Section 4)

Attachment no. 2

C.R.F. S.p.A.:

Subacute Toxicity of Fructose-1,6-Diphosphate,

1976

VOL. I

RPT 188

CRF centro ricerca farmaceutica
s.p.a.

NON CLINICAL LABORATORY INSPECTION DATA

OF THE STUDY CRF 022

Dr. ALFREDO NUNZIATA

DIRECTOR OF CRF

AUTORIZ. MIN SAN N 8002/70 273/28258 DEL 3/8/74 - N. 8002/70 273/26860 DEL 12/3/76

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CAPITALE SOCIALE LIRE 1 000 000 000 - C C I A N 375736 REG SOC TRIB DI ROMA N 2828/7

CRF centro ricerca farmaceutica
s.p.a.

STATEMENT OF C.R.F.

The toxicological study of CRF 022: Esafosfina[R] - Subacute toxicity of one month in New Zealand rabbit has been performed by our Centre from 7/3/1974 to 26/7/74.

The researchers of various departments are:

TOXICOLOGY

Piero Mercatelli (B.Sc.)

HISTOPATHOLOGY

Alberta Argentino-Storino (B.Sc.)

BIOCHEMISTRY

Renato Ottavio Salerno (B.S.)

TECHNICAL DIRECTOR - MINISTERIAL EXPERT

Alfredo Nunziata (PHD)

Scientific Director

Giulio Cesare Perri (MD. PHD.)

The "Curricula Vitorum" of the above-mentioned are enclosed.

All the original documents, the specimen, the slides and all the material concerning this experiment are available for inspection in our own files at the following address:

C.R.F. S.p.A. - Via Tito Speri, 14 - Pomezia -Rome - Italy.

Centro Ricerca Farmaceutica S.p.A.
Dr. Alfredo Nunziata

AUTORIZ. MIN. SAN. N. 800 2/70.273/28258 DEL 3/8/74 - N. 800.2/70.273/26860 DEL 12/3/76

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CAPITALE SOCIALE LIRE 500.000.000 - C. C. I. A. N. 375.736 - REG. SOC. TRIB DI ROMA N 2828/7

STUDY C.R.F. O.22: 30 DAY SUB-ACUTE TOXICITY IN RABBIT (1976)

Daily Registers:	They show weights and dietetic consumptions registered during the test.
File:	It contains the protocol with the notes and corrections dated and signed by responsible.
Row data:	Drafts of reports and copies of tracks of dietetic consumptions. Neither body weights nor symptomatologic notes. Clinical cards, autoptic cards and analytical cards are signed by the responsible.
Specimen:	All the hystological reports are filed with experiment number, sex, date, group and animal number.

Roma, 15.5.1982

R. Costrini

CRF 022

Nonclinical Laboratory Inspection Data

A. TESTING FACILITIES

1. The testing, facility in general is of suitable size, adequate construction and properly located to perform nonclinical laboratory studies. Defined and, if necessary, separate areas are provided.

   Yes - plan of laboratories and facilities are enclosed.

2. Adequate space is provided for administration, supervision, and direction of the testing facility as well as satisfactory facilities for toilets, lockers, showers with hot and cold water, and air driers or single use towels plus all necessary accouterments in accordance with regulations set forth by the OSHA in 29 CFR.

   Yes.

B. PERSONNEL

1. List of personnel at the date of test in February 1976:

Director	Prof. G.C. Perri	
Associate	Dr. A. Nunziata	
Researchers	Dr. P. Mercatelli	Toxicologist
	Dr. A. Argentino	Pathologist
	Mr. R. Salerno	Biochemist
	Mr. T. Bianco	Chemical Analyst
	Dr. M. Nannini	Toxicology Technician
	Dr. R. Campa	" "
	Mr. G. Magnarelli	" "
	Miss. L. Cancelli	Toxicology worker
	Mrs. T. Fusco	" "

9. Procedures are written that describe the responsibilities of the QAU and the records it maintains.

   Responsibilities of the QAU (Responsible for Ministry of Health) are written in Italian Ministry of Health Circular 54 bis and 75.

D. EQUIPMENT

1. Equipment of appropriate design and adequate capacity is available to obtain values reported.

   Yes.

2. Location of equipment permits easy operation, cleaning and maintenance; and,

   Yes.

3. Is cleaned, inspected and maintained regularly.

   Yes.

4. There are written standard operating procedures which describe in detail the methods, materials and schedules to be used in the routine inspection, cleaning, maintenance, testing and calibration of equipment; and,

   Procedures for equipment in respect of the procedures of the suppliers for cleaning etc. are not written procedures but only internal regulations and control of Head of Laboratory.

5. The specific remedial actions to be taken in the event of failure or malfunction of equipment;and,

   Yes.

6. Designates the individual responsible for each of the operations.

   Yes for each laboratory the Head is the individual responsible.

7. Copies of the standard operating procedures are available to laboratory personnel.

   References of the methods and procedures are available to laboratory personnel.

E. TESTING FACILITY OPERATION

1. Separate laboratory space is provided for the performance of routine procedures or categories of procedures; and,

   Yes.

2. Separate laboratory space is provided for the performance of specialized activities such as aseptic surgery, intensive care, necropsy and radiography

   Yes.

3. Spaces of cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study are separate from the areas housing the test system.

   Yes.

4. Studies involving radioactive or other biohazardous materials are carried out in special facilities or areas which provide protection to personnel, test systems, and the external environment against contamination or unnecessary radiation exposure, or infection.

   Yes.

5. Persons possessing and using radioactive materials are licensed in accordance with the Nuclear Regulatory Commission regulations or meet the requirements of an agreement state.

   Yes.

6. Special procedures are employed for the handling of other biohazardous materials.

   Yes in respect of the Italian laws.

7. Written standard operating procedures (which at least meet GLP requirements) are maintained detailing the methods to be used in performing nonclinical laboratory studies.

   No.Detailed methods were written or photocopy of references was made available.

18. Preparation and validation of final study report.

    Idem as E10.

19. A historical file of standard operating procedures annotating effective dates and dates of revisions is maintained.

    No data are only available for all materials of the study that are kept in the archives or in a general file.

20. The relevant standard operating procedures are available at all times in the immediate bench area of personnel performing the procedures.

    Idem as E19.

21. All reagents and solutions in the laboratory area are labeled adequately.

    In respect with Italian regulations.

6. Animals are free of any naturally occuring diseases or conditions that might interfere with the purpose or conduct of the study.

   Yes.

7. The diagnosis, authorization for and description of the treatment (including dates of treatment of animals involved) of test systems is adequately documented.

   Only if it happens, without written authorization.

8. Methods for the unique and permanent identification of all animals when needed have been developed and applied to preclude mixup of animals and/or their tissues; and,

   Yes.

9. Routine of specialized housing of animals of different species, or of the same species used for different studies is adequate to preclude interspecies transmission of infection, mixup, or other events that may affect the outcome of a study or studies.

   Yes.

10. The proper placement of animals which are transferred from one cage to another in the same location is checked by the transferrer and verified by a responsible person appropriately documented, and a record of the procedure maintained.

    No.

12. Animal waste and refuse is collected, stored and disposed of in a safe and sanitary manner so as to preclude vermin infestation, odors, and disease hazards.

    Yes.

13. Animal cages, racks and accessory equipment are cleaned and sanitized at appropriate intervals as recommended in HEW Publication No. (NIH) 74-23 or subsequent revisions.

    Yes.

G. TEST AND CONTROL SUBSTANCES

1. Each container for a test and control substance is appropriately labeled and adequately stored to maintain the identity, strength, quality, and purity of said substances.

   It was labeled by the Sponsor and stored in cold room.

2. An appropriately identified reserve sample selected at random from each batch of test and control substance used in a study of more than 4 weeks duration, is taken, stored in an identical immediate container under appropriate storage conditions, and analyzed at the time the batch is depleted, at the termination of the study, or at the expiration date (whichever occurs first) to assure that the identity, quality, strength, purity, and stability conform to established specifications.

   No.

3. If test or control substances are mixed with a carrier prior to administration each batch of such mixture is tested periodically for the adequacy of the mix to assure uniformity and to determine the concentration of the substance in the mixture. Describe procedures used.

   No only at the beginning by the Sponsor.

4. Enough samples of each batch of the mixture are returned to the Sponsor for such analysis if the study is a blind study.

   No.

5. Each batch of the test and control substance-carrier mix is tested for stability for at least the length of time between mixing and use and to establish storage conditions and an expiration date.

   No.

6. For each batch of the test and control substance, tests are performed to determine the release from the carrier mix and the results documented.

   No.

H. STUDY IMPLEMENTATIONS AND CONDUCT

1. Scientists or other professional persons are available to provide assistance and consultation to subordinates and to handle unforseen issues.

   Yes.

2. Specimens are identified by test system number, study number, nature of specimen and date. Explain identification system.

   Yes. Specimens are coded either by test number date or animal number or code number depending of the specimen.

I. STORAGE AND RETRIEVAL OF RECORDS AND DATA

1. The testing facility maintains and retains all raw data, documentation and other information, protocols, specimens, and final reports generated during and as the result of a nonclinical laboratory study and they are retained in an archive of adequate space and design and are indexed to facilitate their orderly and expedient storage and retrieval.

   Yes.

2. The archive provides the proper conditions to minimize deterioration of all stored material for as long as they are required to be retained.

   Yes.

3. The archive contains specific reference to other locations in which documents and specimens may be stored.

   All materials are kept in the archive.

4. Documents and specimens required to be maintained in the archive and not physically present there have appropriate and specific reference to their location filed in the archive.

   Yes.

5. An individual responsible for the archive is identified.

   Yes.

6. Only authorized personnel enter the archive and whenever a custodian of the archive is not present the suitable repositories for the documents and specimens are locked.

   Yes.

7. Whenever the original material is transferred to the sponsor's archive at the sponsor's request at the completion of the study, duplicates of all material required to be in the archive are retained there, when the nature of the material permits.

   Original material is never transferred to the sponsor's archive.

8. All material required to be retained in the archive is available for inspection to authorized employees of the Food and Drug Administration.

   Yes.

9. If the archive has been contracted out to a commercial archive not belonging to the research facility or sponsor, then the name and address of the commercial archieve has been provided to the sponsor in the submission of the final study report.

   Not applicable.

J. RETENTION OF RECORDS

1. All protocols, raw data, specimens, final reports and other required documents pertinent to the conduct of the study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, are stored in an archive, and retained for the specified time.

   All materials pertinent to the study are kept in the archive. Time depends on the sponsor request.

2. Curriculum vitae and job descriptions of all personnel engaged in conducting the study are retained for the specified period of time, either in the facility employment records, or the archive; and are available for inspection.

   Data are kept in the administration office.

3. The master schedule sheet, records of inspection or evaluation and status reports of the quality assurance unit are retained for specified period of time.

   No.

K. PERSONNEL

1. Adequate periodic training is provided by well-qualified individuals to assure that each person engaged in a laboratory study continues to be qualified for his/her function.

   Personnel is examined by the Head of Laboratory and by Technical direction.

2. A current curriculum vitae (C.V.) is maintained along with a current job description for each person engaged in the conduct of the study. The testing facility also retains the last available C.V. and job description after termination of employment. (Obtain copies of C.V.

   Yes.

3. The testing facility has a sufficient number of personnel to accomplish the activities specified by the protocol.

   Yes.

4. Persons found to have an apparent illness that may adversely affect the integrity of the study are removed from direct contact with any or all applicable aspects of the study until the condition is corrected. Such facts are documented in the records of the study.

   Yes but these facts are not documented.

L. QUALITY ASSURANCE UNIT

1. Each phase of a study is periodically inspected, written reports are prepared, and corrective actions when required are documented.

   Each phase of a study is not periodically inspected by the Responsible of Ministry of Health.

2. All studies are evaluated for conformity to the protocol as required, deviations from the protocol or standard operating procedures are not made without prior approval, and written records of these activities are maintained. The quality and reliability of work performed by contractors and grantees is monitored.

   Deviations are only written on the final report and on laboratory record.

3. Status reports are submitted to management periodically.

   No.

M. EQUIPMENT

1. Equipment, procedures and materials used to protect the integrity and health of test systems, including pest control, are of appropriate design and type, and do not interfere with the conduct of the study; and,

   Yes.

2. Can be easily cleaned and maintained; and,

   Yes.

3. Is cleaned, inspected and maintained regularly.

   Yes.

4. Equipment and materials used to prepare and administer test and/or control substances are of adequate design to assure accurate administration of these substances; and,

   Yes.

5. To preclude contamination of test and control substances; and,

   Yes.

6. Can be easily cleaned and maintained; and,

   Yes.

7. Is cleaned, inspected, maintained and calibrated regularly.

   Yes.

8. Written records are kept which accurately document all inspection, cleaning, testing, and calibrating operations; and,

   No.

9. Nonroutine maintenance and remedial actions taken because of failure or malfunction.

   Yes.

10. The use of all cleaning, maintenance, and pest control materials which might interfere with the conduct of the study or be hazardous to the test system is adequately documented and does not contaminate test systems.

    Yes.

N. ANIMAL CARE

1. Needs for deviation from the standards for animal care are adequately documented and incorporated in the records of the study.

   Not completely.

2. Environmental factors such as the caging and housing systems, sanitation practices, diet, handling, ventilation, lighting, temperature and noise control are maintained uniformly throughout the course of the studies; and,

   Yes.

3. Changes to new locations, or of environmental factors, are not made during the course of the study without written permission from the study director; and the record of the approval and details of the changes are maintained.

   Changes are not made during the course of the study.

4. All newly received animals are kept in quarantine for a predetermined period of time during which their health status is evaluated. (State length of quarantine period for species involved in this study and reasons for disqualifying animals from tje study if applicable).

   Animals (rabbits) were kept in quarantine for 20 days in some area of the study.

5. Bedding used in animal cages or pens does not interfere with purpose or conduct of the study.

   Sawdust was used in bottom wire cages.

O. TEST AND CONTROL SUBSTANCES

1. Each batch of a test and control substance is assayed for identity, strength, quality, and purity prior to initiation of the study either by the laboratory or the sponsor who provides verifying documentation with the substances.

   These actions were performed by the Sponsor.

2. Prior to initiation of the study the stability of each test and control substance is determined, where possible, and if not previously determined by the sponsor, unless stability is the purpose of the study.

   Idem as G1.

3. The test and control substances are derived from the smallest number of production batches consistent with their stability and necessary to fulfill the requirements of the study.

   Test substance was derived from one batch.

4. A system for the distribution of the test and control substances is established with procedures to assure that proper storage at all times maintains the identity, strength, quality, purity, and stability of the substances; and,

   Procedures were used "de facto" by verbal indication of the Head of Toxicology.

5. the possibility of cross-contamination of the substance, is precluded; and,

   Yes.

6. appropriate identification of the substance is maintained throughout the distribution process; and,

   Yes.

7. the receipt and distribution of each batch of the substance is properly documented.

   The receipt of batch from the Sponsor is properly documented.

8. If batches of test and control substances are returned from distribution for redistribution, test and control substances are quarantined in a separate and identificable area; the source of the return and the reason for the return are documented.

   Every day of administration new flask with lyophilized product was allowed.

9. Batches of the test and control substances to be redistributed are reanalyzed to determine conformance to established specifications and redistributed only if all appropriate standards and specifications are met.

   No.

10. Batches of returned test and control substances tha do not conform to appropriate standards and specifications are not distributed without documentation of further appropriate investigations made and corrective actions taken.

    No.

P. STUDY IMPLEMENTATION AND CONDUCT

1. A written detailed protocol including statistical methods is available and approved before the study initiation.

   Yes.

2. The protocol contains the name of the sponsor, a descriptive title and statement of purpose; and,

   Initial protocol contains descriptive title and statement of purpose.

3. The name of Study Director, as well as of scientists or professional persons, laboratory assistants and animal care personnel; and,

   only the name of the Study Director.

4. The name and address of any contractors; and,

   name and address of lab. testing.

5. Identification and stability of test and control substances; and,

   Identification of the test substance.

6. Proposed dates for starting completion and submission of final reports; and,

   No.

7. Specifications for thr test systems including source (obtain name and address) and,

   No.

8. Procedure for unique identification of test system if needed, the method for randomization, if any, and its justification: and,

   No, but the rabbits were caged individually.

9. Description of the diet used in the study as well as solvents, emulsified and/or other material (s) used to solubilize or suspend the test and control substance before mixing in the carrier.

   No.

10. Route of administration of test and control substances and reason for its selection; and,

    Yes.

11. Dosage levels (s), method and frequency of administration, and method to measure absorption; and,

    Yes, except method to measure absorption.

12. Types and frequency of tests, analyses and measurements, and records to be maintained; and,

    Yes.

13. Nonroutine procedures required to assure personnel health and safety.

    No.

14. Changes or revisions to an approved protocol are documented, signed by the Study Director, dated and retained with the protocol.

    Yes.

15. The Study Director assured that the approved protocol, including revisions is followed precisely and,

    Yes in the protocol attached to the final report.

16. Test and control substances are appropriately tested; and,

    No.

17. Test systems are appropriate for the study; and,

    Yes.

18. Personnel recources, facilities, and methodologies are available and,

    Yes are dexcribed in the final report.

19. Personnel involved in the study understand their responsibilities; and,

    Yes in the final report.

20. All data are accurately and promptly verified and recorded including: The administration of the test and control substances to the appropriate test systems in the appropriate dosage, by the approproate method and at the appropriate time, as specified in the protocol (describe in detail; and,

    Control of all raw data was made when final report was written.

21. The tracking of a test system life history in order to assure the accuracy and consistency of all responses and manifestations observed during the course of the study. (Describe the tracking system in details and

    Partially described in the final report.

22. The age at sacrifice/death for each test and control test system; and,

    Yes.

23. Gross pathology findings which are available to the pathologist examining the specimen microscopically, and

    Yes.

24. Unforseen circumstances that may affect the quality and integrity of the study are noted and documented; and,

    Yes.

25. Unexpected health hazards to test systems are promptly reported to the appropriate supervisor and that corrective action taken is documented; and,

    Yes corrective actions were taken if available and documented in the record.

26. The responses of test systems are documented; and,

    Yes.

27. All required GLPs are followed; and

    At he time when the study was conducted GLP were not available.

28. The study is carried out in a manner that provides for safety for laboratory personnel, and,

    Yes.

29. All data, documentation, other information, protocols, specimens and final reports are transmitted to the archive.

Yes.

30. All data generated during the study are recorded, signed and dated in the required manner.

Not always. It was not ufficially requested at this period.

31. Test systems are monitored in conformity with the protocol.

Yes.

32. Animals moribund or found dead during a study are necropsied as specified in the protocol. Explain the operational procedures.

Yes Procedures of the action are documented in the record and final report.

O. REQUIRED DESCRIPTIVE OR QUANTITATIVE INFORMATION FOR COMPLETED ANIMAL STUDIES ONLY

a. Species being used in the study

New Zealand rabbits.

b. Length of time that the animals were on study

20 days for quarantine; 30 days for treatment.

c. Number of animals loaded into the study:

1. on test substance : 20
2. on control : 10

d. Number of animals:

1. on test substance found dead : 1
2. on test substance sacrificed : 19
3. on control found dead : none
4. on control sacrificed : 10

R. REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS

1. The final report shall contain the name and address of the facility performing the study, and

   Yes.

2. dates on which study was initiated and completed; and,

   Yes.

3. the identity of the test and control substances; and,

   Yes.

4. the name of the Study Director, and

   Yes.

5. A summary of data, and analysis of data, and a statement of the conclusions drawn from the analysis, and

   Yes.

6. Reports of each individual scientist or other professional persons involved in the study, appropriately signed and dated and,

   No.

7. the location where all raw data and the final report are to be stored.

   Yes, but not precisely the room and the rack.

8. The final report describes the objectives and procedures stated in the approved protocol, and

   Yes

9. the data elements collected during the study, and

   Yes

10. the statistical methods employed for analysing the data, and

    Yes

11. the stability of the test and control substances under the conditions of administration, and

    No, see the report, the test substance was lyophilized and solution was prepared at the moment of the administration.

12. the methods used, and

    Yes

13. the test system used, and

    Yes

14. the dosage, dosage regimen, route of administration and duration; and,

    Yes

15. any unforeseen circumstances that may have affected the quality or integrity of the nonclinical laboratory study.

    Yes, if it is available.

16. Amendments to the final report are clearly identified, justified, signed and dated.

No, the final report relates the correct execution of the study.

C. R. F.
Centro Ricerca Farmaceutica S.p.A

C R F - 022

TOXICOLOGICAL REPORT ON ESAFOSFINA PRODUCED BY BIOMEDICA FOSCAMA - ROME

30 DAY SUB-ACUTE TOXICITY IN RABBIT

BIOMEDICA FOSCAMA S.p.A.

Chemical Pharmaceutical Industry

ROME-ITALY

0

TOXICOLOGICAL REPORT ON ESAFOSFINA R PRODUCED BY BIOMEDICA FOSCAMA - ROME

C R F - 022

30 DAY SUB-ACUTE TOXICITY IN RABBIT

PROTOCOL

30 DAY SUB-ACUTE TOXICITY IN RABBIT

PURPOSE

To study possible toxic effects produced by fructose 1-6 diphosphate administered for a 30 day period.

PRODUCTS AND DOSES

The product doses are selected on the basis of use in human therapy and maximum concentration obtainable.

Dose I	=	200 mg/Kg equal to 3 DTS
Dose II	=	100 ml/Kg equal to 1.5 DTS

Controls receive apyrogenic saline. The doses will be administered i.v. in a volume of 4 ml/Kg. The solutions are prepared by diluting 5 g of ESAFOSFINA^{R} in 25 ml of bidistilled water which are brought to 100 ml for Dose I and to 200 ml for Dose II with sterile apyrogenic saline.

EXPERIMENTAL CONDITIONS

The test is carried out on 30 New Zeeland rabbits (body weight 2200-2400 g). The animals are kept in single cages in standard conditions (22-24° C temperature and 50-55% relative humidity). They are randomly divided in 6 groups. The substance being tested is administered i.v. 6 days per week. (If administration is required 7 days per week, then the cost of overtime will be charged). The controls receive saline in equal volume to the volume per kilogram administered to the treated animals.

CONTROLS

Behaviour and general conditions of the animals are controlled every day. Body weight and diet consumption are controlled every five days. On day 30 of treatment, 5 males and 5 females per dose level are sacrificed and on each animals the following analyses are performed :

BLOOD TESTS

Glucose	Chlorides
Uric nitrogen	Potassium
SGPT	Total proteins
Bilirubin	Albumin
Alkali phosphatase	Inorganic phosphates
CO_2	Cholesterol
Sodium	LDH
SGOT	Ca^{+2}

HAEMATOLOGIC TESTS

Hemoglobin	Erythrocyte count
Hematocrit	Leucocyte count
MCV	Leucocyte formula

URINE ANALYSES

pH	Blood
Proteins	Ketone bodies
Glucose	Bilirubin
Sediment	Urobilinogenous

AUTOPTIC EXAMS

After sacrifice on day 30, a microscopic examination of the internal organs is performed and the following are removed : brain, pituitary gland, thymus gland, heart, liver, spleen kidneys, adrenal glands, gonads, uterus or prostate. Any other organ which on macroscopic examination presents lesions of any kind is also removed.

HISTOPATHOLOGICAL EXAM

The following tissues are removed during autopsy and, following fixation, embedding and staining, are examined histologically. Ematossilina Eosina and Van Gieson dyes are routinely used.

Adrenal glands	Pancreas
Brain	Pituitary glands
Gonads	Thymus gland
Heart	Spleen
Kidneys	Stomach
Thyroid	Liver
Uterus or prostate	Lung
Intestine (3 levels)	Bone (femur)

Complete histological exams will be performed only on the animals on the highest dose and the controls.

FINAL REPORT

Once the experiments are complete, a final report, containing, in addition to the experiment's purpose, all laboratory data, will be drawn up. The report will also include the individual clinical cards for each animal. All parameters will be processed statistically with a computer and the data will be attached.

BIOMEDICA FOSCAMA 9

Industria Chimico-Farmaceutica s.p.a.
00131 - Roma via Tiburtina Km. 15 - tel. 619.03.41

CRF 022

LABORATORIO DI CONTROLLO CHIMICO **Controllo N.** 10178

Materiale FRUCTOSE-1,6-DIPHOSPHATE SODIUM SALT LYOPHILIZED

N. lotto o di preparazione 02 Data di arrivo o preparazione 22/1/76

Fornitore _____ Quantità _____

RISULTATI ANALITICI

humidity	:	7,8%	
sol. colour 10%	:	390-400	
Chlorides	:	below 500 ppm	
heavy metals	:	" 10 ppm	
oxalic acid	:	absent	
arsenic	:	below 5 ppm	
pH sol. 5%	:	5,75	
tot. phosphorus %	:	13,21 stq	14,32 ss
inorganic %	:	2,05 "	2,22 "
organic %		11,16 "	12,10 "
enzymatic titre	:	72,5% stq	78,6 % ss

OSSERVAZIONI

approved

ANALISTI **TEMPO** **FIRMA**

Data 31/1/76

C. R. F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nunziata

Reponsabile Laboratorio

C R F - 022

SUB-ACUTE TOXICITY IN RABBIT

The Biomedica Foscama Company requested a toxicological study of their product ESAFOSFINA^R administered i.v. The substance, a white liophylized powder, was given to us in 5 g containers taken from production lot no. 02 of January 22, 1976. The experiment was numbered CRF-022 for our records. A liophylized container of the product, together with its analytical certificate, control no. 10478, January 30, 1976 (a photocopy of which is attached) has been saved and marked BF CRF-022 and is available for control.

With the same classification number the following documents and materials have also been filed in our archives:

1) Books and original clinical cards
2) Copy of the final report
3) Microscopic glass slides of :
   a) each animal's blood smear
   b) histological sections of every organ removed.
4) Organs removed during autopsy under 10% neutral formaldehyde.

The materials will be available for 5 years from the date of the final report.

A) EXPERIMENTAL PROTOCOL

30 New Zeeland rabbits (15 males and 15 females) (body weight 2200-2600 g) supplied by the Pellizzari Firm (Bergamo) were used for the experiment.

The animals were randomly divided in 6 groups of 5 animals each (Group I, III, V males and Group II, IV, VI females).he animals were identified by an individual and group number. They were kept in single cages under standard conditions (22-24° C temperature and 50-55% relative humidity). The animals were nourished with a standard Mill-rabbit feed furnished by the Morini Firm (S. Polo d'Enza) with water ad libitum.

The doses were selected on the basis of the human therapeutical dose and the maximum concentration solution and they are : 200 mg/kg to Groups I, II 100 mg/Kg to Groups III, IV The doses were administered i.v. in a volume of 4 ml/Kg. The solutions are prepared by diluting 5 g of ESAFOSFINA^{R} in 25 ml of bidistilled water which are brought to 100 ml for Dose I and to 200 ml for Dose II with apyrogenic saline. The solutions are injected slowly (2 ml/min) once a day six days a week into the ears' marginal vein. General conditions and behaviour of the animals were controlled daily, diet consumption and body weight every five days.

LABORATORY TESTS

Hematologic and biochemical controls (Table 1 and 2) were performed before the experiment (zero time control) and after 1 month of treatment. Before every sampling and at sacrifice, the animals were placed in a metabolic cage to collect the urine, on which the tests listed in Table 3 were performed. During autopsy, all the organs were examined carefully and those listed in Table 4 were removed.

The organs and tissues listed in Table 5 were fixed, embedded and examined histologically after routine staining (Ematossina-Eosina dn Van Gieson).

TABLE 1

Hematological tests performed after sacrifice of animal

The following haematological blood tests are performed :

Red blood cell count	(A)
White blood cell count	(A)
Haemoglobin determination	(A)
Haematocrit	(A)
Leucocyte formula	(M)
MCV	(A)

Tests marked (A) were performed with a SMA 4 Analyzer of Technicon Instruments Corp.

Ratios were calculated by eletronically.

Tests marked (M) were done manually according to classical procedures.

BIBLIOGRAPHY

1. Staining Procedures, The Williams and Wilkins Co., Baltimore, 1973

2. Methods in Toxicology, Paget G. E., Blackwell S.Pub., 338-371, 1970

3. The Blood Morphology of Laboratory Animals, Schermer S., F. A. Davis Co., Philadelphia, 1970

TABLE 2

BIOCHEMICAL BLOOD TESTS PERFORMED AFTER SACRIFICE

1. SGOT	(A)	2. SGPT	(A)
3. Albumin	(A)	4. Total protein	(A)
5. Alakli phosphatase	(A)	6. CO_2	(A)
7. Urea	(A)	8. Glucose	(A)
9. Total bilirubin	(A)	10. Cholesterol	(A)
11. Inorganica phosphorous	(A)	12. LDH	(A)
13. Na^+	(C)	14. K^+	(C)
15. Chlorides	(B)	16. Ca^{++}	(B)

The tests marked (A) were performed simultaneously on a single blood sample with a SMA 12 Micro-Plus Analyzer, those marked (B) separately on a Technicon II Generaltion Analyzer.

BIBLIOGRAPHY

The following methods were used :

1. S. G. O. T.

Rush et All., Ame. Ass. Clin. Chem. Symposium, Buffalo 1970

2. S. G. .O.T.

Rush et All., Ame. Ass. Clin. Chem. Symposium, Buffalo 1970

Methods 1 and 2 are based on spectrophotometric readings of the change in optical density of NADH.

3. ALBUMIN

Boumas Watson, Clin. Chem. Acta 31, 87-96, 1971

Bromocreosole green which lacks affinity to bilirubin and drugs is used.

4. TOTAL PROTEINS

Based on the Biureto reaction, it is the standard method for autoanalyzers.

5. ALKALI PHOSPHATASE

Morgensterns et Al., Clin. Chem. 11, 876, 1965

Based on the enzymatic hydrolysis of p-Nitrophynel phosphate and on the quantity of freed p-Nitrophenol.

6. CO_2

Based on the method of H. Hochstrasser, U.S. Pat. 3,572,1964 adapted to automation.

7. UREA

Marsh et All., Clin. Chem. II, 624, 1965

The urea reacts with diacetylmonoxima in the presence of thiosemicarbazide and ferric ions in an acid environment giving a colored compound.

8. GLUCOSE

Bittner McCleary, Ame. Jour. Clin. Path. 11, 423, 1963

9. TOTAL BILIRUBIN

Jendrassik and Grop, Bioch. Z. 297, 81, 1938

Modified by Gambino and Schriber.

Automation in Anal. Chemistry, Mediad Inc., N.Y., 1964

10. CHOLESTEROL

Huang, Anal. Chem. 33, 1405, 1961

11. INORGANIC PHOSPHOROUS

Robinson et Al., Ann. Clin. Bioch. 8, 168, 1971

12. LDH

Wacher et All., N. Eng. J. Med. 255, 449, 1956

Modified by Kessler et Al. in Advances in Automated Analyses 1, 6-7, 1970

13. Na^{+}- and K^{+}

14. Flame spectrophotometer (Coleman)

15. CHLORIDES

Skeggs and Hochstrasser, Clin.Chem. 10, 918, 1964

16. Ca^{++}

Wells R. Moorhead and Homer G. Biggs, Clin. Chem. 20/11, 14581460, 1974

TABLE 3

URINE ANALYSES

1.	pH	5.	Ketone bodies
2.	Proteins	6.	Bilirubin
3.	Glucose	7.	Urobilinogenous
4.	Blood	8.	Sediment

The determinations were carried out according to classical clinical laboratory procedures.

See for example : HANDBOOK OF CLINICAL LABORATORY DATA
THE CHEMICAL RUBBER COMPANY
CLEVELAND OHIO, 2nd EDITION 1968

TABLE 4

Organs that are removed and weighed after sacrifice and whose weights are used for statistical correlations :

Brain	Spleen
Pituitary gland	Kidneys
Thymus gland	Adrenal glands
Heart	Gonads
Liver	Uterus or prostate
Seminal vescicles	

TABLE 5

Organs and tissues which are removed for autopsy and fixed for inclusion and histopathological examination :

Adrenal glands	Gonads
Pituitary glands	Liver
Spleen	Intestine (3 levels)
Heart	Pancreas
Bladder	Stomach
Lung	Kidneys
Thymus gland	Uterus or prostate
Brain	Bone (femus)

B) EXPERIMENTAL SCHEDULE

March 3, 1976	Animals under diuresis
March 8, 1976	Zero time endocardiac blood sample drawn (15 M + 15 F)
March 10, 1976	Treatment begins
April 5, 1976	Animal no. 5 Group I dies from pneumonia
April 14, 1976	Drug administration having been completed, the rabbits are placed in metabolic cages.
April 15, 1976	Endocardiac blood samples drawn for 1 month control.
April 20, 1976	The following animals are sacrificed :
	Rabbits no. 1 2 3 4 Group I
	Rabbits no. 1 2 3 4 5 Group II
	Rabbits no. 1 2 3 4 5 Group III
April 21, 1976	The following animals are sacrificed :
	Rabbits no. 1 2 3 4 5 Group IV
	Rabbits no. 1 2 3 4 5 Group V
	Rabbits no. 1 2 3 4 5 Group VI
	Death is provoked by the injection of air in the marginal vein; the animals are then bled by means of an incision in the carotid.

C) RESULTS

Statistical Calculations

The animals's growth curve results are reported in graphic form according to the method of Gray and Addis, in which the logarithm of the weight is an inverse function of time; a linear function is thus obtained that allows comparison by means of a statistical analysis of the lines' angular coefficient which it represents.

Diet consumption, reported on the individual clinical cards, indicates the weight consumed in 5 days.

Average weights per Group are reported on the graph.

The biochemical, haematological and autoptic data were processed statistically by means of one-way variance analysis for several groups (1) to which Bartlett's variance homogenuity test was applied.

Summary table with averages, +/- S.E. and confidence limits are reported for each group. Fisher's F'S and their relative significance are also given in the variance analysis tables, and the groups which compared to the controls have a significance of p 0,05 are also indicated.

1) W. G. Snedecor, G. W. Cochran, Statistical Methods, VI ed. Iowa State University Press, 258, 1967

C - 1) General behaviour and clinical tests

No changes in behaviour or general conditions were observed in the rabbits treated with 30 injections of ESAFOSFINA^{R}. Nor were changes noted in the respiratory apparatus, the cardiovascular system and the C.N.S.

C - 2) Body weight and diet consumtion

During administration, body growth (see graph) was normal in all groups. Treatment did not cause a noticeable change in trend. The trend of diet consumption is the same for all types of treatment, showing a slight drop back in the initial 15 days of treatment, but remaining constant thereafter.

C- 3) AUTOPTIC RESULTS

During the experiment there was one case of spontaneous death (No. 5 Group I). The autopsy revealed an increase in the volume of the lung tissue, which was gray-pink in color. Under pressure a white mucoid exudate outflowed from the bronchi. Death was attributed to pneumonia.

The autoptic examination carried out after sacrifice at the end of the experiment did not reveal pathological conditions and the organs appeared to be in good conditions.

The places were the injections had been made (marginal vein in both ears) showed no alterations or necrotic areas.

C - 3 a) Absolute weight of organs

The one-way variance analysis applied to these values indicates that there is a significant variance in the absolute weight of the liver and heart in the males. These values, lower in the treated animals, are not correlated to the

dose, as a result of which, the variance cannot be related to the treatment. In none of the female values is there a significant difference between treated and controls.

C - 3 b) Relative weight of organs

The relative weight of the liver of the treated males is statistically lower than that of the controls, but in a way that cannot be correlated to the dose. No significant alteration is found in the females.

C - 4) HAEMATOLOGICAL EXAM

The average haematological values at zero time show the homogeneity of the animals and their initial excellent clinical conditions. The treated animals (males and females) show a significant increase of HCT and red blood corpuscles compared to the controls. This trend is correlated to the dose. There is a significant decrease of neutrophyles in the males and a relative increase of lymphocytes at both doses compared to the controls. All values range within standard average values for rabbits.

C - 5) BIOCHEMICAL TESTS

The average biochemical values at zero time show the homogeneity of the animals and their initial excellent clinical conditions. Significant values for males are distributed as follows :

Total proteins	: lower for both doses
Cholesterol	: lower for both doses
Bun	: lower for both doses
Glucose	: higher in treated for both doses
Ca^{+2}	: higher in treated for both doses
Alkali phosphatase	: higher for the 200 mg/Kg i.v. dose

Significant values for females are :

Total proteins	: lower for both doses
Cholesterol	: lower for both doses
Cl^-	: lower for the 200 mg/Kg i.v. dose

Nevertheless, the animals' biochemical values do not differ from normal values for rabbits.

Urine constans

There is no alteration in these values.

D) CONCLUSIONS AND COMMENTS

The examination of the data in this report shows that, in our experimental conditions and at our doses, ESAFOSFINA^R produced by BIOMEDICA FOSCAMA of Rome has no toxic effect.

The doses selected are higher than normally used in human therapy :

200 mg/Kg i.v.	=	2.60 DTS
100 mg/Kg i.v.	=	1.30 DTS

Statistically significant biological and hematological variations were noted; however, the biological significance of these variations is accidental and not correlated to treatment. The variations are normal in the species used and derive from the individual animal's capacity to reestablish the homeostatic equilibrium that had been broken by repeated administration of non physiological volumes of liquids and salts.

The small variations in the individual biochemical values derive from each

animal's capacity in contrasting exogenous action.

On average, the values range within normal limits. It can thus be concluded that ESAFOSFINA^{R} is a product that is well tolerated by animal organisms, even in case of repeated administrations and that it lacks toxic effects.

Pomezia, July 26, 1976.

G) HISTOLOGICAL REPORT

RABBITS - TIME = 1 MONTH

30 days after the experiment has begun, the organs of the rabbits treated with ESAFOSFINA^R, administered i.v., at two different dose levels plus a control group, are examined histologically. Fixation and staining procedures are described in the protocol.

These are the results of the microscopic examination for each animal:

Group I	No. 1 2 3 4	N. S.
Group II	No. 1 2 3 4 5	N. S.
Group III	No. 1 2 3 4 5	N. S.
Group IV	No. 1 2 3 4 5	N. S.
Group V	No. 1 2 3 4 5	N. S.
Group VI	No. 1 2 3 4 5	N. S.

The histological examination performed at t= 1 month on rabbits treated with ESAFOSFINA^R does not reveal lesions in any of the organs. Microscopic examination shows shows normal functions of the various parts of the organism throughout treatment that enables us to exclude that the substance administered may have toxic effects.

Pomezia, July 26, 1976

C.R.F. TOXICOLOGIC DEPARTMENT

32

BIOCHEMICAL VALUES ANALYSIS OF VARIANCE EXPERIMENT n 022 SEX M STRAIN NEW.ZEL. - TIME -1 MONTH

		GROUP I		GROUP III		GROUP V		F	SIGNIF.	+
CO 2	meq/l	15.500	± 0.6455	16.600	± 1.8055	14.400	± 0.9274	0.76	N.S.	
Prot.Tot.	g%	7.575	± 0.2323	7.960	± 0.3600	9.140	± 0.4632	4.52	0.05	1
Albumine	g%	5.050	± 0.1443	5.080	± 0.2922	5.680	± 0.2245	2.24	N.S.	
P inorg.	mg%	8.150	± 1.0774	7.880	± 0.3382	8.440	± 0.1720	0.25	N.S.	
Cholest.	mg%	58.750	± 2.3936	78.000	± 7.6811	93.000	± 4.0620	9.08	0.01	1
Glucose	mg%	156.250	± 3.1458	168.000	± 4.6368	156.000	± 1.0000	4.39	0.05	2
BUN	mg%	21.000	± 1.4720	20.200	± 0.9695	28.600	± 1.8601	10.10	0.01	1 2
Bilirub.T.	mg%	0.425	± 0.0250	0.440	± 0.0400	0.470	± 0.0490	0.30	N.S.	
Alk.phos.	mU/ml	191.250	± 6.5749	139.000	±16.9853	145.000	±10.8397	4.46	0.05	1
LDH	mmU/ml	0.385	± 0.0359	0.308	± 0.0372	0.384	± 0.0435	1.27	N.S.	
SGPT	mU/ml	53.750	± 5.5434	46.000	± 7.6485	55.000	±13.1339	0.25	N.S.	
SGOT	mU/ml	93.750	±24.0978	65.000	±11.9373	72.000	±13.2853	0.80	N.S.	
Cl ion	meq/l	107.750	± 4.0901	121.000	± 1.0000	119.200	± 4.7476	3.63	N.S.	
Na ion	meq/l	133.750	± 3.7053	126.000	± 2.4495	127.600	± 0.9274	2.63	N.S.	
K ion	meq/l	4.200	± 0.4564	3.340	± 0.2462	3.440	± 0.0678	2.74	N.S.	
Ca^{++}	mg%	14.125	± 0.3146	15.200	± 0.2550	13.840	± 0.2358	7.74	0.01	2

+ GROUP SIGNIFICANT COMPARED TO THE LAST ONE.

DATA: 29/4 76 FIRMA: C.R.F. Consorzio Ricerca Farmaceutica S.p.A. Dr. Alfredo Vanzetta

C.R.F. TOXICOLOGIC DEPARTMENT

BIOCHEMICAL VALUES — ANALYSIS OF VARIANCE — EXPERIMENT n 022 — SEX F — STRAIN NEW.ZEL. - 1 MONTH

		GROUP II		GROUP IV		GROUP VI		F	SIGNIF.	+
CO 2	meq/l	16.800	± 1.4629	14.800	± 1.6553	12.800	± 1.1576	1.92	N.S.	
Prot.Tot.	g%	7.560	± 0.0400	7.880	± 0.2853	8.640	± 0.4106	3.66	N.S.	1
Albumine	g%	4.980	± 0.1800	5.000	± 0.1140	5.740	± 0.3415	3.47	N.S.	
P inorg.	mg%	9.600	± 0.6293	8.280	± 0.2059	8.360	± 0.2315	3.33	N.S.	
Cholest.	mg%	92.000	± 2.5495	84.000	± 5.3385	122.000	±10.559[illegible]	8.21	0.01	1 2
Glucose	mg%	164.000	± 8.7178	161.000	± 5.7879	163.000	± 5.6125	0.04	N.S.	
BUN	mg%	25.600	± 2.1119	30.000	± 0.8944	30.000	± 3.4205	1.14	N.S.	
Bilirub.T.	mg%	0.410	± 0.0400	0.460	± 0.0678	0.460	± 0.0510	0.28	N.S.	
Alk.phos.	mU/ml	182.000	±30.2324	160.000	± 9.8742	146.000	±13.7295	0.82	N.S.	
LDH	mmU/ml	0.304	± 0.039[illegible]	0.428	± 0.1037	0.308	± 0.0516	0.99	N.S.	
SGPT	mU/ml	57.000	± 9.0277	49.000	± 5.3385	48.000	± 5.8310	0.50	N.S.	
SGOT	mU/ml	71.000	±13.5462	91.000	±34.2199	51.000	± 8.8600	0.83	N.S.	
Cl ion*	meq/l	115.800	± 1.90[illegible]9	127.400	± 3.5014	124.600	± 3.2650	4.13	0.05	1
Na ion	meq/l	137.200	± 6.9886	127.200	± 3.2924	127.000	± 2.0000	1.60	N.S.	
K ion	meq/l	4.760	± 0.8778	3.520	± 0.3105	3.560	± 0.2205	1.62	N.S.	
Ca^{++}	mg%	14.200	± 0.2550	15.900	± 0.8426	13.880	± 0.5152	3.39	N.S.	

DATA: 29/4/76 FIRMA: Dr. Alfredo [illegible]

+ GROUP SIGNIFICANT COMPARED TO THE LAST ONE -

CRF

1 MONTH

GROUP I SEX M STRAIN NEW.ZEL. EXPERIMENT 022 TREATMENT 200mg/Kg 4ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	4.	M.	L.F.		±E.S.
CO_2	meq/l	17.00	16.00	14.00	15.00	15.50	17.55	13.45	0.645
Prot.Tot.	g%	7.00	7.90	7.40	8.00	7.58	8.31	6.84	0.232
Albumine	g%	4.80	5.30	4.80	5.30	5.05	5.51	4.59	0.144
P inorg.	mg%	5.00	8.40	9.60	9.60	8.15	11.61	4.69	1.087
Cholest.	mg%	55.00	65.00	55.00	60.00	58.75	66.37	51.13	2.394
Glucose	mg%	165.00	155.00	155.00	150.00	156.25	166.26	146.24	3.146
BUN	mg%	18.00	21.00	20.00	25.00	21.00	25.68	16.32	1.472
Bilirub.T.	mg%	0.40	0.50	0.40	0.40	0.43	0.50	0.35	0.025
Alk.phos.	mU/ml	205.00	180.00	200.00	180.00	191.25	212.17	170.33	6.575
LDH	mmU/ml	0.34	0.48	0.32	0.40	0.39	0.50	0.27	0.036
SGPT	mU/ml	50.00	70.00	45.00	50.00	53.75	71.39	36.11	5.543
SGOT	mU/ml	45.00	130.00	60.00	140.00	93.75	170.44	17.06	24.09
Cl ion	meq/l	96.00	110.00	115.00	110.00	107.75	120.77	94.73	4.090
Na ion	meq/l	128.00	138.00	142.00	127.00	133.75	145.54	121.96	3.705
K ion	meq/l	3.50	4.60	5.30	3.40	4.20	5.65	2.75	0.456
Ca^{++}	mg%	13.50	15.00	14.00	14.00	14.13	15.13	13.12	0.315

DATA:

C. R. F.
CONSOR.IO PICENO CERTIFICATO S.r.l.
FIRMA: Dr. Giuseppe Pavanziata

1 MONTH

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GROUP 1(SEX F STRAIN NEW.ZEL. EXPERIMENT . 02 TREATMENT 100mg/Kg BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S
CO 2	meq/l	17.00	16.00	18.00	21.00	12.00	16.80	20.86	12.74	1.463
Tot. Prot.	g%	7.70	7.60	7.50	7.50	7.50	7.56	7.67	7.45	0.040
Albumine	g%	4.60	5.40	4.50	5.20	5.20	4.98	5.48	4.48	0.180
Inorg. P.	mg%	8.40	9.00	11.40	8.40	10.80	9.60	11.35	7.85	0.629
Cholest.	mg%	100.00	95.00	90.00	90.00	85.00	92.00	99.07	84.92	2.550
Glucose	mg%	170.00	155.00	145.00	195.00	155.00	164.00	188.20	139.80	8.718
BUN	mg%	18.00	27.00	31.00	26.00	26.00	25.60	31.46	19.74	2.112
Bilirub.T.	mg%	0.35	0.30	0.40	0.50	0.50	0.41	0.52	0.30	0.040
Alk.phos.	mU/ml	185.00	280.00	135.00	105.00	205.00	182.00	265.94	98.06	30.232
LDH	mmU/ml	0.36	0.34	0.40	0.22	0.20	0.30	0.41	0.19	0.040
SGPT	mU/ml	55.00	90.00	55.00	35.00	50.00	57.00	82.06	31.94	9.028
SGOT	mU/ml	75.00	120.00	55.00	65.00	40.00	71.00	108.61	33.39	13.546
Cl ione	meq/l	120.00	115.00	110.00	114.00	120.00	115.80	121.10	110.50	1.908
Na ione	meq/l	125.00	125.00	145.00	130.00	161.00	137.20	156.60	117.80	6.989
K ione	meq/l	3.00	3.50	6.00	3.70	7.60	4.78	7.20	2.32	0.878
Ca^{++}	mg%	14.00	14.00	13.50	15.00	14.50	14.20	14.91	13.49	0.255

GROUP III SEX M STRAIN NEW.ZEL. EXPERIMENT 022 TREATMENT 100mg/Kg 4ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	15.00	13.00	23.00	18.00	14.00	16.60	21.61	11.59	1.806
Prot.Tot.	g%	7.70	8.90	7.90	6.80	8.50	7.96	8.96	6.96	0.360
Albumine	g%	5.20	5.60	4.80	4.10	5.70	5.07	5.89	4.27	0.292
P inorg.	mg%	7.60	8.20	7.60	7.00	9.00	7.88	8.82	6.94	0.338
Cholest.	mg%	95.00	55.00	70.00	75.00	95.00	78.00	99.33	56.67	7.681
Glucos	mg%	160.00	175.00	170.00	155.00	180.00	168.00	180.87	155.13	4.637
BUN	mg%	23.00	18.00	19.00	19.00	22.00	20.20	22.89	17.51	0.970
Bilirub.T.	mg%	0.50	0.50	0.40	0.30	0.50	0.44	0.55	0.33	0.040
Alk.phos.	mU/ml	195.00	145.00	125.00	90.00	140.00	139.00	186.16	91.84	16.985
LDH	mmU/ml	0.32	0.34	0.20	0.26	0.42	0.31	0.41	0.20	0.037
SGPT	mU/ml	75.00	45.00	30.00	40.00	40.00	46.00	67.24	24.76	7.649
SGOT	mU/ml	75.00	80.00	30.00	45.00	95.00	65.00	98.14	31.86	11.937
Cl ion	meq/l	120.00	120.00	125.00	120.00	120.00	121.00	123.78	118.22	1.000
Na ion	meq/l	125.00	125.00	125.00	120.00	135.00	126.00	132.80	119.20	2.449
K ion	meq/l	3.20	3.20	3.10	2.90	4.30	3.34	4.02	2.66	0.246
Ca^{++}	mg%	15.00	15.00	15.50	14.50	16.00	15.20	15.91	14.49	0.255

DATA: 29/4/76 FIRMA: C.R.F. Dr. Alfredo Nunziata

GROUP IV SEX F STRAIN NEW.ZEL. EXPERIMENT 022 TREATMENT 100mg/Kg 4ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	20.00	10.00	15.00	16.00	13.00	14.80	19.40	10.20	1.655
Prot.Tot.	g%	7.50	7.80	9.00	7.50	7.60	7.88	8.6	7.09	0.285
Albumine	g%	5.40	5.00	5.00	4.70	4.90	5.00	5.32	4.68	0.114
P inorg.	mg%	7.60	8.20	8.20	8.60	8.80	8.28	8.85	7.71	0.206
Cholest.	mg%	85.00	70.00	100.00	90.00	75.00	84.00	98.82	69.18	5.339
Glucose	mg%	180.00	160.00	165.00	155.00	145.00	161.00	177.07	144.93	5.788
BUN	mg%	29.00	29.00	33.00	28.00	31.00	30.00	32.48	27.52	0.894
Bilirub.T.	mg%	0.40	0.40	0.70	0.50	0.30	0.46	0.65	0.27	0.068
Alk.phos	mU/ml	190.00	165.00	130.00	150.00	165.00	160.00	187.41	132.59	9.874
LDH	mmU/ml	0.50	0.32	0.80	0.22	0.30	0.43	0.72	0.14	0.104
SGPT	mU/ml	50.00	55.00	65.00	40.00	35.00	49.00	63.82	34.18	5.339
SGOT	mU/ml	95.00	30.00	220.00	40.00	70.00	91.00	186.01	-4.01	34.220
Cl ion	meq/l	135.00	125.00	130.00	132.00	115.00	127.40	137.12	117.68	3.501
Na ion	meq/l	125.00	140.00	125.00	125.00	121.00	127.20	136.34	118.06	3.292
K ion	meq/l	3.30	4.70	3.50	3.20	2.90	3.52	4.38	2.66	0.310
Ca^{++}	mg%	19.00	15.00	16.00	15.50	14.00	15.90	18.24	13.56	0.843

DATA: 29/4/76

C. R. A. CONSORZIO RICERCA FARMACEUTICA S.p.A.

FIRMA: Dr. Alfredo Nunziata

CRF
Consorzio Ricerca Farmacologica S.p.A.

1 month

38

GROUP V SEX M STRAIN NEW.ZEL EXPERIMENT 022 TREATMENT PHYSIOL. SOL. 4ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	12.00	17.00	13.00	14.00	16.00	14.40	16.97	11.83	0.927
Prot.Tot.	g%	9.30	7.60	10.20	9.90	8.70	9.14	10.43	7.85	0.463
Albumin	g%	6.10	4.90	5.50	6.10	5.80	5.68	6.30	5.06	0.224
P inorg.	mg%	8.60	8.40	8.20	8.00	9.00	8.44	8.92	7.96	0.172
Cholest.	mg%	100.00	90.00	105.00	85.00	85.00	93.00	104.28	81.72	4.062
Glucose	mg%	155.00	155.00	155.00	160.00	155.00	156.00	158.78	153.22	1.000
BUN	mg%	25.00	29.00	34.00	24.00	31.00	28.60	33.76	23.44	1.860
Bilirub.T.	mg%	0.30	0.50	0.45	0.60	0.50	0.47	0.61	0.33	0.049
Alk.phos.	mU/ml	120.00	125.00	145.00	180.00	155.00	145.00	175.10	114.90	10.840
LDH	mmU/ml	0.40	0.28	0.34	0.54	0.36	0.38	0.50	0.26	0.044
SGPT	mU/ml	105.00	40.00	30.00	45.00	55.00	55.00	91.47	18.53	13.134
SGOT	mU/ml	115.00	45.00	50.00	60.00	90.00	72.00	108.89	35.11	13.285
Cl ion	meq/l	103.00	120.00	130.00	116.00	127.00	119.20	132.38	106.02	4.748
Na ion	meq/l	126.00	130.00	128.00	129.00	125.00	127.60	130.17	125.03	0.927
K ion	meq/l	3.40	3.60	3.30	3.60	3.30	3.44	3.63	3.25	0.068
Ca^{++}	mg%	14.70	14.00	13.50	13.50	13.50	13.84	14.49	13.19	0.236

DAT: 29/4/76

FIRMA: C.R.F. Consorzio Ricerca Farmacologica S.p.A. Dr. Alfredo Nunziata

CRF
Consorzio Ricerca Farmaceutica

1 month

GROUP VI SEX F STRAIN NEW.ZEL. EXPERIMENT 022 TREATMENT 4ml/Kg ev BIOCHEMICAL . CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	14.00	10.00	10.00	15.00	15.00	12.80	16.01	9.59	1.158
Prot.Tot.	g%	9.00	9.70	8.20	7.30	9.00	8.64	9.78	7.50	0.411
Albumin	g%	5.40	6.50	5.30	4.90	6.60	5.74	6.69	4.79	0.341
P inorg.	mg%	8.00	8.20	9.00	8.80	7.80	8.36	9.00	7.72	0.232
Cholest.	mg%	160.00	100.00	125.00	105.00	120.00	122.00	151.32	92.68	10.559
Glucos	mg%	180.00	165.00	160.00	145.00	165.00	163.00	178.58	147.42	5.612
BUN	mg%	18.00	31.00	36.00	37.00	28.00	30.00	39.50	20.50	3.421
Bilirub.T.	mg%	0.60	0.30	0.50	0.40	0.50	0.46	0.60	0.32	0.051
Alk.phos.	mU/ml	110.00	155.00	150.00	125.00	190.00	146.00	184.12	107.88	13.730
LDH	mmU/ml	0.46	0.14	0.34	0.28	0.32	0.31	0.45	0.16	0.052
SGPT	mU/ml	45.00	55.00	45.00	30.00	65.00	48.00	64.19	31.81	5.831
SGOT	mU/ml	55.00	35.00	80.00	30.00	55.00	51.00	75.60	26.40	8.860
Cl ion	meq/l	130.00	133.00	115.00	125.00	120.00	124.60	133.66	115.54	3.265
Na ion	meq/l	125.00	125.00	135.00	125.00	125.00	127.00	132.55	121.45	2.000
K ion	meq/l	3.30	3.30	4.40	3.20	3.60	3.56	4.17	2.95	0.220
Ca^{++}	mg%	14.00	15.00	12.70	12.70	15.00	13.88	15.31	12.45	0.515

DATA: 29/4/76

FIRMA: C.R.F. Consorzio Ricerca Farmaceutica S.p.A. Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica s.p.a.
[illegible] Telefono [illegible]

1 month

C.R.F. TOXICOLOGIC DEPARTMENT

HEMATOLOGIC VALUES VARIANCE ANALYSIS EXPERIMENT n° 022 SEX M STRAIN NEW ZEELAND

	GROUP	GROUP I	GROUP III	GROUP V	F	Signf.
Hct %	37.500 ± 0.5000	36.600 ± 0.9274	33.600 ± 0.6000	7.81	0.01	1 2
Leuk.x 1000	4.100 ± 0.6[illegible]56	4.640 ± 0.5036	5.820 ± 0.4152	2.76	N.S.	
Hb g% ml	13.100 ± 0.3000	13.220 ± 0.4903	1[illegible].300 ± 0.4025	2.50	N.S.	
Erythroc. x millions	7.750 ± 0.2630	7.320 ± 0.2634	6.460 ± 0.1778	7.64	0.01	1 2
MCV	48.550 ± 1.9414	50.100 ± 1.259[illegible]	52.120 ± 1.2110	1.49	N.S.	
FORMULA Neutr.	11.750 ± 2.2500	19.600 ± 3.1241	27.400 ± 5.4369	3.54	0.01	1
Lymph.	87.500 ± 2.6300	80.000 ± 3.0332	72.400 ± 5.6000	3.13	0.01	
Mon.	-	-	-	-		
Eosin.	-	-	-	-		
Bas.	-	-	-	-		

Data: 29/4/76

Firma C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica S.p.A.
[illegible] Telefono [illegible]

1 month

C.R.F. TOXICOLOGIC DEPARTMENT

HEMATOLOGIC VALUES VARIANCE ANALYSIS EXPERIMENT n° 022 SEX F STRAIN NEW ZEELAND

GROUP	GROUP II	GROUP IV	GROUP VI	F	Signf.	
Hct %	37.000 ± 0.3162	33.600 ± 0.4000	32.600 ± 0.9274	14.25	0.01	1
Leuk.x 1000	4.220 ± 0.2332	4.360 ± 0.8328	5.120 ± 0.7813	0.51	N.S.	
Hb g% ml	12.400 ± 0.3017	13.540 ± 0.2600	13.540 ± 0.5741	2.66	N.S.	
Erythroc. x millions	7.020 ± 0.1655	6.500 ± 0.1483	6.160 ± 0.3429	3.37	0.01	
M V	52.800 ± 1.0922	51.800 ± 1.5215	53.340 ± 2.1738	0.22	N.S.	
FORMULA Neutr.	18.000 ± 3.5777	24.800 ± 6.0983	28.000 ± 4.6043	1.09	N.S.	
Lymph.	781.200 ± 3.7202	74.200 ± 6.1838	67.600 ± 4.3543	1.95	N.S.	1
Mon.	-	-	-	-		
Eosin.	-	-	-	-		
Bas.	-	-	-	-		

Data: 29/4/76 Firma

C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo [illegible]

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farmaceutica s.p.a.
[illegible]
Telefono [illegible]

1 month

GROUP I SEX M STRAIN NZ EXPERIMENT 022 TREATMENT 200 mg / Kg or HEMATOLOGIC CARD

Animal N	1.	2.	3.	4.	M.	L.F.		±E.S.
Hct %	38.00	36.00	38.00	38.00	37.50	39.09	35.91	0.500
Leuk.x1000	3.20	4.60	5.80	2.80	4.10	6.28	1.92	0.686
Hb g%ml	12.60	12.60	13.40	13.80	13.10	14.05	12.15	0.300
Erythroc. x millions	7.00	7.80	8.00	8.20	7.75	8.59	6.91	0.263
MCV	54.30	46.10	47.50	46.30	48.55	54.73	42.37	1.941
Leukocitic formula								
Neutr.	9.00	18.00	8.00	12.00	11.75	18.91	4.59	2.250
Lymph.	90.00	80.00	92.00	88.00	87.50	95.87	79.13	2.630
Mon.	0.0	0.0	0.0	0.0	0.0	-	-	-
Eosin.	0.0	2.0	0.0	0.0	0.5	-	-	-
Bas.	1.0	0.0	0.0	0.0	0.2	-	-	-

DATA: 29/4/76

FIRMA: C. R. F. CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nunziata

1 month

GROUP II SEX B STRAIN NZ EXPERIMENT 022 TREATMENT 200mg /Kg HEMATOLOGIC CARD

Animal N	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	37.00	36.00	38.00	37.00	37.00	37.00	37.88	36.12	0.316
Leuk.x1000	5.00	4.50	3.80	3.80	4.00	4.22	4.87	3.57	0.233
Hb g%ml	12.10	11.60	12.10	13.00	13.20	12.40	13.24	11.56	0.302
Frythroc. x millions	6.90	6.50	7.00	7.20	7.50	7.02	7.48	6.56	0.166
MCV	53.60	55.40	54.30	51.40	49.30	52.80	55.83	49.77	1.092
Leukocitic Formula									
Neutr.	8.00	20.00	22.00	12.00	28.00	18.00	27.93	8.0	3.5 B
Lymph.	92.00	70.00	78.00	76.00	70.00	71.20	91.53	70.87	3.720
Mon.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Eosin.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Bas.	0.0	0.0	0.0	2.0	2.0	0.8	-	-	-

DATA: 29/4/76

FIRMA: S.R.F. LABORATORIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

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farmaceutica s.p.a.

1 month

Group III SEX M STRAIN N2 EXPERIMENT 022 TREATMENT 100 mg/ Kg HEMATOLOGIC CARD

Animal N	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	38.00	39.00	37.00	34.00	35.00	36.60	39.18	34.02	0.927
Leuk.x% 00	3.20	4.80	6.20	4.00	5.00	4.64	6.04	3.24	0.504
Hb g%ml	13.00	13.80	12.40	12.10	14.80	13.22	14.58	11.86	0.490
Erythroc. x millions	7.30	8.00	[illegible].30	6.40	7.60	[illegible].32	8.05	6.59	0.263
MCV	52.00	48.70	50.70	53.10	46.00	50.10	53.60	46.60	1.260
Leukocitic Formula									
Neutr.	28.00	16.00	12.00	16.00	26.00	19.60	28.28	10.92	3.124
Lymph.	72.00	82.00	88.00	84.00	74.00	80.00	[illegible]8.43	71.57	3.033
Mon.	0.0	1.0	0.0	0.0	0.0	0.1	-	-	-
Eosin.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Bas.	0.0	1.0	0.0	0.0	0.0	0.2	-	-	-

DATA: 29/4/76 FIRMA: C.R.F. Consorzio Ricerca Farmaceutica S.p.A. Dr. Alfredo Nunziata

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GROUP IV SEX ♂ STRAIN NZ EXPERIMENT 022 TREATMENT 100 mg/Kg 1 month HEMATOLOGIC CARD

Animal N	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	35.00	33.00	34.00	33.00	33.00	33.60	34.71	32.49	0.400
Leuk.x1000	2.20	5.00	6.80	5.00	2.80	4.36	6.67	2.05	0.833
Hb g%m	13.00	13.60	14.50	13.40	13.20	13.54	14.26	12.82	0.260
Erythroc.x millions	6.20	7.00	6.60	6.50	6.20	6.50	6.91	6.09	0.148
MCV	56.40	47.10	51.50	50.80	53.20	51.80	56.02	47.58	1.522
Leukocitic Formula									
Neutr.	32.00	20.00	45.00	12.00	15.00	24.80	41.72	7.88	6.094
Lymph.	66.00	80.00	54.00	86.00	85.00	74.20	91.37	57.03	6.184
Mon.	2.0	0.0	0.0	0.0	0.0	0.4	-	-	-
Eosin.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Bas.	0.0	0.0	2.0	1.0	0.0	0.6	-	-	-

DATA: 29/4/76 FIRMA: C.R.F. Consorzio Ricerca Farmaceutica S.p.A. Dr. Alfredo Nunziata

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1 month

Group V SEX M STRAIN NZ EXPERIMENT 022 TREATMENT PHYSIOL. SOL HEMATOLOGIC CARD

Animal N	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	33.00	33.00	35.00	32.00	35.00	33.60	35.27	31.93	0.600
Leuk.x1000	4.60	6.40	6.80	6.20	5.10	5.82	6.97	4.67	0.415
Hb g%ml	12.80	14.60	14.80	14.20	15.10	14.30	15.42	13.18	0.402
Erythroc.x millions	5.90	6.20	6.80	6.60	6.80	6.46	6.95	5.97	0.178
MCV	55.90	53.20	51.50	48.50	51.50	52.12	55.48	48.76	1.211
Leukocitic Formula									
Neutr.	22.00	14.00	34.00	22.00	45.00	27.40	42.50	12.30	5.437
Lymph.	78.00	86.00	66.00	38.00	54.00	72.40	87.95	56.85	5.600
Mon.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Eosin.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Bas.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-

DATA: 29/4/76 FIRMA: C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

CRF
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farmaceutica s.p.a.

1 month

GROUP VI SEX F STRAIN N2 EXPERIMENT 022 TREATMENT PHYSIOL. SOL. HEMATOLOGIC CARD

Animal N.	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	31.00	34.00	33.00	30.00	35.00	32.60	35.17	30.03	0.927
Leuk.x1000	5.60	5.40	7.60	4.00	3.00	5.12	7.29	2.95	0.781
Hb g%ml	12.30	15.00	13.60	12.20	14.60	13.54	15.13	11.95	0.574
Erythroc. x millions	5.20	[illegible]	6.80	5.60	6.20	6.16	7.11	5.21	0.343
MCV	59.60	48.60	48.50	53.60	56.40	53.34	59.38	47.30	2.174
Leukocitic Formula									
Neutr.	38.00	40.00	18.00	24.00	20.00	28.00	40.78	15.22	4.604
Lymph.	62.00	58.00	62.00	76.00	80.00	67.60	79.69	55.51	4.354
Mon.	0.0	2.0	2.0	0.0	0.0	0.8	-	-	-
Eosin.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
Bas.	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-

DATA: 29/4/76 FIRMA: C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

C.R.F. TOXICOLOGICAL DEPARTMENT

1 MONTH

n 022 SEX M STRAIN NEW.ZEL.

48

RELATIVE AUTOPTIC VALUES — VARIANCE ANALYSIS — EXPERIMENT

		GROUP I	GROUP III	GROUP V	F	SIGNIF. +
BRAIN	g	9.075 ± 0.2955	9.620 ± 0.1772	9.140 ± 0.3487	1.12	N.S.
HYPOPHYSIS	g	0.018 ± 0.0027	0.028 ± 0.0032	0.022 ± 0.0027	2.95	N.S.
THYMUS	g	3.850 ± 0.3279	3.860 ± 0.3530	3.740 ± 0.4534	0.03	N.S.
HEART	g	5.850 ± 0.1658	7.080 ± 0.2871	6.420 ± 0.2417	5.9	0.05
LIVER	g	62.300 ± 1.2295	60.180 ± 2.1242	70.680 ± 3.5896	4.56	0.05 2
SPLEEN	g	1.250 ± 0.1258	1.360 ± 0.1806	1.440 ± 0.1327	0.36	N.S.
SUPR. G	g	0.250 ± 0.0289	0.280 ± 0.0200	0.300 ± 0.0316	0.80	N.S.
KIDNEYS	g	16.100 ± 0.3536	16.660 ± 0.9800	14.780 ± 0.6200	1.89	N.S.
GONADS	g	4.500 ± 0.7326	4.440 ± 0.2502	4.360 ± 0.2943	0.02	N.S.
SEMINAL VESICLES	g	=	=	=	=	
PROSTATE UTERUS	g	1.400 ± 0.5017	1.740 ± 0.1249	1.280 ± 0.1497	0.82	N.S.
WEIGHT AT DEATH	g	2887.500 ±55.4339	2960.000 ±25.8968	2810.000 ±00.4978	0.55	N.S.

significant compared to the last.

Data: 29/4/76

Firma

C. R. F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nunziata

C.R.F. TOXICOLOGICAL DEPARTMENT

1 MONTH

RELATIVE AUTOPTIC VALUES — VARIANCE ANALYSIS — EXPERIMENT n 022 SEX F STRAIN NEW.ZEL.

49

		GROUP II	GROUP IV	GROUP VI	F	SIGN. +
brain	g	9.167 ± 0.1581	9.540 ± 0.2088	8.920 ± 0.2764	1.86	N.S.
hypophysis	g	0.024 ± 0.0026	0.023 ± 0.0009	0.026 ± 0.0054	0.21	N.S.
thymus	g	3.300 ± 0.3162	2.600 ± 0.2168	2.880 ± 0.3970	1.21	N.S.
heart	g	7.000 ± 0.4990	6.380 ± 0.2577	5.880 ± 0.3247	2.24	N.S.
liver	g	58.120 ± 3.0766	54.620 ± 2.8289	63.720 ± 7.0320	0.94	N.S.
spleen	g	1.560 ± 0.1166	1.380 ± 0.0970	1.460 ± 0.2638	0.26	N.S.
supr. g	g	0.260 ± 0.0400	0.236 ± 0.0264	0.226 ± 0.0194	0.34	N.S.
kidneys	g	14.220 ± 0.9211	14.100 ± 0.8337	14.040 ± 1.2086	0.008	N.S.
gonads	g	0.203 ± 0.0269	0.293 ± 0.0374	0.290 ± 0.0601	1.35	N.S.
seminal vesicles	g	=	=	=	=	
prostate uterus	g	3.540 ± 0.8041	4.880 ± 1.2575	3.500 ± 1.4061	0.44	N.S.
Weight at death	g	2710.000 ±46.9699	2620.000 ±80.0000	2590.000 ±87.1780	0.32	N.S.

+ group significant compared to the last.

Data: 29/4/76

Firma C. R. F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nuzzaca

C.R.F. TOXICOLOGICAL DEPARTMENT

1 MONTH

RELATIVE AUTOPTIC VALUES — VARIANCE ANALYSIS — EXPERIMENT n 022 SEX M STRAIN NEW.ZEL. 50

		GROUP I	GROUP III	GROUP V	F	SIGNIF.	+
brain	g	0.314 ± 0.0046	0.327 ± 0.0146	0.329 ± 0.0232	0.19	N.S.	
hypophysis	g	0.602 ± 0.0811	0.923 ± 0.0703	0.772 ± 0.1049	3.17	N.S.	
thymus	g	0.133 ± 0.0117	0.130 ± 0.0081	0.133 ± 0.0150	0.02	N.S.	
heart	g	0.203 ± 0.0040	0.241 ± 0.0157	0.230 ± 0.0113	2.43	N.S.	
liver	g	2.160 ± 0.0543	2.037 ± 0.0355	2.518 ± 0.1126	10.82	0.01	1 2
spleen	g	0.043 ± 0.0040	0.046 ± 0.0066	0.052 ± 0.0054	0.54	N.S.	
supr. g	g	8.720 ± 1.1560	9.606 ± 0.9549	10.627 ± 0.9369	0.86	N.S.	
kidneys	g	0.558 ± 0.0070	0.563 ± 0.0199	0.528 ± 0.0264	0.84	N.S.	
gonads	g	0.155 ± 0.0228	0.150 ± 0.0054	0.157 ± 0.0143	0.05	N.S.	
seminal vesicles	g	=	=	=	=		
prostate uterus	g	0.048 ± 0.0163	0.059 ± 0.0037	0.046 ± 0.0064	0.59	N.S.	
weight at death	g	=	=	=	=		

[illegible] significant compared to the last.

Date 29/4/76

C. R. F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.
Firma [illegible]

C.R.F. TOXICOLOGICAL DEPARTMENT 1 MONTH

RELATIVE AUTOPTIC VALUES VARIANCE ANALYSIS EXPERIMENT n 022 SEX F STRAIN NEW.ZEL.

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		GROUP II	GROUP IV	GROUP VI	F	SIGNI. +
brain	g	0.340 ± 0.0114	0.365 ± 0.0102	0.345 ± 0.0108	1.53	N.S.
hypophysis	g	0.893 ± 0.0904	0.864 ± 0.0365	0.987 ± 0.1811	0.29	N.S.
thymus	g	0.121 ± 0.0057	0.099 ± 0.0078	0.112 ± 0.0160	1.01	N.S.
heart	g	0.258 ± 0.0074	0.244 ± 0.0096	0.227 ± 0.0084	3.27	N.S. 1
liver	g	2.155 ± 0.1101	2.080 ± 0.0527	2.455 ± 0.2632	1.40	N.S.
spleen	g	0.058 ± 0.0049	0.053 ± 0.0043	0.057 ± 0.0102	0.14	N.S.
supr. g.	g	9.490 ± 1.0997	9.042 ± 1.0515	8.850 ± 1.0731	0.09	N.S.
kidneys	g	0.527 ± 0.0341	0.538 ± 0.0281	0.542 ± 0.0416	0.04	N.S.
gonads	g	0.007 ± 0.0006	0.011 ± 0.0016	0.011 ± 0.0021	1.96	N.S.
seminal vesicles	g	=	=	=	=	
prostate or uterus	g	0.127 ± 0.0218	0.188 ± 0.050	0.132 ± 0.0488	0.64	N.S.
Weight at death	g	=	=	=	=	

+ group significant compared to the last.

Data: 29/4/76

Firma C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica s.p.a.

N I SEX M STRAIN NEW.Z EXPERIMENT 022 TREATMENT 200mg/Kg in4ml/Kg ev AUTOPTIC CARD

Animal		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	M.	L.F.	±E.S.
brain	g	8.300	9.300	9.000	9.700	=	=	=	=	=	=	9.075	10.015 8.135	0.2955
	g%	0.302	0.315	0.316	0.323	=	=	=	=	=	=	0.314	0.328 0.300	0.0045
hypophysis	g	0.012	0.021	0.014	0.023	=	=	=	=	=	=	0.018	0.026 0.009	0.0027
	g%	0.436	0.712	0.491	0.767	=	=	=	=	=	=	0.602	0.860 0.344	0.0811
thymus	g	3.500	3.200	4.700	4.000	=	=	=	=	=	=	3.850	4.893 2.807	0.3279
	g%	0.127	0.1[illegible]	0.165	0.133	=	=	=	=	=	=	0.[illegible]	0.171 0.096	0.0117
heart	g	5.600	6.300	5.600	5.900	=	=	=	=	=	=	5.850	6.378 5.322	0.1658
	g%	0.204	0.214	0.196	0.197	=	=	=	=	=	=	0.203	0.245 0.190	0.0040
liver	g	60.100	60.800	65.600	62.700	=	=	=	=	=	=	62.300	66.21258.3[illegible]8	1.2295
	g%	2.185	2.061	2.302	2.090	=	=	=	=	=	=	2.160	2.333 1.987	0.0543
spleen	g	1.200	1.000	1.200	1.600	=	=	=	=	=	=	1.250	1.650 0.850	0.1258
	g%	0.044	0.0[illegible]4	0.042	0.053	=	=	=	=	=	=	0.043	0.056 0.031	0.0040
supr. g.	g	0.300	0.200	0.300	0.200	=	=	=	=	=	=	0.250	0.342 0.158	0.0289
	g%	10.909	6.780	10.526	6.667	=	=	=	=	=	=	8.720	12.399 5.042	1.1560
kidneys	g	15.700	16.300	15.400	17.000	=	=	=	=	=	=	16.100	17.22514.975	0.3536
	g%	0.571	0.553	0.540	0.567	=	=	=	=	=	=	0.558	0.580 0.535	0.0070
gonads	g	2.800	6.000	3.800	5.400	=	=	=	=	=	=	4.500	6.831 2.169	0.7326
	g%	0.102	0.203	0.133	0.180	=	=	=	=	=	=	0.155	0.227 0.082	0.0228
seminal vesicles	g	=	=	=	=	=	=	=	=	=	=			
	g%	=	=	=	=	=	=	=	=	=	=			
prostate or	g	0.900	1.000	0.800	2.900	=	=	=	=	=	=	1.400	2.996-0.196	0.5017
uterus	g%	0.033	0.034	0.028	0.09[illegible]	=	=	=	=	=	=	0.0[illegible]8	0.100-0.00[illegible]	0.0163
weight at death	g	2750	2950	2850	3000	=	=	=	=	=	=	2888	3064 2711	55.4

DATA: 29/4/76

FIRMA: Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica s.p.a.

1 MESE

N II SEX F STRAIN NEW.Z. EXPERIMENT 022 TREATMENT 200mg/Kg 4ml/Kg ev AUTOPTIC CARD

Animal		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	M.	L.F.	±E.S.
brain	g	9.300	78L 9.000	8.500	9.200	9.800	=	=	=	=	=	9.167	9.606 8.728	0.1581
	g%	0.332	0.356	0.340	0.368	0.302	=	=	=	=	=	0.340	0.371 0.308	0.0114
hypophysis	g	0.027	0.022	0.029	0.015	0.028	=	=	=	=	=	0.024	0.031 0.017	0.0026
	g%	0.964	0.880	1.160	0.600	0.862	=	=	=	=	=	0.893	1.144 0.642	0.0904
thymus	g	3.500	2.800	3.200	2.600	4.400	=	=	=	=	=	3.300	4.178 2.422	0.3162
	g%	0.125	0.112	0.128	0.104	0.135	=	=	=	=	=	0.121	0.137 0.105	0.0057
heart	g	7.600	5.900	6.800	6.100	8.600	=	=	=	=	=	7.000	8.385 5.615	0.4990
	g%	0.271	0.236	0.272	0.244	0.265	=	=	=	=	=	0.258	0.278 0.237	0.0074
liver	g	65.600	59.000	57.500	47.100	61.400	=	=	=	=	=	58.120	66.661 49.579	3.0766
	g%	2.343	2.360	2.300	1.884	1.889	=	=	=	=	=	2.155	2.461 1.850	0.1101
spleen	g	1.700	1.300	1.300	1.900	1.600	=	=	=	=	=	1.560	1.884 1.236	0.1166
	g%	0.061	0.052	0.052	0.076	0.049	=	=	=	=	=	0.058	0.072 0.044	0.0049
supr. g.	g	0.200	0.200	0.300	0.200	0.400	=	=	=	=	=	0.260	0.371 0.149	0.0400
	g%	7.143	8.000	12.000	78L 8.000	12.308	=	=	=	=	=	9.490	12.543 6.437	1.0997
kidneys	g	16.600	15.600	11.800	12.400	14.700	=	=	=	=	=	14.220	16.777 11.663	0.9211
	g%	0.593	0.624	0.472	0.496	0.452	=	=	=	=	=	0.527	0.622 0.433	0.0341
gonads	g	0.200	0.200	0.135	0.182	0.300	=	=	=	=	=	0.203	0.278 0.129	0.0269
	g%	0.007	0.008	0.005	0.007	0.009	=	=	=	=	=	0.007	0.009 0.006	0.0006
seminal vesicles	g	=	=	=	=	=	=	=	=	=	=			
	g%	=	=	=	=	=	=	=	=	=	=			
prostate or uterus	g	2.400	2.300	2.700	3.700	6.600	=	=	=	=	=	3.540	5.772 1.308	0.8041
	g%	0.076	0.092	0.108	0.148	0.203	=	=	=	=	=	0.127	0.188 0.067	0.0218
Weight at death	g	2800	2500	2500	2500	3250	=	=	=	=	=	2710	3178L 2302	147.0

DATA: 29/4/76

FIRMA: C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica s.p.a.

1 MESE

N III SEX M STRAIN N.ZEL EXPERIMENT O22 TREATMENT IOOmg/Kg 4ml/Kg ev AUTOPTIC CARD

Animal		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	M.	L.F.		±E.S.
brain	g	10.200	9.700	9.200	9.700	9.300	=	=	=	=	=	9.620	10.112	9.128	0.1772
	g%	0.329	0.380	0.323	0.294	0.310	=	=	=	=	=	0.327	0.368	0.287	0.0146
hypophysis	g	0.029	0.021	0.021	0.038	0.029	=	=	=	=	=	0.028	0.036	0.019	0.0032
	g%	0.935	0.824	0.737	1.152	0.967	=	=	=	=	=	0.923	1.118	0.728	0.0703
thymus	g	3.500	3.200	3.900	5.200	3.500	=	=	=	=	=	3.860	4.840	2.880	0.3530
	g%	0.113	0.125	0.137	0.158	0.117	=	=	=	=	=	0.130	0.152	0.107	0.0081
heart	g	6.800	7.600	7.000	7.800	6.200	=	=	=	=	=	7.080	7.877	6.283	0.2871
	g%	0.219	0.297	0.246	0.236	0.207	=	=	=	=	=	0.241	0.285	0.197	0.0157
liver	g	63.700	52.000	60.200	62.800	62.200	=	=	=	=	=	60.180	66.077	54.283	2.1242
	g%	2.055	2.039	2.112	1.903	2.073	=	=	=	=	=	2.037	2.135	1.938	0.0355
spleen	g	1.200	1.000	2.000	1.100	1.500	=	=	=	=	=	1.360	1.861	0.859	0.1806
	g%	0.039	0.039	0.070	0.033	0.050	=	=	=	=	=	0.046	0.064	0.028	0.0066
supr. g.	g	0.300	0.300	0.300	0.200	0.300	=	=	=	=	=	0.280	0.336	0.224	0.0200
	g%	9.677	11.765	10.526	6.061	10.000	=	=	=	=	=	9.606	12.257	6.955	0.9549
kidneys	g	18.900	13.400	16.200	16.800	18.000	=	=	=	=	=	16.660	19.269	14.051	0.9400
	g%	0.610	0.525	0.568	0.509	0.600	=	=	=	=	=	0.563	0.618	0.507	0.0199
gonads	g	4.600	4.000	4.400	5.300	3.900	=	=	=	=	=	4.440	5.135	3.745	0.2502
	g%	0.148	0.157	0.154	0.161	0.130	=	=	=	=	=	0.150	0.165	0.135	0.0054
seminal vesicles	g	=	=	=	=	=	=	=	=	=	=				
	g%	=	=	=	=	=	=	=	=	=	=				
prostate or uterus	g	1.400	1.500	1.800	2.000	2.000	=	=	=	=	=	1.740	2.087	1.393	0.1249
	g%	0.045	0.059	0.063	0.061	0.067	=	=	=	=	=	0.059	0.069	0.049	0.0037
weight at death	g	3100	2550	2850	3300	3000	=	=	=	=		2960	3309	2611	125.9

DATA: 29/4/76 FIRMA: C. R. F. consorzio ricerca farmaceutica s.p.a. Dr. Alfredo Sanzieni

Consorzio ricerca farmaceutica S.p.A.

1 MESE

N IV SEX F STRAIN N.ZEL EXPERIMENT 022 TREATMENT 100mg/Kg 4ml/Kg ev AUTOPTIC CARD

Animal		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Brain	g	10.200	9.800	9.700	9.600	9.400	9.540	10.120	8.960	0.2078
	g%	0.352	0.368	0.388	0.384	0.333	0.365	0.393	0.337	0.0102
hypophysis	g	0.024	0.020	0.025	0.022	0.022	0.023	0.025	0.020	0.0009
	g%	0.828	0.800	1.000	0.880	0.815	0.864	0.966	0.763	0.0365
thymus	g	2.700	2.600	1.800	2.800	3.100	2.600	3.202	1.997	0.2168
	g%	0.093	0.104	0.072	0.112	0.115	0.099	0.121	0.078	0.0078
Heart	g	6.500	5.600	6.000	6.800	7.000	6.380	7.095	5.665	0.2577
	g%	0.224	0.224	0.240	0.272	0.259	0.244	0.270	0.217	0.0096
Liver	g	62.800	47.700	50.800	52.200	59.600	54.620	62.473	46.767	2.8289
	g%	2.166	1.908	2.032	2.088	2.207	2.080	2.226	1.934	0.0527
Spleeng.	g	1.500	1.500	1.400	1.500	1.000	1.380	1.649	1.111	0.0970
	g%	0.052	0.060	0.056	0.060	0.037	0.053	0.065	0.041	0.0043
supr. g.	g	0.200	0.300	0.200	0.180	0.300	0.236	0.309	0.163	0.0264
	g%	6.897	12.000	8.000	7.200	11.111	9.042	11.960	6.123	1.0515
kidney	g	15.700	11.600	12.800	15.900	14.500	14.100	16.414	11.786	0.8337
	g%	0.541	0.464	0.512	0.636	0.537	0.538	0.616	0.460	0.0281
gonads	g	0.200	0.310	0.225	0.410	0.320	0.293	0.397	0.189	0.0374
	g%	0.007	0.012	0.009	0.016	0.012	0.011	0.016	0.007	0.0016
Seminal vesicles	g	=	=	=	=	=				
	g%	=	=	=	=	=				
Prostate or uterus	g	5.500	6.800	8.000	3.000	1.100	4.880	8.371	1.389	1.2575
	g%	0.190	0.272	0.320	0.120	0.041	0.188	0.328	0.049	0.0504
Weight at death	g	2900	2500	2500	2500	2700	2620	2842	2398	80.0

DATA: 29/4/76 FIRMA: Dr. Alfredo Ivanissevich

CRF consorzio ricerca farmaceutica s.p.a.

1 MESE

N V SEX M STRAIN N.ZEL. EXPERIMENT 022 TREATMENT PHYSIOL. .4ml/Kg ev AUTOPTIC CARD

Animal		1.	2.	3.	4.	5.	M.	L.F.	±E.S.
Brain	g	9.500	8.200	9.200	10.200	8.600	9.140	10.108	8.172	0.3487
	g%	0.352	0.265	0.347	0.392	0.287	0.329	0.393	0.264	0.0232
hypophysis	g	0.019	0.024	0.031	0.015	0.019	0.022	0.029	0.014	0.0027
	g%	0.704	0.774	1.170	0.577	0.633	0.772	1.063	0.480	0.1049
thymus	g	2.000	4.400	4.200	3.700	4.400	3.740	4.999	2.481	0.4534
	g%	0.074	0.142	0.158	0.142	0.147	0.133	0.174	0.091	0.0150
heart	g	5.800	6.000	6.800	6.400	7.100	6.420	7.091	5.749	0.2417
	g%	0.215	0.194	0.257	0.246	0.237	0.230	0.261	0.198	0.0113
Liver	g	69.800	74.500	57.300	73.800	78.000	70.680	80.645	60.715	3.5896
	g%	2.585	2.403	2.162	2.838	2.600	2.518	2.830	2.205	0.1126
Spleen	g	1.700	1.500	1.000	1.700	1.300	1.440	1.880	1.072	0.1327
	g%	0.063	0.048	0.038	0.065	0.043	0.052	0.067	0.036	0.0054
supr. g.	g	0.300	0.300	0.300	0.200	0.400	0.300	0.388	0.212	0.0316
	g%	11.111	9.677	11.321	7.692	13.333	10.627	13.228	8.026	0.9369
kidneys	g	16.800	15.200	13.000	14.300	14.600	14.780	16.501	13.059	0.6200
	g%	0.622	0.490	0.491	0.550	0.487	0.528	0.601	0.455	0.0264
gonads	g	5.300	4.000	3.900	4.800	3.800	4.360	5.177	3.543	0.2943
	g%	0.196	0.129	0.147	0.185	0.127	0.157	0.197	0.117	0.0143
Seminal vesicles	g	-	-	-	-	-				
	g%	-	-	-	-	-				
Prostate or Uterus	g	1.400	1.300	1.500	1.500	0.700	1.280	1.695	0.865	0.1497
	g%	0.052	0.042	0.057	0.058	0.023	0.046	0.064	0.029	0.0064
Weight at death	g	2700	3100	2650	2600	3000	2810	3089	2531	100.5

DATA: 29/4/76

C. R. F. CONSORZIO RICERCA FARMACEUTICA S.p.A.

FIRMA: Dr. [illegible] Nunziata

CRF consorzio ricerca farmaceutica s.p.a.

1 MESE

N VI SEX F STRAIN N.ZELE. EXPERIMENT022 TREATMENT RHYSIOL .4ml/Kgev AUTOPTIC CARD.

Animal		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Brain	g	8.900	9.100	8.700	8.100	9.800	8.920	9.687	8.153	0.2764
	g%	0.336	0.325	0.378	0.324	0.363	0.345	0.375	0.315	0.0107
Hypophysis	g	0.014	0.046	0.022	0.023	0.024	0.026	0.041	0.011	0.0054
	g%	0.528	1.643	0.957	0.920	0.889	0.987	1.490	0.485	0.1811
Thymus	g	1.400	3.000	3.200	3.000	3.800	2.880	3.985	1.775	0.3970
	g%	0.053	0.107	0.139	0.120	0.141	0.112	0.157	0.067	0.0160
Heart	g	5.600	7.100	5.200	5.900	5.600	5.880	6.781	4.979	0.3247
	g%	0.211	0.254	0.226	0.236	0.207	0.227	0.250	0.204	0.0084
Liver	g	67.400	68.300	41.900	84.400	56.600	63.720	83.241	44.199	7.0320
	g%	2.543	2.439	1.822	3.376	2.096	2.455	3.186	1.725	0.2632
Spleen	g	2.400	1.200	1.400	1.500	0.800	1.460	2.192	0.728	0.2638
	g%	0.091	0.043	0.061	0.060	0.030	0.057	0.075	0.028	0.0102
Supr.G.	g	0.200	0.200	0.300	0.200	0.230	0.226	0.280	0.172	0.0198
	g%	7.547	7.143	13.043	8,000	8.519	8.850	11.829	5.872	1.0731
Kidneys	g	18.400	12.800	12.100	12.000	14.900	14.040	17.395	10.685	1.2086
	g%	0.694	0.457	0.526	0.480	0.552	0.542	0.657	0.426	0.0416
Gonads	g	0.215	0.520	0.300	0.215	0.200	0.290	0.457	0.123	0.0601
	g%	0.008	0.019	0.013	0.009	0.007	0.011	0.017	0.005	0.0021
Seminal Vesicles	g	-	-	-	-	-				
	g%	-	-	-	-	-				
Prostate or Uterus	g	2.000	9.100	2.500	1.700	2.200	3.500	7.403	-0.403	1.4061
	g%	0.075	0.325	0.109	0.071	0.071	0.132	0.267	-0.004	0.0488
Weight at death	g	2650	2800	2300	2500	2700	2590	2832	2348	87.2

R. F.

DATA: 29/4/76

FIRMA: Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica s.p.a.

TIME 0

GROUP I SEX M STRAIN N.ZEL. EXPERIMENT 022 TREATMENT 200mg/Kg in 4ml/Kgev BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	13.00	22.00	16.00	11.00	20.00	16.40	22.13	10.67	2.064
Tot. Prot.	g%	6.30	6.60	5.90	6.70	5.80	6.26	6.76	5.76	0.181
Albumine	g%	4.30	4.60	4.40	4.30	4.20	4.36	4.55	4.17	0.0681
Inorg. P.	mg%	6.70	9.90	10.00	8.80	9.20	8.92	10.58	7.26	0.598
Cholest.	mg%	45.00	115.00	65.00	60.00	60.00	69.00	102.24	35.76	11.979
Glucose	mg%	175.00	170.00	220.00	170.00	175.00	182.00	208.54	155.46	9.566
BUN	mg%	12.00	14.00	15.00	14.00	13.00	13.60	15.01	12.19	0.510
Bilirub.T.	mg%	0.40	0.40	0.30	0.40	0.20	0.34	0.45	0.23	0.040
Alk.Phos.	mU/ml	185.00	150.00	215.00	240.00	210.00	200.00	242.31	157.69	15.248
LDH	mmU/ml	0.60	1.70	1.32	0.50	0.56	0.94	1.61	0.26	0.242
SGPT	mU/ml	55.00	70.00	50.00	60.00	75.00	62.00	74.87	49.13	4.637
SGOT	mU/ml	65.00	150.00	235.00	65.00	170.00	137.00	227.40	46.60	32.581
Cl ion	meq/l	105.00	100.00	97.00	105.00	101.00	101.80	105.66	97.94	1.393
Na ion	meq/l	140.00	149.00	137.00	146.00	138.00	141.80	148.09	135.51	2.267
K ion	meq/l	5.50	7.30	5.00	6.10	4.60	5.70	7.01	4.39	0.472
Ca^{++}	mg%	16.00	15.00	15.00	15.00	15.00	15.20	15.75	14.65	0.200

DATA: 26/3/76 FIRMA:

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TIME 0

GROUP II SEX F STRAIN N.ZEL. EXPERIMENT 022 TREATMENT 200mg/Kg in 4ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	10.00	13.00	18.00	20.00	21.00	16.40	22.26	10.54	2.112
Tot. Prot.	g%	6.90	6.60	6.90	5.90	7.10	6.68	7.27	6.09	0.211
Albumin	g%	5.80	4.20	4.80	4.00	4.60	4.68	5.55	3.81	0.314
Inorg. P.	mg%	10.00	9.20	8.60	10.00	6.80	8.92	10.56	7.28	0.592
Cholest.	mg%	110.00	65.00	60.00	70.00	120.00	85.00	119.57	50.43	12.450
Glucose	mg%	160.00	165.00	190.00	190.00	195.00	180.00	200.12	159.88	7.246
BUN	mg%	16.00	12.00	10.00	12.00	15.00	13.00	16.04	9.96	1.095
Bilirub.T.	mg%	0.70	0.30	0.30	0.25	0.40	0.39	0.62	0.16	0.081
Alk.phos.	mU/ml	225.00	175.00	185.00	140.00	140.00	173.00	217.03	128.97	15.859
LDH	mmU/ml	2.08	0.30	0.60	0.70	0.46	0.83	1.72	-0.06	0.320
SGPT	mU/ml	35.00	65.00	55.00	70.00	40.00	53.00	71.93	34.07	6.819
SGOT	mU/ml	160.00	50.00	85.00	155.00	85.00	107.00	166.9[illegible]	47.03	21.599
Cl ion	meq/l	108.00	106.00	106.00	102.00	97.00	103.80	109.24	98.36	1.960
Na ion	meq/l	165.00	140.00	145.00	139.00	143.00	146.40	159.65	133.15	4.771
K ion	meq/l	9.60	5.40	5.90	4.90	5.00	6.16	8.60	3.72	0.878
Ca^{++}	mg%	15.00	14.00	15.00	13.00	16.00	14.60	16.02	13.18	0.510

DATA: 26/3/76 FIRMA:

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TIME 0

GROUP III SEX M STRAIN N.ZEL. EXPERIMENT 22 TREATMENT 100mg/Kg in 4ml/Kg eVS BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	22.00	25.00	26.00	25.00	21.00	23.80	26.49	21.11	0.970
Tot. Prot.	g%	6.50	7.00	6.80	6.00	5.90	6.44	7.0[illegible]	5.84	0.216
Albumin	g%	4.20	3.90	4.20	3.80	4.00	4.02	4.24	3.80	0.080
Inorg. P.	mg%	7.10	4.90	6.30	5.10	5.80	5.84	6.95	4.73	0.402
Cholest.	mg%	75.00	135.00	95.00	100.00	75.00	96.00	126.47	65.53	11.000
Glucose	mg%	170.00	150.00	170.00	170.00	165.00	165.00	175.73	154.27	3.873
BUN	mg%	12.00	20.00	15.00	12.00	12.00	14.20	18.53	9.87	1.562
Bilirub.T.	mg%	0.30	0.30	0.10	0.70	0.70	0.42	0.75	0.09	0.120
Alk.phosp.	mU/ml	155.00	50.00	95.00	75.00	105.00	96.00	144.46	47.54	17.493
LDH	mmU/ml	0.72	0.66	0.44	0.68	0.34	0.57	0.78	0.36	0.075
SGPT	mU/ml	75.00	55.00	45.00	35.00	40.00	50.00	69.59	30.41	7.071
SGOT	mU/ml	95.00	85.00	55.00	65.00	40.00	68.00	95.56	40.44	9.950
Cl ion	meq/l	103.00	103.00	103.00	112.00	107.00	105.60	110.52	100.68	1.778
Na ion	meq/l	144.00	140.00	152,00	140.00	148.00	144.80	151.26	138.34	2.332
K ion	meq/l	5.20	5.80	6.40	4.90	5.90	5.64	6.38	4.90	0.266
Ca^{++}	mg%	15.00	15.00	16.00	14.00	14.00	14.80	15.84	13.76	0.374

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Dr. Alfredo Nunziata

TIME

GROUP IV SEX F STRAIN NEW.ZEL. EXPERIMENT 022 TREATMENT 100mg/Kg 4ml/Kg ev BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	14.00	22.00	18.00	24.00	16.00	18.80	23.95	13.65	1.855
Tot. Prot.	g%	6.50	5.60	7.80	6.80	6.10	6.56	7.59	5.53	0.370
Albumin	g%	3.90	3.70	4.60	4.40	3.90	4.10	4.57	3.63	0.170
Inorg. P.	mg%	7.20	5.40	5.90	5.00	4.70	5.64	6.86	4.42	0.439
Cholest.	mg%	65.00	55.00	95.00	125.00	55.00	79.00	116.87	41.13	13.638
Glucose	mg%	185.00	175.00	170.00	150.00	180.00	172.00	188.77	155.23	6.042
BUN	mg%	13.00	15.00	12.00	35.00	18.00	18.60	30.33	6.87	4.226
Bilirub.T.	mg%	0.70	0.70	0.70	0.70	0.60	0.68	0.74	0.62	0.020
Alk.Phosp.	mU/ml	170.00	135.00	110.00	100.00	130.00	129.00	162.55	95.45	12.083
LDH	mmU/ml	0.14	0.42	0.78	0.92	0.40	0.53	0.92	0.14	0.141
SGPT	mU/ml	50.00	80.00	55.00	50.00	55.00	58.00	3 3.58	42.42	5.612
SGOT	mU/ml	25.00	145.00	140.00	150.00	165.00	125.00	195.3 1	54.62	25.348
Cl ion	meq/l	115.00	105.00	103.00	99.00	108.00	106.00	113.45	98.55	2.683
Na ion	meq/l	140.00	139.00	139.00	147.00	145.00	142.00	146.65	137.35	1.673
K ion	meq/l	4.90	4.70	4.90	6.00	6.10	5.32	6.15	4.49	0.301
Ca^{++}	mg%	14.00	12.00	15.00	16.00	15.00	14.40	16.28	12.52	0.6 8

DATA: 26/3/76 FIRMA: C. R. F. CONSORZIO RICERCA FARMACEUTICA SpA Dr. Alfredo Nunziata

TIME 0

GROUP V SEX M STRAINN.2EL. EXPERIMENT Q22 TREATMENT PHYSIOL. SOL. in4ml/Kg$_{ev}$ BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	22.00	15.00	20.00	17.00	13.00	17.40	21.93	12.87	1.631
Tot. Prot.	g%	7.30	6.60	7.40	7.70	6.80	7.16	7.72	6.60	0.201
Albumin	g%	5.30	4.20	4.20	5.00	4.50	4.64	5.25	4.03	0.220
Inorg. P.	mg%	7.90	8.10	7.10	7.10	6.70	7.38	8.12	6.64	0.265
Cholest.	mg%	95.00	90.00	90.00	75.00	60.00	82.00	99.87	64.13	6.442
Glucos.	mg%	190.00	175.00	150.00	175.00	170.00	172.00	189.87	154.13	6.442
BUN	mg%	14.00	11.00	16.00	11.00	11.00	12.60	15.46	9.74	1.030
Bilirub.T.	mg%	0.60	0.60	0.70	0.70	0.65	0.65	0.71	0.59	0.022
Alk.Phos.	mU/ml	220.00	165.00	150.00	325.00	270.00	226.00	316.48	135.52	32.611
LDH	mmU/ml	0.74	0.48	0.60	1.10	0.62	0.71	1.00	0.41	0.106
SGPT	mU/ml	85.00	45.00	55.00	50.00	65.00	60.00	79.62	40.38	7.071
SGOT	mU/ml	85.00	50.00	70.00	135.00	75.00	83.00	122.39	43.61	14.195
Cl ion	meq/l	107.00	110.00	108.00	110.00	117.00	110.40	115.25	105.55	1.749
Na ion	meq/l	167.00	152.00	147.00	160.00	161.00	157.40	167.19	147.61	3.530
K ion	meq/l	7.20	6.50	5.50	6.50	6.50	6.44	7.19	5.69	0.271
Ca^{++}	mg %	16.00	14.00	13.00	14.00	14.00	14.20	15.56	12.84	0.490

DATA: 26/3/76 FIRMA: C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

TIME 0

GROUP VI SEX F STRAIN N.ZEL. EXPERIMENT 022 TREATMENT PHYSIOL. SOL. in 4ml/Kg BIOCHEMICAL CARD

		1.	2.	3.	4.	5.	M.	L.F.		±E.S.
CO 2	meq/l	16.00	16.00	12.00	18.00	16.00	15.60	18.31	12.89	0.980
Prot. Tot.	g%	7.60	7.60	7.20	6.60	7.40	7.28	7.79	6.77	0.185
Albumine	g%	4.90	6.00	5.10	4.50	4.00	4.90	5.82	3.98	0.333
Inorg. P.	mg%	7.60	7.80	7.50	7.80	6.70	7.48	8.04	6.92	0.203
Cholest.	mg%	110.00	150.00	120.00	80.00	65.00	105.00	146.55	63.45	15.000
Glucose	mg%	190.00	170.00	175.00	180.00	175.00	178.00	187.39	168.61	3.391
BUN	mg%	13.00	13.00	12.00	22.00	11.00	14.20	19.70	8.70	1.985
Bilirub.T.	mg%	0.70	0.95	0.80	0.65	0.60	0.74	0.91	0.57	0.062
Alk.Phosp.	mU/ml	190.00	205.00	195.00	135.00	150.00	175.00	212.93	137.07	13.693
LDH	mmU/ml	0.46	2.40	1.56	0.40	0.26	1.02	2.17	-0.14	0.417
SGPT	mU/ml	55.00	60.00	60.00	40.00	40.00	51.00	63.69	38.31	4.583
SGOT	mU/ml	85.00	185.00	110.00	60.00	60.00	100.00	164.22	35.78	23.184
Cl ion	meq/l	107.00	109.00	112.00	126.00	126.00	116.00	127.52	104.48	4.159
Na ion	meq/l	158.00	168.00	173.00	160.00	155.00	162.80	172.05	153.55	3.338
K ion	meq/l	6.80	9.80	9.60	7.30	5.40	7.78	10.12	5.44	0.844
Ca^{++}	mg%	15.00	11.00	14.00	16.00	15.00	14.20	16.58	11.82	0.860

DATA: 26/3/76 FIRMA: Dr. Alfredo Nunziata

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C.R.F. DIPARTIMENTO DI TOSSICOLOGIA

TIME 0

HEMATOLOGIC VALUES ANALYSIS OF VARIANCE EXPERIMENT n° 022 SEX M STRAIN NEW ZELLAND

	GROUP	GROUP I	GROUP III	GROUP V	F	Signf.	
	Hct %	36.200 ± 0.7348	38.600 ± 0.5099	40.600 ± 0.5099	13.73	0.01	1 2
	Leuk.x 1000	3.120 ± 0.8980	4.160 ± 0.418	5.160 ± 0.6431	2.24	N.S.	
	Hb g% ml	12.000 ± 0.5762	11.920 ± 0.3137	13.520 ± 0.2498	4.94	0.01	1 2
	Erythroc. x millions	5.460 ± 0.3655	5.440 ± 0.1364	6.120 ± 0.2417	2.13	N.S.	2
	MCV	67.220 ± 3.6225	71.060 ± 1.4702	66.660 ± 2.0351	0.88	N.S.	
FORMULA	Neutr.	26.200 ± 9.3723	30.400 ± 2.1354	28.800 ± 5.9867	0.10	N.S.	
	Lmph.	73.400 ± 9.3360	69.600 ± 2.1354	71.200 ± 5.9867	0.08	N.S.	
	Mon.	0	0	0	0		
	Eosiph.	0	0	0	0		
	Bas.	0	0	0	0		

Data 26/3/76 Firma

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C.R.F. DIPARTIMENTO DI TOSSICOLOGIA

TIME 0

HEMATOLOGIC VALUES — ANALYSIS OF VARIANCE — EXPERIMENT n° 022 — SEX F — STRAIN NEW ZEELAND

	GROUP	GROUP II	GROUP IV	GROUP VI	F	Signf.	
Hct %		38.600 ± 0.5099	39.000 ± 1.0488	41.000 ± 0.5477	2.98	0.01	1
Leuk.x 1000		4.400 ± 0.4147	4.360 ± 0.5[illegible]41	5.120 ± 0.6621	0.58	N.S.	
Hb gr% ml		13.060 ± 0.3341	13.000 ± 0.3347	13.480 ± 0.5314	0.40	N.S.	
Erythroc. x millions		5.860 ± 0.1806	5.880 ± 0.190[illegible]	6.120 ± 0.3153	0.37	N.S.	
MCV		66.140 ± 2.4109	66.600 ± 2.79[illegible]6	65.560 ± 3.3466	0.03	N.S.	
FORMULA	Neutr.	21.600 ± 4.4900	27.600 ± 6.2338	28.600 ± 5.0160	0.51	N.S.	
	Lymph.	78.400 ± 4.4900	73.000 ± 6.0581	73.000 ± 3.9749	0.40	N.S.	
	Mon.	0	0	0			
	Eosiph.	0	0	0			
	Bas.	0	0	0			

Data: 26/3/78

Firma [illegible] S.p.A.
Dr. Alfredo [illegible]

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t=0

GROUP I SEX M STRAIN NZ EXPERIMENT 022 TREATMENT 200 mg/Kg os HEMATOLOGIC CARD

Animal N.	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	37.00	38.00	34.00	37.00	35.00	36.20	38.24	34.16	0.735
Leuk. x 1000	4.20	4.00	1.00	5.40	1.00	3.12	5.61	0.63	0.898
Hb g ù ml	11.20	13.20	10.40	13.40	11.80	12.00	13.60	10.40	0.576
Erythroc. x millions	4.80	6.00	4.70	6.60	5.20	5.46	6.47	4.45	0.366
MCV	77.10	63.30	72.30	56.10	67.30	67.22	77.28	57.16	3.622
Leukocitic Formula									
Neutr.	22.00	46.00	5.00	50.00	8.00	26.20	52.22	0.18	9.372
Lymph.	76.00	54.00	95.00	50.00	92.00	73.40	99.32	47.48	9.336
Mon.	2.0	0.0	0.0	0.0	0.0	0.2			
Eosiph.	0.0	0.0	0.0	0.0	0.0	0.0			
Bas.	0	0	0	0	0	0			

DATA: 26/3/76 FIRMA: C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

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GROUP II SEX F STRAIN NZ EXPERIMENT 022 TREATMENT 200mg/Kg os t=0 HEMATOLOGIC CARD

Animal N.	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	37.00	39.00	39.00	38.00	40.00	38.60	40.02	37.18	0.510
Leuk. x 1000	4.60	5.20	4.80	2.80	4.60	4.40	5.55	3.25	0.415
Hb g % ml	13.60	13.00	12.20	12.50	14.00	13.06	13.99	12.13	0.334
Erythroc. millions	6.50	5.90	5.70	5.40	5.80	5.86	6.36	5.36	0.181
MCV	56.90	66.10	68.40	70.40	68.90	66.14	72.83	59.45	2.411
Leukocitic Formula									
Neutr.	22.00	6.00	22.00	24.00	34.00	21.60	34.07	9.13	4.490
Lymph.	78.00	94.00	78.00	76.00	66.00	78.40	90.87	65.93	4.490
Mon.	0.0	0.0	0.0	0.0	0.0	0.0			
Eosiph.	0.0	0.0	0.0	0.0	0.0	0.0			
Bas.	0.0	0.0	0.0	0.0	0.0	0.0			

DATA: 26/3/76

FIRMA: C. R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

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GROUP III SEX M STRAIN NZ EXPERIMENT 022 TREATMENT 100mg/kG OS t=0 HEMATOLOGIC CARD

Animal N:	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	37.00	39.00	40.00	39.00	38.00	38.60	40.02	37.18	0.510
Leuk. x 1000	5.40	2.80	4.20	4.40	4.00	4.16	5.32	3.00	0.417
Hb g à ml	11.40	11.20	13.00	12.00	12.00	11.92	12.79	11.05	0.314
Erythroc.x millions	5.20	5.20	5.90	5.30	5.60	5.44	5.82	5.06	0.136
MCV	71.10	75.00	67.80	73.60	67.80	71.06	75.14	66.98	1.470
Leukocitic Formula									
Neutr.	32.00	26.00	38.00	28.00	28.00	30.40	36.33	24.47	2.135
Lymph.	68.00	74.00	62.00	72.00	72.00	69.60	75.53	63.67	2.135
Mon.	0.0	0.0	0.0	0.0	0.0	0.0			
Eosiph.	0.0	0.0	0.0	0.0	0.0	0.0			
Bas.	0.0	0.0	0.0	0.0	0.0	0.0			

DATA: 26/3/76 FIRMA: C. R. CONSORZIO RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Nunziata

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GROUP IV SEX F STRAIN NZ EXPERIMENT 022 TREATMENT 100 mg/Kg os t=0 HEMATOLOGIC CARD

Animal N.	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	40.00	39.00	41.00	40.00	35.00	39.00	41.91	36.09	1.049
Leuk. x 1000	5.00	5.40	5.00	4.20	2.20	4.36	5.95	2.77	0.574
Hb g à ml	13.20	12.80	14.20	12.40	12.40	13.00	13.93	12.07	0.335
Erythroc. x millions	5.[illegible]0	6.30	6.30	5.30	5.80	5.88	6.41	5.35	0.191
MCV	70.20	61.90	65.10	75.50	60.30	66.60	74.36	58.84	2.795
Leukocitic Formula									
Neutr.	33.00	24.00	36.00	40.00	5.00	27.60	44.91	10.29	6.234
Lymph.	67.00	[illegible]6.00	67.00	60.00	95.00	73.00	89.82	56.18	6.058
Mon.	0.0	0.0	2.0	0.0	0.0	0.2			
Eosiph.	0.0	0.0	0.0	0.0	0.0	0.0			
Bas.	0.0	0.0	0.0	0.0	0.0	0.0			

DATA: 26/3/76

FIRMA: C R F Laboratori Farmaceutici S.p.A.
Dr. Alfredo Nunziata

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Consorzio ricerca farmaceutica s.p.a.

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GROUP VI SEX F STRAIN NZ EXPERIMENT 022 TREATMENT PHYSIOL SOL HEMATOLOGIC CARD

Animal N	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	41.00	42.00	42.00	39.00	41.00	41.00	42.52	39.48	0.548
Leuk. x 1000	3.20	4.80	6.80	4.40	6.40	5.12	6.96	3.28	0.662
Hb g % ml	12.20	15.00	14.40	12.60	13.20	13.48	14.96	12.00	0.531
Erythroc.x millions	5.40	6.90	6.80	5.50	6.00	6.12	7.00	5.24	0.315
MCV	75.90	60.90	61.80	70.90	58.30	65.56	74.85	56.27	3.347
Leukocitic Formula									
Neutr.	44.00	26.00	18.00	19.00	36.00	28.60	42.53	14.67	5.016
Lymph.	66.00	74.00	82.00	71.00	62.00	73.00	84.04	61.96	3.9[illegible]5
Mon.	0.0	0.0	0.0	0.0	0.0	0.2			
Eosiph.	0.0	0.0	0.0	0.0	0.0	0.0			
Bas.	0.0	0.0	0.0	0.0	0.0	0.0			

: 26/3/76

C. R. F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nunziata

CRF
Consorzio ricerca farmaceutica S.p.A.

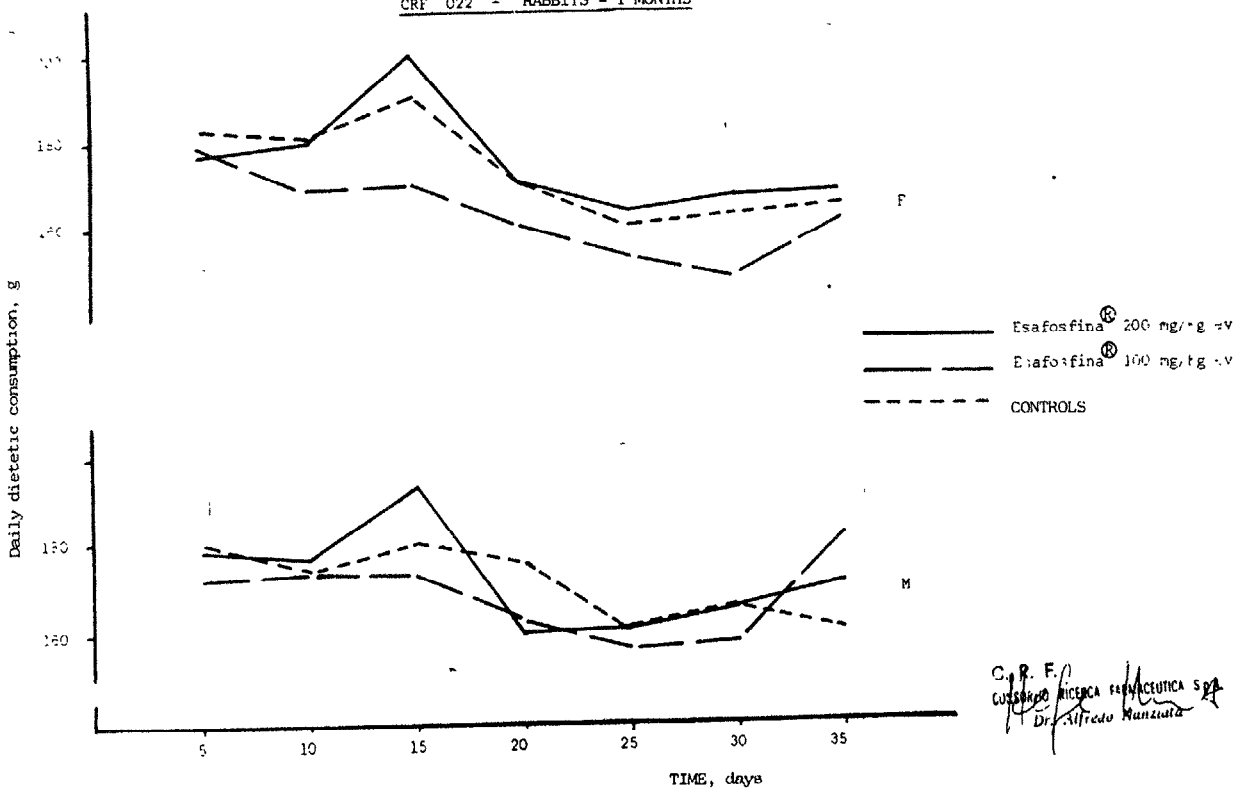
GROUP V SEX M STRAIN NZ EXPERIMENT 022 TREATMENT PHYSIOL. SOL. t=0 HEMATOLOGIC CARD

Animal N.	1.	2.	3.	4.	5.	M.	L.F.		±E.S.
Hct %	41.00	39.00	42.00	41.00	40.00	40.60	42.02	39.18	0.510
Leuk. x 1000	3.40	5.00	7.20	5.80	4.40	5.16	6.95	3.37	0.643
Hb g à ml	13.80	12.60	13.40	14.00	13.80	13.52	14.21	12.83	0.250
Erythroc.x millions	6.30	5.30	6.40	6.70	5.90	6.12	6.79	5.45	0.242
MCV	65.10	73.60	65.60	61.20	67.80	66.66	72.31	61.01	2.035
Leukocitic Formula									
Neutr.	38.00	14.00	46.00	18.00	28.00	28.80	45.42	12.18	5.97
Lymph.	62.00	86.00	54.00	62.00	72.00	71.20	87.82	54.58	5.97
Mon.	0.0	0.0	0.0	0.0	0.0	0.0			
Eosiph.	0.0	0.0	0.0	0.0	0.0	0.0			
Bas.	0	0	0	0	0	0			

DATA: 26/3/76

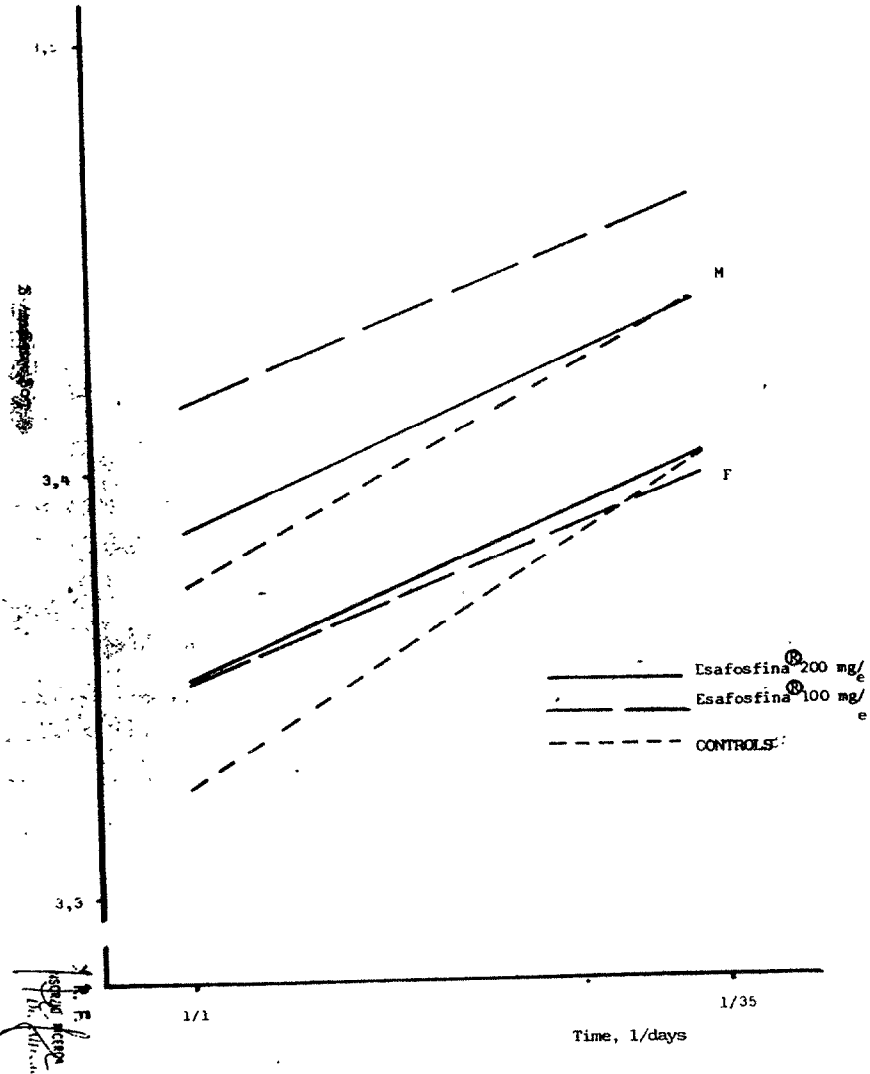
FIRMA C. R. F. CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nunziata

CRF 022 - RABBITS - 1 MONTHS



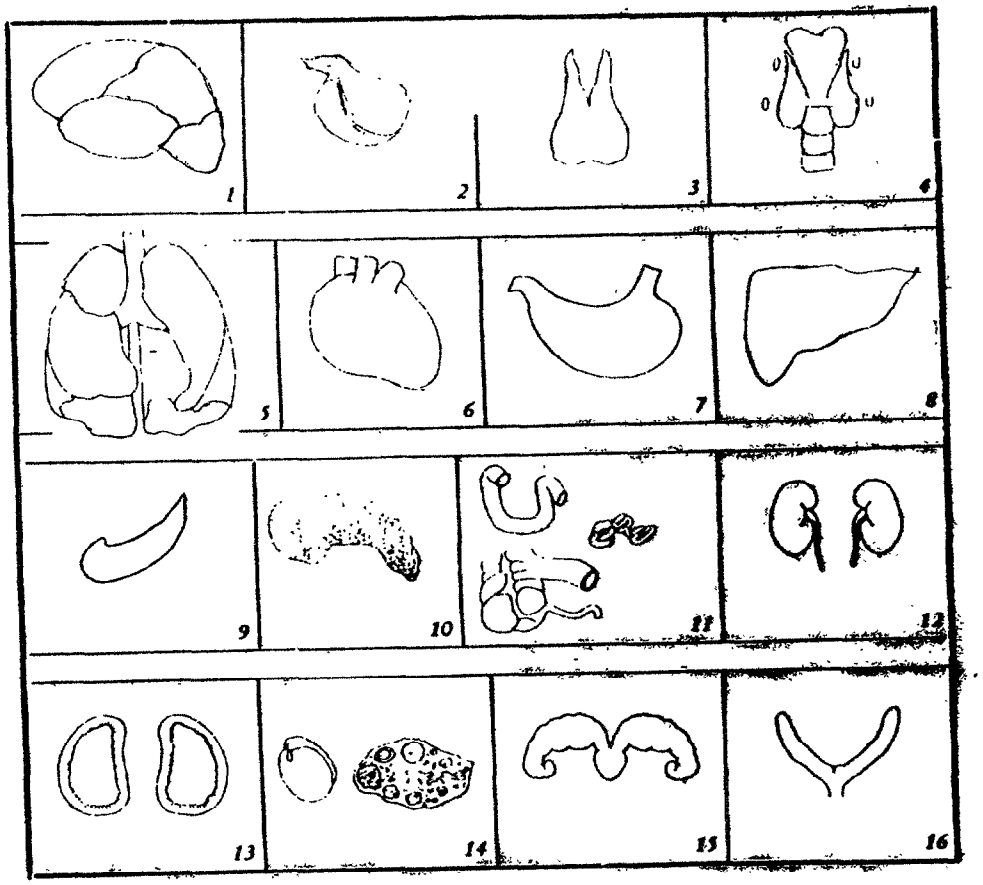
C.R.F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Manzinelli

RABBITS - 1 MONTH-



AUTOPTIC CARD

N.	SEX	STRAIN	EXPERIMENT	TREATMENT
11	M	N. ZEELAND	022	200 mg/kg iv-1 month



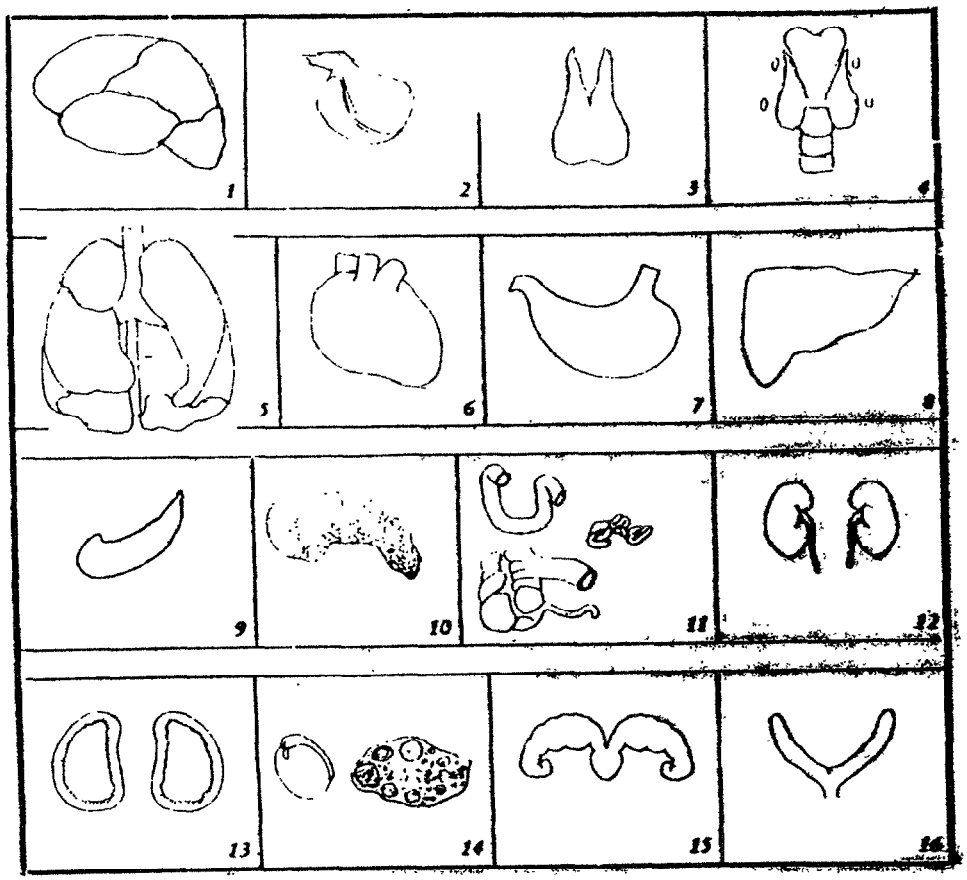
ORGAN

1.BRAIN	g 8,3	6.HEART	g 5,6	11. INTESTINE	
2.HYPOPHYSIS	mg0,01	7.STOMACH		12. KIDNEYS	g 15,7
3.THYMUS	g3,5	8.LIVER	g60,1	13. SUPRARENAL GLANDS	mg 300
4.THYROID		9.SPLEEN	g 1,2	14. GONADS	g 2,8
5.LUNGS		10.PANCREAS		15. SEMINAL VESICLES	
				16. PROSTATE	mg 900

Date 29/4/76

AUTOPTIC CARD

N.	SEX	STRAIN	EXPERIMENT	TREATMENT
31	M	N. ZEELAND	022	200 mg/kg iv-1 month



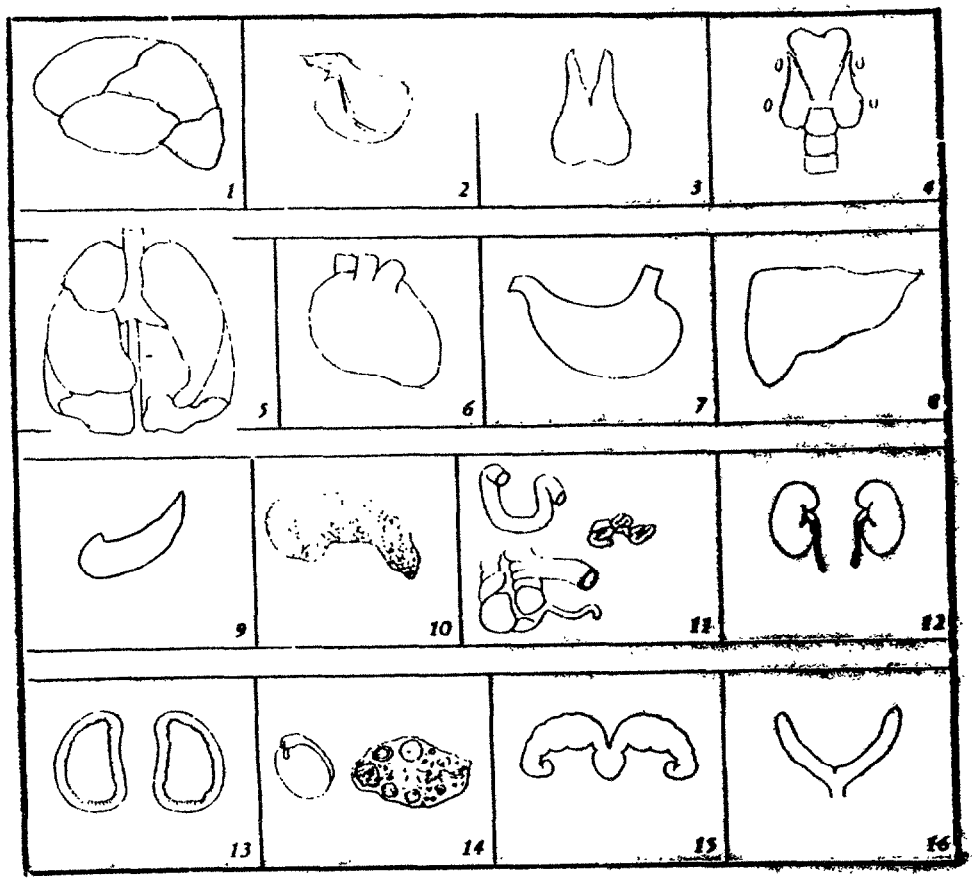
ORGAN

1.BRAIN g 9
2.HYPOPHYSIS g0,014
3.THYMUS g 4,7
4.THYROID
5.LUNGS
6.HEART g9,6
7.STOMACH
8.LIVER g65,6
9.SPLEEN g1,2
10.PANCREAS
11. INTESTINE
12. KIDNEYS g 15,4
13. SUPRARENAL GLANDS mg 300
14. GONADS g 3,8
15. SEMINAL VESICLES
16. PROSTATE mg 800

Date 29/4/76

AUTOPTIC CARD

N. 41	SEX M	STRAIN N. ZEELAND	EXPERIMENT 022	TREATMENT 200 mg/kg iv-1 month



ORGAN

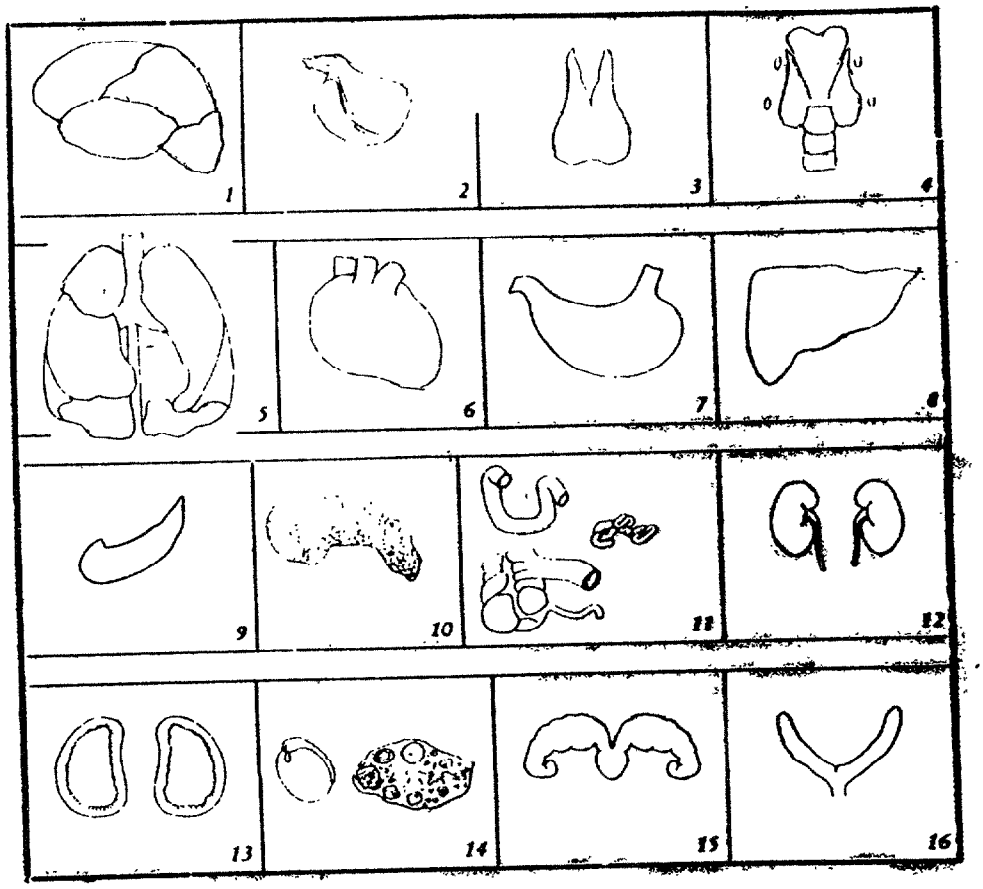
1.BRAIN g9,7
2.HYPOPHYSIS mg0,0237.STOMACH
3.THYMUS g4,0
4.THYROID
5.LUNGS
6.HEART g 5,9
8.LIVER g62,7
9.SPLEEN g 1,6
10.PANCREAS
11. INTESTINE
12. KIDNEYS g 17
13. SUPRARENAL GLANDS mg 200
14. GONADS g 5,4
15. SEMINAL VESICLES
16. PROSTATE mg 2900

Date 29/4/76

C.R.F.
Toxicological Department

AUTOPTIC CARD

N. I II	SEX F	STRAIN N. ZEELAND	EXPERIMENT 022	TREATMENT 200 mg/kg iv-1 month



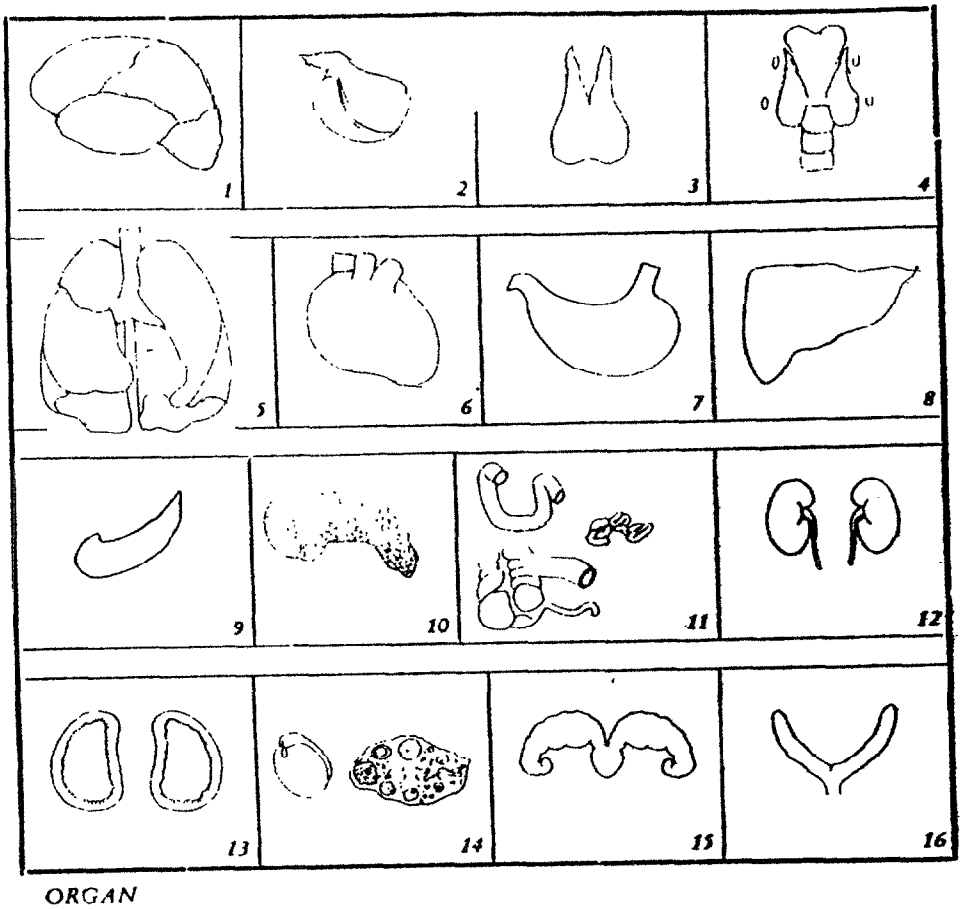
ORGAN

1.BRAIN	g9,3	6.HEART	g 7,6	11. INTESTINE	
2.HYPOPHYSIS	mg0,027	7.STOMACH		12. KIDNEYS	g 16,6
3.THYMUS	g3,5	8.LIVER	g65,6	13. SUPRARENAL GLANDS	mg 200
4.THYROID		9.SPLEEN	g1,7	14. GONADS	g 0,2
5.LUNGS		10.PANCREAS		15. SEMINAL VESICLES	
				16. PROSTATE	mg 2400

Date 29/4/76

AUTOPTIC CARD

N.	SEX	STRAIN	EXPERIMENT	TREATMENT
21	M	N. ZEELAND	022	200 mg/kg iv-1 month



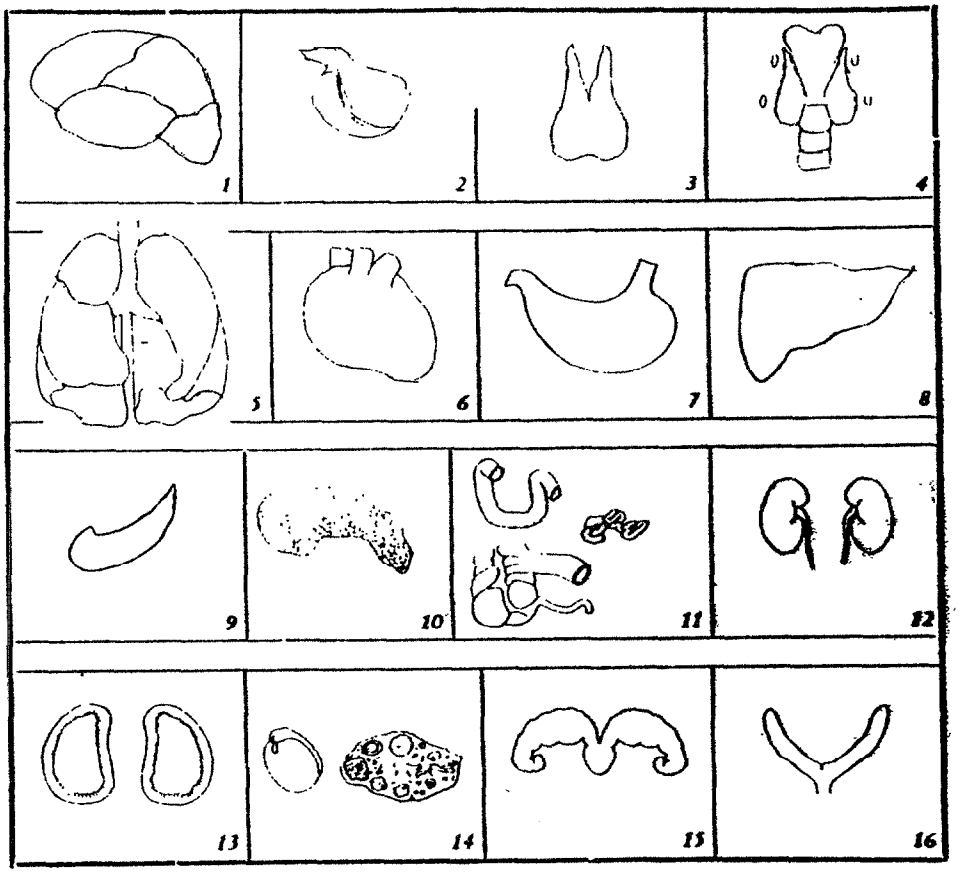
ORGAN

1.BRAIN	g9,3	6.HEART	g6,3	11. INTESTINE	
2.HYPOPHYSIS	mg0,02	7.STOMACH		12. KIDNEYS	g16,3
3.THYMUS	g3,2	8.LIVER	g60,8	13. SUPRARENAL GLANDS	mg200
4.THYROID		9.SPLEEN	g1	14. GONADS	g6
5.LUNGS		10.PANCREAS		15. SEMINAL VESICLES	
				16. PROSTATE	mg1000

Date 29/4/76

AUTOPTIC CARD

N. 2 II	SEX	STRAIN N. ZEELAND	EXPERIMENT 022	TREATMENT 200 mg/kg iv-1 month



ORGAN

1.BRAIN g8,9
2.HYPOPHYSIS mg0,02
3.THYMUS g2,8
4.THYROID
5.LUNGS
6.HEART g5,9
7.STOMACH
8.LIVER --g59
9.SPLEEN g1,3
10.PANCREAS
11. INTESTINE
12. KIDNEYS g 15,6
13. SUPRARENAL GLANDS mg 200
14. GONADS g 0,2
15. SEMINAL VESICLES
16. PROSTATE
UTERUS mg 2300

Date 29/4/76