Health Academy
Radboudumc

Examination	:	**B1RS2 Research, tweede semester**
Date	:	June 20th 2017
Start	:	9:30 h

After finishing the exam, you can take this examination set along with you.
Please hand in the OTHER part (the answering form) to the supervisor.

You are allowed to use a calculator of the type Casio FX-82MS.

The questions must be answered in English. If you cannot remember a specific English term, you are allowed to use the Dutch term.

During the exam, you have access on a computer to these books:

- Baynes & Dominiczak: Medical Biochemistry
- van Oosterom en Oostendorp: Medische Fysica
- Campbell: Statistics at square one
- Fletcher: Clinical Epidemiology
- Turnpenny: Emery's Elements of Medical Genetics

GENERAL INSTRUCTIONS:

- This exam consists of **5** open questions.
- The available time is **2** hours.
- Check if your examination set is complete.
- Please write *your name and student number* on each page of the answering form.
- Write your answers on the answering form in the open space below the questions. Read the questions carefully before phrasing your answers.
- Be concise and complete in your answers.
- If necessary you can also use the *backside* of the pages.
- Refrain from using abbreviations in your answers, and write legibly (illegible answers are considered incorrect).
- Please do not use a pencil.
- The use of audiovisual and technical devices is not allowed, unless it is mentioned explicitly elsewhere on this page. Any inappropriate use of such equipment is regarded as fraud.
- Except for the exam forms, some loose writing material, your student and registration card your table should be empty. No boxes or cases are allowed.
- **After finishing the exam, please hand the answering form to the supervisor. If you have comments about the questions we refer you to the hyperlink of the digital comment form that is included in your "studenten webdossier" below "toetsen".**

SUCCESS

ATTENTION !!

FIRST PUT YOUR NAME AND STUDENT NUMBER ON EVERY PAGE OF THE ANSWERING FORM!

b) The authors describe part of their methods (see also abstract above) as follows:

> Children we studied were recruited from a group of people who had complained to the Taiwan Consumers' Foundation about phthalate exposure. Briefly, main caregivers, mostly mothers, were interviewed to collect food intake information for the period between April and July of 2011. After the questionnaire interview and physical examination, one-spot urine samples were collected. Part of the sample was used for routine urinary analysis. The remaining portion was aliquoted and stored in a − 20 °C freezer for the subsequent analyses of phthalate metabolites and the biomarkers of renal injury.
>
> Urine samples were analyzed for nine phthalate metabolites using mass spectrometry. To prepare urine samples for phthalate analysis, 1 mL of each sample was thawed, transferred to a glass tube, and a small amount of a mixture of radioactively labelled phthalate monoester standards was added, which can be detected separately of urine metabolites by mass spectrometry.

i) What is the reason for adding a small amount of phthalate monoester standards to the patient urine before analysis? (3 pt)

ii) This experimental setup contains critical parameters. Name and explain two experimental parameters in this study that increase the reliability/validity of this study. (4 pt)

iii) Name and explain also two limitations of this study. (4 pt)

c) The authors conclude in their article that intake of DEHP from phthalate-tainted foods may be a potential risk factor for microalbuminuria, a marker of glomerular injury in children. Based upon the results of Figure 1.1, give one argument that supports their conclusion and give one argument that contradicts their conclusion. (4 pt)

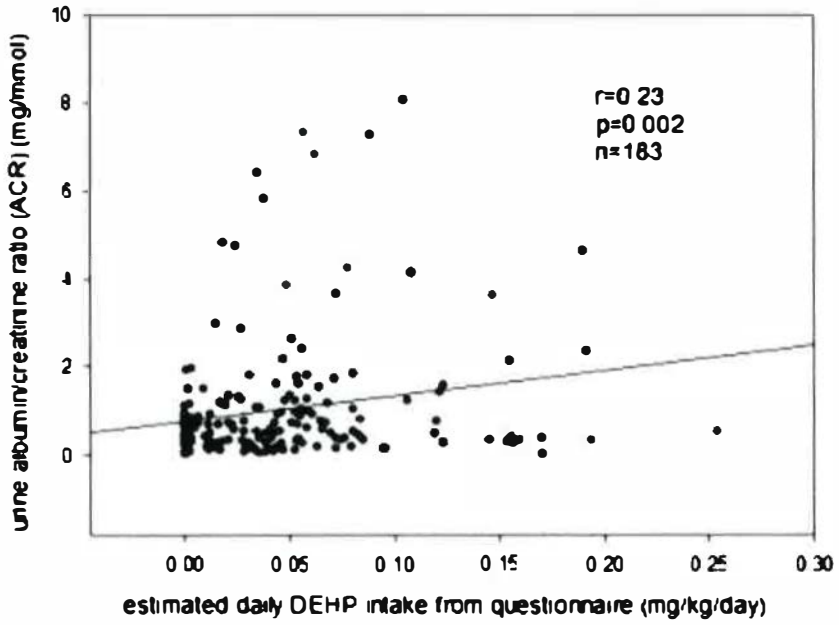


Figure 1.1 The Spearman correlation between intake of estimated daily di-(2-ethylhexyl) phthalate (DEHP) intake (mg/kg/day) from questionnaire and biomarkers of renal injury in the study children. (A) Urine albumin/creatinine ratio.

b. Was the filter that was used to produce the trace in figure 2.2-B a low-pass filter or a high-pass filter? (1 pts)

c. What is an appropriate cut-off frequency for the filter in question b? Explain your answer. (3 pts)

d. Sketch the amplitude response of the filter of question b. Indicate what is plotted along the axes (3 pt)

Question 3

Modelling: Measles and native Americans – dr. T. Oostendorp

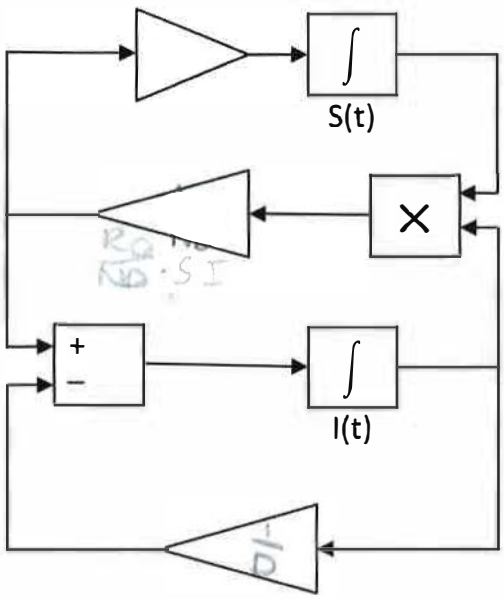
(15 points)

A commonly used model for epidemic outbreaks is the SIR-model. The differential equation for the number of infectious people $I(t)$ in this model is:

$$\frac{d}{dt}I(t) = \frac{R_0}{ND}S(t)I(t) - \frac{1}{D}I(t)$$

Here R_0 is the basic reproductive number, D is the average duration of infectiousness, N is the population size, and $I(t)$ is the number of infectious people.

a. Below the corresponding Simulink-model is displayed. Add the correct values and/or symbols to the Gain blocks (the triangular blocks) so that the model complies to the above differential equation (4 pt)



In the SIR-model it is commonly assumed that (almost) nobody dies as the result of the disease. This assumption is definitively incorrect for the spread of measles among the native population in the Americas; according to some estimates (W.H. McNeill: Plagues and peoples. Oxford: Basil Blackwell,1976), that population decreased by more than 50% in the 100 years after the arrival of Columbus, mainly as the result of measles.

We will adopt the standard SIR-model above to include death from measles.

Table III.
RR of incident atrial fibrillation with fish intake in 5184 Dutch men and women aged 55 years and older

	Categories of fish intake (g/d)		
	<20 (Reference)	0-20	≥20
No. of subjects	1527	2030	1627
Median intake (g/d)	0	9.6	32.1
All subjects			
No. of events	84	124	104
Person-years	9938	13 000	10 385
Incidence/1000 y	8.4	9.5	10.0
RR, model 1*	1	1.17 (0.89-1.54)	1.27 (0.95-1.70)
RR, model 2†	1	1.07 (0.81-1.42)	1.17 (0.87-1.57)
Subjects without previous MI			
No. of events	67	93	81
Person-years	8767	11 220	9217
Incidence/1000 y	7.6	8.3	8.8
RR, model 1*	1	1.14 (0.83-1.56)	1.24 (0.89-1.71)
RR, model 2†	1	1.12 (0.81-1.53)	1.16 (0.84-1.62)

RRs were obtained by Cox proportional hazard analysis, with 95% CI in parentheses.

* Model includes age, sex, and energy intake.

† Model includes age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction (except for subgroup analyses excluding subjects with a history of myocardial infarction).

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b. What is the research question in the study of Brouwer et al.? (3 pt). → doelstelling niet ethisch

ob c. In this study, a prospective cohort study design was used. Why is it hardly feasible to address the same research question in a clinical trial? Explain your answer. (4 pts)

1 c d. What is the meaning of the results mentioned near the bottom of the last column of table III: 1.24 (0.89 – 1.71)? (4 pts) 1,24 mean RR- 0,89 t/m 1,71 95% CI

2 d e. Explain why age is a possible confounder in the research of Brouwer et al. (3 pts) kan ook art. uitkomstmaten

0 e h. What has been done in the research of Brouwer et al. to control for confounders? (2 pts) in RR age als gewogen gem (iedere leeftijdsgroep)

The fish consumption may have been measured incorrectly, assume that subjects with atrial fibrillation have reported higher fish intake than in reality.

2 f i. Which kind of bias may be the result of this incorrect measurement of fish intake? (2 pt)

information bias

The next two tables list the antibodies available to the student.

TLR4 antibodies					
Name	P1	P2	P3	P4	P5
Reactivity	Mouse	Human	Human	Human, Mouse, Rat	Human
Immunogen	extracellular domain of mouse TLR4	synthetic peptide corresponding to residues surrounding serine 681 of human TLR4	aa24-631 of human TLR4	aa100-200 of human TLR4	Ba/F3 cell line expressing human TLR4 cell surface antigen
Host species	Rat	Rabbit	Goat	Mouse	Mouse
Isotype	IgG	IgG	IgG	IgG	IgG
Clonality	Polyclonal	Polyclonal	Polyclonal	Monoclonal	Monoclonal
Conjugation	none	none	none	none	none
Applications	IHC, Western blot, ELISA	Western blot	IHC Paraffin, Western blot, Flow cytometry	IHC Frozen/Paraffin, Western blot, Flow cytometry, ChIP	IHC, Flow cytometry

c. Which antibody pair should you use to detect the anti-histone antibody levels in the blood of the patient? (3 pt) zie linker pagina

d. Which negative control should you include for your assay? (3 pt) antigen, geen antistof

FCM

In figure 5.1 the combination of CD45 plotted against the side scatter (SS) is an important combination in an immunophenotype of cell populations.

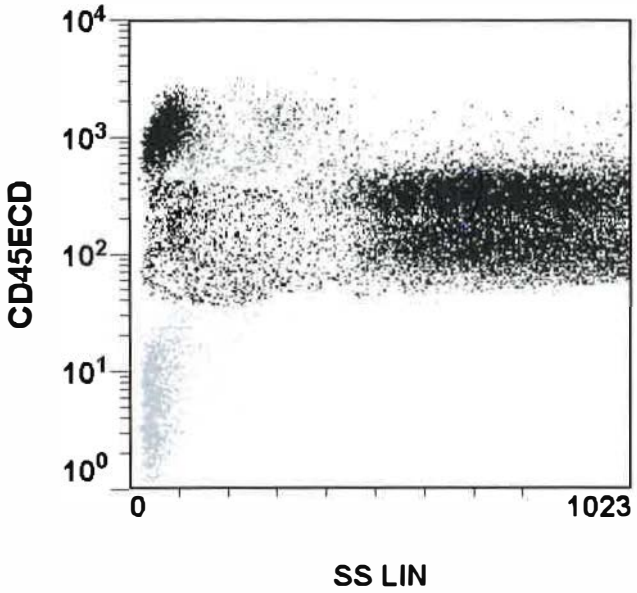

Figure 5.1 CD45ECD against SS.

e. Which information is provided by the combination of "CD45" and "SS" in the flow cytometrical determination in bone marrow? Explain your answer. (4 pts) massa en granulariteit ↑ SS ↑ FS/CD45.

f. Name two advantages of this combination (4 pts) Meer info makkelijker uit eenmaar kaler. Je kunt zien of er een correlatie is.