



# **TOXICOLOGY FOR PREVENTION**

**MAIN TASKS IN PRIMARY  
PREVENTION**

# 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 EXPERIMENTS (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 REALLY 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 conjugated 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 / TERRATOGEN

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



# THE „ZERO“ EXPOSURE

- IS NOT REALISTIC
- EVEN AT THE BEGINNING OF THE EVOLUTION, HISTORIC „PEOPLE“ WERE 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, inspired 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?
- DISCUSSION ABOUT RISKS – journalists, VIP persons
- TO CONVINCING 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