TOXICOLOGY FOR PREVENTION

MAIN TASKS IN PRIMARY PREVENTION

https://is.muni.cz/el/1411/podzim2012/VLPL9X1a/seminar-30-31.qwarp

TOPICS in RESEARCH

- DISCOVERY of HAZARDS
- MEASUREMENT of EXPOSURE
- IDENTIFICATION THE RISK
- WAYS of CONTROL
- ACTION

HAZARD

- CHARACTERISTIC PROPERTIES OF CHEMICAL(s)
- AND THEIR MIXTURES
- (*BOTH NATURAL AND INDUSTRIAL)*
- TO CAUSE DAMAGES OF HEALTH
- ACCUTE, CHRONICAL, LATE

DISCOVERY OF HAZARDS

- MATHEMATIC MODELS
- IN VITRO EXPERIMENTS
- ANIMAL EXPERIMENTS
- CLINICAL STUDIES
- EPIDEMIOLOGICAL STUDIES
- ETHIC RULES

PROBLEMS

- CHOICE THE „RIGHT“ ANIMALS FOR EXPERIMENS (thalidomid – Contergan, DDT, sacharin, …)
- MOTIVATION of VOLUNTEERS for PARTICIPATION IN CLINICAL and EPIDEMIOLOGIC STUDIES (smokers, catastrophes)

PROBLEMS continue

- EXTRAPOLATION OF RESULTS OBTAINED IN EXPERIMENTS (high levels of exposure doses)
- TO HUMAN EXPOSED TO LOW DOSES
- IS THE LINEAR MODEL REALY RIGHT?
- Does the „SAFE TRESHOLD“ exist?

PROBLEMS continue

- TO ESTABLISH THE DOSE-EFFECT RELATIONSHIPS IS CRUCIAL
- MANY CHEMICALS HAVE DIFFERENT (even oposite) EFFECTS IN LOW AND HIGH LEVELS (narcotics´excitation phase)
- HORMESE (U or J curve): vitamins, minerals, alcohol, radioactivity, …

SAFE LIMITS

- ARE DEPENDED DIRECTLY ON THE DOSE-RESPONSE CURVE
- THE VERY LOW LIMITS:

- MAY BE HARMFUL (in the case of „hormese“), and
- ARE VERY EXPENSIVE

EXPOSURE

- THE DOSE WHICH REACHES
- **THE TARGET ORGAN**
- IS CRUCIAL FOR THE EFFECT OF CHEMICAL

EVALUATION

- OF EXTERNAL EXPOSURE =
- **INTAKE**
- IS THE MOST EXACT STEP:
- ANALYSIS OF AIR, FOOD, WATER, DRUGS, COSMETICS and
- CALCULATION OF USUAL DAILY INTAKE

NEXT STEPS of EXPOSURE: UPTAKE

- **UPTAKE = RATE of RESORPTION** in DIFFERENT WAYS of INTAKE
- Heavy metals: 1-10 % in GIT but
  50-70% in lungs
- LACK OF KNOWLEDGES ABOUT RATES

METABOLISM

- MANY CHEMICALS ARE ACTIVATED BY THE 1st PHASE OF METABOLISM (oxidation – free radicals)
- INDIVIDUAL DIFFERENCES due to
- GENETIC POLYMORPHISMS
- in production of MICROSOMAL ENZYMES

METABOLISM

- NO – HYDROSOLUBLE CHEMICALS
- CONJUGATION – POLAR CHEM.
- TWO-STEPS METABOLISM:

- 1st: REDUCTION, HYDROLYSIS, OXIDATION
- 2nd: CONJUGATION (sulfids, glucuronides,…)

ENZYMES

- 1 st phase: CYTOCHROM P 450
  (CYP … - CYP1A1) =>
  ACTIVATION due to FREE RADICALS

- 2nd phase: TRANSFERASES
  DE-ACTIVATION, QUICK EXCRETION

GENETIC POLYMORPHISM

- THE INDIVIDUAL ABILITY OF RELEASE OF EACH ENZYME IS HEREDITARY DETERMINATED
- CAN BE SLIGHTLY MODIFICATED BY SOME CHEMICALS

„HAPPY and UNHAPPY“

- People with LOW CYP…(s) AND HIGH TRANSFERASES = ☻
- People with HIGH CYP(s) and LOW TRANSFERASES = produce many free radicals which cannot be conjucated and excreted
- MAJORITY of people have MIXED VULNERABILITY

THE PREVENTIVE TASK

- TO IDENTIFICATE THE MORE VULNERABLE PERSONS, and
- TO PROTECT THEM FROM THE EXPOSURE
- ARE IN SOME ETHICAL CONFLICTS

FINAL EXPOSURE:

- ONLY PART OF ENVIRONMENTAL CHEMICALS ARE INTAKEN
- ONLY PART OF THEM ARE UPTAKEN
- ONLY PART ARE ACTIVATED
- ONLY PART REACHES THE TARGET ORGAN

RISK

- DEFINITION THE HEALTH DAMAGES CAUSED BY EXPOSURE:
- THE EXACT EVALUATION OF BIOLOGICAL EXPOSURE IS EXTREMELY DIFFICULT
- INTER- and INTRA- INDIVIDUAL DIFFERENCES

BIOLOGIC TESTS of EXPOSURE

- SPECIFIC: MATERNAL CHEMICAL or its SPECIFIC METABOLITES
- NON-SPECIFIC:
- CONJUGATES
- REACTION OF THE BODY

BIOLOGIC MATERIALS:

- URINE, FAECES, EXPIRATED AIR
- BLOOD, SALIVA, HAIR, 1st DENTICE
- FOLLICULAR FLUID, EJACULATE, BREAST MILK
- BONES, FAT, TISSUES

EVALUATION of CHEMICALS

- ACCORDING TO LD 50:
- INERT
- HARMFUL
- POISONS
- EXTREMELY HARMFUL POISONS

CARCINOGENS / TERRATOGENS

- 1A - EVIDENT HUMAN C / T
- 1B - HIGHLY PROBABLE HUMAN C/T
- 2 - PROBABLE C/T
- 3 - POSSIBLE C/T
- 4 - NON-PROBABLE C/T

CARCINOGENS / TERRATOGENT

- 73 CARCINOGENS CLASS 1A+B
- 67 of them IN CIGARETTE SMOKE
- 1A TERRATOGENS: alcohol, smoking, nicotine, organic mercury, thalidomid
- 1B : cadmium, lead, heroin, coccain

THE „ZERO“ EXPOSURE

- IS NOT REALISTIC
- EVEN AT THE BEGINNING OF THE EVOLUTION, HISTORIC „PEOPLE“ VERE EXPOSED TO THOUSANDS CHEMICALS (through air, food, water)

NATURAL PESTICIDES

- ARE IN ALL FRUITS, VEGETABLES and OTHER PLANT SOURCES OF NUTRITION
- PLANTS CAN CHANGE THEIR CONCENTRATIONS, and even
- THEIR SORTS

CHEMICAL STRUCTURE

- OF „NATURAL PESTICIDES“ IS SIMILAR / THE SAME,
- AS FOR „INDUSTRIAL PESTICIDES“
- IN EXPERIMENTS, 50 % of both NATURAL AND INDUSTRIAL CHEMICALS ARE RHODENT CARCINOGENS

DAILY INTAKE:

- INDUSTRIAL PESTICIDES…..0.09 mg
- NATURAL PESTICIDES…1500 mg
- NO KNOWLEDGE ABOUT THE HEALTH EFFECTS OF NAT.PESTIC.
- PROTECTIVE EFFECT OF FRUIT and VEGETABLES INTAKE IS ACCEPTED

HUMAN PROTECTION:

- EXPOSURE DURING THE EVOLUTION =>
- DEVELOPMENT OF NON-SPECIFIC PROTECTION:

-MUCOCILLIAL TRANSPORT OF DUST

-RATE OF UPTAKE

-CONTINUAL EXCHANGES THE SURFACE LAYERS OF SKIN / MUCOUS MEMBRANES

PROTECTION - continue

-METABOLIC TRANSFORMATION

-QUICK EXCRETION OF HYDROSOLUBLE COMPOUNDS

-DNA REPAIR

-BARRIERS (hematoencephalic, placental)

CHILD x ADULT DIFFERENCES

- HIGHER LEVEL OF INTAKE: water, food, inspirated air per kg/weight
- HIGHER RATE OF UPTAKE in GIT
- LOWER ACTIVITY OF ENZYMES
- HIGHER VULNERABILITY TO EFFECTS
- LONGER CUMULATIVE TIME

IN DEVELOPED COUNTRIES

- THE MOST IMPORTANT SOURCE OF CHILDREN´ EXPOSURE TO HARMFUL CHEMICALS IS
- ENVIRONMENTAL TOBACCO SMOKE (SECONDHAND and THIRDHAND SMOKING at homes /cars)

WAYS FOR CONTROL

- LEVEL of ACCEPTABLE DAILY INTAKE (ADI) = WHO
- MAXIMAL LIMITS FOR WATER, FOOD, AIR (occupational, ambient) =
- NATIONAL LAWS and NORMS
- WORLD-WIDE COOPERATION

ACTION

- SETTING THE PRIORITIES = WHICH RISK IS THE MOST IMPORTANT?
- DISCUSION ABOUT RISKS – journalists, VIP persons
- TO CONVICE POLITICIANS to preferent interest about public health against their individual profit

CONCLUSIONS:

- MORE THAN 10.000.000 CHEMICALS WERE IDENTIFICATED
- WE ARE IN DIALY/ OFTEN CONTACT WITH 500.000 CHEMICALS
- WE HAVE QUITE GOOD MEDICAL INFORMATIONS ABOUT 1.000 CHEMICALS

CONCLUSIONS:

- WE HAVE MANY OPEN PROBLEMS IN TOXICOLOGY
- WE ALLOW TO CONFUSE PEOPLE WITH UNCORRECT INFORMATIONS
- WE UNDERESTIMATE THE MAIN TOXICOLOGIC RISK FOR HEALTH = **SMOKING**

PREVENTIVE TOXICOLOGY in the FUTURE

- BASIC RESEARCH IN EVALUATION OF EXPOSURE AND EFFECTS
- METHODS FOR SEEKING THE VULNERABLE PEOPLE esp. CHILDREN
- WAYS OF PROTECTION OF VULNERABLE PEOPLE/CHILDREN