

Re-exam TOKS3001
Medical (human) toxicology

Thursday December 9th 2010, 9.00 am - 1.00 pm

ECTS credits: 7.5

Number of pages (included front-page and semilogarithmic paper): 4

Examination support: Calculator and English/Norwegian or
Norwegian/English dictionary.

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Exam results: January 10th 2011
Examination results are announced on <http://studweb.ntnu.no/>

Problem 1

- a) What do we understand by the expression “volume of distribution” in the toxicokinetics
- b) What do we understand by the expression “first order kinetics” in the toxicokinetics
- c) What do we understand by the expression ”steady state” in the toxicokinetics.
- d) A shipment of fruit is contaminated with two different pesticides; A and B. Pesticide A in a concentration of 10 mg/kg and B in 20 mg/kg. When Sigrid has eaten some of the fruit, she is feeling unwell and goes to a close by hospital where they find evidence for a slight pesticide poisoning. Parallel to treatment, one of the doctors collects frequent blood samples from Sigrid for the next eight hours in order to identify the existence and elimination profile of possible pesticides. He identifies the two pesticides A and B and plasma concentrations were measured as shown in the table below. In literature the oral absorption rate of both pesticides are very high.

Time after intake (hours)	Plasma concentrations (ng/ml)	
	A	B
1	17	2.8
2	13	2.7
3	10	2.6
4	8	2.4
6	4.6	2.2
8	2.8	2.0

Give possible explanations to why A reaches a higher plasma concentration than B

- e) Make semi logarithmic plots of the plasma concentration versus time curves of the two pesticides.
- f) Estimate or calculate the biological elimination half-life ($T_{1/2}$) and the total elimination rate constant (k_e) for both pesticides as accurate as possible. Assume that both pesticides follow a one compartment model and possess first order kinetics.
- g) Calculate (by formulas) how long time that will elapse (from the 8 hours point) before the two pesticides will achieve the same plasma concentration.
- h) Anticipate that the volume of distribution, V , is equal for A and B and that A has a bioavailability, F , of 100 % and B of 9.4 %. If Sigrid continued eating the fruit, which pesticide would then have the highest mean plasma concentration after 4 weeks and what would the mean plasma concentration ratio be between A and B.
- i) How did you reason for your answer to question h)?

Problem 2

- a) A risk assessment procedure consists usually of five different points or areas. Name these.
- b) What does the expression NOAEL stand for?
- c) Show how you can determine NOAEL for a chemical.
- d) Explain in detail the assumed mechanism of urinary bladder cancer for β -naphthylamine in man.
- e) Why do we not find urinary bladder cancer in rats after exposure to β -naphthylamine?
- f) The dose of an exposure is crucial for the development of toxicity both in animals and humans. Anticipate that an adult man is exposed over a lifetime to a specific toxic environmental chemical both by inhalation and by oral ingestion. Calculate the total daily exposure (TDE) of the chemical assuming a continuous daily (24 hrs) inhalation of an air concentration of $1.5 \mu\text{g}/\text{m}^3$ and a daily (24 hrs) intake of 2 L of water containing the chemical in question in a concentration of $5 \mu\text{g}/\text{L}$.
- g) Toxicity trials had been performed earlier for establishment of NOAEL values for the chemical in rats. An NOAEL value was established for neurological effects at an exposure of $20 \mu\text{g}/\text{kg} \times \text{dag}$, fatty liver at $200 \mu\text{g}/\text{kg} \times \text{dag}$ and kidney damage at $1000 \mu\text{g}/\text{kg} \times \text{dag}$. Calculate the acceptable daily exposure (ADE) for humans and comment on the safety factors used in the extrapolation.
- h) What do we mean by the expression ADE?
- i) Is the exposure of the adult man to the environmental chemical acceptable or unacceptable? Explain.

Problem 3

- a) Many forms of cancer increase in numbers in Norway while some decrease. What are the major reasons for reduced incidence of stomach cancer in both sexes and what are the reasons for the increased incidence of lung cancer among women compared with men?
- b) What is a chemical carcinogen?
- c) What are the hallmarks of cancer cells?
- d) Explain shortly how a carcinogenic chemical acts from it enters the body and until a genetic damage is induced.
- e) Give an example of metabolic activation of a pro carcinogenic chemical substance and describe its effect on DNA.
- f) Explain how Ras takes part in development of cancer in humans.
- g) Explain which quality of a carcinogenic chemical is the most important with reference to how a risk evaluation of that substance should be performed?

