

TAKEDA

Subacute Toxicity
of
NEOSUGAR G

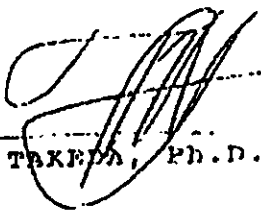
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Subacute toxicity
of
Neosugar G

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Time Period;

Sept. 1, 1982 ~ Jul. 31, 1984

Subacute Toxicity of Neosugar G

Introduction

Neosugar is a mixture of fructooligo saccharides obtained by β binding of 1 to 3 molecules of fructose to fructose residue of sucrose at the position of 1-2 through enzymatic reaction between fructose transferase produced by organisms of *Asperigillus* and *Aureobasidium* genera. In nature fructooligo saccharides are distributed widespreadly, chiefly in higher plants. Neosugar G is a new sweetener consisting of about 50% of fructooligo saccharides, monosaccharide and sucrose.

The aim of the present study is to describe the results of our subacute toxicity study on Neosugar G.

Materials and Methods

1. Test substance

The test substance used was a 75% aqueous solution of Neosugar G (Lot No. ACT-6) consisting of a mixture of 51% of Neosugar (a product of Meiji Seika Kaisha, Ltd.), 38% of monosaccharide and 11% of sucrose.

2. Animals

Both sexes of JCI-SD rats (SPF), purchased from Japan CLEAR at the age of 4 weeks, were used in groups of 30 rats

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TELEPHONE: 03-3273-3441, 3442
FAX: 03-3271-5617Sugar composition of Neosugar G;

Sugar composition of the NEOSUGAR G (Lot No. ACT-6) is, G+F; 38%, sucrose; 11%, GF2; 21%, GF3; 24% and GF4; 6%. There are no other analytical results such as level of heavy metals etc.

Concerning feed composition and feed preparation;

Neosugar G was added to the basal diet (Oriental Yeast MF-R) as is base. So the concentration of FOS in the feed of Neosugar G group is calculated by the equation, $1.875\% \times 75\% \times 51\%$ for the Neosugar G 1.875% group.

Composition of the basal feed MF-R is,

moisture	7.6%	crude protein	24.6
crude lipid	5.6	crude ash	6.3
crude fiber	3.1	soluble non-N	
calorie	360kcal	substances	52.8
vitA	1810IU	vitD3	80 IU
vitK3	0.04mg	vitB1	2.04mg
vitB6	0.92mg	niacin	9.68mg
biotin	25.9ug	follic a.	0.15mg
choline	0.23mg	vitB12	6.0 ug
		vitE	10.4mg
		vitB2	1.21mg
		pantothenic a.	3.05mg
		inositol	433mg
		vitC	4mg

The test diets of Neosugar G groups were prepared without correcting the balance of nutrients above. For example, 10% neosugar G diet was made of 90g of MF-R and 10g of Neosugar G.

I am sorry but there is no analytical records of FOS in the diets.

each at the age of 5 to 6 weeks after 1 to 2 weeks of quarantine and acclimatization.

3. Feeding condition of animals

Animals were maintained in a feeding room controlled of temperature and relative humidity at 21 to 25°C and 45 to 65%, respectively. As to the light and dark cycle, the animal room was lighted using an artificial room lighting from 7:00 to 19:00. Two each animals were housed in a stainless cage of 24.5 cm in width, 34 cm in depth and 18 cm in height. As the feed, commercially available powdered feed (product of Oriental Yeast, MF-R) added with Neosugar G in five different concentrations as described below was used. The drinking water was tap water added with chlorine and adjusted of chlorine concentration at about 2 ppm. Animals were fed with free access to thus prepared feed and drinking water. Excreta of animals were removed once a day at about the same hour of the day. Animals were identified by cage No. and staining with picric acid.

4. Administration route, dose level and group of animals

Since Neosugar is usually taken orally, it was administered for 91 days by free access to a commercially available powdered feed added with Neosugar G in five different concentrations of 1.875, 3.75, 7.5, 15 and 30%. The group

of animals fed with the feed without addition of Neosugar G was used as the control group.

5. Test items

Test items included general condition, body weight, feed and water intakes, audiometry, hematological tests, urinalysis, and pathological studies.

General condition of animals was observed once or twice daily, and body weight and feed and water intakes were determined once a week. Audiometry was performed once before start of administration and then once a month. Namely, in all animals 5,000, 8,000 and 16,000 Hz of sound was loaded to the auricle from a distance of about 30 cm using a Galton's whistle and presence or absence of auricular reflex was examined.

Urinalysis was performed once a month by pooling urine of 10 animals as one test material (3 test materials for each group).

Hematological tests, serum biochemical tests and pathological studies were performed on day 36 and the following day of the final feeding day. These tests were performed in the last numbered 10 animals on day 36 and in all of the remaining animals on the following day of the final feeding day. Blood samples for general hematological tests were collected from the inferior vena cava under anesthesia with

	Item of measurement	Abbreviation	Unit	Remarks	
Blood	blood platelet white blood cell red blood cell hemoglobin hematocrit mean corpuscular volume mean corpuscular hemoglobin mean corpuscular hemoglobin concentration	PBC WBC RBC Hgb Hct MCV MCH MCHC	$\times 10^3/\text{mm}^3$ $\times 10^3/\text{mm}^3$ $\times 10^6/\text{mm}^3$ g/dl % μm^3 pg %	TECHNICON Hemalog 8/90	
	basophilic leukocyte eosinophilic leukocyte staff neutrophil segmented neutrophil lymphocyte monocyte	Bas Eos Ne(St) Ne(Seq) Lympho. Ly. Mono... Mon.	% % % % % %	May-Giemsa	
Serum	glutamic pyruvic transaminase glutamic oxaloacetic transaminase leucine aminopeptidase cholinesterase alkaline phosphatase lactate dehydrogenase creatinine phosphokinase blood urea nitrogen creatinine total protein albumin calcium cholesterol triglyceride glucose albumin/globulin ratio glutathione Inorganic Phosphorus Phospholipid	GPT GOT LAP ChE ALP LDH CPK BUN Cre. TP Alb. Ca Chol. TG Glu A/G GSH InP PL	IU IU IU ΔpH IU IU IU mg/dl mg/dl g/dl g/dl mg/dl mg/dl mg/dl mg/dl mg/dl mg/dl mg/dl	HITACHI-718 Automatic Analyzer	
	sodium potassium chloride	Na K Cl	U. Na U. K U. Cl	mEq/l mEq/l mEq/l	TECHNICON Stat/Imm II
urine	pH value protein glucose ketone bilirubin occult blood urobilinogen	pH Pro. Gluc. Ket. Bili. OB Urobili.		Qualitative	MULTI STICKS
	specific gravity	SG			Waco URIPST
	osmotic pressure	OP		mOsm/kg	Advanced CRYO-MATIC Osmometer
	urine volume	UV		ml	

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ANALYTICAL METHODS.

1 GPT (Glutamic Pyruvic Transaminase)

method ; UV method

reference ; Wróblewski, Proc. Soc. Exp. Med.,
91, 96 (1956)

2 GOT (Glutamic Oxaloacetic Transaminase)

method ; UV method

reference ; Karmen, J. Clin. Invest.,
34. 126 (1955)

3 LAP (Leucin Aminopeptidase)

method ; L-leucyl p-diethyl aminoanilide method

principle ;

p-Diethyl aniline liberated from L-leucyl p-diethyl aminoanilide by LAP in a test sample was colored to blue with 1-Naphthol-2-sulfonic Acid as a coupler and meta-Sodium-Periodate as an oxidative reagent. The color intensity indicates LAP activity.

4 CHE (Choline Esterase)

method ; delta-pH method

principle ;

Acetate liberated from acetyl-choline by CHE in a sample decreases pH and color of phenol-red turns pale. Alteration of the color indicates CHE activity of the sample.

5 ALP (Alkaline Phosphatase)

method ; modified Kind-King method

reference ; Watanabe et al, Japanese J. Clin. Pathol.,
15, 708 (1967)

6 LDH (Lactate Dehydrogenase)

method ; Wróblewski-La Due method

principle ;

Pyruvic acid as a substrate reduces to lactic acid by the action of LDH with oxidation of NADH to NAD. The change of absorption at 340 nm of NAD indicates LDH activity.

7 CPK (Creatine Phosphokinase)

method ; modified Oliver method

reference ; Rosalki, J. Lab. and Clin. Med.,
69, 696 (1967)

8 BUN (Blood Urea Nitrogen)

method ; modified Urease-Indophenol method

principle ;

Uric acid in the sample liberates ammonium and bicarbonate by the action of urease.

Ammonium changes to Indophenol with Salicylic acid and Sodium Chlorite by catalytic action of Sodium Nitroprusside. The color intensity of produced indophenol indicates the amount of BUN.

9 CREA (Creatinine)

method ; Jaffé method

principle ;

Creatinine with Picric acid produces a specific red compound (Jaffé reaction). The color intensity indicates the amount of creatinine.

10 TP (Total Protein)

method ; Biuret method

reference ; Cornall, J. Biol. Chem.,
177, 751 (1949)**11 ALB (Albumin)**

method ; BCG method

reference ; Dumas et al., Clin. Chim. Acta,
31, 87 (1971)**12 CA (Calcium)**

method ; OCPC method

reference ; Connerty et al., Am. J. Clin. Path.,
45, 290 (1966)**13 CHO (Cholesterol)**

method ; enzyme method

reference ; Allain, C. C. et al., Clin. Chem.
20, 470 (1974)

14 TG (Triacyl Glycerol)

method ; LPL-GK-GPO (lipoprotein lipase-glycero
kinase-glycerol 3 phosphate oxidase)
enzyme method

principle ;

H_2O_2 liberated from glycerol-3-phosphate, 4-amino
antipyrine and p-chlorphenol makes quantitatively
oxidative-condensation compound. Intensity of the
color (red) indicates the amount of triacyl glycerol.

15 GLU (Glucose)

method ; GOD-POD (glucoseoxidase-peroxidase) method
reference ; Trinder, Ann. Clin. Biochem.,
6, 24 (1979)

16 GSH (Glutathione)

method ; DTNB method

principle ;

SH group in Glutathione reacts with DTNB(5,5'-dithio-
bis(2-nitrobenzoic acid)) quantitatively and colors
to yellow.

17 InP (Inorganic Phosphorus)

method ; direct Molybdic-blue method

principle ;

Ammonium molybdate catches inorganic phosphorus and
turns to phosphomolybdic acid. Sulfic acid:methyl-
aminophenol reduces the phosphomolybdic acid to
molybdic-blue (blue pigment).

18 PL (Phospholipid)

method ; enzymatic method

principle ;

Phospholipase D liberates choline from phospholipid
and Cholineoxidase liberates H_2O_2 from the choline.
The amount of H_2O_2 is determined by POD as described
in GLU.

nembutal. A portion of blood samples collected was treated with anticoagulant and subjected to hematological tests. The remainder was separated of serum to be subjected to serum biochemical tests. Items of urinalysis, hematological tests and serum biochemical tests are shown in the attached table.

Immediately after collection of blood samples, necropsy was performed and visceral organs were removed for pathological examination. The visceral organs resected were weighed and fixed in neutral formalin. According to the ordinary method, HE stained preparations were prepared and examined histologically under an optical microscope. For histologic preparations of the liver, kidney and spleen obtained on day 92, electron microscopic studies were also performed. For these electron microscopic studies 2 animals with two lowest odd numbers of each group were used. A portion of visceral organs to be studied were resected before fixation with formalin, fixed with glutalaldehyde and prepared into preparations for electron microscopic studies.

6. Statistical analysis

For each measurements the mean \pm SD values were calculated in each group and examined of presence or absence of significant difference between the control group and the group fed with Neosugar G. For analysis of significant of difference t-test was used.

Results

1) Mortality

One male animal each died on day 35 and day 77 in Neosugar G 30% group. For the animal which died on day 35, the death was judged as accidental since it was found dead caught between the feeder and the cage. On the other hand, among females death occurred in 1 animal each in Neosugar G 1.875% group on day 63, in Neosugar G 7.5% group on day 77 and in Neosugar G 3% group on day 10.

2) General condition

In males, 1 case showed coarse coat and hair loss in the facial area from day 65 to day 80.

In Neosugar G 1.875% group one case developed hair loss under the right ear from day 50 through the end of the study period. In another 1 case smudge of the right and left palpebral was seen from days 21 to 28 and hair loss and crust formation from day 57 through the end of the study period.

Neosugar G at 3.75% caused hair loss and crust formation under the right ear from day 71 to day 82 in 1 case and swelling of the right ankle from day 55 to day 64 in 1 case. Moreover, hematoma of the right auricle from day 84 and hair loss and crust formation under the right ear from day 71 were observed through the end of the study period in 1 case

each.

At the dose level of 7.5% of Neosugar G, smudge of the left palpebra was seen in 1 case from day 71 to day 74 and coarse coat over the right shoulder to ventral side in 1 case from day 71 to day 83. One each case showed hair loss of the back area from day 84, hair loss and crust formation under the left ear from day 84, and hair loss and crust formation under the right ear from day 71, respectively. All of these symptoms persisted until the end of the study period. In 1 case smudge of the palpebra and the area around the mouth and nose as well as dyspnea appeared on day 36. Since it was predetermined that this animal was to be subjected to hematological and pathological studies on day 36, blood samples were collected and necropsy was conducted on day 26.

In Neosugar G 15% group, bloody stool was observed only on day 5 in 1 case. One case showed smudge around the nose from day 28 to day 31. In about one third of the animals of this group, passages of soft stool and diarrhea were observed from day 3 to day 11.

At the dose level of 30% of Neosugar G, one case showed coarse coat from the right and left facial area to the shoulder from day 64 and one case coarse coat in the right facial area from day 71 through the end of the study period, respectively. Almost all cases passed soft stool or diarrheal stool from day 2 to day 27. Subsequently, the number of animals show-

ing these symptoms decreased gradually, and from day 37 thereafter only 1 to 2 cases showed passages of diarrheal or soft stool.

The findings observed in female animals were as follows. In no-treatment group, smudge of the palpebra developed from day 41 in 1 case, and coarse coat of the facial area from day 75 in 1 case and from day 88 in 1 case through the end of the study period, respectively. In another 1 case, hair loss was noted in the lumbar region from day 64 to day 79.

In Neosugar G 1.875% group, one case showed coarse coat of the right facial area from day 57 to day 69, 1 case developed discharge of the right palpebra (on day 38 only) and smudge of the right palpebra from day 38 to the end of the study period, respectively. In another 1 case slight smudge of the right palpebra was seen from day 53 to day 56.

One case of Neosugar G 3.75% group showed smudge of the fur coat in the lumbar region from day 88 through the end of the study period.

In Neosugar G 7.5% group, smudge of bilateral palpebrae and that of the left palpebra were seen in 1 case each from day 4 and day 57, respectively. Coarse coat appeared from day 78 in the left cervical area in 1 case and in the proximal area of the left ear in 1 case, respectively, through the end of the study period. In almost all cases slightly

soft stool was passed on days 6 and 7.

In Neosugar 15% group smudge of the right palpebra from day 68 in 1 case, hair loss of the left nose from day 70 in 1 case, and coarse coat from the cervical area to the shoulder from day 68 in 1 case were observed through the end of the study period. One case showed coarse coat in the cervical area to the head from day 50 to day 77 and 1 case displayed coarse coat in the neck, shoulder, face and head from day 12 to day 63. Passage of soft stool or diarrheal stool was seen in about half of the animals on days 2 to 4, in almost all of animals on days 4 to 8 and in sporadic animals on days 9 to 18.

In the group fed with Neosugar G at 30%, coarse coat was seen from the right shoulder to the lumber region from day 38 through the end of the study period. On days 2 to 27 passage of diarrheal or soft stool appeared in almost all cases. Subsequently, the number of animals showing these symptoms decreased to disappear from day 62 thereafter.

3) Body weight (Table - 1)

In male animals the body weight was higher than that of the control group in Neosugar G 3.75% group on day 50 and from day 64 thereafter, in Neosugar G 7.5% group from day 43 thereafter, and on the final day of determination in Neosugar G 15% group.

The body weight recorded for female animals was superior to that of the control group on days 64 and 78 in Neosugar G 1.875% group, on days 29 and from day 43 thereafter in Neosugar G 3.75% group, from day 22 thereafter in Neosugar G 7.5% group, and from day 15 thereafter in Neosugar G 15 and 30% group, respectively.

4) Feed intake (Table 2)

The feed intake of male animals was higher than that of the control group on days 1 and 8 and from day 57 thereafter in Neosugar G 1.875% group, on days 1 and 8, 22 to 50 and from day 64 thereafter in Neosugar G 3.75% group, on days 1 to 29 and from day 43 thereafter in Neosugar G 7.5% group, on day 8 and from day 22 thereafter in Neosugar G 15% group, and on day 8 and from day 29 thereafter in Neosugar G 30% group. Less feed was consumed in Neosugar G 30% group as compared to the control groups on day 1.

In females more feed was consumed on days 8, 29 and 50 and from day 78 thereafter in Neosugar G 1.875% group, on days 8 to 36, 50 and from day 78 thereafter in Neosugar G 3.75% group, on days 8 to 26, 57 and from day 78 thereafter in Neosugar G 7.5% group, on days 8 to 36 and from day 50 thereafter in Neosugar G 15 and 30% groups. Less feed was consumed on day 1 in Neosugar G 1.875% group, on day 71 in Neosugar G 7.5% group, and on day 1 in Neosugar G 30% group.

5) Water intake (Table 3)

The water intake for male animals was higher than that of the control group on day 43 in Neosugar G 1.875% group, on days 43, 71 and 78 in on days 29, 43 and 64 to 85 in Neosugar G 15% group and on days 8, 15, 29 to 57 and 71 to 85 in Neosugar G 30% group. On the other hand, the water intake lower than that of the control group was recorded on days 8, 50 and 92 in Neosugar G 1.875% group, on day 8 in Neosugar G 3.75% group, on days 8 and 15 in Neosugar G 7.5% group and on days 1 and 8 in Neosugar G 15% group.

The water intake for females was higher than that of the control group on days 8, 22, 29, 78 and 92 in Neosugar G 1.875% group, on day 1 in Neosugar G 15% group and on days 1 and 8 in Neosugar G 30% group. A decrease in water intake was observed on day 1 in Neosugar G 1.875% group, on days 1 and 15 in Neosugar G 7.5%, on day 50 in Neosugar G 15% group and on days 50 and 85 in Neosugar G 30% group.

6) Audiometry

No abnormalities were observed on any of the assessment days in either females or males.

7) Urinalysis (Table - 4)

In male animals the urine became positive for Bili at 1 month Neosugar G7.5 and 15% groups and also for Ket in

Neosugar G 15% group. At 2 months urine became positive for protein and occult blood reaction in Neosugar G 7.5% group and for protein, Ket and occult blood reaction in Neosugar G 15% group. The findings of urinalysis at 3 months revealed positive results for protien and occult blood in Neosugar G 1.875% group, for protein and Bili in Neosugar G 3.75 and 7.5% groups, for protein, glucose, Ket, Bili and occult blood reaction in Neosugar G 15% group, and for protein and Ket in Neosugar G 30% group.

In female animals the urinalysis gave positive results for occult blood at 1 month in Neosugar G 1.875 to 15% groups and also for protein in Neosugar G 1.875 and 15% groups. At 2 months urine showed positive results for protein and occult blood in Neosugar G 7.5 and 15% groups and moreover for Ket in Neosugar G 15% group. Urinalysis conducted at 3 months revealed that urine became positive for protein in all groups and moreover for occult blood reaction in Neosugar G 1.875% group, for Bili in Neosugar G 3.75, 7.5 and 15% groups and also for Glu and Ket in Neosugar G 15% group. In Neosugar G 30% group the urine became positive for Ket. In both male and female animals the urinalysis conducted before start of administration of the test substance also gave positive results for protein, Ket and Bili. In addition, in the no-treatment group also urinalyses gave positive results for pritein and occult blood

reaction at almost all of the assessment periods.

8) Hematological tests (Table - 5)

(1) Findings of hematological tests on day 36 were as described below

The hematological findings recorded for male animals revealed an increase in Hct and decreases in MCHC and Ne (Seg) in Neosugar 1.875% group, increases in Hct, MCV and Eos and a decrease in MCHC in Neosugar G 3.75% group, an increase in MCV and a decrease in MCHC in Neosugar G 15% group, and increases in MCV and Eos and a decrease in MCHC in Neosugar G 30% group. In Neosugar G 7.5% group no remarkable changes were observed.

As to female animals, a decrease in PBC was observed in Neosugar G 1.875% group. Except for this finding, no abnormal changes were seen in any of the other groups.

(2) Findings of hematological tests on day 92 were as described below.

Findings for male animals showed a decrease in Hgb in all groups and moreover a decrease in RBC and Hct in groups fed with Neosugar G at 7.5% or more. In groups fed with Neosugar G at 15% or more MCHC also showed a decrease. In addition, an increase in Ne (Seg) and a decrease in Ly were observed in Neosugar G 1.875, 7.5 and 30% groups, an increase in WBC and a decrease in Hct in Neosugar G 1.875% group, an

increase in WBC and a decrease in MCHC in Neosugar G 3.75% group, and a decrease in Mon in Neosugar G 30% group.

In female animals WBC showed a decrease in groups fed with Neosugar G at 7.5% or more, although no dose-response correlation was seen. Other than these findings, a decrease in MCV and a decrease in Hct were observed in Neosugar G 1.875% group and Neosugar G 7.5 and 30% groups, respectively.

All of the above described findings were mild in nature and showed no dose-response relation.

9) Results of serum biochemical tests (Table - 6)

(1) Findings of serum biochemical tests performed on day 36 revealed following changes.

The changes observed in male animals included increases in Cl and α_1 -globulin fraction, a decrease in TP and an elevation in A/G ratio in Neosugar G 1.875% group, decrease in ChE and Ca and an increase in Cl in Neosugar G 3.75% group, increases in P.L, Cl and α_1 -globulin fraction and decreases in ChE, Al-P, TP and Ca in 7.5% group, decreases in GPT, ChE, BUN and γ -globulin fraction, increases in P.L, Na, Cl and Alb fraction and an elevation in A/G ratio in Neosugar G 15% group, and increases in Na, Cl, Alb fraction and LAP, decreases in ChE, BUN and α_1 -globulin fraction and an elevation in A/G ratio in Neosugar G 30% group.

For females, the results of serum biochemical tests

showed decreases in LDH, Alb and α_2 -globulin fraction and increases in TP, Alb, Ca and α_1 -globulin fraction in Neosugar G 1.875% group, increases in CRE, TP, Alb, Ca, TG and P.L in Neosugar G 3.75% group, increases in TP, Alb, Ca, Glu, P.L and Na in Neosugar G 7.5% group, a decrease in BUN, and increase in Na, K, and α_2 -globulin fraction in Neosugar G 15% group, and decreases in GPT and BUN and increases in TP, Alb, Ca, P.L, Na, K, α_2 -globulin fraction and γ -globulin fraction in Neosugar G 50% group.

(2) Findings of serum biochemical tests performed on day 92 revealed following changes.

In male animals decreases in ChE, Al-P and BUN were seen in groups fed with Neosugar G at 3.75% or more and increases in LAP, Cl and γ -globulin fraction in groups fed with Neosugar G at 7.5% or more. Other findings included increases in CPK, Na, Cl, α_2 -globulin fraction and decreases in Alb, GSH and β -globulin in Neosugar G 1.875% group, increases in CPK, Chol, TG and α_2 -globulin fraction and a decrease in P.L in Neosugar G 3.75% group, increases in LAP, LDG, CPK, Glu, Na and α_1 -globulin fraction and decreases in Alb and Alb fraction in Neosugar G 7.5% group, increases in GPT, GPT, Na and α_2 -globulin fraction and decreases in TP and Alb in Neosugar G 15% group, and increases in CPK, Ca, TG and α_2 -globulin fraction, an elevation in A/G ratio and decreases in TP, GSH, P.L and α_1 -globulin fraction in Neosugar G 30% group.

The changes recorded for female animals were increases in Na, Cl and Alb fraction and decreases in α_1 - and α_2 -globulin

fractions in Neosugar G 1.875% group, decreases in P.L and α_1 -globulin fraction in Neosugar G 3.75% group, decrease in BUN and α_2 -globulin fraction and increase in Na, Cl and γ -globulin fraction in Neosugar G 7.5% group, decreases in Alb, Al-P and β -globulin fraction, increases in Ca, Na and Cl, and an elevation in A/G ratio for Neosugar G 15% group, and a decrease in BUN, increase in LAP, ChE, TP, Alb, Ca and α_1 -globulin fraction and an elevation in A/G ratio in Neosugar G 30% group.

10) Organ weight (Table - 7)

(1) Findings obtained on day 36 were as described below.

a) Absolute organ weight

The absolute organ weight of male animals revealed a decrease in thymus weight for Neosugar G 3.75% group, an increase in intestine weight for Neosugar G 15% group, decreases in weights of the lung, liver and right kidney and an increase in intestine weight for Neosugar G 30% group.

The absolute organ weight for females showed a decrease in adrenal weight for 3.75% group and an increase in intestine weight for Neosugar G 30% group.

b) Relative organ weight

As to relative organ weight of males, a decrease

in thymus weight was recorded for Neosugar G 3.75% group, a decrease in pulmonary weight and an increase in intestine weight for Neosugar G 15% group, and a decrease in liver weight and an increase in intestine weight for Neosugar G 30% group.

The absolute organ weight for females showed a decrease in adrenal weight for Neosugar G 15% group and an increase in intestine weight for Neosugar G 30% group.

(2) Findings obtained on day 92 were as described below.

a) Absolute organ weight

The changes observed in absolute organ weight of male animals were an increase in heart weight for Neosugar G 7.5% group, increases in weight of heart, hypophysis and intestines for Neosugar G 15% group and an increase in intestine weight for Neosugar G 30% group.

The absolute organ weight of female animals showed an increase in ovary weight for Neosugar G 1.875% group, increases in heart, spleen and intestine weights for 7.5% group, increases in heart, spleen, adrenal and intestine weights for Neosugar G 15% group, and increases in brain, heart, liver, adrenal, hypophysis and intestine weights for Neosugar G 30% group.

b) Relative organ weight

Regarding relative organ weight of male animals,

a decrease was seen in the left testicle weight for Neosugar G 1.875% group, decreases in cerebral, left renal and right and left testicles weights for Neosugar G 3.75% group, decreases in brain, spleen and left renal weights for Neosugar G 7.5% group, decreases in right and left testicle weights and an increase in intestine weight for Neosugar G 15% group, and a decrease in the left renal weight and an increase in intestine weight for Neosugar G 30% group.

Changes in relative organ weight observed in females included decreases in pulmonary and uterine weights for Neosugar G 1.875% group, decreases in brain, lung, right and left renal, uterine and hypophysis weights for Neosugar G 3.75% group, a decrease in brain weight for Neosugar G 7.5% group, decreases in brain and lung weights and an increase in intestine weight for Neosugar G 15% group, and decreases in brain, lung and right and left renal weights and an increase in intestine weight for Neosugar G 30% group.

11) Necropsy findings (Table - 8)

(1) Necropsy findings on day 36 were as described below.

In male animals, gastrointestinal bleeding and retention of gas were observed in 1 case of Neosugar G 7.5% group.

In Neosugar G 15% group distension of the cecum was shown in 3 cases. At the dose level of 30%, distension of the cecum was noted in 6 cases and small right testis in 1 case.

Among females, distension of the cecum was observed in 8 cases of Neosugar G 30% group.

In any of the other groups no abnormalities were observed for either males or females.

(2) Necropsy findings on day 92 were as described below.

In male animals, intestinal hemorrhage and distension of the cecum were seen in 1 case each of Neosugar G 15% group. At the dose level of 30% distension of the cecum was observed in 13 cases and small right testis and distension of the cecum in 1 case. As to fatal cases (2 cases) of Neosugar G 30% group, congestion of the thymus and distension and congestion of the cecum were seen in 1 case and distension of the cecum and blood like ascite in the other case (accidental death).

Regarding female animals, edema of the uterus was observed in 1 case of no-treatment group. In 1 case of Neosugar G 1.875% group (fatal case), hypertrophy of adrenal glands (right and left), mucoid deposition of the gastric mucosa, scattering of white spots on the surface of kidneys, and hemorrhage of the urinary bladder were encountered. In 1 case (fatal case) of Neosugar G 7.5% group, hypertrophy of the right and

left adrenal glands, hypertrophy of the right kidney and hemorrhage of the urinary bladder were present. In Neosugar G 30% group the cecum was distended in 5 cases. In 1 fatal case, necropsy findings revealed fluid like contents within the stomach, hemorrhage of the glandular stomach, and distention and hemorrhage of the cecum.

In any of the other groups no abnormalities were observed for either males or females.

12) Optical microscopic findings (Table 8)

(1) Optical microscopic findings on day 36 were as described below.

The optical microscopic findings observed in male animals included round cell infiltration of the renal cortex (one side) in 1 case and round cell infiltration of the interstitium of the prostate in 1 case for Neosugar G 1.875% group; round cell infiltration of the interstitium of the prostate in 2 cases for Neosugar G 3.75% group; desquamation of the gastrointestinal mucosa in 1 case and retention of hemoglobinuria in the urinary bladder in 1 case for Neosugar G 7.5% group; round cell infiltration of the interstitium of the prostate in 1 case and atrophy of the cecum mucosa in 2 cases for Neosugar G 15% group; and hyperplasia of the renal pelvic mucosa (one side) in 1 case, aspermatogenesis (one side) of the right testis in 1 case and atrophy of the cecum mucosa

in 1 case for Neosugar G 30% group.

As to female animals round cell infiltration of the renal pelvis or cortical interstitium of the kidney was encountered in 1 case each for no-treatment group and Neosugar G 3.75 and 7.5% groups.

(2) Optical microscopic findings on day 92 were as described below.

As to male animals, round cell infiltration of the heart was noted in 1 case and vacuolization of hepatocytes in 1 case for no-treatment group. Regarding group fed with Neosugar G, aspermatogenesis of the testis (one side) and round cell infiltration of the interstitium of the prostate in 1 case, respectively, for Neosugar G 1.875% group. For Neosugar G 3.75% group vacuolization of hepatocytes was shown in 1 case, round cell infiltration of the renal cortex in 1 case and round cell infiltration of the interstitium of the prostate in 1 case. The findings observed for Neosugar G 7.5% group were round cell infiltration of the renal cortex (one side) in 1 case, round cell infiltration of the interstitium of the prostate in 1 case and fibrosis of Langerhans' islets in 1 case. For Neosugar G 15% group, small cyst of the renal cortex (one side) was noted in 1 case, round cell infiltration of the interstitium of the prostate in 1 case, atrophy of the cecal mucosa in 1 case and fibrosis around the pancreas in 1 case. The findings recorded for

Neosugar G 30% group were congestion of the thymus in 1 case (fatal case), aspermatogenesis of the testis in 1 case and desquamation of the cecal mucosa in 4 cases.

On the other hand, as to the findings obtained for female animals round cell infiltration of the cortical interstitium and regeneration of epithelial cells of the uriniferous tubules were shown in 2 cases and hyperemia of the uterine mucosa in 1 case of no-treatment group. In Neosugar G 1.875% group 2 cases exhibited round cell infiltration of the cortical interstitium and regeneration of epithelial cells of the uriniferous tubules, and 1 case (fatal case) showed severe pyelonephritis of both kidneys, congestion of both adrenal cortex, atrophy, necrosis and desquamation of the gastric mucosa, and necrosis calcification and round cell infiltration of the mucosa of the urinary bladder. Among animals of Neosugar G 7.5% group, 1 case (fatal case) showed extended necrosis of the kidney (one side), round cell infiltration of the cortical interstitium, edema and congestion of the lung, and congestion and vacuolization of the adrenal cortex, and another 1 case exhibited round cell infiltration of the cortical interstitium of the kidney. In 1 case of Neosugar G 15% group, round cell infiltration of the interstitium of the cortex and regeneration of epithelial cells of the uriniferous tubules were present. In Neosugar G 30% group vacuolization of hepatocytes was seen in 2 cases, atrophy of the cecal mucosa

in 3 cases and hyperemia of the gastric mucosa and hemorrhage of the cecal membrane in 1 case (fatal case).

13) Electron microscopic findings (Table - 9)

In male animals the electron microscopic findings of the liver showed fatty degeneration in all groups and a decrease and fractionation of RER in Neosugar G 3.75 and 15% groups. As to the kidney an increase in lysosome was seen in no-treatment group and Neosugar G 7.5 and 30% groups. Degeneration of β -cells was noted in no-treatment group and 7.5% group.

In female animals fatty degeneration was observed in all groups. In Neosugar G 7.5% group, swelling of mitochondria was encountered. Focal cytoplasmic degeneration was noted in Neosugar G 15% group. In some animals of groups fed with Neosugar G at 3.75% or more, the kidney showed swelling of mitochondria. At the dose level of Neosugar G 30%, the spleen showed decreased enzymogen granules of exocrine gland and alterative changes of acinoar cells were noted.

Discussion

Neosugar is obtained by binding of fructose to Fructose (F) of succrose (GF), made up through conjugation of glucose (G) with Fructose (F), by reacting fructose transferase produced by microorganisms and it is a mixture of fructooligo

saccharides consisting of 1 ketose GF , nistose GF and 1-fructranosylnistose GF . Neosugar G is a mixture of about 50% of fructooligo saccharides, monosaccharide and sucrose.

It has been elucidated that Neosugar has various advantageous properties as described below. Namely, Neosugar is a sweetener which is not decomposed by saliva of humans or animals or by intestinal digestive enzymes, but it is slightly decomposed by intestinal flora. When administered orally in experimental animals, it causes no changes in blood glucose levels or insulin levels. In rats induced of diabetes by alloxan or streptozotosin, it decreases blood sugar levels.⁴⁾ Neosugar decreases hypercholesterolemia and controls elevation of blood pressure in SHR rats. It also decreases hypertriglycemia in rats induced of diabetes by streptozotosin and in mice induced of obesity by glodthiogluucose. Moreover, it is selectively consumed by Bifidobacteria in the intestines of humans and helps growth of these bacteria.

Its efficacy to decrease total cholesterol, triglyceride, and fatty acid levels, and glycemia as well as its hypotensive effect have been confirmed in clinical trials in patients with hyperlipedemia.

In the present study subacute toxicity of Neosugar G was determined with following results.

Death occurred in 2 male cases in Neosugar G 30% group and in 1 female case each in Neosugar G 1.875%, 7.5% and 30% group, respectively. As to general conditions various

changes such as hair loss, coarse fur coat, and smudge were observed. However, the changes which were considered to have dose-response relationship were only the nature of stool. Reversible passages of soft stool or diarrheal stool were observed at dose levels of 15% or more for males and at 7.5% or more for females. The duration of soft stool and diarrhea was approximately in proportion to the dose level of Neosugar G, showing a prolonging tendency in the highest dosed group. Feed intake showed both male and female animals in treated group. No special tendency was seen in water intake. Regarding body weight, an increase was noted from about middle through the end of the experimental period only in Neosugar G 3.75 and 7.5% group for male animals. For female animals weight gain was observed in almost all groups. The increase in body weight was also proportional to the dose level of Neosugar G, appearing from the earlier period in higher dosed groups.

In the results of audiometry no abnormalities were seen.

Urinalysis revealed changes in some parameters such as levels of Bili, Ket and P as well as occult blood reaction in sporadic cases for both males and females in each group. However, some of these changes were also seen before start of feeding of animals with the feed added with Neosugar G. Moreover, since similar changes were observed in no-treatment group also, none of the changes of these parameters were considered to be attributable to feeding with Neosugar G.

On the other hand, hematological tests and serum biochemical tests revealed fluctuations of many parameters for both male and female animals. The main changes observed were as follows.

The male animals the results of studies at the assessment period of day 36 revealed a decrease in ChE at dose levels of 3.75% or more and in addition to this change a decrease in BUN at dose levels of 15% or more. At the assessment period of day 92, a decrease in Hgb was seen in all groups and decreases in Che, Al-P and BUN in groups fed with Neosugar G at 3.75 or more. In addition to these changes, at dose levels of 7.5% or more decreases in RBC and Hct as well as an increase in γ -globulin fraction were observed.

The findings recorded for female animals on day 36 included increases in TP, Alb, Ca and P.L in all groups and an increase in α_2 -globulin fraction in groups fed with Neosugar G at 15% or more. Moreover, γ -globulin showed an increase at dose levels of 30% or more. On day 92 WBC showed a decrease at dose levels of 7.5% or more and moreover a decrease in BUN and increases in ChE, TP, Alb and Ca were seen at dose levels of 30% or more.

As described above, many parameters showed fluctuations in both male and female animals. However, all of these changes were mild in nature and no correlative relations existed between changes and the dose levels of Neoguar G for

most of them. Moreover, none of the patterns of these fluctuations were indicative of disturbances of any particular visceral organs. Therefore, it is difficult to consider that changes of various parameters observed for both male and female animals were attributable to toxic effects of the test substance.

Pathologically, the following findings were obtained.

In males at necropsies on both day 36 and day 92 there were some animals which showed gastrointestinal bleeding, distension of the cecum, and small testis. Among these changes only cecum distension observed in the groups with the test substance at 15% or more showed dose-response relation. All of the other findings were observed in only 1 case each with no dose-response relation at either of the assessment periods, and they were judged as incidental changes. As to visceral organ weight, many organ showed changes in weight at both assessment periods of day 36 and day 92. The only changes that were recorded for both absolute and relative organ weights were an increase in organ weight of the intestines at dose levels of 15% or more and a decrease in liver weight observed in animals of Neosugar G 30% group on day 36. Light microscopic findings revealed some histologic abnormalities in sporadic animals of various groups including no-treatment group. The change which was considered to be correlated with the dose level was slight atrophy of the cecal

mucosa. In Neosugar G 30% group the liver weight showed a decrease on day 36. However, since no abnormalities were found in the liver histologically, this organ weight loss of the liver is considered to be of no importance. The findings of electron microscopy revealed some changes in liver, kidney and spleen. All of these changes are observed usually and not considered to be attributable to feeding with Neosugar G.

The necropsy findings obtained for female animals revealed distension of the cecum in Neosugar G 30% group on both day 36 and day 92. Regarding visceral organ weight, changes were observed in many organs at both assessment periods of day 36 and day 92. However, changes observed in both absolute and relative organ weights were only the increase intestinal weight for the assessment period of day 36, and increased intestinal weight in groups fed with Neosugar G at 15% or more and, in addition, decreased brain weight in Neosugar G 30% for the assessment period of day 92. The decrease in brain weight may be attributable to the fact that the body weight recorded for Neosugar G 30% group was higher than that of no-treatment group by 11%. By light microscopic examination histologic abnormalities were observed in sporadic cases of all groups including no-treatment group similar to male animals. However, dose-response relation was shown only for the slight atrophy of the cecal mucosa observed in the

highest dose group on day 92. In Neosugar G 30% group no histologic abnormalities were seen in the brain on day 92. These findings also indicated that the decrease in brain weight found at necropsy was of no importance. Electron microscopic studies of the liver, kidney and pancreas also revealed no abnormal findings which could be attributable to feeding of Neosugar G similar to male cases.

As described above, changes which were considered to be clearly attributable to feeding with Neosugar G were development of diarrhea and soft stool, increase in intestinal weight and distension of the cecum and slight atrophy of the cecal mucosa observed in high dosed groups. All of these changes are generally seen in rats when fed with hardly digestable polysaccharides and not specific for Neosugar G.

Death occurred in a total of 5 cases including both males and females. Death of 1 male case of Neosugar G 30% group was accidental. In 1 female case each of Neosugar G 1.875 and 7.5% groups which died during the study period pronounced pyelonephritis or extensive necrosis of the renal cortex was encountered. In the present study, some female cases including those of no-treatment group showed nephritis like findings such as round cell infiltration in the kidney. Moreover, urinary occult blood reaction became positive in no-treatment also. From these findings occurrence of urinary tract infection was suspected. Therefore, there is a high

possibility that fatal animals of Neosugar G 1.875 and 7.5% groups developed serious urinary tract infections, resulting in death. In 1 female fatal case and 1 male fatal case of Neosugar G 30% group severe distension of the cecum was observed as a common finding. In addition, hemorrhage of the cecum, and congestion, hemorrhage and thickening of the gastric mucosa or congestion of the cecum were observed. However, in either of these cases no abnormal findings which were considered to be the direct cause of death were shown. Moreover, no abnormalities were seen in general condition just before death with uneventful body weight gain. Therefore, in these 2 cases also there is a high possibility that the death is incidental.

As described above, in the present study on subacute toxicity following treatment with Neosugar G mixed in feed for 91 days no toxic effect which could be attributable to treatment with Neosugar G appeared even in Neosugar G 30% group, the highest dose group, except for soft stool, diarrhea and distension of the cecum.

Conclusion

Both sexes of SD rats in groups of 30 animals each were fed with free access to feed added with Neosugar G at five different concentrations of 1.875, 3.75, 7.5, 15 and 30% for 92 days to determine subacute toxicity.

In higher dosed groups various symptoms such as soft stool, diarrhea and distension of the cecum which are ordinarily seen following oral administration of hardly digestable polysaccharides were observed. Apart from these findings, there were no abnormal findings attributable to feeding with Neosugar G. From these results it was concluded that Neosugar G gives no toxic effect on rats when it is given orally for 91 days mixed in feed at a level of 30%.

Table 1-1. Changes in body weights of male rats fed with Neosugar G for 91 days

Day	Neosugar G					
	No treatment	1.875%	3.75%	7.5%	15%	30%
	N	N	N	N	N	N
1	30 111.1 3.06	30 111.2 2.76	30 110.9 3.45	30 111.0 3.09	30 111.3 3.06	30 111.1 4.45
8	30 178.6 6.88	30 177.2 8.25	30 180.0 6.41	30 178.5 7.52	30 178.4 8.07	30 176.6 11.21
15	30 234.6 9.64	30 235.5 10.81	30 237.4 10.39	30 236.3 10.97	30 232.0 12.10	30 229.4 21.05
22	30 288.8 12.81	30 291.0 15.37	30 295.2 14.26	30 293.5 15.34	30 286.0 25.66	30 280.2 22.11
29	30 325.3 17.64	30 328.9 18.43	30 333.0 19.59	30 333.5 18.90	30 326.2 30.88	30 316.0 28.18
36	30 359.4 23.45	30 360.0 23.98	30 366.3 21.05	30 366.0 25.72	30 364.1 31.08	29 350.6 32.71
43	20 385.3 28.81	20 391.0 28.84	20 400.5 22.56	20 405.1* 26.41	20 395.3 30.69	19 380.8 36.03
50	20 410.6 32.01	20 414.6 31.72	20 430.0* 25.15	20 431.1* 28.96	20 423.4 36.36	19 405.6 41.17
57	20 430.4 34.77	20 433.6 34.62	20 449.3 28.94	20 452.2* 29.15	20 443.6 39.18	19 424.2 39.44
64	20 445.9 36.82	20 450.5 38.58	20 470.6* 30.25	20 473.1* 31.43	20 464.3 41.49	19 448.4 43.43
71	20 455.5 38.20	20 467.1 41.94	20 485.9** 31.53	20 485.5* 32.79	20 479.5 43.43	19 464.4 45.39
78	20 470.4 38.39	20 481.9 43.85	20 502.1** 33.09	20 503.8** 34.87	20 492.6 48.19	18 484.7 50.63
85	20 481.7 39.36	20 495.9 44.65	20 515.6** 35.04	20 515.3** 37.41	20 510.0 49.18	18 502.4 56.17
92	20 497.2 42.09	20 512.3 45.64	20 533.3** 34.67	20 533.4** 39.25	20 528.5* 50.75	18 523.6 60.10

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 1-2. Changes in body weights of female rats fed with Neosugar G for 91 days:

Day	No treatment		Neosugar G				
			1.875%	3.75%	7.5%	15%	30%
	N	N	N	N	N	N	
1	30 112.5 3.61	30 111.8 4.64	30 112.3 3.01	30 113.3 3.60	30 112.5 3.38	30 113.0 3.64	
8	30 155.3 9.22	30 158.9 7.35	30 158.2 8.23	30 157.9 9.70	30 157.4 7.58	30 159.1 8.69	
15	30 177.7 9.23	30 179.2 9.34	30 179.8 9.53	30 179.7 11.65	30 182.7* 9.18	29 183.2* 10.96	
22	30 197.7 13.19	30 201.3 14.43	30 202.8 14.58	30 206.5* 12.50	30 207.7** 12.26	29 210.1** 14.92	
29	30 209.8 12.88	30 216.0 13.54	30 217.7* 14.52	30 222.8** 14.32	30 223.8** 12.01	29 225.8** 16.77	
36	30 229.0 16.00	30 225.4 24.04	30 236.2 15.19	30 239.1* 15.04	30 242.5** 15.27	29 242.3** 17.13	
43	20 234.4 13.26	20 241.8 19.54	20 252.5** 15.87	20 249.4** 14.59	20 253.8** 16.42	19 250.6* 22.88	
50	20 247.8 14.77	20 254.8 22.22	20 264.8** 16.07	20 262.3** 14.79	20 268.7** 15.74	19 268.7** 24.31	
57	20 255.3 14.43	20 266.5 22.29	20 274.0** 18.09	20 273.0** 12.93	20 277.3** 15.64	19 276.9** 24.64	
64	20 263.2 13.43	19 276.3* 20.45	20 282.4** 16.58	20 279.3** 16.63	20 283.8** 13.82	19 287.8** 25.09	
71	20 267.8 16.56	19 277.5 20.14	20 286.8** 20.18	20 283.2** 15.30	20 289.3** 17.46	19 292.7** 26.91	
78	20 273.3 14.92	19 285.9* 22.68	20 295.1** 21.05	19 293.2** 17.61	20 295.3** 20.62	19 302.9** 28.08	
85	20 277.4 16.34	19 287.8 23.31	20 301.1** 24.05	19 294.5** 15.54	20 300.5** 18.52	19 303.9** 27.37	
92	20 281.8 16.83	19 294.7 25.19	20 308.6** 25.39	19 301.5** 14.85	20 306.1** 18.57	19 312.7** 30.90	

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 2-1. Changes in food intakes of male rats fed with Neosugar G for 91 days

Day	No treatment		Neosugar G									
			1.875%		3.75%		7.5%		15%		30%	
	N		N		N		N		N		N	
1	30	14.8 1.35	30	15.8** 0.94	30	16.0** 0.92	30	16.5** 1.08	30	14.1 1.64	30	11.2** 1.65
8	30	19.1 1.15	30	19.5* 1.00	30	20.2** 1.34	30	20.4** 1.39	30	21.3** 1.40	30	22.0** 2.37
15	30	20.2 1.40	30	20.7 1.00	30	20.6 0.97	30	21.2** 0.94	30	21.1 2.82	30	21.7 3.85
22	30	22.0 1.04	30	21.6 3.21	30	22.8* 1.66	30	23.2** 1.11	30	23.8** 2.48	30	22.7 2.56
29	30	20.2 2.07	30	20.0 2.26	30	22.6** 2.73	30	22.9** 0.98	30	22.8** 1.03	30	23.4** 1.73
36	30	23.4 3.27	30	23.2 2.20	30	25.3* 2.48	30	24.0 3.74	30	28.1** 2.86	29	28.6** 3.19
43	20	23.3 2.29	20	24.2 1.63	20	24.8* 2.12	20	26.1** 1.33	20	26.3** 2.00	19	27.5** 2.27
50	20	22.8 3.07	20	22.6 1.52	20	25.0** 1.26	20	25.2** 1.75	20	27.8** 2.14	19	27.1** 2.55
57	20	22.1 1.32	20	23.6* 2.25	20	23.0 2.79	20	24.3** 1.51	20	25.9** 1.56	19	26.9** 2.68
64	20	21.4 2.19	20	23.0* 1.93	20	24.3** 1.78	20	25.8** 0.97	20	28.3** 1.72	19	29.4** 2.72
71	20	19.8 2.90	20	22.7** 2.12	20	24.2** 2.33	20	24.5** 1.89	20	29.1** 6.40	19	28.1** 3.40
78	20	21.7 1.36	20	22.8* 1.69	20	24.5** 1.86	20	24.8** 0.90	20	27.7** 3.37	18	27.9** 3.54
85	20	21.9 1.54	20	24.2** 1.45	20	26.2** 3.29	20	25.5** 1.75	20	28.3** 3.54	18	29.9** 2.42
92	20	20.7 1.58	20	21.8* 1.38	20	22.8** 1.11	20	24.0** 1.75	20	27.2** 2.26	18	27.7** 3.22

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 2-2. Changes in food intakes of female rats fed with Neosugar C for 91 days

Day	No treatment		Neosugar G									
			1.875%		3.75%		7.5%		15%		30%	
	N		N		N		N		N		N	
1	30	13.3 1.14	30	12.4** 1.21	30	13.5 2.24	30	13.7 1.10	30	13.5 1.36	30	9.4** 1.82
8	30	13.5 1.93	30	14.6** 1.06	30	15.1** 1.46	30	15.4** 1.73	30	16.1** 2.22	30	17.5** 2.52
15	30	15.6 1.35	30	15.2 1.67	30	17.4** 1.18	30	17.0** 2.19	30	19.2** 3.44	29	20.9** 7.39
22	30	15.8 1.44	30	19.3 10.11	30	17.6* 3.78	30	19.8** 2.96	30	22.7** 12.40	29	23.4** 3.70
29	30	13.8 2.63	30	15.1* 1.32	30	15.5** 2.00	30	17.2** 1.72	30	18.1** 2.26	29	20.8** 2.89
36	30	14.3 2.68	30	13.7 3.91	30	15.9* 2.07	30	15.9* 2.03	30	16.5** 2.65	29	16.9** 1.81
43	20	20.5 18.87	20	16.2 2.17	20	16.3 2.77	20	15.9 4.25	20	18.6 3.39	19	18.2 1.81
50	20	14.6 1.56	20	15.6* 1.42	20	16.8** 2.14	20	15.4 2.02	20	17.3** 2.08	19	18.6** 2.27
57	20	15.9 3.33	20	17.0 1.49	20	16.9 2.97	20	18.3** 1.11	20	19.4** 2.02	19	21.1** 1.78
64	20	16.3 5.00	19	17.7 0.80	20	17.6 2.10	20	18.0 2.87	20	20.2** 2.43	19	22.3** 2.63
71	20	15.4 2.99	19	14.8 2.34	20	14.9 3.00	20	13.5* 2.18	20	17.7* 2.63	19	20.0** 2.18
78	20	14.2 1.74	19	16.6** 1.85	20	16.8** 2.75	19	18.2** 2.06	20	16.3** 1.71	19	19.7** 2.28
85	20	14.9 1.94	19	16.1* 1.48	20	17.1** 2.71	19	16.4* 2.38	20	19.3** 1.52	19	19.2** 1.43
92	20	15.3 1.42	19	17.0** 1.89	20	17.4** 1.52	19	17.7** 2.74	20	18.1** 1.79	19	20.6** 2.01

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 3-1. Changes in water intakes of male rats fed with Neosugar G for 91 days

Day	Neosugar G											
	No treatment		1.875%		3.75%		7.5%		15%		30%	
	N		N		N		N		N		N	
1	30	22.7 2.40	30	22.3 2.64	30	23.3 2.39	30	22.5 2.03	30	21.1* 3.42	30	21.7 4.79
8	30	31.1 2.49	30	27.7** 4.72	30	27.8** 2.58	30	28.2** 3.55	30	28.1* 6.05	30	39.5** 4.68
15	30	33.6 4.10	30	33.1 3.53	30	32.6 4.08	30	30.9* 5.99	30	31.8 4.70	30	39.8** 4.30
22	30	32.5 6.95	30	33.9 7.75	30	33.7 3.45	30	32.1 4.49	30	32.1 6.96	30	34.5 4.15
29	30	34.7 7.57	30	32.9 9.24	30	35.7 8.34	30	37.8 7.41	30	42.7** 9.34	30	39.7** 6.22
36	30	38.1 3.63	30	35.9 6.24	30	36.9 5.01	30	36.1 5.93	30	40.1 6.98	29	43.6** 7.38
43	20	36.8 2.97	20	39.5* 4.95	20	40.1** 3.51	20	40.0* 5.43	20	41.9** 5.20	19	42.7** 4.60
50	20	38.5 3.12	20	35.7* 3.89	20	39.9 4.73	20	37.3 6.87	20	39.1 4.91	19	43.7** 5.73
57	20	37.9 3.82	20	36.7 5.80	20	38.2 6.34	20	39.2 8.45	20	41.5 6.90	19	45.7** 5.97
64	20	37.4 4.48	20	34.8 8.50	20	40.0 6.65	20	38.8 9.19	20	40.5* 3.55	19	40.1 8.71
71	20	35.0 4.70	20	35.8 9.46	20	41.5** 6.09	20	48.7** 15.43	20	39.8* 8.50	19	44.8** 10.09
78	20	32.8 5.21	20	34.2 8.32	20	37.9** 2.49	20	40.7** 5.93	20	39.6** 8.02	18	40.4** 2.50
85	20	33.1 4.36	20	32.5 8.84	20	34.4 4.16	20	39.6** 7.11	20	42.7** 7.99	18	38.7** 6.04
92	20	36.1 2.40	20	32.3* 6.39	20	35.5 6.67	20	34.5 9.80	20	36.7 4.23	18	36.3 6.84

Each value represents the mean and standard deviation.

Significantly different from No treatment : *--- $P < 0.05$, **--- $P < 0.01$

Table 3-2. Changes in water intakes of female rats fed with Neosugar G for 91 day

Day	No treatment		Neosugar G									
			1.875%		3.75%		7.5%		15%		30%	
	N		N		N		N		N		N	
1	30	24.2 1.35	30	22.9* 2.98	30	24.0 2.99	30	22.2** 3.31	30	25.4* 2.62	30	25.8* 3.26
8	30	21.2 3.37	30	24.1* 5.24	30	22.9 3.19	30	22.5 4.30	30	21.3 3.74	30	27.5** 5.49
15	30	29.5 5.69	30	29.0 4.84	30	29.9 7.17	30	24.5** 4.83	30	27.1 5.29	29	30.0 5.70
22	30	23.5 9.45	30	31.7** 9.78	30	27.2 8.46	30	26.3 6.06	30	24.6 5.42	29	25.7 5.78
29	30	27.1 7.12	30	32.6* 9.44	30	27.9 6.74	30	29.5 7.74	30	28.5 9.52	29	31.3 11.10
36	30	26.9 5.61	30	29.0 5.69	30	28.3 4.65	30	28.1 4.40	30	28.6 4.50	29	27.9 5.56
43	20	35.5 8.35	20	34.6 4.82	20	33.8 7.89	20	30.6 7.32	20	36.0 6.07	19	35.2 6.63
50	20	39.8 8.18	20	39.1 8.14	20	36.2 9.73	20	37.2 9.82	20	32.3* 9.78	19	30.3** 3.33
57	20	32.1 6.75	20	34.5 6.43	20	31.5 5.74	20	32.3 5.97	20	33.3 4.13	19	30.8 6.29
64	20	31.5 5.26	19	31.4 6.13	20	30.9 5.08	20	28.4 5.55	20	29.3 4.99	19	31.8 7.60
71	20	27.2 8.24	19	31.3 5.18	20	28.8 9.07	20	28.3 8.66	20	31.5 9.02	19	31.1 6.43
78	20	27.3 5.88	19	31.6* 6.11	20	28.8 5.63	19	30.7 7.18	20	25.8 6.49	19	29.9 4.30
85	20	36.6 6.04	19	39.5 5.65	20	37.5 8.54	19	37.5 15.44	20	36.0 5.62	19	31.0* 7.01
92	20	30.9 4.53	19	37.1** 6.13	20	33.4 5.35	19	32.8 8.71	20	29.8 5.94	19	29.3 5.78

Each value represents the mean and standard deviation.
Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 4-1. Urinalysis of male rats fed with Mesosugar C for 91 days

Day	Group (X)		U.Na	U.K	U.Cl	O P	pH	P	Glu	Ket	Bill	OB	Uro
Initial	No treatment	A	271	250	208	1906	9	+	-	-	+	-	+
		B	318	195	230	1872	9	+	-	-	+	-	+
		C	297	202	217	2062	9	+	-	-	+	-	+
	Mesosugar C 1.875	A	276	221	221	2104	9	+	-	-	+	-	+
		B	245	185	186	2046	9	+	-	-	+	-	+
		C	349	226	274	2412	8	+	-	-	+	-	+
	3.75	A	347	215	257	2248	9	+	-	-	+	-	+
		B	320	188	225	2118	9	+	-	-	+	-	+
		C	323	200	251	2094	8	+	-	-	+	-	+
	7.5	A	272	202	200	1986	8	+	-	-	+	-	+
		B	307	207	227	2050	9	+	-	-	+	-	+
		C	297	220	237	2136	9	+	-	-	+	-	+
	15	A	268	197	216	1914	9	+	-	-	+	-	+
		B	329	195	235	2086	9	+	-	-	+	-	+
		C	261	228	212	2082	8	+	-	-	+	-	+
	30	A	312	216	235	2162	8	+	-	-	+	-	+
		B	280	230	239	2168	9	+	-	-	+	-	+
		C	265	184	192	1934	9	+	-	-	+	-	+
31	No treatment	A	207	137	157	1622	8	+	-	-	-	-	±
		B	202	147	162	1594	9	+	-	-	-	-	±
		C	186	114	129	1312	8	+	-	-	-	-	±
	Mesosugar C 1.875	A	257	160	187	1776	8	+	-	-	-	-	±
		B	234	163	171	1660	9	+	-	-	-	-	±
		C	212	150	158	1604	7	+	-	-	-	-	±
	3.75	A	167	131	158	1588	6	+	-	-	-	-	±
		B	226	158	170	1738	8	+	-	-	-	-	±
		C	178	103	126	1296	8	+	-	-	-	-	±
	7.5	A	183	141	144	1476	8	+	-	-	-	-	±
		B	211	212	188	1938	8	+	-	-	-	-	±
		C	165	129	136	1412	7	+	-	-	-	-	±
	15	A	172	107	133	1210	7	+	-	-	-	-	±
		B	206	125	160	1456	7	+	-	-	-	-	±
		C	258	189	214	1890	6	+	-	-	-	-	±
	30	A	185	143	222	2130	5	+	-	-	-	-	±
		B	154	130	179	1574	5	+	-	-	-	-	±
		C	150	150	198	1626	5	+	-	-	-	-	±
60	No treatment	A	118	74	83	880	9	+	-	-	-	+++	±
		B	145	107	109	1190	9	-	-	-	-	-	±
	Mesosugar C 1.875	A	126	72	84	950	9	-	-	-	-	-	±
		B	133	84	76	998	9	-	-	-	-	-	±
	3.75	A	117	63	68	1036	9	-	-	-	-	-	±
		B	114	85	72	962	9	-	-	-	-	-	±
	7.5	A	114	69	73	888	9	-	-	-	-	-	±
		B	112	124	109	1248	7	+	-	-	-	+	±
	15	A	85	85	68	936	7	+	-	-	-	++	±
		B	45	58	63	538	8	-	-	-	-	-	±
	30	A	62	51	58	780	7	-	-	-	-	-	±
		B	98	40	90	1048	6	-	-	-	-	-	±
91	No treatment	A	141	143	117	1706	7	++	-	-	-	++	+
		B	205	219	190	2252	7	+	-	-	-	-	±
	Mesosugar C 1.875	A	112	147	116	1614	6	++	-	-	-	+++	±
		B	137	159	116	1782	6	+	-	-	-	+	±
	3.75	A	128	188	111	1660	6	+	-	-	-	+	±
		B	146	172	134	1954	7	+	-	-	-	+	±
	7.5	A	166	190	142	1988	6	++	-	-	-	+	±
		B	133	158	113	1560	6	+	-	-	-	-	±
	15	A	141	194	133	1756	6	++	±	+	+	++	+
		B	118	158	107	1378	6	+	-	-	-	-	±
	30	A	126	190	149	1856	6	++	-	+	-	-	+
		B	125	165	152	1788	6	+	-	-	-	-	±

- = not detectable, ± = slight, + = moderate, ++ = severe, +++ = very severe
A, B and C show the respectively parts of the first, middle and last of each group that was divided into three.

Table 4-2. Urinalysis of female rats fed with Mesosugar C for 91 days

Day	Group (2)		U.Na	U.K	U.Cl	O.P	pH	P	Clu	Ket	Bili	SG	Ure
Initial	No treatment	A	164	154	140	1384	9	-	-	-	+	-	+
		B	155	123	132	1318	8	-	-	-	-	-	±
		C	144	156	158	1496	8	-	-	-	-	-	±
	Mesosugar C 1.875	A	166	124	134	1242	9	-	-	-	-	-	±
		B	192	494	156	1346	9	-	-	-	-	-	±
		C	163	119	129	1092	9	-	-	-	-	-	±
	3.75	A	187	163	169	1434	8	+	-	-	-	-	+
		B	162	140	135	1250	9	-	-	-	+	-	±
		C	202	133	150	1260	9	-	-	-	+	-	±
	7.5	A	204	168	153	1708	8	+	-	-	-	-	+
		B	221	156	167	1444	9	+	-	-	+	-	+
		C	180	133	134	1246	9	-	-	-	-	-	+
	15	A	212	164	185	1576	9	+	-	-	+	-	+
		B	165	137	123	1320	9	-	-	-	-	-	±
		C	200	150	140	1430	8	+	-	-	+	-	+
	30	A	217	151	174	1544	8	+	-	+	+	-	±
		B	207	141	173	1412	9	+	-	-	+	-	+
		C	181	128	146	1076	9	-	-	-	-	-	±
31	No treatment	A	126	95	196	1008	9	+	-	-	-	+++	±
		B	116	101	74	1104	8	-	-	-	-	-	±
		C	101	99	87	980	8	-	-	-	-	-	±
	Mesosugar C 1.875	A	99	100	85	996	7	-	-	-	-	-	±
		B	115	99	94	1008	9	+	-	-	-	+++	±
		C	116	104	87	1000	7	-	-	-	-	-	±
	3.75	A	122	101	101	1038	8	-	-	-	-	-	±
		B	119	92	92	984	8	-	-	-	-	-	±
		C	108	115	104	1016	8	-	-	-	-	++	±
	7.5	A	107	89	93	1024	7	-	-	-	-	-	±
		B	108	112	92	1142	7	-	-	-	-	-	±
		C	108	72	81	786	8	-	-	-	-	++	±
	15	A	92	69	81	796	7	+	-	-	-	+++	±
		B	85	75	67	776	7	-	-	-	-	+	±
		C	94	81	77	830	8	-	-	-	-	-	±
	30	A	66	99	80	1176	6	-	-	-	-	-	±
		B	57	49	49	602	6	-	-	-	-	-	±
		C	93	89	81	1046	6	-	-	-	-	-	±
60	No treatment	A	118	76	63	880	9	+	-	-	-	+++	±
		B	143	107	109	1198	9	-	-	-	-	-	±
		C	126	72	84	950	9	-	-	-	-	-	±
	Mesosugar C 1.875	A	126	72	84	950	9	-	-	-	-	-	±
		B	133	84	74	998	9	-	-	-	-	-	±
		C	119	85	88	1036	9	-	-	-	-	-	+
	3.75	A	114	85	72	962	9	-	-	-	-	-	±
		B	114	85	72	962	9	-	-	-	-	-	±
		C	114	85	72	962	9	-	-	-	-	-	±
	7.5	A	114	69	73	888	9	-	-	-	-	-	±
		B	112	124	109	1248	7	+	-	-	-	+	±
		C	112	124	109	1248	7	+	-	-	-	+	±
	15	A	83	85	68	936	7	+	-	+	-	++	±
		B	65	58	63	538	8	-	-	-	-	-	±
		C	65	58	63	538	8	-	-	-	-	-	±
	30	A	62	51	50	700	7	-	-	-	-	-	±
		B	98	88	90	1068	6	-	-	-	-	-	±
		C	98	88	90	1068	6	-	-	-	-	-	±
91	No treatment	A	141	163	117	1704	7	++	-	-	-	++	+
		B	205	219	190	2232	7	+	-	-	-	-	±
		C	205	219	190	2232	7	+	-	-	-	-	±
	Mesosugar C 1.875	A	112	167	116	1414	6	++	-	-	-	+++	±
		B	137	159	116	1702	6	+	-	-	-	+	±
		C	137	159	116	1702	6	+	-	-	-	+	±
	3.75	A	128	188	111	1640	6	+	-	-	+	-	±
		B	146	192	134	1954	7	+	-	-	+	-	±
		C	146	192	134	1954	7	+	-	-	+	-	±
	7.5	A	166	190	142	1988	6	++	-	-	+	-	±
		B	137	150	113	1540	6	+	-	-	-	-	±
		C	137	150	113	1540	6	+	-	-	-	-	±
	15	A	141	194	133	1756	6	++	±	+	+	++	+
		B	110	158	107	1370	6	+	-	-	-	-	±
		C	110	158	107	1370	6	+	-	-	-	-	±
	30	A	126	190	149	1856	6	++	-	+	-	-	+
		B	125	185	152	1780	6	+	-	+	-	-	±
		C	125	185	152	1780	6	+	-	+	-	-	±

- = not detectable, ± = slight, + = moderate, ++ = severe, +++ = very severe.

A, B and C show the respectively parts of the first, middle and last of each group that was divided into three.

Table 3-1. Hematology of male and female rats fed with Neosugar C for 35 days.

male																
Day	Group (%)	N	PBC	WBC	RBC	Hgb	Hct	HCV	MCH	MCHC	Bas	Eos	He(St)	He(Seg)	Ly	Mon
36	No treatment	10	527.2	9.73	7.436	13.79	34.53	46.7	18.57	39.91	0.0	0.2	0.0	21.6	78.2	0.0
			52.25	1.494	0.3053	0.499	0.778	1.34	0.745	1.135	0.0	0.42	0.0	6.42	6.56	0.0
			522.4	9.16	7.635	13.92	36.28**	47.7	18.25	38.34**	0.0	0.7	0.0	15.5*	82.2	0.0
Neosugar C	1.575	10	512.1	1.105	0.3475	0.449	0.966	1.89	0.800	0.911	0.0	0.95	0.0	5.25	5.43	0.0
			527.6	9.07	7.322	13.83	35.92*	49.23*	18.91	38.48**	0.0	1.2*	0.0	16.3	82.5	0.0
			59.71	1.974	0.3741	0.529	1.315	1.99	1.002	1.005	0.0	1.23	0.0	6.92	6.69	0.0
Neosugar C	3.75	10	571.8	10.53	6.832	12.61	32.89	49.7	18.57	37.92	0.0	0.7	0.0	18.7	80.5	0.1
			31.28	2.785	1.5564	2.748	5.962	6.25	0.735	3.038	0.0	0.95	0.0	8.47	8.53	0.32
			954.8	8.72	7.343	13.56	35.41	48.42	18.47	38.25**	0.0	0.7	0.0	19.5	79.6	0.2
Neosugar C	15	10	954.8	1.377	0.4564	0.591	1.665	1.71	0.739	0.853	0.0	0.95	0.0	8.07	8.42	0.53
			955.4	9.76	7.149	13.53	35.18	49.64	18.37	38.46*	0.0	0.9*	0.0	23.1	76.0	0.0
			95.60	1.708	0.4512	0.536	1.340	3.27	0.835	1.259	0.0	0.98	0.0	7.05	6.96	0.0
female																
Day	Group (%)	N	PBC	WBC	RBC	Hgb	Hct	HCV	MCH	MCHC	Bas	Eos	He(St)	He(Seg)	Ly	Mon
36	No treatment	10	778.6	5.00	6.647	13.33	35.60	53.8	20.06	37.42	0.0	1.7	0.0	18.9	79.3	0.1
			59.33	1.097	0.3345	0.455	1.018	1.55	0.560	0.792	0.0	1.49	0.0	6.14	5.40	0.32
			708.0**	5.22	6.766	13.63	35.84	53.4	20.16	38.02	0.1	0.9	0.0	17.9	81.1	0.0
Neosugar C	1.575	10	47.79	1.579	0.3566	0.337	1.039	2.01	0.680	0.543	0.32	0.88	0.0	6.57	6.64	0.0
			761.8	5.05	6.663	13.41	35.96	54.1	20.14	37.28	0.1	0.9	0.0	19.1	79.9	0.0
			96.80	0.876	0.2797	0.482	1.180	0.99	0.597	0.597	0.32	0.88	0.0	3.07	3.28	0.0
Neosugar C	3.75	10	723.4	5.19	6.631	13.52	35.84	54.2	20.37	37.65	0.0	1.6	0.1	15.7	82.6	0.0
			58.81	1.043	0.3707	0.828	1.859	2.10	0.648	0.530	0.0	1.84	0.32	7.89	7.60	0.0
			758.2	5.73	6.418	13.10	35.07	54.9	20.45	37.38	0.0	1.1	0.0	16.7	82.2	0.0
Neosugar C	15	10	38.95	0.833	0.3788	0.627	1.434	1.52	0.670	0.582	0.0	1.45	0.0	7.41	7.98	0.0
			765.2	5.45	6.411	12.99	34.95	54.8	20.30	37.19	0.0	0.9	0.0	17.9	81.3	0.0
			41.12	0.984	0.2226	0.338	1.164	1.32	0.614	0.817	0.0	0.74	0.0	4.39	4.37	0.0

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 5-2. Hematology of male and female rats fed with Neosugar C for 91 days.

male																
Day	Group (%)	N	PBC	WBC	RBC	Hgb	Hct	HCV	HCH	HCHC	Bas	Eos	Ne(St)	Ne(Seg)	Ly	Hon
92	No treatment	20	678.6	7.19	8.663	14.25	38.07	44.0	16.47	37.45	0.0	0.2	0.1	21.0	78.3	0.3
			68.16	1.203	0.4471	0.491	1.345	2.13	0.668	1.187	0.0	0.41	0.31	3.09	3.27	0.47
	Neosugar C 1.875	20	724.5	8.30	8.349	13.52	36.63	44.1	16.18	36.78	0.0	0.3	0.3	23.9	75.4	0.1
			108.52	1.667	0.7064	1.123	2.192	1.73	0.506	1.370	0.0	0.55	0.44	4.37	4.33	0.21
	3.75	20	695.3	8.26	8.428	13.63	37.21	44.3	16.25	36.78	0.0	0.3	0.3	23.3	76.0	0.2
			65.22	1.443	0.6457	0.942	2.334	1.53	0.628	0.783	0.0	0.55	0.44	7.00	7.24	0.41
	7.5	20	690.5	7.71	8.267	13.79	36.86	44.6	16.62	37.40	0.0	0.3	0.2	25.8	73.5	0.1
			58.42	1.376	0.3538	0.544	1.286	1.73	0.625	0.799	0.0	0.57	0.41	8.04	8.08	0.37
	15	20	692.3	6.56	8.316	13.69	37.24	44.9	16.47	36.76	0.0	0.3	0.1	24.2	75.2	0.1
			55.50	1.559	0.3775	0.527	1.248	1.65	0.601	0.823	0.0	0.59	0.31	7.51	7.37	0.37
	30	18	685.9	7.09	8.141	13.49	36.74	45.3	16.59	36.71	0.0	0.4	0.1	26.6	72.9	0.1
			50.16	1.231	0.3995	0.614	1.128	2.08	0.848	0.722	0.0	0.70	0.24	7.93	8.20	0.24
female																
Day	Group (%)	N	PBC	WBC	RBC	Hgb	Hct	HCV	HCH	HCHC	Bas	Eos	Ne(St)	Ne(Seg)	Ly	Hon
92	No treatment	20	671.8	6.36	7.571	13.58	36.09	47.9	17.95	37.58	0.0	1.1	0.0	20.3	78.5	0.0
			84.92	1.263	0.3837	0.640	1.324	1.21	0.539	0.831	0.0	1.09	0.0	7.22	7.94	0.0
	Neosugar C 1.875	19	639.6	6.30	7.808	13.77	36.45	46.8	17.65	37.74	0.0	0.6	0.0	18.9	80.4	0.1
			58.03	1.515	0.4446	0.812	1.740	0.98	0.564	0.972	0.0	0.77	0.0	6.31	6.95	0.23
	3.75	20	664.8	5.71	7.735	13.82	36.41	47.1	17.90	38.00	0.0	0.9	0.0	21.3	77.8	0.0
			84.04	1.115	0.2537	0.416	1.023	1.14	0.547	0.915	0.0	1.05	0.0	5.50	5.47	0.22
	7.5	19	629.5	5.16	7.358	13.30	34.94	47.2	18.11	38.06	0.0	1.3	0.0	20.6	79.2	0.0
			87.52	0.985	0.3138	0.456	1.028	1.33	0.766	0.654	0.0	1.24	0.0	7.00	6.71	0.0
	15	20	679.1	5.02	7.352	13.32	34.93	47.8	18.15	38.10	0.0	1.4	0.0	21.4	77.1	0.0
			75.72	1.061	0.5482	0.866	2.297	1.84	0.533	0.969	0.0	1.28	0.0	7.16	7.20	0.0
	30	19	690.6	5.36	7.388	13.29	35.12	47.7	18.02	37.85	0.0	1.9	0.0	18.6	79.5	0.0
			68.16	1.131	0.3580	0.516	1.274	1.34	0.564	0.850	0.0	1.56	0.0	5.99	6.09	0.0

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 6-1. Serum biochemistry of male and female rats fed with Neosugar C for 35 days.

male

Day	Group (%)	N	CPT	COT	LAP	CNE	Al-P	LDH	CPK	BUN	CNE	T P	Alb	Ca	Chol	T C	Clu	A
36	No treatment	10	16.3	71.2	55.5	0.206	212.6	640.2	606.6	17.57	0.56	4.26	2.15	10.3	43.4	235.4	149.6	1.0
			4.22	10.41	3.81	0.0255	63.93	223.87	167.96	2.144	0.171	0.171	0.095	0.31	4.50	59.55	8.48	0.0
	Neosugar C. 1.675	10	14.1	66.3	55.0	0.183	194.4	594.2	526.7	17.65	0.47	4.07	2.12	10.2	42.1	212.5	155.0	1.0
			2.77	9.39	3.23	0.0249	50.08	236.73	188.08	1.374	0.106	0.177	0.063	0.21	5.15	35.72	9.64	0.0
	3.75	10	15.5	70.4	53.1	0.179	178.7	646.9	610.9	18.03	0.52	4.15	2.14	10.0	46.6	238.3	155.9	1.0
			5.40	16.63	5.30	0.0281	52.19	214.63	200.72	1.621	0.114	0.263	0.117	0.24	6.35	83.27	9.45	0.0
	7.5	10	17.0	76.5	51.4	0.151	159.1	615.2	615.2	19.50	0.54	4.02	2.09	9.8	44.3	257.8	159.8	1.0
			6.09	17.55	7.78	0.0357	38.84	254.34	255.35	6.553	0.070	0.312	0.152	0.46	3.37	60.08	12.77	0.0
	15	10	12.7	67.7	56.4	0.154	152.6	623.6	573.1	15.53	0.44	4.06	2.13	10.6	45.9	242.1	149.5	1.1
			1.42	4.32	6.95	0.0375	36.05	117.98	91.84	1.470	0.107	0.337	0.134	0.78	5.24	54.20	15.81	0.0
	30	10	15.8	81.0	59.5	0.163	225.2	740.5	728.3	15.60	0.54	4.23	2.23	10.5	48.0	194.5	151.2	1.1
			5.45	16.29	3.98	0.0408	65.63	222.87	201.54	1.352	0.107	0.260	0.106	0.30	5.62	66.97	15.88	0.0

female

Day	Group (%)	N	CPT	COT	LAP	CNE	Al-P	LDH	CPK	BUN	CNE	T P	Alb	Ca	Chol	T C	Clu	A
36	No treatment	10	14.3	61.1	50.3	0.827	194.9	497.6	540.5	23.64	0.51	4.36	2.27	10.3	47.7	108.8	148.7	1.05
			0.95	11.07	5.81	0.1227	62.73	245.69	283.65	2.750	0.160	0.151	0.106	0.35	7.78	41.50	10.87	0.07
	Neosugar C. 1.675	10	15.4	53.4	52.5	0.802	174.4	264.7	348.8	22.12	0.55	4.60	2.39	10.7	50.7	133.4	156.0	1.08
			2.07	5.91	4.74	0.1722	56.89	130.57	124.08	1.731	0.108	0.216	0.137	0.23	6.53	60.56	6.16	0.07
	3.75	10	15.2	67.1	53.0	0.872	160.7	639.5	619.8	22.88	0.73	4.68	2.43	10.7	48.9	185.0	154.2	1.08
			3.97	7.99	5.25	0.1423	39.93	182.08	164.88	2.508	0.170	0.346	0.164	0.29	9.59	62.63	8.98	0.05
	7.5	10	15.8	59.4	52.0	0.790	154.7	426.5	474.8	22.89	0.59	4.69	2.41	10.7	53.4	156.3	163.9	1.06
			2.39	8.33	4.88	0.1455	58.81	261.56	218.60	4.169	0.129	0.233	0.166	0.24	9.11	65.50	12.45	0.09
	15	10	13.2	63.2	54.6	0.735	154.9	538.4	507.8	20.14	0.51	4.53	2.33	10.4	48.9	104.2	145.3	1.06
			1.40	9.03	4.65	0.1637	51.95	140.99	98.01	3.323	0.088	0.298	0.134	0.26	3.91	31.46	9.08	0.11
	30	10	12.1	56.8	52.3	0.879	164.5	435.8	475.9	19.72	0.59	4.82	2.50	10.6	52.4	129.1	148.8	1.08
			1.45	8.94	5.62	0.1774	60.68	174.71	149.97	2.274	0.110	0.349	0.189	0.22	7.78	60.14	12.74	0.04

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 6-2. Serum biochemistry of male and female rats fed with Neosugar C for 35 days.

male													
Day	Group (%)	n	CSH	InP	P.L	HA	K	Cl	Alb	Serum protein			
										α_1	α_2	β	γ
36	No treatment	10	12.1	3.91	135.5	144.0	4.49	101.5	61.461	10.829	5.850	15.675	6.185
			1.03	0.273	5.17	1.15	0.145	1.08	1.5076	0.7114	0.4575	1.2489	0.8852
	Neosugar C 1.675	10	12.2	3.88	131.2	144.3	4.44	103.4	60.333	12.393	5.554	15.630	6.180
			1.55	0.368	6.23	0.82	0.158	1.35	2.7429	1.3306	0.5537	1.7799	0.9740
	3.75	10	11.7	3.93	138.5	144.1	4.36	102.9	60.923	11.489	6.217	15.066	6.305
			1.45	0.283	6.67	1.29	0.232	0.88	2.1427	1.0530	0.5493	1.4232	0.7722
	7.5	10	12.0	3.89	169.8	144.0	4.36	102.8	60.725	11.799	6.093	15.194	6.189
			1.43	0.260	11.93	1.33	0.165	1.32	1.2966	0.7519	0.5831	0.6797	1.1450
	15	10	11.8	3.96	147.7	145.2	4.96	103.8	63.089	10.258	5.475	16.077	5.101
			1.43	0.207	8.27	1.32	1.707	1.55	1.4390	0.8709	0.8392	1.0516	0.7597
	30	10	11.4	4.03	138.6	146.1	4.63	103.7	63.531	9.706	5.581	15.683	5.499
			1.30	0.283	8.25	1.10	0.200	1.83	2.1756	1.4750	0.6367	1.1814	0.9183
female													
Day	Group (%)	n	CSH	InP	P.L	HA	K	Cl	Alb	Serum protein			
										α_1	α_2	β	γ
36	No treatment	10	11.8	4.44	129.3	139.9	4.00	107.1	64.572	10.076	5.107	15.154	5.085
			0.98	0.587	12.16	1.66	0.240	1.73	1.3031	1.1583	0.6686	0.6603	1.3608
	Neosugar C 1.875	10	12.3	4.26	137.0	140.9	3.80	107.9	62.313	11.749	4.247	15.900	5.782
			1.24	0.556	14.15	1.29	0.240	1.45	2.5125	1.3431	0.6534	0.5422	1.3049
	3.75	10	12.2	4.65	144.9	141.3	4.10	107.3	64.382	9.150	5.791	14.783	5.352
			1.07	0.417	9.75	1.34	0.170	2.06	1.3629	2.8246	1.1137	1.3822	1.2390
	7.5	10	11.4	4.36	146.6	142.1	4.02	108.5	64.738	9.174	5.816	14.930	5.337
			1.39	0.677	12.83	1.85	0.240	2.32	1.9436	1.5196	0.8608	1.1635	0.8693
	15	10	12.8	4.55	137.9	141.8	4.25	108.0	64.159	8.956	6.014	15.233	5.629
			1.30	0.595	4.73	1.40	0.242	1.56	1.4905	1.5151	1.0919	0.7194	1.4662
	30	10	11.3	4.80	150.5	142.4	4.29	107.8	62.228	9.749	6.043	14.638	7.339
			1.01	0.535	18.93	0.97	0.197	2.20	4.3022	2.3972	0.6279	1.1979	2.0637

Each value represents the mean and standard deviation.
Significantly different from No treatment: *-- $P < 0.05$, ***-- $P < 0.01$

Table 6-3. Serum biochemistry of male and female rats fed with Neosugar C for 91 days.

male

Day	Group (%)	N	CPT	COT	LAP	CHE	ALP	LDH	CPK	BUN	CRE	T P	Alb	Ca	Chol	T C	Clu
92	No treatment	20	17.6	71.5	57.1	0.296	206.1	692.5	471.3	23.26	0.66	4.70	2.24	9.8	42.5	234.8	164.4
			5.22	12.98	4.85	0.0396	63.81	218.03	153.19	2.221	0.180	0.336	0.114	0.33	8.21	70.71	11.16
																	0.0
Neosugar C 1.675		20	18.9	78.3	56.3	0.293	168.6	810.3	575.6	22.65	0.68	4.53	2.14	9.9	46.8	263.3	168.1
			6.94	19.42	5.13	0.0415	55.38	292.31	164.28	2.146	0.124	0.268	0.127	0.33	10.46	80.90	12.51
																	0.0
3.75		20	18.5	75.4	59.4	0.249	165.0	795.3	594.8	20.73	0.75	4.71	2.22	10.0	50.3	311.8	170.8
			2.65	10.81	3.98	0.0314	50.62	291.09	144.78	1.794	0.250	0.336	0.125	0.31	6.81	97.94	14.09
																	0.0
7.5		20	17.5	76.8	60.5	0.222	151.3	887.4	735.3	19.16	0.65	4.52	2.16	9.8	48.1	253.9	176.3
			3.69	12.80	4.67	0.0325	44.07	236.59	266.22	1.381	0.139	0.200	0.109	0.27	10.49	87.62	14.84
																	0.0
15		20	25.1	82.4	63.0	0.197	164.9	771.8	555.8	18.97	0.66	4.45	2.16	9.9	45.3	280.9	164.1
			12.35	18.77	4.79	0.0281	59.49	207.73	144.36	1.393	0.109	0.204	0.114	0.35	8.31	74.81	17.51
																	0.0
30		18	18.9	76.0	61.1	0.168	147.0	724.2	584.7	15.92	0.62	4.50	2.23	10.1	45.4	292.7	164.8
			7.79	11.42	5.83	0.0342	48.99	197.39	184.29	1.458	0.125	0.243	0.136	0.31	6.57	99.79	13.47
																	0.0

female

Day	Group (%)	N	CPT	COT	LAP	CHE	ALP	LDH	CPK	BUN	CRE	T P	Alb	Ca	Chol	T C	Clu
92	No treatment	20	18.0	71.3	50.0	1.013	124.9	560.1	479.3	21.86	0.90	5.12	2.60	10.7	60.8	265.3	149.6
			11.29	43.74	5.47	0.1654	42.84	209.45	205.77	2.251	0.454	0.305	0.170	0.23	13.23	167.74	9.21
																	0.0
Neosugar C 1.675		19	17.3	67.5	52.5	1.006	116.6	593.4	485.4	20.68	0.81	5.23	2.64	10.9	55.4	239.2	151.3
			5.32	15.97	4.35	0.2029	42.64	200.39	185.74	2.493	0.170	0.364	0.198	0.33	8.51	75.60	11.67
																	0.0
3.75		20	18.9	67.3	52.3	0.919	119.0	571.2	471.4	21.36	0.84	5.13	2.62	10.7	56.4	226.8	145.5
			7.52	16.04	5.63	0.1765	48.58	165.27	129.54	2.378	0.201	0.291	0.189	0.34	9.28	70.79	14.99
																	0.0
7.5		19	17.2	64.6	50.3	1.034	122.3	588.8	478.6	20.32	0.74	5.30	2.74	10.8	59.8	223.1	152.2
			5.38	18.19	5.43	0.1548	38.12	227.36	175.60	2.294	0.171	0.540	0.304	0.55	10.48	99.44	11.03
																	0.0
15		20	16.1	61.1	51.0	1.085	82.3	534.8	477.3	20.15	0.80	5.15	2.68	10.9	58.8	218.8	154.1
			3.60	12.19	5.19	0.1803	30.76	150.90	190.30	2.146	0.277	0.435	0.232	0.39	10.49	103.98	13.75
																	0.0
30		19	23.1	102.0	54.6	1.179	125.6	658.0	536.9	18.17	0.89	5.50	2.39	11.2	61.6	258.8	150.2
			24.10	89.22	6.50	0.2311	50.30	237.06	180.93	2.537	0.476	0.437	0.233	0.35	10.94	165.88	12.95
																	0.0

Each value represents the mean and standard deviation.
Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 6-4 Serum biochemistry of male and female rats fed with Neosugar C for 91 days.

Male													
Day	Group (%)	N	CSH	InP	P.L	Na	K	Cl	Alb	Serum protein			
										α_1	α_2	β	γ
92 No treatment													
		20	12.1	3.98	175.6	143.5	4.14	102.2	63.983	9.975	4.638	15.982	5.421
			1.21	0.217	11.60	0.76	0.185	1.58	1.4202	1.3011	0.5746	1.1918	0.6682
Neosugar C 1.875 30													
		20	11.3	3.92	172.7	144.7	4.12	103.5	63.969	10.259	5.569	15.161	5.042
			1.25	0.252	12.80	1.03	0.177	1.57	1.3636	1.1947	0.5998	0.9513	0.7912
	3.75	20	11.9	3.98	163.4	143.8	4.21	102.4	62.903	9.840	5.655	16.210	5.540
			1.50	0.232	9.19	0.93	0.208	0.95	2.2758	1.2806	1.0467	1.0428	0.7927
	7.5	20	11.4	3.98	177.6	144.9	4.17	103.3	61.756	11.421	5.021	15.300	6.001
			1.58	0.246	15.46	1.00	0.213	1.53	2.7747	1.3955	0.7132	1.0336	1.0380
	15	20	11.5	3.99	180.9	144.8	4.15	103.4	63.431	9.855	5.269	15.299	6.144
			1.04	0.271	13.24	0.95	0.212	1.85	2.2991	1.7433	0.6926	0.9896	1.1750
	30	18	10.5	4.01	165.6	143.8	4.20	103.6	63.253	9.053	5.671	15.315	6.708
			0.84	0.207	9.78	1.35	0.245	1.79	2.1690	1.0516	0.7087	1.2894	1.2846
Female													
Day	Group (%)	N	CSH	InP	P.L	Na	K	Cl	Alb	Serum protein			
										α_1	α_2	β	γ
92 No treatment													
		20	12.1	3.93	170.4	142.8	4.26	107.9	60.106	11.285	6.149	14.966	7.409
			1.44	0.337	18.37	1.18	0.278	1.94	2.2571	2.0941	0.7950	0.9627	1.3658
Neosugar C 1.875 19													
		19	12.1	3.96	166.1	144.6	4.17	110.1	61.984	9.452	5.580	15.036	7.944
			0.96	0.284	17.40	1.80	0.185	1.91	2.4606	2.1102	0.8029	1.0468	1.2840
	3.75	20	11.5	3.91	148.1	143.9	4.17	109.2	61.632	9.556	6.251	14.674	7.927
			1.10	0.381	16.23	2.63	0.227	2.76	2.7442	1.7762	0.8701	1.3347	1.2615
	7.5	19	11.9	3.81	170.3	144.4	4.26	109.8	58.665	13.668	5.612	14.692	7.144
			1.27	0.345	20.11	1.22	0.350	2.20	4.2169	2.3902	0.8505	1.7045	1.3601
	15	20	11.6	4.02	166.6	144.3	4.33	109.5	60.363	11.825	6.107	14.251	7.450
			1.43	0.477	19.13	1.41	0.237	1.79	2.4123	2.1813	0.6702	1.2536	0.9262
	30	19	12.3	3.99	166.6	143.2	4.15	108.6	58.591	13.552	6.034	14.542	7.277
			1.14	0.767	27.55	1.39	0.337	2.22	3.3662	2.1627	0.6078	1.5911	1.4657

Each value represents the mean and standard deviation.
Significantly different from No treatment: *--- $P < 0.05$, **--- $P < 0.01$

Table 7-1. Organ weight of male rats fed with Neosugar C for 35 days.

Organ	Absolute organ weight (g)						Relative organ weight (%)					
	No treatment	1.875%	3.75%	7.5%	15%	30%	No treatment	1.875%	3.75%	7.5%	15%	30%
	1C	10	10	10	10	10	10	10	10	10	10	10
Brain	1.563 0.030	1.938 0.085	1.963 0.037	1.935 0.049	1.934 0.083	1.934 0.085	0.552 0.046	0.543 0.038	0.558 0.043	0.550 0.051	0.536 0.058	0.556 0.029
Thymus	0.546 0.125	0.656 0.068	0.536* 0.071	0.589 0.105	0.563 0.131	0.556 0.120	0.180 0.028	0.183 0.015	0.150* 0.020	0.166 0.024	0.160 0.030	0.159 0.031
Heart	1.249 0.102	1.204 0.108	1.285 0.136	1.140 0.081	1.343 0.122	1.166 0.168	0.350 0.033	0.337 0.032	0.361 0.048	0.324 0.117	0.371 0.038	0.333 0.028
Lung	1.891 0.258	1.737 0.185	1.731 0.162	1.793 0.257	1.691 0.185	1.865* 0.206	0.529 0.071	0.485 0.042	0.484 0.041	0.507 0.059	0.465* 0.036	0.477 0.045
Liver	15.313 1.597	15.680 2.228	17.162 1.748	16.395 2.887	16.686 1.988	13.564* 2.964	4.736 0.477	4.379 0.564	4.800 0.400	4.620 0.680	4.595 0.527	3.862** 0.651
Spleen	0.537 0.124	0.838 0.101	0.619 0.072	0.771 0.126	0.664 0.103	0.842 0.112	0.234 0.031	0.233 0.018	0.229 0.019	0.217 0.030	0.238 0.027	0.241 0.027
Kidney (L)	1.453 0.177	1.491 0.076	1.607 0.109	1.507 0.150	1.506 0.168	1.372 0.177	0.418 0.048	0.417 0.025	0.451 0.038	0.427 0.045	0.416 0.053	0.393 0.034
Kidney (R)	1.508 0.156	1.476 0.098	1.600 0.121	1.498 0.133	1.545 0.145	1.280* 0.111	0.422 0.046	0.413 0.024	0.448 0.037	0.425 0.041	0.427 0.049	0.386- 0.024
Adrenal	0.062 0.014	0.064 0.009	0.075 0.020	0.066 0.009	0.067 0.015	0.066 0.012	0.017 0.004	0.018 0.002	0.021 0.005	0.019 0.004	0.019 0.004	0.019 0.003
Testis (L)	1.728 0.101	1.772 0.153	1.784 0.153	1.704 0.098	1.762 0.092	1.728 0.122	0.484 0.037	0.496 0.046	0.500 0.047	0.483 0.038	0.487 0.049	0.500 0.069
Testis (R)	1.718 0.058	1.741 0.127	1.739 0.174	1.700 0.090	1.772 0.087	1.649 0.209	0.481 0.037	0.486 0.030	0.487 0.046	0.482 0.038	0.490 0.052	0.474 0.066
Prostate	0.556 0.140	0.517 0.109	0.524 0.099	0.574 0.114	0.564 0.120	0.457 0.093	0.155 0.033	0.145 0.031	0.147 0.030	0.163 0.036	0.155 0.031	0.130 0.021
Hypophysis	0.012 0.003	0.012 0.003	0.012 0.003	0.012 0.002	0.012 0.001	0.010 0.003	0.003 0.001	0.003 0.001	0.003 0.001	0.003 0.001	0.003 0.000	0.003 0.001
Intestine	22.606 2.487	21.083 2.311	21.011 2.141	20.406 4.001	26.263* 4.668	31.818* 5.116	6.318 0.619	5.875 0.351	5.874 0.469	5.734 0.690	7.172* 0.754	9.106* 1.149
Body weight	357.90 22.03	358.10 19.73	357.60 21.10	353.90 26.07	364.10 33.48	349.40 32.34						

Each value represents the mean and standard deviation.

Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 7-2. Organ weight of female rats fed with Neosugar C for 35 days.

Organ	Absolute organ weight (g)						Relative organ weight (%)					
	No treatment	1.675%	3.75%	7.5%	15%	30%	No treatment	1.675%	3.75%	7.5%	15%	30%
Brain	1.941 0.223	1.999 0.139	1.978 0.174	2.010 0.112	2.021 0.195	2.070 0.190	0.849 0.089	0.855 0.075	0.863 0.063	0.844 0.051	0.838 0.085	0.857 0.094
Thymus	0.560 0.165	0.569 0.082	0.490 0.093	0.615 0.116	0.573 0.111	0.614 0.110	0.243 0.060	0.244 0.036	0.215 0.038	0.257 0.042	0.238 0.049	0.254 0.047
Heart	0.984 0.126	0.962 0.094	0.979 0.085	1.008 0.113	0.976 0.128	1.027 0.114	0.429 0.032	0.412 0.029	0.430 0.027	0.422 0.023	0.404 0.051	0.425 0.056
Lung	1.475 0.227	1.493 0.204	1.389 0.198	1.491 0.163	1.500 0.152	1.489 0.083	0.643 0.078	0.641 0.087	0.609 0.075	0.624 0.056	0.622 0.065	0.620 0.043
Liver	10.862 1.599	11.190 1.268	10.329 0.768	10.629 1.081	10.837 1.472	11.419 1.176	4.728 0.486	4.788 0.406	4.536 0.240	4.451 0.258	4.485 0.344	4.714 0.422
Spleen	0.681 0.169	0.714 0.137	0.627 0.083	0.689 0.138	0.731 0.127	0.656 0.125	0.295 0.058	0.307 0.061	0.275 0.031	0.287 0.047	0.303 0.049	0.271 0.050
Kidney (L)	1.058 0.085	1.047 0.086	1.060 0.101	1.005 0.072	1.055 0.155	1.087 0.115	0.463 0.040	0.449 0.036	0.465 0.044	0.455 0.016	0.436 0.053	0.447 0.049
Kidney (R)	1.042 0.116	1.085 0.101	1.045 0.083	1.103 0.099	1.062 0.130	1.086 0.115	0.455 0.041	0.465 0.037	0.458 0.031	0.462 0.019	0.440 0.045	0.449 0.041
Adrenal	0.1005 0.01220	0.0946 0.01372	0.0894 0.01115	0.0935 0.00955	0.0882 0.01387	0.0910 0.01286	0.0441 0.00651	0.0407 0.00636	0.0395 0.00662	0.0392 0.00358	0.0365** 0.00518	0.0401 0.00527
Ovary (L)	0.086 0.011	0.088 0.011	0.090 0.012	0.091 0.012	0.081 0.009	0.085 0.020	0.036 0.005	0.038 0.005	0.040 0.004	0.038 0.005	0.038 0.004	0.036 0.008
Ovary (R)	0.086 0.011	0.088 0.011	0.090 0.012	0.091 0.012	0.081 0.009	0.085 0.020	0.036 0.005	0.038 0.005	0.040 0.004	0.038 0.005	0.038 0.004	0.036 0.008
Uterus	0.782 0.470	0.753 0.0164	0.629 0.0161	0.638 0.146	0.741 0.200	0.823 0.310	0.337 0.0076	0.325 0.0070	0.325 0.0071	0.267 0.0073	0.309 0.0071	0.341 0.0016
Hypophysis	0.0175 0.00363	0.0175 0.00222	0.0175 0.00227	0.0174 0.00276	0.0170 0.00284	0.0185 0.00280	0.00116 0.00116	0.00087 0.00087	0.00087 0.00132	0.00119 0.00119	0.00113 0.00113	0.00104 0.00104
Intestine	16.852 2.711	17.895 2.233	17.475 2.239	17.874 1.990	18.885 3.605	25.987** 2.495	7.341 0.946	7.662 0.791	7.657 0.746	7.500 0.768	8.127 1.253	7.731** 0.889
Body weight	229.20 19.515	233.40 14.362	227.90 15.184	238.70 16.050	241.80 17.249	242.10 9.516						

Each value represents the mean and standard deviation.
Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 7-3. Organ weight of male rats fed with Nicotinic G for 91 days.

Organ	Absolute organ weight (g)						Relative organ weight (%)					
	No treatment	1.875%	3.75%	7.5%	15%	30%	No treatment	1.875%	3.75%	7.5%	15%	30%
	20	20	20	20	20	15	20	20	20	20	20	18
Brain	2.092 0.118	2.077 0.102	2.074 0.105	2.118 0.098	2.150 0.055	2.089 0.082	0.423 0.039	0.408 0.034	0.390** 0.030	0.399* 0.026	0.410 0.040	0.405 0.041
Thymus	0.535 0.119	0.611 0.155	0.604 0.135	0.623 0.182	0.628 0.172	0.584 0.145	0.108 0.022	0.120 0.032	0.114 0.028	0.116 0.031	0.119 0.049	0.111 0.023
Heart	1.483 0.120	1.581 0.255	1.563 0.154	1.605* 0.185	1.623** 0.169	1.567 0.141	0.299 0.017	0.308 0.028	0.294 0.029	0.301 0.022	0.308 0.031	0.300 0.030
Lung	2.155 0.304	2.187 0.342	2.180 0.346	2.356 0.605	2.305 0.487	2.179 0.276	0.434 0.053	0.427 0.055	0.409 0.062	0.442 0.109	0.439 0.097	0.420 0.060
Liver	18.901 3.076	19.933 4.341	20.571 2.909	20.759 3.471	20.820 4.010	19.669 3.259	3.786 0.404	3.880 0.542	3.864 0.542	3.875 0.431	3.918 0.542	3.743 0.302
Spleen	1.010 0.153	1.020 0.130	1.032 0.120	0.938 0.133	0.993 0.120	1.021 0.141	0.030 0.020	0.026 0.026	0.026 0.026	0.026 0.026	0.026 0.026	0.026 0.026
Kidney (L)	0.198 1.742	0.207 1.716	0.181 1.772	0.206 1.760	0.226 1.764	0.197 1.652	0.021 0.032	0.041 0.041	0.032 0.032	0.026 0.026	0.036 0.036	0.030 0.030
Kidney (R)	0.218 0.067	0.264 0.013	0.175 0.010	0.214 0.011	0.224 0.016	0.200 0.012	0.025 0.014	0.045 0.013	0.036 0.013	0.022 0.013	0.035 0.013	0.032 0.014
Adrenal	0.013 1.937	0.013 1.860	0.010 1.900	0.011 1.971	0.016 1.824	0.012 1.954	0.014 0.003	0.013 0.002	0.013 0.002	0.013 0.002	0.013 0.002	0.014 0.002
Testis (L)	0.106 1.911	0.165 1.892	0.111 1.905	0.147 1.970	0.185 1.912	0.089 1.904	0.033 0.033	0.041 0.037	0.026 0.036**	0.029 0.037	0.041 0.036	0.04 0.036
Testis (R)	0.114 0.804	0.139 0.862	0.127 0.804	0.128 0.908	0.129 0.879	0.174 0.809	0.033 0.162	0.040 0.169	0.036 0.169	0.035 0.170	0.037 0.166	0.031 0.172
Prostate	0.015 0.004	0.015 0.004	0.014 0.004	0.016 0.004	0.014 0.004	0.017 0.003	0.003 0.003	0.003 0.001	0.003 0.001	0.003 0.001	0.003 0.001	0.003 0.001
Hypophysis	26.760 3.018	26.873 4.717	26.922 3.138	27.461 3.586	27.780** 5.258	27.443** 5.065	5.180 0.394	5.230 0.642	5.055 0.545	5.142 0.496	5.000** 0.579	7.154** 0.592
Intestine	497.20 42.09	512.30 46.64	533.35** 34.67	533.40** 39.2	528.55* 50.7	523.61 60.10						
Body weight												

Each value represents the mean and standard deviation.
Significantly different from No treatment : *---P<0.05, **---P<0.01

Table 7-4. Organ weight of female rats fed with Neosugar C for 91 days.

Organ	Absolute organ weight (g)						Relative organ weight (%)					
	No treatment	1.875%	3.75%	7.5%	15%	30%	No treatment	1.875%	3.75%	7.5%	15%	30%
Brain	1.892 0.084	1.938 0.064	1.942 0.097	1.924 0.096	1.921 0.072	1.953 0.074	0.673 0.042	0.662 0.037	0.632 0.049	0.640 0.042	0.639 0.041	0.625 0.054
Thymus	0.376 0.133	0.406 0.099	0.419 0.136	0.380 0.061	0.391 0.082	0.419 0.103	0.133 0.044	0.128 0.029	0.136 0.044	0.126 0.022	0.128 0.028	0.135 0.037
Heart	0.943 0.091	0.983 0.126	1.005 0.111	1.054 0.088	1.042 0.088	1.044 0.111	0.335 0.033	0.334 0.041	0.326 0.030	0.350 0.030	0.341 0.033	0.335 0.034
Lung	1.604 0.271	1.511 0.138	1.548 0.195	1.608 0.182	1.601 0.178	1.538 0.106	0.569 0.090	0.513 0.030	0.503 0.061	0.537 0.052	0.523 0.046	0.495 0.046
Liver	11.102 1.358	11.262 1.131	11.814 1.452	11.688 1.352	11.604 1.412	12.179 1.351	3.941 0.427	3.830 0.354	3.833 0.426	3.880 0.454	3.786 0.361	3.899 0.292
Spleen	0.621 0.106	0.631 0.123	0.647 0.075	0.683 0.097	0.684 0.067	0.641 0.082	0.221 0.039	0.214 0.021	0.211 0.028	0.230 0.034	0.224 0.024	0.206 0.030
Kidney (L)	1.062 0.176	1.096 0.227	1.038 0.098	1.092 0.102	1.101 0.191	1.057 0.097	0.378 0.065	0.372 0.072	0.337 0.026	0.363 0.040	0.360 0.061	0.340 0.036
Kidney (R)	1.088 0.208	1.107 0.223	1.028 0.088	1.096 0.095	1.130 0.231	1.068 0.095	0.387 0.076	0.376 0.072	0.334 0.027	0.364 0.037	0.370 0.074	0.343 0.031
Adrenal	0.0726 0.01142	0.0766 0.01313	0.0729 0.01189	0.0771 0.01275	0.0822 0.01321	0.0827 0.01474	0.0258 0.00376	0.0262 0.00486	0.0237 0.00411	0.0256 0.00456	0.0210 0.00478	0.0267 0.00550
Ovary (L)	0.075 0.014	0.086 0.011	0.082 0.010	0.080 0.010	0.079 0.012	0.078 0.011	0.027 0.004	0.029 0.006	0.027 0.004	0.027 0.003	0.027 0.004	0.025 0.004
Ovary (R)	0.075 0.014	0.086 0.011	0.082 0.010	0.080 0.010	0.079 0.012	0.078 0.011	0.027 0.004	0.029 0.006	0.027 0.004	0.027 0.003	0.027 0.004	0.025 0.004
Uterus	0.866 0.235	0.734 0.171	0.761 0.180	0.882 0.291	0.803 0.186	0.917 0.328	0.308 0.086	0.251 0.063	0.247 0.057	0.284 0.099	0.264 0.065	0.295 0.110
Hypophysis	0.0175 0.00235	0.0170 0.00245	0.0169 0.00221	0.0185 0.00278	0.0179 0.00326	0.0194 0.00331	0.0062 0.00082	0.0058 0.00094	0.0055 0.00077	0.0062 0.00094	0.0059 0.00108	0.0062 0.00104
Intestine	16.353 1.942	17.393 2.489	18.130 2.665	18.513 2.424	20.084 2.930	25.220 2.936	5.811 0.676	5.890 0.561	6.202 0.744	5.152 0.831	6.552 0.783	8.089 0.837
Body weight	281.75 16.832	294.74 25.188	308.65 25.395	301.47 14.849	306.15 18.566	312.74 30.898						

Each value represents the mean and standard deviation.
Significantly different from No treatment : *---P<0.05, ****P<0.01

Table 8-1. Gross and microscope observation of male rats fed with Haasugar C for 35 days

Observation	Organ	Finding	No treatment									
			1.875% 3.75% 7.5% 15% 30%									
			H	10	10	10	10	10	10	10	10	10
Gross	Digestive tract	Small (one slide)	+	0	0	0	0	0	0	0	1j)	0
			+	0	0	0	0	1d)	0	0	0	0
			+	0	0	0	0	0	0	0	2f)	1k)
			+	0	0	0	0	0	0	0	1g)	5l)
Microscopic	Kidney	Round cell infiltration (one slide, cortex)	+	0	1a)	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	1m)
			+	0	0	0	0	0	0	0	0	1j)
			+	0	0	0	0	0	0	0	0	1j)
Microscopic	Prostate	Round cell infiltration (interstitium)	+	0	1b)	2c)	0	0	1h)	0	0	0
			+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
Microscopic	Digestive tract	Desquamation of mucous membrane	+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
Microscopic	Urinary bladder	Hemoglobinuria retention	+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0
			+	0	0	0	0	0	0	0	0	0

± = slight, + = moderate

Letter) = animal no. --- a)=53, b)=59, c)=81, 89, d)=113, e)=112, f)=142, 144, g)=147, h)=149, i)=144, 147, j)=179, k)=177, l)=171, 173, 174, 178, 180, m)=176, n)=180

Table 8-2. Gross and microscopic observation of female rats fed with Neosugar C for 35 days

Observation	Organ	Finding	No treatment						
			1.075% 3.75% 7.5% 15% 30%						
			N	10	10	10	10	10	10
Gross	Digestive tract	Distention of cecum	±	0	0	0	0	0	4 ^{a)}
			+	0	0	0	0	0	4 ^{b)}
Microscopic	Kidney	Round cell infiltration (mucosa of renal pelvis or interstitium of cortex, both sides)	±	1 ^{c)}	0	1 ^{d)}	1 ^{e)}	0	0

± = slight, + = moderate
 Letter) = animal no. --- a) = 371, 373, 377, 379, b) = 372, 376, 378, 380, c) = 221, d) = 288, e) = 320

Table 8-3. Gross and microscopic observation of male rats fed with Neosugar G for 91 days.

Observation	Organ	Finding	No treatment									
			1.075% 3.75% 7.5% 15% 30%									
			N	20	20	20	20	20	20	20	10	
Gross	Testis	Small (one side)	±	0	0	0	0	0	0	0	1 ^{o)}	
		Hemorrhage of intestine	+	0	0	0	0	0	0	1 ^{j)}	0	
	Digestive tract	Distention of cecum	+	0	0	0	0	0	0	1 ^{k)}	10 ^{p)}	
			+	0	0	0	0	0	0	0	3 ^{q)}	
Microscopic	Heart	Round cell infiltration	±	1 ^{a)}	0	0	0	0	0	0	0	
	Liver	Vacuolization	±	1 ^{b)}	0	1 ^{c)}	0	0	0	0	0	
	Kidney	Round cell infiltration (one side, cortex)	±	0	0	1 ^{f)}	1 ^{g)}	0	0	0	0	
		Small cyst (one side, cortex)	±	0	0	0	0	0	0	1 ^{l)}	0	
	Testis	Aspermatogenesis (one side)	+	0	1 ^{c)}	0	0	0	0	0	1 ^{o)}	
	Prostate	Round cell infiltration (interstitium)	±	0	1 ^{d)}	1 ^{f)}	1 ^{h)}	1 ^{m)}	0	0	0	
	Digestive tract	Atrophy of cecum mucous membrane	±	0	0	0	0	0	0	1 ^{k)}	4 ^{r)}	
	Pancreas	Fibrosis of Langerhans's Islets	+	0	0	0	0	1 ^{l)}	0	0	0	
		Fibrosis of peripancreas	±	0	0	0	0	0	0	1 ⁿ⁾	0	

± = slight, + = moderate, ++ = severe

letter) = animal no. --- a)=9, b)=15, c)=39, d)=48, e)=61, f)=69, g)=97, h)=92, i)=104, j)=137, k)=132, l)=126, m)=122, n)=138, o)=169, p)=151,153,157,161,165 170, q)=160,162,164, r)=151,157,160,162

Observation of dead animal :

30%, no.155 --- Gross : Congestion(+) of thymus, and distention(++) and congestion(+) of cecum

Microscopic : Congestion(+) of thymus

30%, no.163 --- Gross : Ulcer e ascites, and distention(++) of cc (an accidental death)

Table 8-4. Gross and microscopic observation of female rats fed with H₂ O₂ for 91 days

Observation	Organ	Finding	H ₂ O ₂ treatment					
			N	20	19	20	19	20
Gross	Uterus	Edema	++	1 ^{a)}	0	0	0	0
	Digestive tract	Distention of cecum	±	0	0	0	0	5 ^{a)}
	Liver	Vacuolization	±	0	0	0	0	2 ^{b)}
	Kidney	Round cell infiltration of cortex interstitium and/or regeneration of tubular epithelial cells	±	0	1 ^{d)}	0	1 ^{f)}	0
Microscopic	Uterus	Hypertrophy of mucosa	+	1 ^{c)}	0	0	0	0
	Digestive tract	Atrophy of cecum mucosa	±	0	0	0	0	3 ^{l)}

± = slight, + = moderate, ++ = severe

Letter) = animal no. --- a)=358,361~363,365, b)=201,204, c)=217, d)=242, e)=239, f)=306, g)=326, h)=354,364, i)=361,362,365

Observation of dead animal :

1.875%, no.233 --- Gross : White spots of surface(+) of kidneys, hypertrophy(+) of adrenal glands, mucoid deposition or fluid content(+) of gastric mucosa, and hemorrhage(+) of urinary bladder

Microscopic : Pyelonephritis(++) of kidneys, congestion(±) of adrenal cortex(both sides), atrophy, necrosis and desquamation(+) of gastric mucosa, and necrosis, calcification and round cell infiltration(+) of urinary bladder

7.5%, no.292 --- Gross : Hypertrophy(±) of kidney(one side) and adrenal glands, and hemorrhage(+) of urinary bladder

Microscopic : Massive necrosis(++) of cortex of kidney(one side), round cell infiltration(±) of cortex interstitium of kidneys, congestion and edema(±) of lung, and congestion(+) and vacuolization(±) of adrenal cortex(both sides), and necrosis(+) and round cell infiltration(±) of urinary bladder

30%, no.352 --- Gross : Distention(++) and hemorrhage(+) of cecum, and mucoid deposition or fluid content, hypertrophy and hemorrhage(+) of gastric mucosa

Microscopic : Hemorrhage(++) of cecum mucosa and hypertrophy(±) of gastric mucosa

Table 9-1. Electronmicroscopic observation of male rats fed with Neosugar G for 91 days

Organ	Finding	No. of rats												
		treatment												
		No. 1	3	31	33	61	63	91	93	121	123	151	153	
Liver	Fatty changes	++	++	+	+	+	+	+	+	+	+	+	+	
	Decrease in glycogen granules	-	-	-	-	-	-	-	-	-	-	-	-	
	Swelling of mitochondria	-	-	-	-	-	-	-	-	-	-	-	-	
	Increase in SER	-	-	-	-	-	-	-	-	-	-	-	-	
	Fragmentation of RER	-	-	-	-	+	+	-	-	+	+	-	-	
	Increase in lysosome	-	-	-	-	-	-	-	-	-	-	-	-	
	Focal cytoplasmic degradation	-	-	-	-	-	-	-	-	-	-	-	-	
	Activation of Kupffer cell	-	-	-	-	-	-	-	-	-	-	-	-	
Kidney	Degeneration of epithelial cell	-	-	-	-	-	-	-	-	-	-	-	-	
	Degeneration of endothelial cell	-	-	-	-	-	-	-	-	-	-	-	-	
	Thickening of basement membrane	-	-	-	-	-	-	-	-	-	-	-	-	
	Increase in mesangium	-	-	-	-	-	-	-	-	-	-	-	-	
	Foot process fusion	-	-	-	-	-	-	-	-	-	-	-	-	
	Disarrangement of brush border	-	-	-	-	-	-	-	-	-	-	-	-	
	Increase in lysosome	-	+	-	-	-	-	-	+	-	-	+	+	
	Swelling of mitochondria	-	-	-	-	-	-	-	-	-	-	-	-	
Pancreas	Flattening of basal infoldings	-	-	-	-	-	-	-	-	-	-	-	-	
	Alterative changes of β cell	+	-	-	-	-	-	-	+	-	-	-	-	
	Alterative changes of α cell	-	-	-	-	-	-	-	-	-	-	-	-	
	Degranulation of β cell	-	-	-	-	-	-	-	-	-	-	-	-	
Exocrine gland	Degranulation of α cell	-	-	-	-	-	-	-	-	-	-	-	-	
	Decrease in zymogen granules	-	-	-	-	-	-	-	-	-	-	-	-	
	Alterative changes of acinar cell	-	-	-	-	-	-	-	-	-	-	-	-	

- = no abnormality detected + = moderate, ++ = severe

Table 9-2. Electronmicroscopic observation of female rats fed with Neosugar C for 91 days

Organ	Finding	H ₂ O treat- ment										
		No.201	203	231	235	261	263	291	293	321	323	351 353
Liver	Fatty changes	++	++	+	+	+	+	+	+	+	+	+
	Decrease in glycogen granules	-	-	-	-	-	-	-	-	-	-	-
	Swelling of mitochondria	-	-	-	-	-	-	-	+	-	-	-
	Increase in SER	-	-	-	-	-	-	-	-	-	-	-
	Fragmentation of RER	-	-	-	-	-	-	-	-	-	-	-
	Increase in lysosome	-	-	-	-	-	-	-	-	-	-	-
	Focal cytoplasmic degradation	-	-	-	-	-	-	-	-	-	+	-
Kidney	Activation of Kupffer cell	-	-	-	-	-	-	-	-	-	-	-
	Degeneration of epithelial cell	-	-	-	-	-	-	-	-	-	-	-
	Degeneration of endothelial cell	-	-	-	-	-	-	-	-	-	-	-
	Thickening of basement membrane	-	-	-	-	-	-	-	-	-	-	-
	Increase in mesangium	-	-	-	-	-	-	-	-	-	-	-
	Food process fusion	-	-	-	-	-	-	-	-	-	-	-
	Disarrangement of brush border	-	-	-	-	-	-	-	-	-	-	-
Pancreas	Increase in lysosome	-	-	-	-	-	-	-	-	-	-	-
	Swelling of mitochondria	-	-	-	-	-	+	+	+	+	+	+
	Flattening of basal infoldings	-	-	-	-	-	-	-	-	-	-	-
	Alterative changes of β cell	-	-	-	-	-	-	-	-	-	-	-
Endocrine gland	Alterative changes of α cell	-	-	-	-	-	-	-	-	-	-	-
	Degranulation of β cell	-	-	-	-	-	-	-	-	-	-	-
	Degranulation of α cell	-	-	-	-	-	-	-	-	-	-	-
	Decrease in zymogen granules	-	-	-	-	-	-	-	-	-	-	+
Exocrine gland	Alterative changes of acinar cell	-	-	-	-	-	-	-	-	-	-	+

- = no abnormality detected, + = moderate, ++ = severe