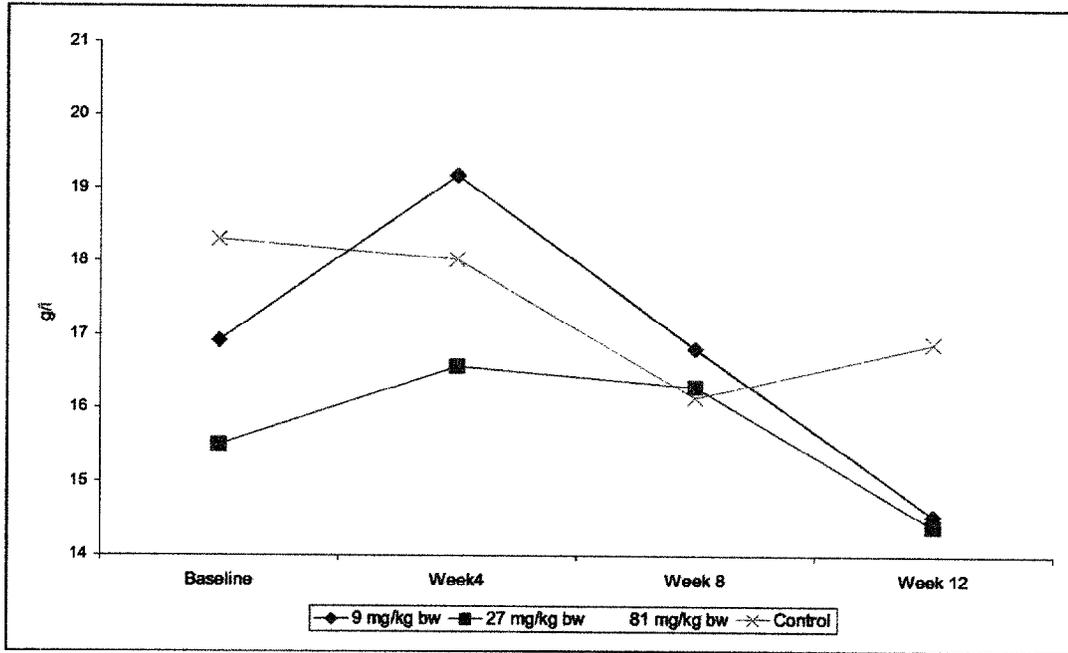


Figure 21. Globulin

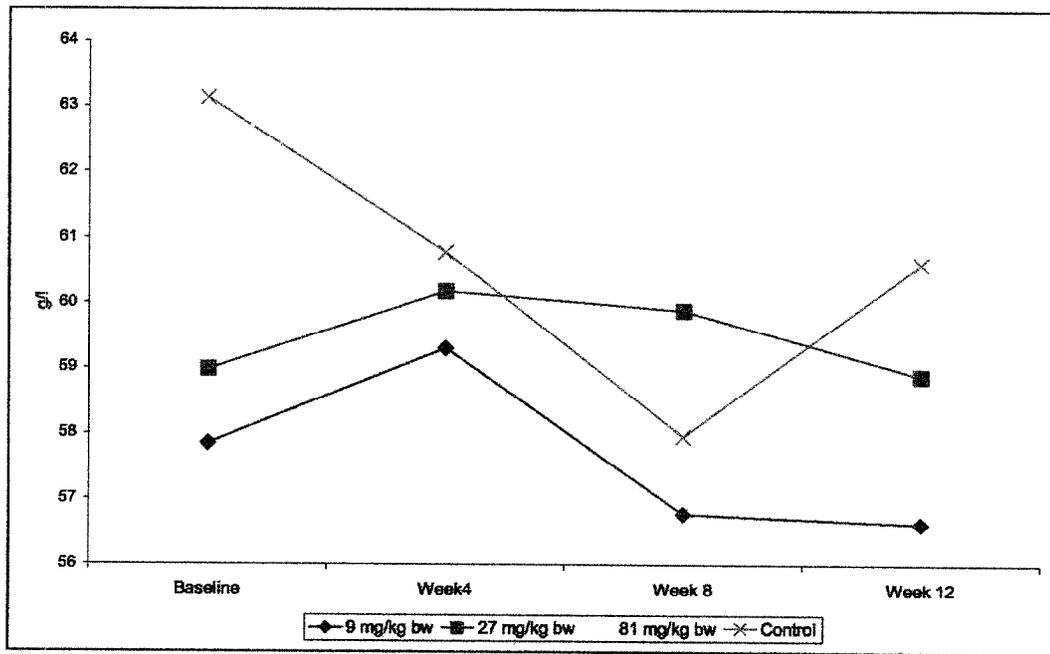


Figure 22. Total protein

APPENDIX II: Biochemistry, continued

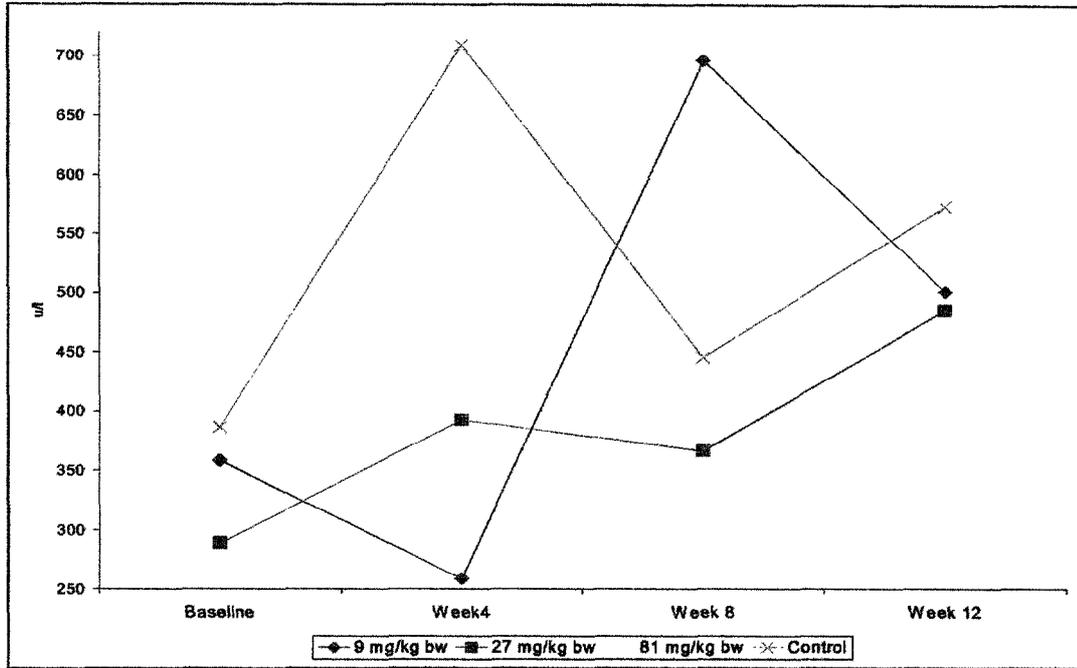


Figure 23. Creatinine kinase

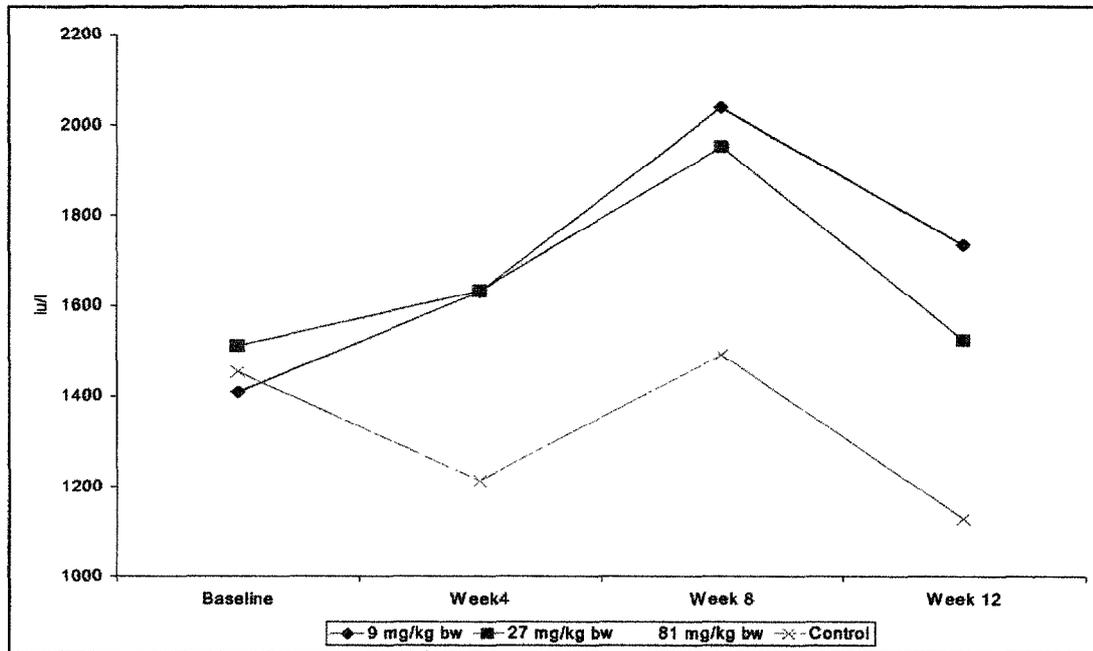


Figure 24. Lactate dehydrogenase

APPENDIX II: Biochemistry, continued

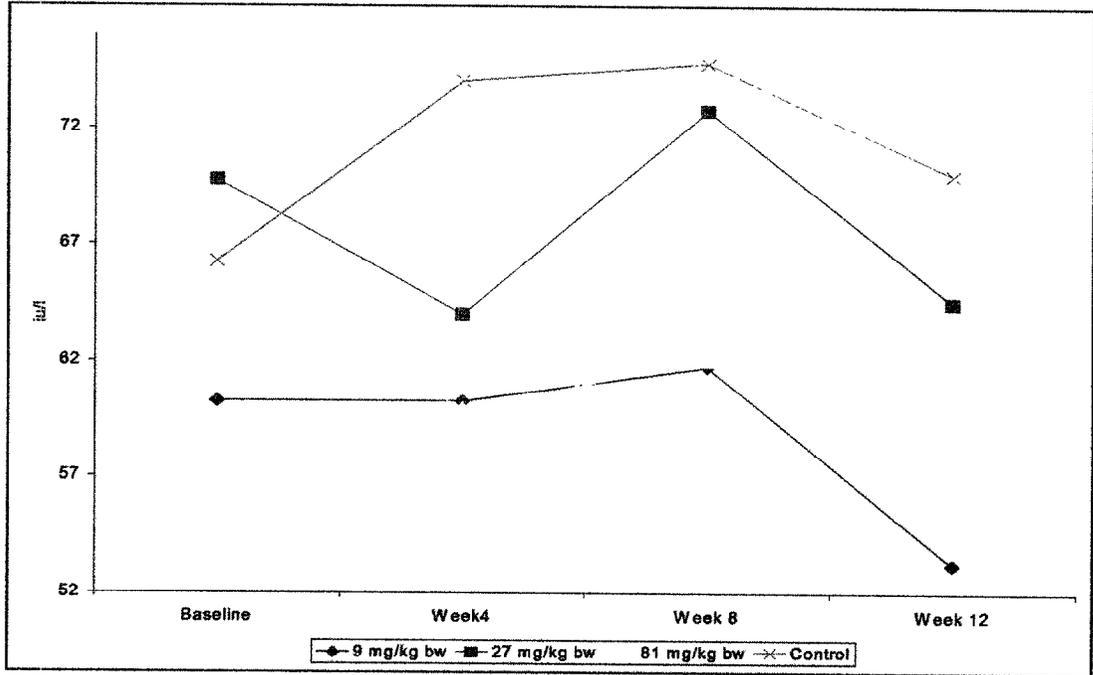


Figure 25. Gamma-glutamyl transferase

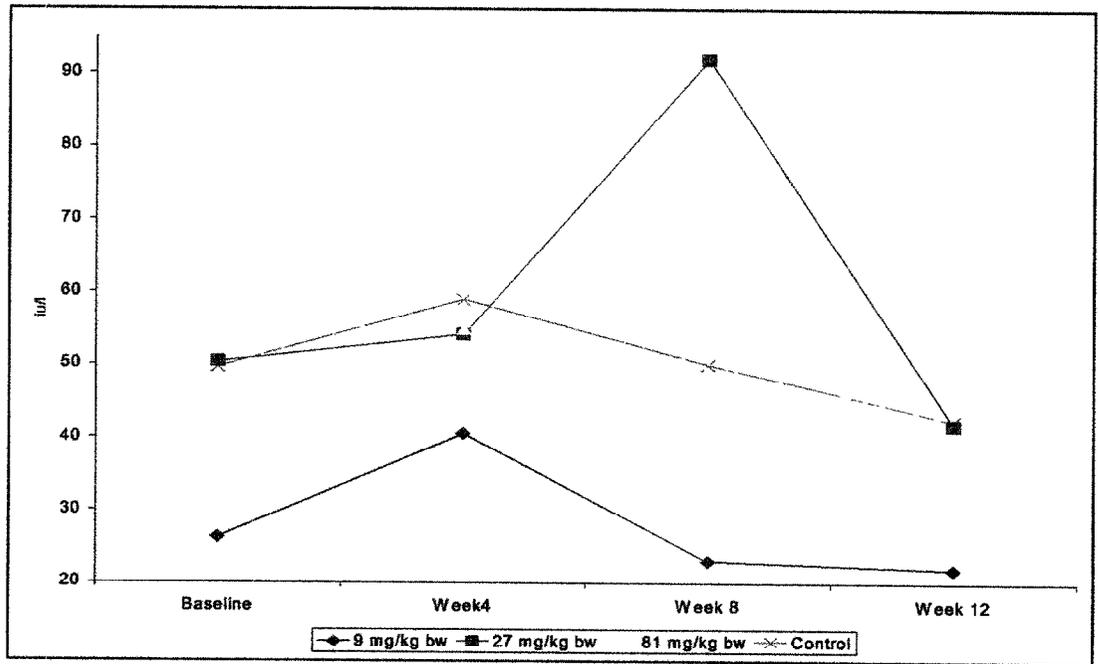


Figure 26. Alanine aminotransferase
APPENDIX II: Biochemistry, continued

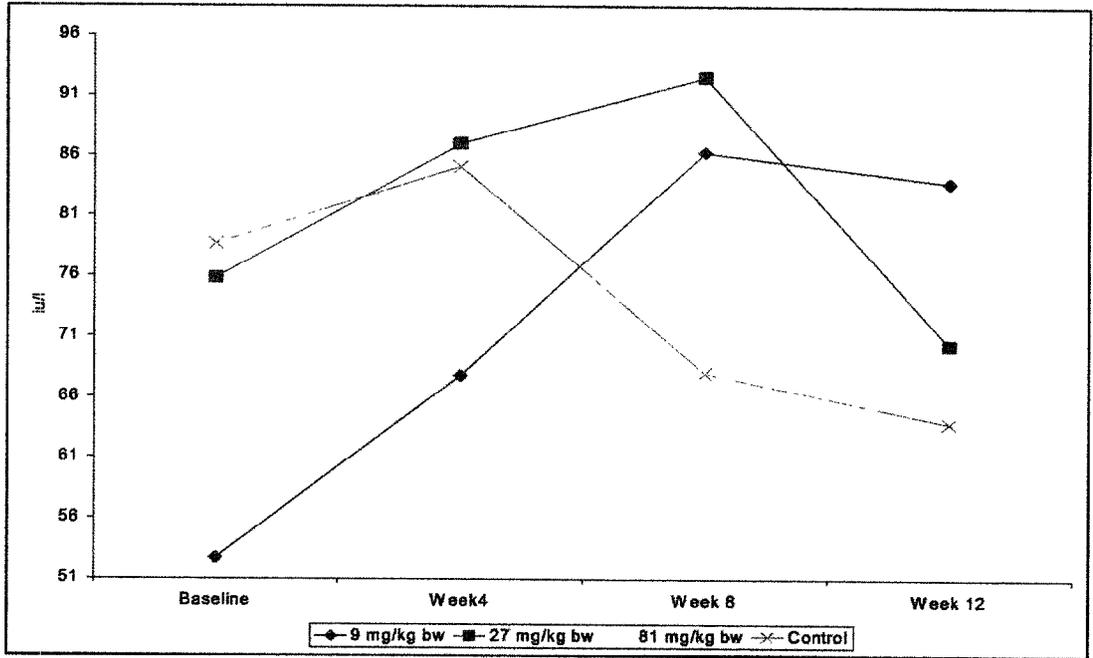


Figure 27. Aspartate aminotransferase

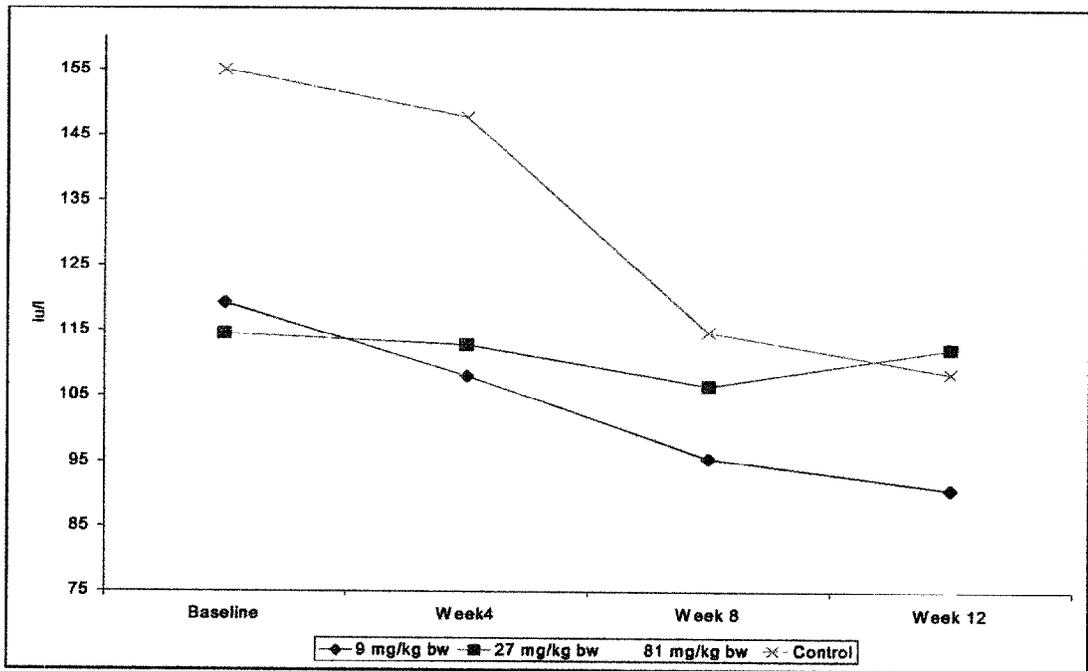


Figure 28. Alkaline phosphatase

APPENDIX II: Biochemistry, continued

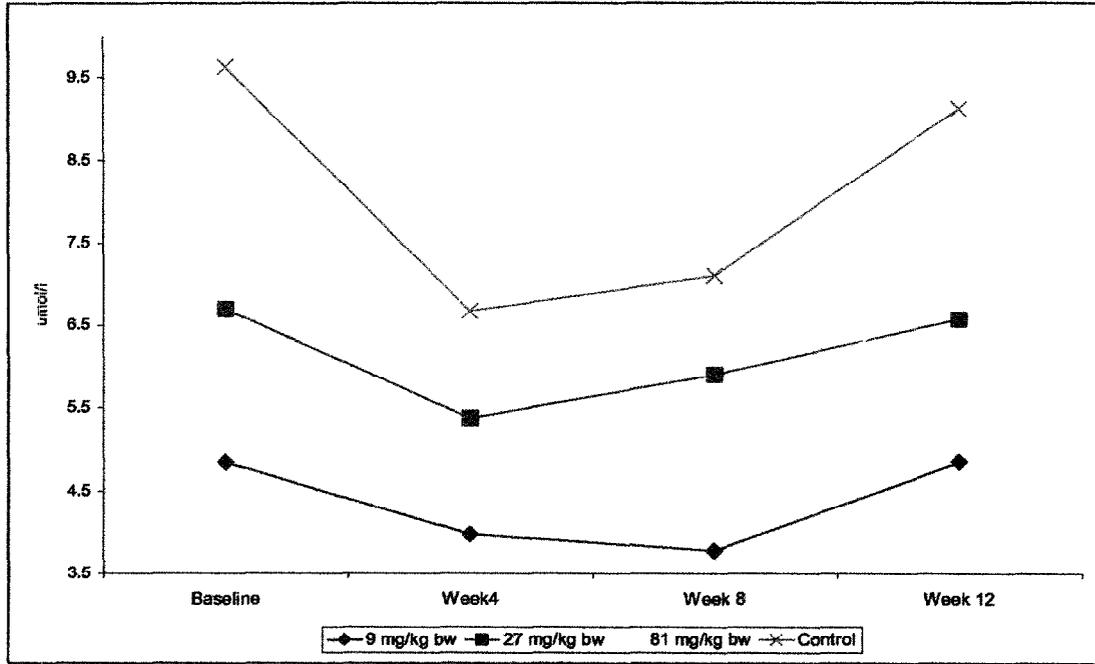


Figure 29. Total bilirubin

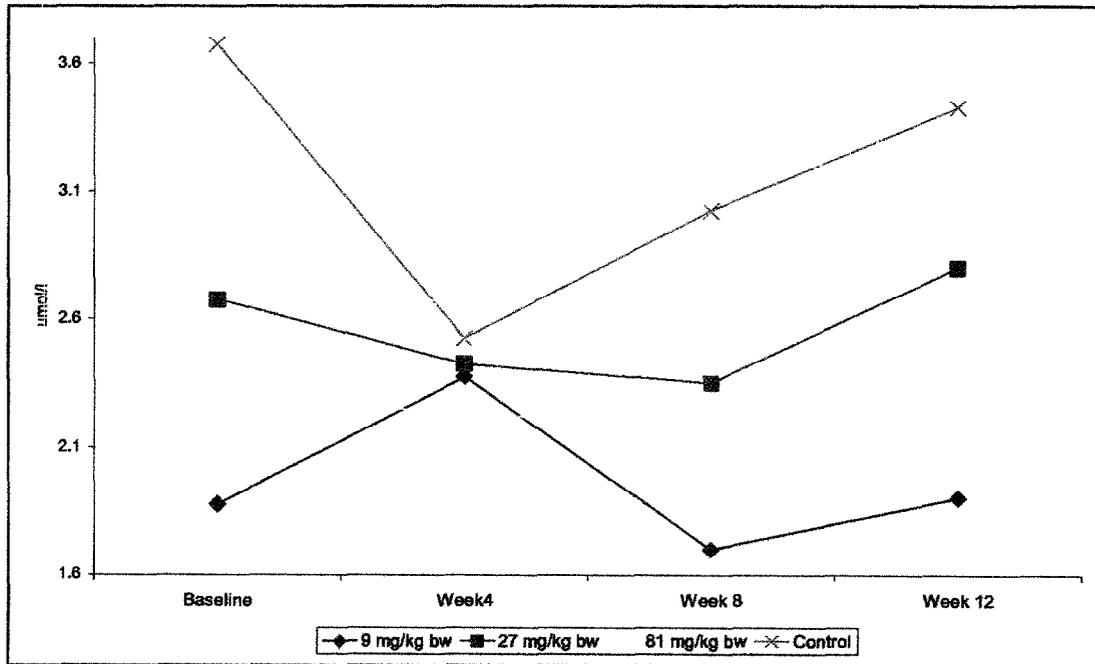


Figure 30. Unconjugated bilirubin
APPENDIX II: Biochemistry, continued

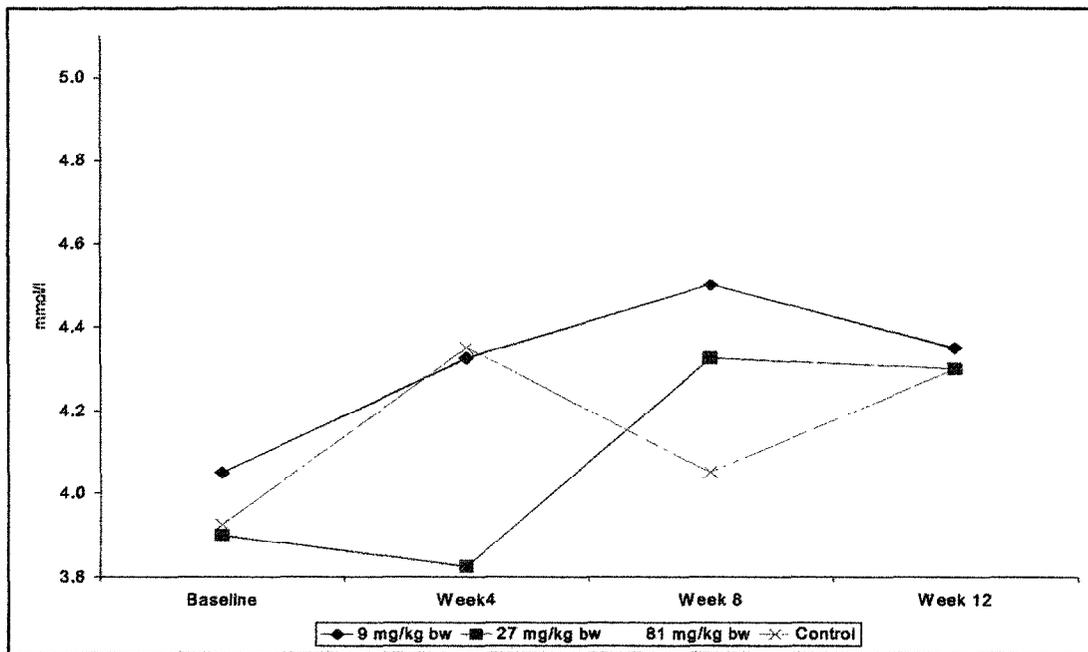


Figure 31. Glucose

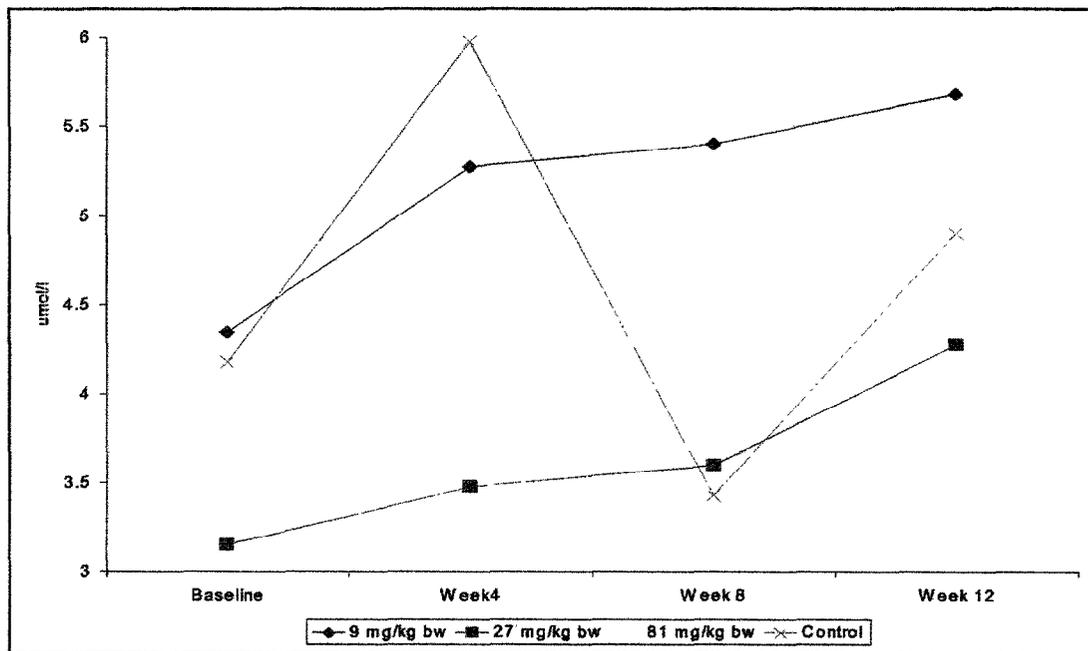


Figure 32. Urea
APPENDIX II: Biochemistry, continued

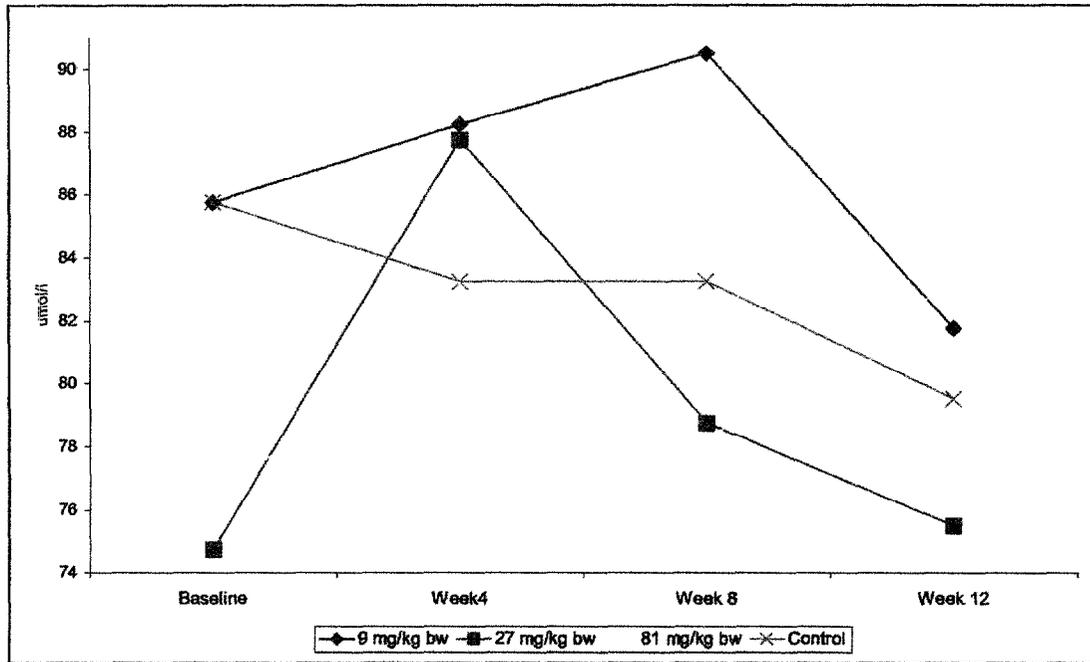


Figure 33. Creatinine

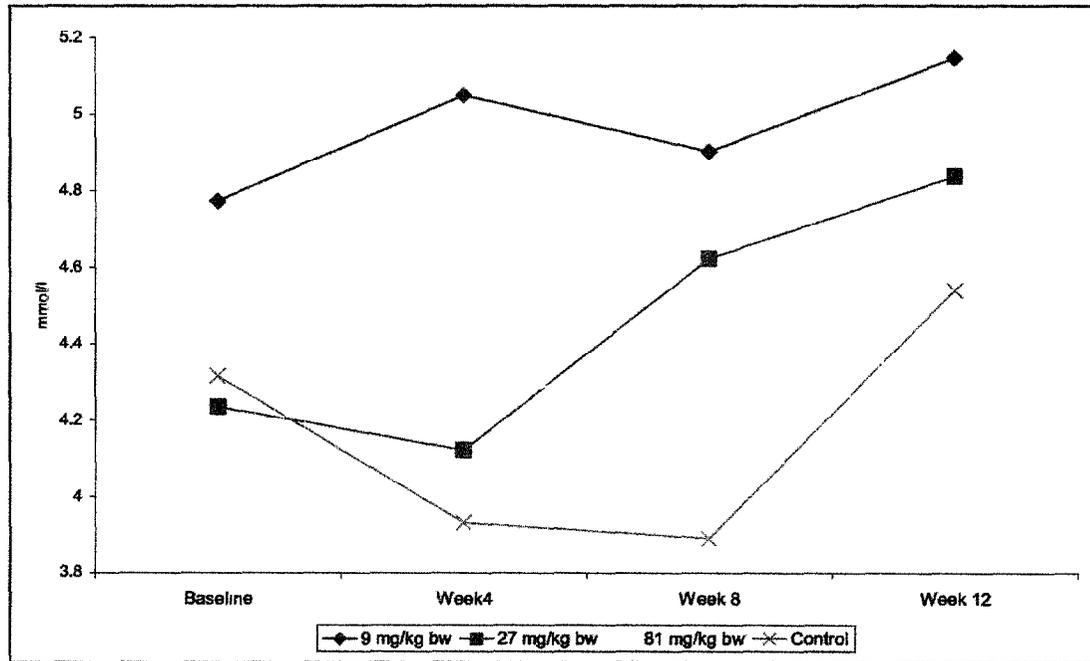


Figure 34. Total cholesterol
APPENDIX II: Biochemistry, continued

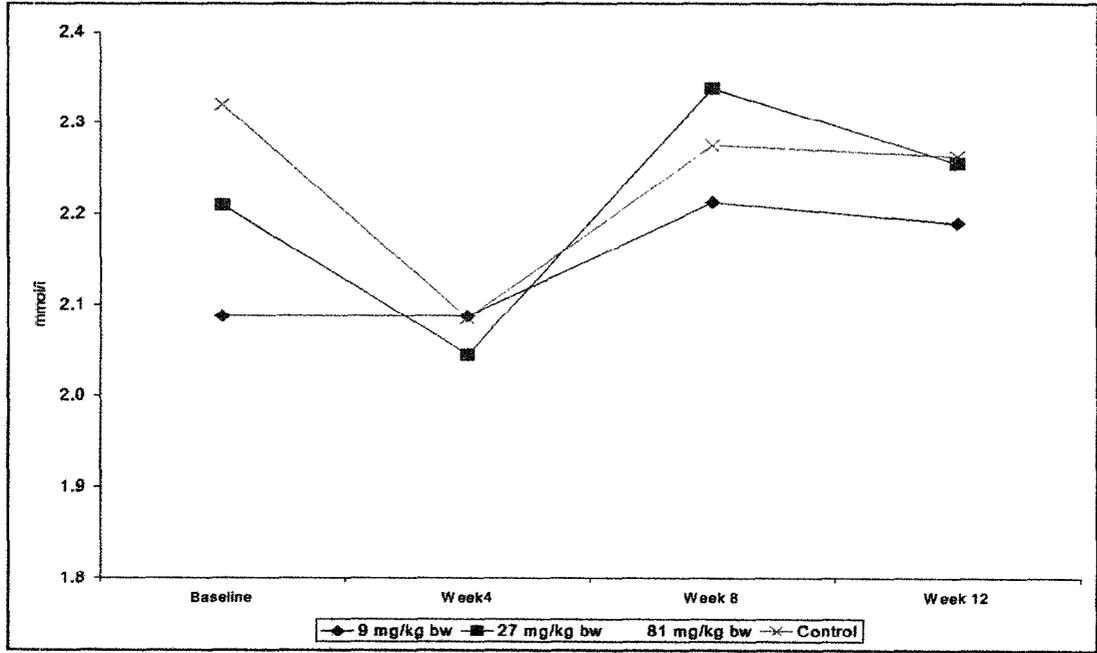


Figure 35. High density lipoprotein-cholesterol

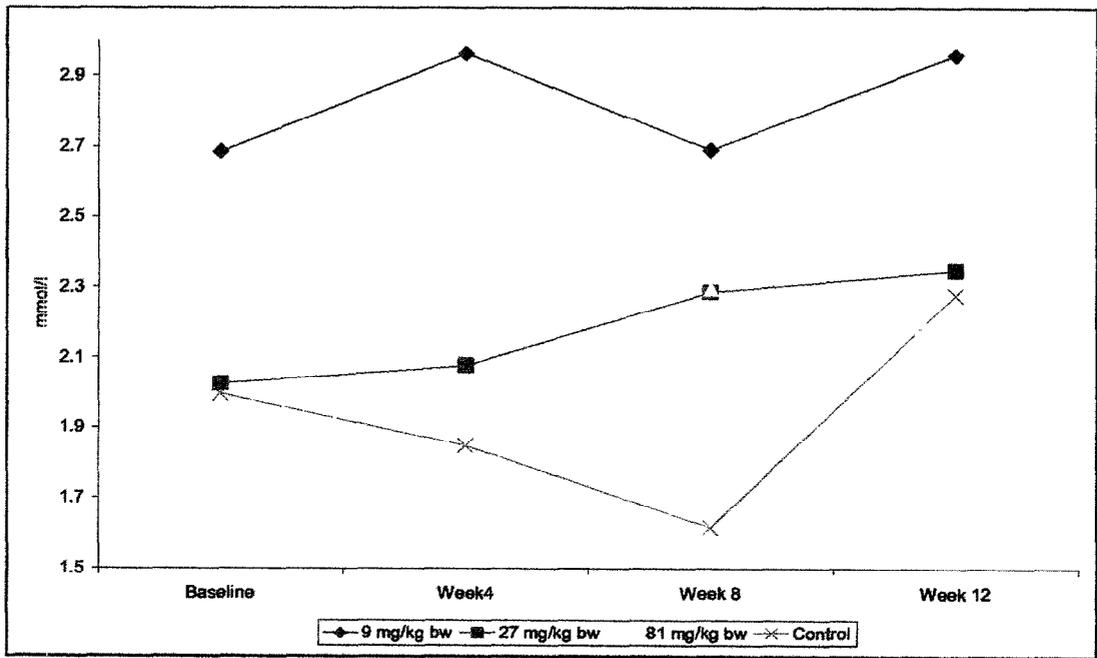


Figure 36. Low density lipoprotein-cholesterol

APPENDIX III: Physical and physiological variables

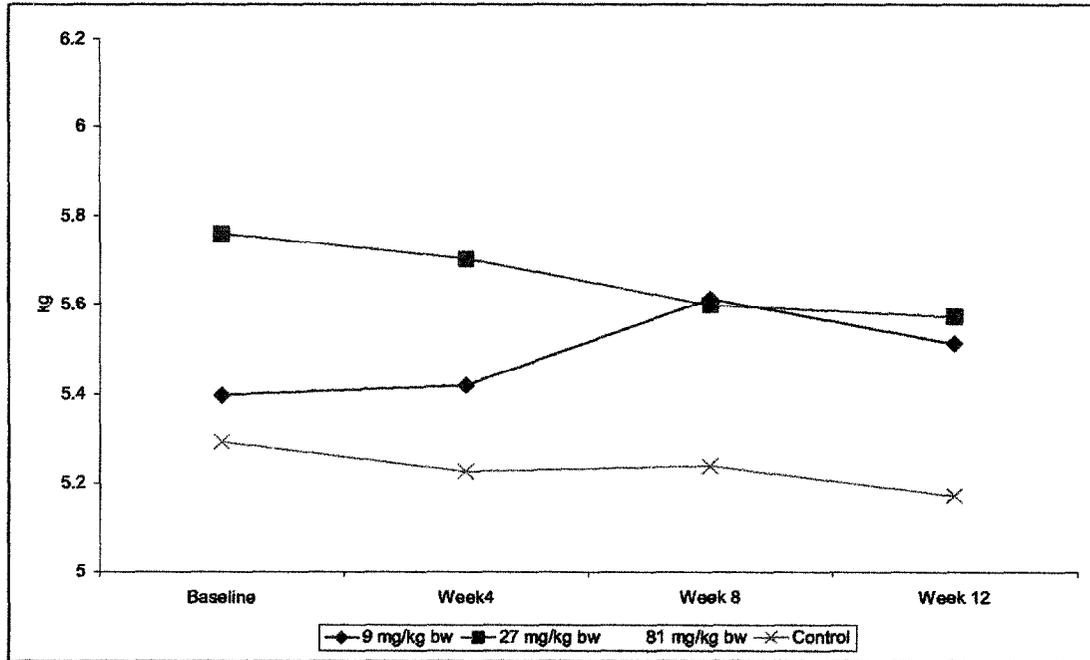


Figure 37. Bodyweight

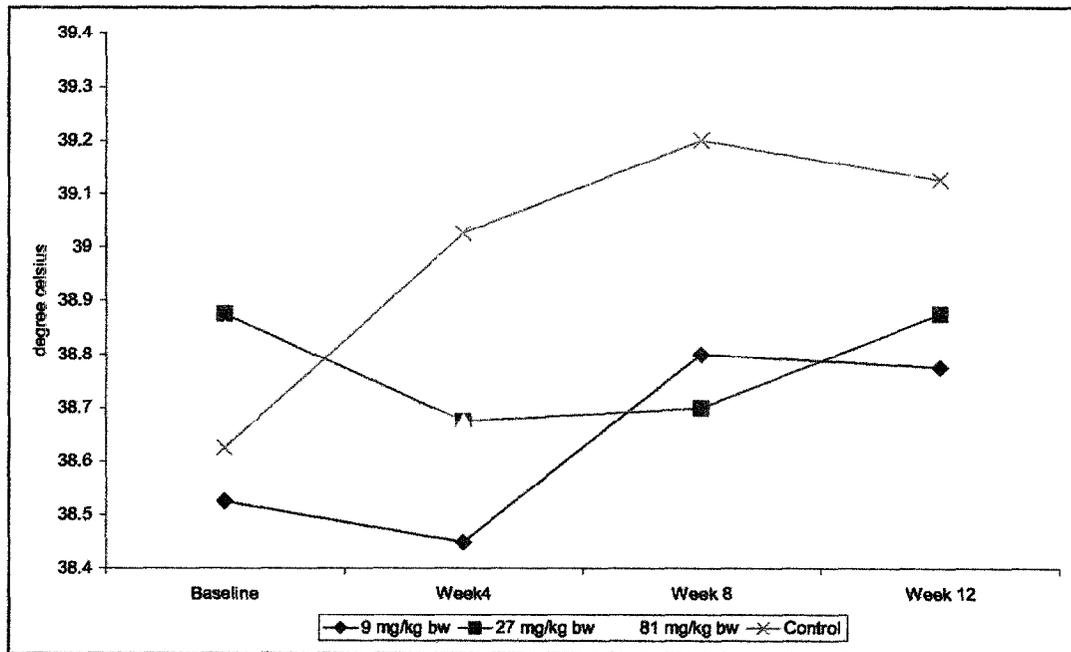


Figure 38. Body temperature

APPENDIX III: Physical and physiological variables, continued

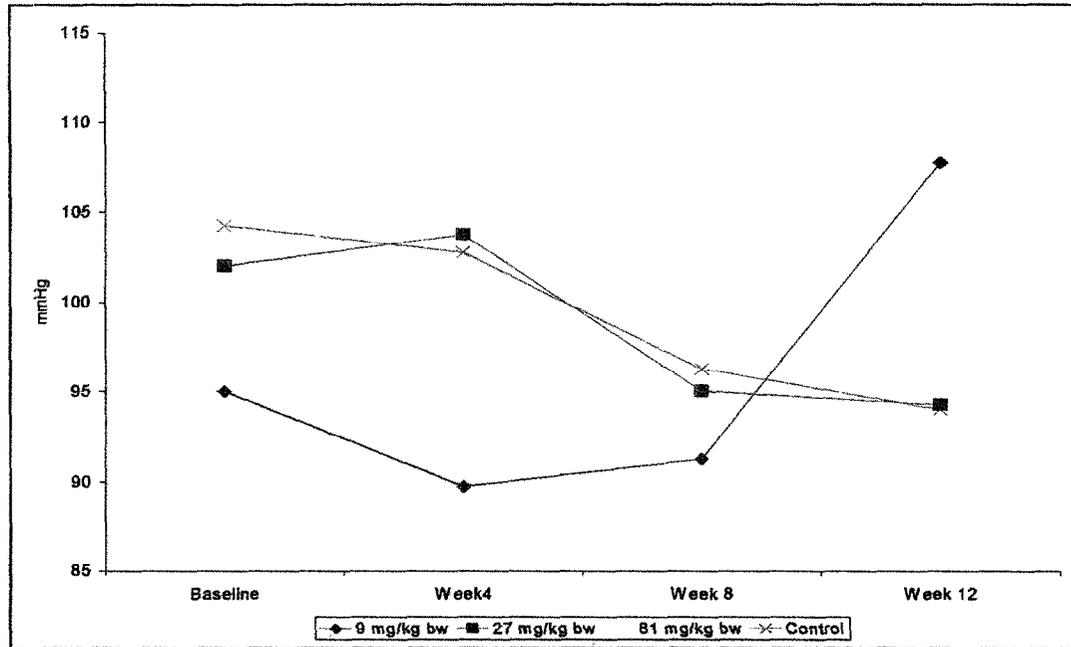


Figure 39. Systolic blood pressure

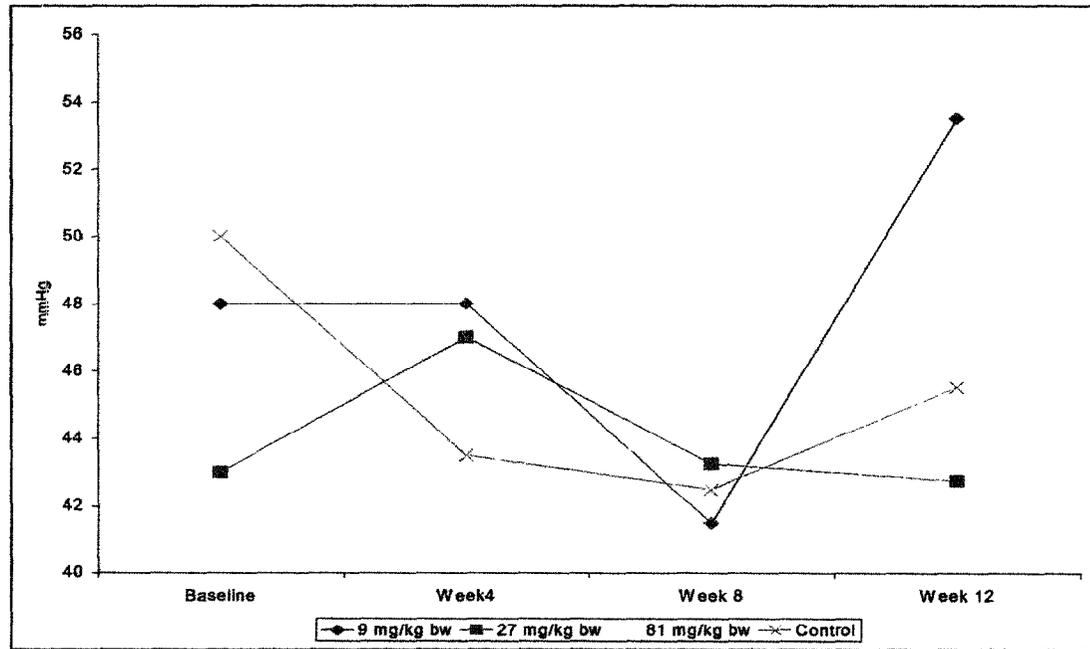


Figure 40. Diastolic blood pressure

APPENDIX III: Physical and physiological variables, continued

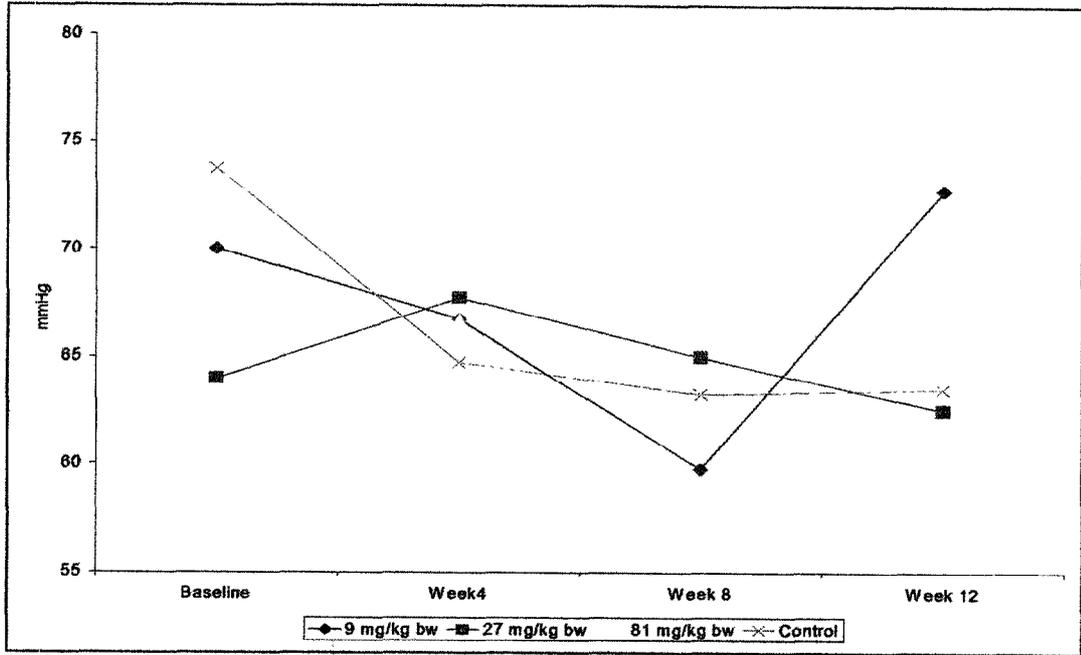


Figure 41. Mean arterial pressure

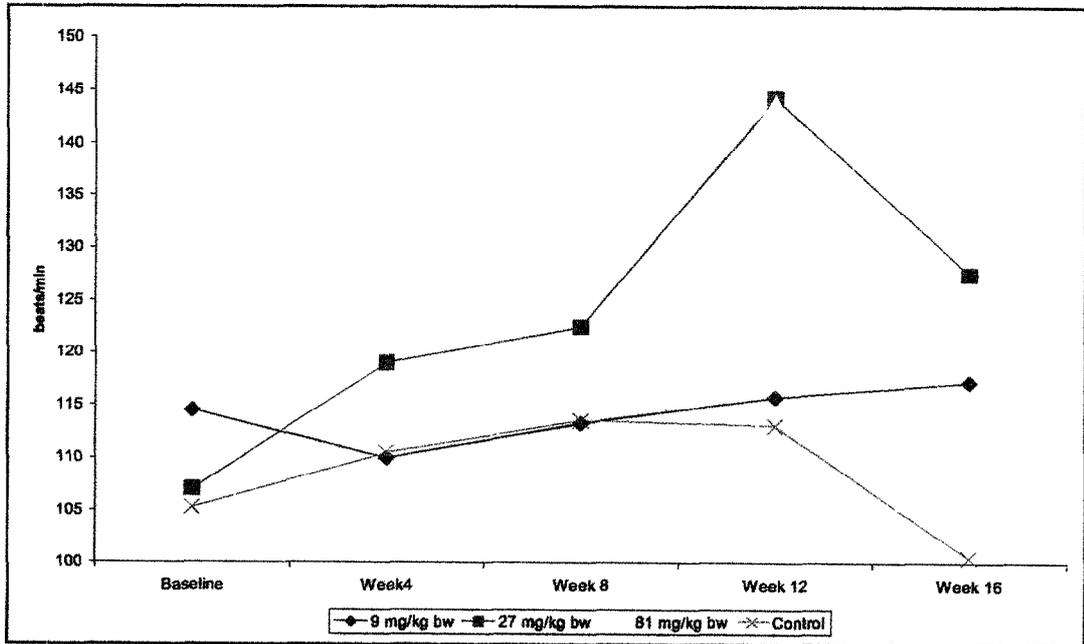


Figure 42. Heart rate

APPENDIX III: Physical and physiological variables, continued

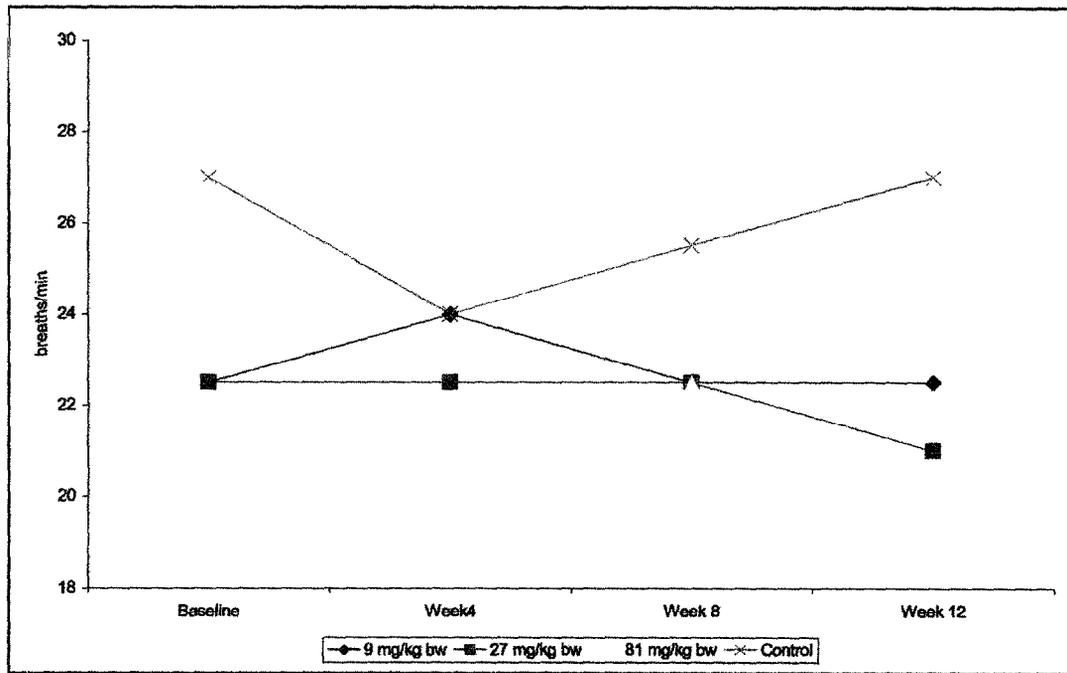


Figure 43. Respiratory rate

Sutherlandia is a South African medicinal plant that has been used as a multi-purpose "tonic" in the region for generations. Because of its efficacy as a safe tonic for diverse health conditions, it has enjoyed a long history of use by all cultures in southern Africa. It is currently used as a "quality of life" tonic by individuals and at various clinics in southern Africa. It is also shipped elsewhere in Africa and to Europe. In keeping with World Health Organization (WHO) guidelines on the assessment of herbal medicines, *Sutherlandia* is generally regarded as safe on the basis of its long history of safe use in South Africa.

In addition, there were no deaths in mice given 1,500 mg/kg by mouth. } 2-10-11

The innovative South African phytomedicines company, Phyto Nova, has been distributing tablets and capsules from this plant for the past five years. Phyto Nova works closely with physicians and clinics (by phone and also through frequent clinic visits) that are dispensing the product and to date no adverse effects have been reported.

Capsules are manufactured according to Phyto Nova's specifications by registered pharmaceutical manufacturer Impilo Drugs (1966) (Pty) Ltd. This means that Phyto Nova's *Sutherlandia* is manufactured according to Good Manufacturing Practice (GMP) – please see enclosure from Impilo Drugs.

We propose importing these capsules directly from Phyto Nova.

The long history of use of *Sutherlandia* in South Africa, coupled with the conclusions of the exhaustive independent safety study seem to suggest that, when used under the conditions recommended, *Sutherlandia* will reasonably be expected to be safe.

The attached list – "Traditional Uses of *Sutherlandia* – Published Indications" is submitted in order to give an idea of the length of time that *Sutherlandia* has been in general use in southern Africa. The diverse indications listed in this publication are not intended to imply that *Sutherlandia* will be distributed in the United States as anything other than a general tonic.

Andrew Laing

TRADITIONAL USES OF *SUTHERLANDIA* - PUBLISHED INDICATIONS

LIST OF REFERENCES:

(INDICATIONS INDICATED IN BOLD)

A. PUBLICATIONS UP TO 1962

(many subsequent publications merely cited/repeated the information in Watt & Breyer-Brandwijk and others; for comprehensive list of references see list B below)

- Dykman, E.J.** 1908. *De Suid Afrikaanse Kook-, Koek- en Resepte Boek* (14th improved impression. Paarl Printers Ltd, Paarl (Cape Colony), South Africa.
(page 145: infusion of bark and leaves for **cancer, stomach ailments and blood purification** - one cup three times a day until it starts working, then a little less)
- Kling, H.** 1923. *Die Sieketrooster*. Van de Sandt de Villiers Ltd, Cape Town.
(page 20): leaf juice mixed with fat or (leaf-) lard as blisterplaster - "trcksalf" - for **infections, pustules and carbuncles**)
- Laidler, P. W.** 1928. The magic medicine of the Hottentots. *South African Journal of Science* 25: 433-447.
(page 443: decoctions for **washing wounds**; given to drink for **fevers**; also used for **consumption, chicken pox, etc.** - the "etc." implies a wide range of ailments, i.e. a general medicine or tonic used)
- Pappe, L.** 1847. *A list South African indigenous plants used as remedies by the colonists of the Cape of Good Hope*. O. I. Pike, Cape Town.
(page 6: dried and pulverised roots and leaves used for **eye diseases**)
- Smith, A.** 1895. *A contribution to the South African materia medica*, 3rd edition. Lovedale, South Africa.
(page 62: preparation of leaves as **tonic**; page 66: pinch of leaves in boiling water taken twice or thrice a day for **extreme weakness and sinking at the stomach**; page 86: **blood purifier**; page 116 & 117: leaf decoction for **dysenteric diarrhoea**; page 188 & 189: curing of **malignant tumours, cancerous in appearance**; also used as **blood purifier and tonic** ... to **delay the progress of true cancer and much prolonged life**)
- Watt, J.M. & Breyer-Brandwijk, M.G.** 1962. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, 2nd edn. Livingstone, London.
(page 649: Infusions or decoctions of the leaf and bark are used for **influenza, stomach complaints, intestinal complaints, internal cancers, uterine troubles, liver diseases, rheumatism, inflammations, haemorrhoids, dropsy, backache** and as a **tonic**; infusions are taken in **amenorrhoea**, as **blood tonic** and as **cancer prophylactic**; powdered leaf in syrup is used to treat cough; weak infusions taken before meals seem to act as a **bitter tonic** to **improve appetite and digestion**; may cause sweating. may be slightly purgative and may be emetic if too strong)

B. COMPREHENSIVE LIST

Anonymous, 1962. *Oupa en Ouma se Boererate* ("Grandfather's and Grandmother's Farm Remedies"). Tafelberg Publishers, Cape Town.

(page 146: knife tip of powdered dried leaves after each meal for liver ailment – "lewerkwaal").

Archer, F.M. 1990. Planning with people - ethnobotany and African uses of plants in Namaqualand (South Africa). *Mitt. Inst. Allg. Bot. Hamburg* 23: 959-972.

(page 966: infusion of leaves and flowers used for stomach complaints; page 967: basic ingredient in most medicines in Namaqualand – mostly for stomach ailments, in Table 3, also listed specifically for influenza, wounds, pains aches and skin disorders)

Cillié, A.M. 1992. *Kruie op witblits, resepte en feite*, p. 43. Unpublished notes, Worcester Museum.

(page 17: leaves steeped in brandy used for back ailments and kidney ailments; leaf infusion ("tea") made from the whole plant used to treat cancer and also to wash wounds)

Dykman, E.J. 1908. *De Suid Afrikaanse Kook-, Koek- en Resepte Boek* (14th improved impression. Paarl Printers Ltd, Paarl (Cape Colony), South Africa.

(page 145: infusion of bark and leaves for cancer, stomach ailments and blood purification – one cup three times a day until it starts working, then a little less)

Kling, H. 1923. *Die Sieketrooster*. Van de Sandt de Villiers Ltd, Cape Town.

(page 20): leaf juice mixed with fat or (leaf-) lard as blisterplaster – "treksalf" – for infections, pustules and carbuncles)

Laidler, P. W. 1928. The magic medicine of the Hottentots. *South African Journal of Science* 25: 433-447.

(page 443: decoctions for washing wounds; given to drink for fevers; also used for consumption, chicken pox, etc. – the "etc." implies a wide range of ailments, i.e. a general medicine or tonic used)

Palmer, E. 1985. *The South African Herbal*. Tafelberg Publishers, Cape Town.

(page 124: half cup of infusion or decoction three times a day for cancer, fever and as blood purifier; decoction of root and leaves as eye wash).

Pappe, L. 1847. *A list South African indigenous plants used as remedies by the colonists of the Cape of Good Hope*. O. I. Pike, Cape Town.

(page 6: dried and pulverised roots and leaves used for eye diseases)

Roberts, M. 1990. *Indigenous healing plants*. Southern Book Publishers, Halfway House. (p. ...????)

Rood, B. 1994. *Uit die veldapteeke*. Tafelberg, Cape Town.

(pages 53 & 54: decoction of leaves for cancer growths; leaf infusions used for influenza, stomach complaints, cancer, chicken-pox, and the common cold; dried powdered leaves snuffed for head cancer and nose cancer; leaf infusion used for diabetes and as eye wash for weak eyes; flowers in strong decoction for fever and to wash wounds; decoction also drunk (taken internally) for "stomach nerves" and varicose veins; infusion of bark and leaves used as tea, mainly to cure haemorrhoids)

Shearing, D. 1994. *Karoo. South African Wild Flower Guide No. 6*. Botanical Society of South Africa, Cape Town.

(page 82: washing wounds, fevers, chicken-pox and cancer)

Smith, C.A. 1966. *Common names of South African Plants. Memoirs of the botanical Survey of South Africa No. 35.* Botanical Research Institute, Department of Agricultural Technical Services, South Africa.

(pages 275 & 276: decoctions used for washing wounds and taken internally for fevers, chicken-pox and especially for cancer)

Smith, A. 1895. *A contribution to the South African materia medica*, 3rd edition. Lovedale, South Africa.

(page 62: preparation of leaves as tonic; page 66: pinch of leaves in boiling water taken twice or thrice a day for extreme weakness and sinking at the stomach; page 86: blood purifier; page 116 & 117: leaf decoction for dysenteric diarrhoea; page 188 & 189: curing of malignant tumours, cancerous in appearance; also used as blood purifier and tonic ... to delay the progress of true cancer and much prolonged life)

Van Breda, P.A.B. & Barnard, S.A. 1986. *Veldplante. Kankerbos*. Leaflet A.7 of series *Veldweiding*, reprinted from *Boerdery in Suid-Afrika*. Department of Agriculture and Water Supply, Pretoria.

(page 1 & 2: dried leaf and flower used as snuff for head cancer and infusion of leaf used for stomach cancer)

Van Wyk, B-E., Van Oudtshoorn, B. & Gericke, N. 1997. *Medicinal plants of South Africa*. Briza publications, Pretoria (2nd improved impression, 2000).

(page 246: stomach problems, cancer; bitter tonic, good general medicine; colds, influenza, chicken-pox, diabetes, varicose veins, piles, inflammation, liver problems, backache, rheumatism; washing of wounds, fever)

Van Wyk, B-E. & Gericke, N. 2000. *People's Plants: a guide to useful plants of southern Africa*. Briza publications, Pretoria.

(page 148: tonic to treat fever, poor appetite, indigestion, gastritis, oesophagitis, peptic ulcer, dysentery, cancer prevention, cancer treatment, diabetes, colds, influenza, cough, asthma, chronic bronchitis, kidney conditions, liver conditions, rheumatism, heart failure, urinary tract infections, stress and anxiety; pancreatic cancer, other cancer, improved quality of life in patients with terminal metastatic breast cancer; rheumatoid arthritis)

Vergoes Houwens, N.F. no date. *Medicine from the Veld*. Unpublished notes, Worcester Museum.

(page 2: weak leaf infusion taken for internal cancers; also for fever, as blood purifier and to wash wounds; root and leaf infusion for eye bath)

Watt, J.M. & Breyer-Brandwijk, M.G. 1962. *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, 2nd edn. Livingstone, London.

(page 649: Infusions or decoctions of the leaf and bark are used for influenza, stomach complaints, intestinal complaints, internal cancers, uterine troubles, liver diseases, rheumatism, inflammations, haemorrhoids, dropsy, backache and as a tonic; infusions are taken in amenorrhoea, as blood tonic and as cancer prophylactic; powdered leaf in syrup is used to treat cough; weak infusions taken before meals seem to act as a bitter tonic to improve appetite and digestion; may cause sweating, may be slightly purgative and may be emetic if too strong)

Wileman, L. no date. *The Uses of our Karoo Plants in Bygone Times*. Unpublished notes, Worcester Museum.

(page 7: washing wounds, fevers, chicken-pox, cancer, eye wash)

Youted, G. (ed.) no date. *Dictionary of South African traditional medicinal plants of the Eastern Cape*. Pharmaceutical Society of South Africa, Johannesburg (unpublished).

(page 158: leaves, stems and roots used for blood purification, as tonic, for chest colds – powdered leaf mixed with sugar – and abdominal complaints; said to delay the course of cancer)



IMPiLO

DRUGS (1966) (PTY) LTD

CERTIFICATE OF ANALYSIS

Batch No. :S3421
Product :SUTHERLANDIA CAPSULES
Alternative names :
Packaging :WHITE PVC JARS (60's)
Expiry Date :04/2003

	SPECIFICATION	METHOD	RESULT
Description	:Transparent capsule/green powder fill.	Visual	Complies
Average mass	:580 - 620 mg	Balance	601,2 mg
Length	:21,0 - 22 mm	Vernier	21,43 mm
Disintegration	:NMT 60 mins	USP 24 (Discs)	35 mins
Uniformity of mass	Wts. of NMT 2 capsules (of 20) may deviate from ave. by MT 7,5 % and none by more than 15 %	Balance	Complies

Willem Laas
QA Manager

Impilo Drugs (1966) Pty Ltd • Reg No: 06/00027/07

Director: A.M. Tshibane, B.Sc. - M.S. Tshibane, M.Pharm. (Hons)

9 Green St. Lebowale, Maseru, Botswana - PO Box 3222, SOUTHWEST AFRICA

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