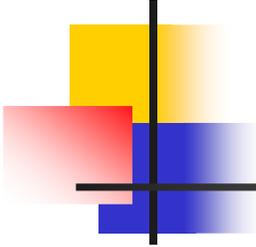


# TOXICOLOGY

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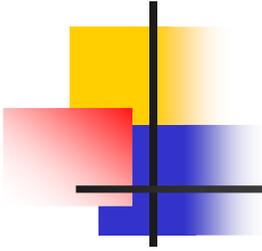
FOR ENGLISH SPEAKING  
STUDENTS



# DEFINITION

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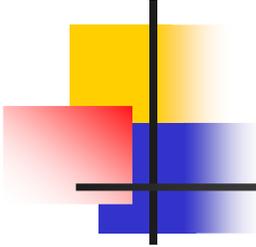
- THE STUDY ABOUT THE NATURE AND MECHANISMS OF CHEMICALS' EFFECTS ON LIVING ORGANISMUS AND OTHER BIOLOGIC SYSTEMS
- QUANTITATIVE ASSESSMENT OF THE SEVERITY AND FREQUENCY OF SUCH EFFECTS



# GOALS FOR PREVENTION

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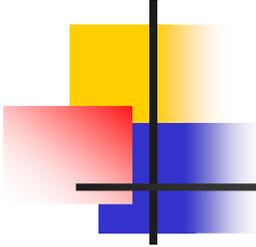
- PROTECTION THE PUBLIC HEALTH
- PROTECTION THE WORKERS
- HEALTH PROMOTION
- DEVELOPMENT OF SAFER CHEMICALS  
USED AS DRUGS, FOOD ADDITIVES,  
PESTICIDES, INDUSTRIAL CHEMICALS



# SORTS OF TOXICOLOGY

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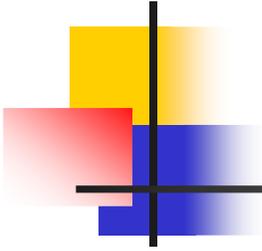
- ANALYTICAL
- CLINICAL
- FORENSIC
- OCCUPATIONAL
- ENVIRONMENTAL
- REGULATORY
- CONVENTIONAL, ...



# SCOPES OF TOXICOLOGY

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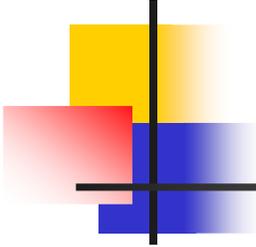
- **MEDICINE:** diagnosis, prevention, treatment
- **FOOD INDUSTRY:** additives
- **AGRICULTURE:** pesticides, growth regulators, animal food additives, veterinary drugs
- **INDUSTRY**



# EPIDEMIES OF POISONING

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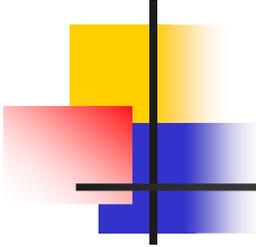
- POMPEII – VESUVE,  $\text{SO}_2$
- SMOG REDUCTIVE (dust, CO, PAH):  
Donora, London
- SMOG OXIDATIVE ( $\text{O}_3$ ,  $\text{No}_x$ ,  $\text{CO}_2$   
hydrocarbons): Los Angeles



# EPIDEMIES - continue

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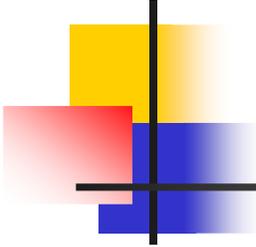
- MINAMATA, NIIGATA, IRAQ, USA - METHYLMERCURY
- ITAI-ITAI - CADMIUM
- YUSHO, YUCHENG - PCBs
- MICHIGAN – PBBs
- SEVESO – PCDD (TCDD)
- BHOPALE - METHYLISOCYANATE



# ROUTES OF INTAKE

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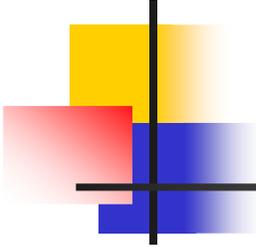
- GASTROINTESTINAL TRACT
- RESPIRATORY TRACT
- SKIN
- VAGINA, RECTUM, EAR, EYES
- PARENTERAL APPLICATION



# BARRIERS

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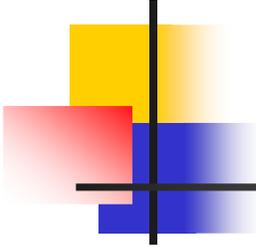
- MUCOCILLIAL CLEARANCE
- SKIN FILM (ACID AND FATTY)
- PLACENTAL
- CEREBRO-VASCULAR
- RATE OF ABSORPTION



# TYPES OF UPTAKE

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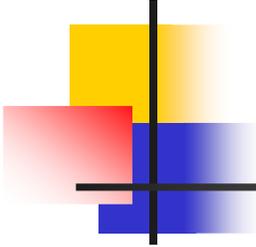
- PASSIVE DIFFUSION
- FILTRATION
- CARRIER-MEDIATED TRANSPORT
- ENGULFING BY THE CELLS



# BIOTRANSFORMATION

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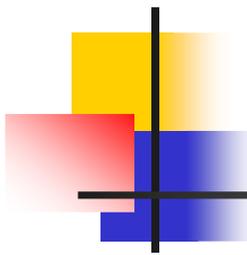
- The main influencing factor:
- WATER / LIPO – SOLUBILITY
  
- WATER – SOLUBLE => EXCRETION WITHOUT METABOLISATION
- POLARIC = > AFTER CONJUGATION
- LIPO-SOLUBLE => 2 STEPS METABOLISM



# Ist STEP /PHASE

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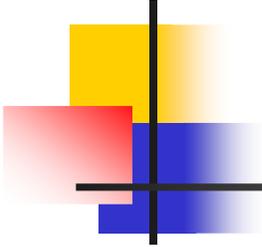
- OXIDATION, REDUCTION, HYDROLYSIS
- CATALYTIC MICROSOMAL ENZYMES
- METABOLITES DEVELOPED BY OXIDATION ARE BOTH LESS AND MORE ACTIVE THAN THE MATERNAL COMPOUND
- DUE TO OXYGEN / FREE RADICALS



# OXIDATIVE BIOTRANSFORMATION

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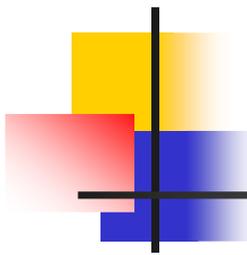
- MICROSOMAL ENZYMES – COMPLEX of
- CYTOCHROM P450
- GENETIC DIFFERENCES IN GENOTYPE  
– GENETIC POLYMORPHISM



# CYTOCHROM P450

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- ENVIRONMENTAL INFLUENCE ON FENOTYPE:
- SOME DRUGS, DDT, PCBs, PCDDs, chemicals in VEGETABLES
- CAN INDUCE THE RELEASE OF OXIDATIVE ENZYMES P450



# CYTOCHROM P 450 – exampl.

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- CYP 1A1: lungs, placenta

PAH

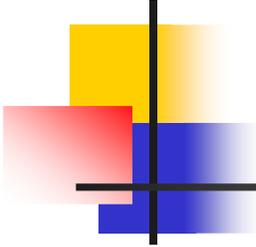
- CYP 1A2: liver

AFLATOXINS, NITROSAMINES

- CYP 2A6: lungs, liver, ...

NITROSAMINES, NICOTINE

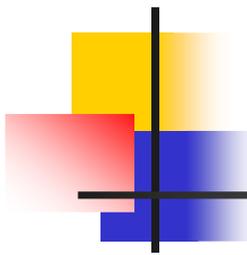
CYP 1B1, 2C9, 2C19, 2D6, 2E1, 3A...



## 2nd STEP / PHASE

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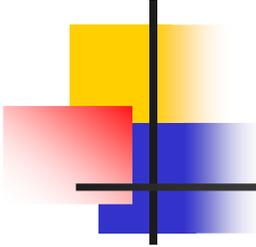
- CONJUGATION:
- **GLUCURONIDES** FORMATION: the most important and common way,
- Catalyzing enzymes:
- UDP- GLUCURONYL TRANSFERASEs:
- Aliphatic and aromatic alcohols, amines, sulfhydryl compounds, ...



## 2 nd STEP /PHASE

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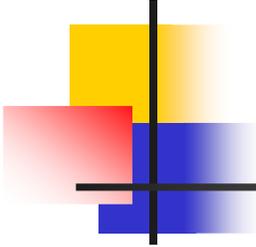
- **GLUTATHIONE** FORMATION
- Enzymes GLUTATHION-S-  
TRANSPHERASEs:
- Polycyclic aromatic hydrocarbons
- **ACETYLATION:** enzymes N-ACETYL  
TRANSPHERASEs: SLOW/FAST  
ACETYLATORS



## 2nd STEP /PHASE

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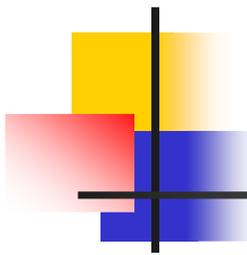
- SULPHATES FORMATION – enzymes  
SULPHOTRANSFERASES
- METHYLATION
  
- GENETIC POLYMORPHISM:
- „HAPPY“ / „UNHAPPY“ PEOPLE



# EXCRETION OF CHEMICALS

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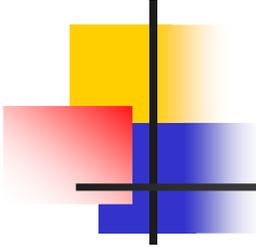
- URINARY
- BILIARY
- EXPIRATED AIR
- SALIVA
- EVAPORATION
- SKIN ADNEXES (HAIR, NAILS)
- MOTHER'S MILK



# TESTs OF EXPOSURE

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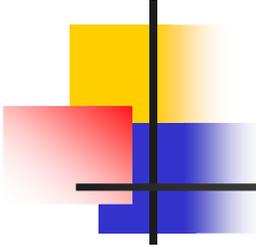
- LEVELS OF THE SUBSTANCE or IT'S SPECIFIC METABOLITE: CO in the expired air, cotinine, BaP DNA adducts
- LEVELS OF NON-SPECIFIC METABOLITES: urinary glucuronides, thioethers



# TESTs OF EXPOSURE

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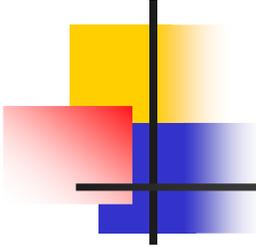
- ASSESSMENT OF THE ORGANISM'S RESPONSE: anemia in the Pb chronic exposure, Chromosomal aberations in the exposure to mutagens
- ASSESSMENT OF THE INDIVIDUAL VULNERABILITY: genetic polymorphism in induction of microsomal enzymes, sexual /ethnic /age differences



# SPECTRUM OF EFFECTS

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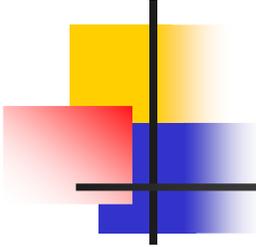
- LOCAL x SYSTEMIC
- REVERSIBLE x IRREVERSIBLE
- IMMEDIATE x DELAYED
- MORPHOLOGIC x FUNCTIONAL x BIOCHEMICAL
- ALLERGIC x IDIOSYNCRATIC



# SPECTRUM OF EFFECTS

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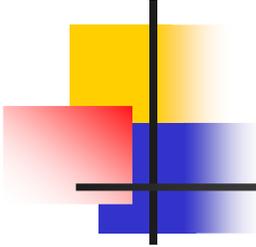
- IRRITATION, INFLAMMATION
- TOXICITY (according to the target organ): hemato-, hepato-, neuro-, nephro-, cardio-, ...
- EMBRYOTOXICITY
- TERRATOGENICITY
- MUTAGENICITY
- CARCINOGENICITY



# DIFFICULTIES IN RESEARCH

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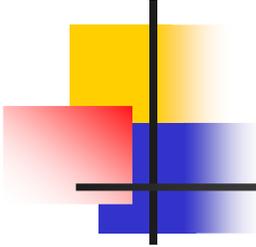
- EXTRAPOLATION from the ANIMAL EXPERIMENTS to the HUMAN REALITY
- DOSE – RESPONSE RELATIONSHIP
- THE (upper) LIMITS FOR THE PHYSIOLOGIC RESPONSE
- INTERACTION OF CHEMICALS IN MIXTURES



# ANTI-CHEMICAL DEFENSE

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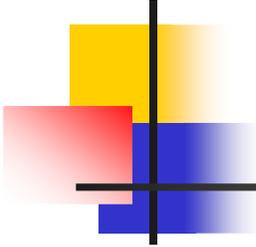
- CONTINUAL EXCHANGE/REPLACEMENT OF DAMAGED CELLS
- INDUCTION OF DETOXIFYING BIOTRANSFORMATION
- ACTIVE EXCRETION OF HYDRO-SOLUBLE SUBSTANCES
- DNA REPAIR



# IS THE NATURE SAFE?

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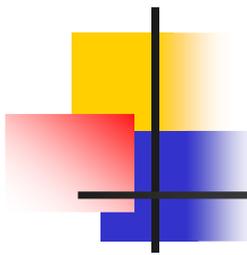
- DEFENSE HAS DEVELOPED IN THE EVOLUTION DUE TO EXPOSURE TO NATURAL CHEMICAL COMPOUNDS
  - ALL SURVIVE PLANTS HAVE DEVELOPED THEIR PROTECTION AGAINST THEIR NATURAL ENEMIES = **NATURAL PESTICIDES**



# NATURAL PESTICIDES

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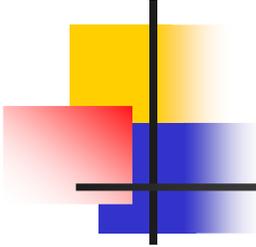
- ARE CHEMICALLY SIMILAR TO THOSE PRODUCED BY INDUSTRY
- SOME OF THEM ARE STRONG TOXINS AND CARCINOGENS (botulotoxine, aflatoxine)
- PLANTS CAN CHANGE both the CONCENTRATIONS and the SORT



# TOO MANY RHODENT CARCINOGENS

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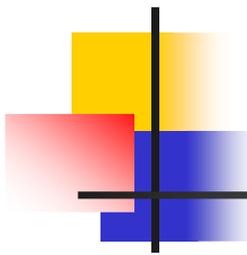
- There were tested more than
- 1000 INDUSTRIAL CHEMICALS and
- 50 NATURAL CHEMICALS
- In both groups, about
- 50% are RHODENT CARCINOGENS



# EXPERIMENTAL TESTS

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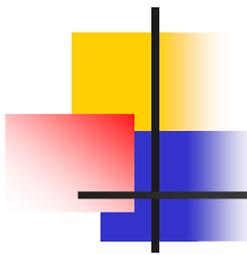
- The MAXIMAL TOLERATED DOSES, and their fractions ( $1/2$   $1/4$ ) ARE USED
- WHICH MATHEMATIC MODEL OF EXTRAPOLATION FOR HUMAN EXPOSURE IS THE BEST?
- LINEAR? EXPONENTIAL?
- DOES THE SAFE TRESHOLD EXISTS?



# EPIDEMIOLOGIC/CLINIC STUDIES

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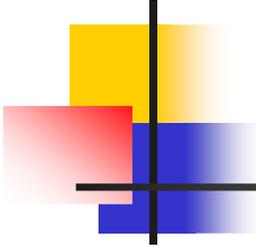
- ARE ONLY ACCEPTABLE FOR HUMAN RISK ASSESSMENT = >
- CHEMICAL ACCIDENTS and DISASTERS ARE ASSESSED IN LONGITUDINAL PROSPECTIVE STUDIES
- Also PROFESSIONAL EXPOSURES are the sources of IMPORTANT DATA



# CARCINOGENS' CLASSIFICATION

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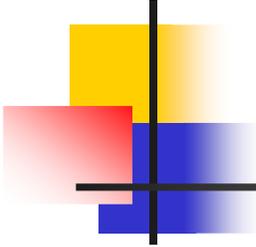
■ CATEGORIES	HUMAN	/	ANIMAL DATA
■ HUMAN C. 1A	suffic.		suffic./limited
■ PROBABLE 2A	limited		sufficient
■ POSSIBLE 2B	inadeq.		Suffic/limited
■ NO-CLASSIF. 3	absent		inadeq/absen
■ NOT CARCIN.4	absent		negative in 2 species



# CARCINOGENIC EFFECTS

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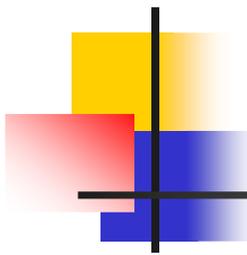
- OF CHEMICAL SUBSTANCES RISE THE MAJOR CONCERN OF RESEARCHES:
- GENOTOXIC THEORY OF CARCINOGENESIS: INITIATION of DNA MUTAGENIC CHANGES – REPLICATION – PROMOTION – MANIFESTATION
- EPIGENETIC (non-mutagenic) THEORY



# WHAT DO WE KNOW?

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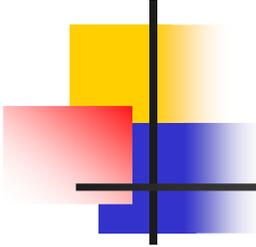
- WE CAN MEASURE THE MUTAGENICITY (Ames 's test) AND RESPONSE (Chromosomal abberations, sister chromatide exchanges, DNA adducts...)
- THERE ARE RELATIONSHIPS BETWEEN SHORT-TERM MARKERS and CANCER INCIDENCE
- CELLS PROLIFERATION IS IMPORTANT



# WHAT WE DON'T KNOW?

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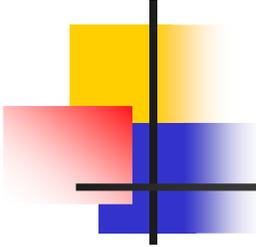
- WHICH MODEL FOR EXTRAPOLATION IS THE MOST PRECIOUS ?
- WHICH IS THE ROLE OF NATURAL CHEMICALS and CONDITIONS ?
- WHICH SIGNALS OF RESPONSE ON EXPOSURE ARE IMPORTANT FOR USE THEM TO ESTABLISH THE ACCEPTABLE LIMITS ?



# POLITICAL POINT OF VIEW:

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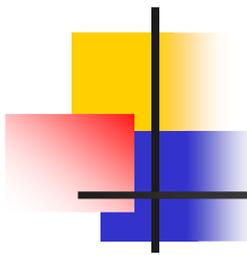
- TO KEEP LIMITS IN MORE DIFFICULT THAN TO ESTABLISH THEM
- HOW MANY VULNERABLE PEOPLE WE WILL PROTECT BY THE LIMITS
- CAN WE ACCEPT SOME SPECIFIC PROTECTION OF VULNERABLE PART OF POPULATION



# ENVIRONMENTAL HYSTERY

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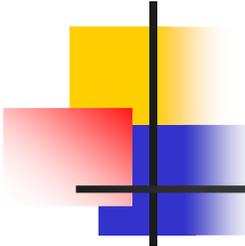
- VERY OFTEN ENHANCES THE PUBLIC INTEREST ABOUT LOW-RISK FACTORS (sacharin, DDT, PBCs, Alar, ...)
- AND
- OBSCURES / UNDERESTIMATES THE REAL RISKS (nutrition, smoking, poor hygiene, ...)



# ALL CANCER MORTALITY:

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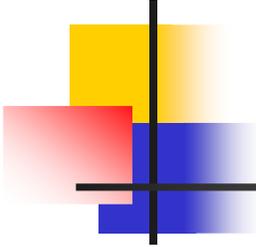
- ATTRIBUTIVE RISK IN LIFE STYLE
- NUTRITION ..... 35%
- SMOKING ..... 30%
- INFECTIOUS AGENTS ..... 10%
- SEXUAL BEHAVIOUR ..... 7%
- ALCOHOL ..... 4%
- TOGETHER ..... **87%**



# ALL CANCER MORTALITY

---

- ATTRIBUTIVE RISK IN ENVIRONMENT
- OCCUPATION ..... 4%
- MEDICAL TREATMENT ..... 3%
- GEOPHYSICAL FACTORS ..... 3%
- POLLUTED AIR, WATER ..... 2%
- FOOD ADDITIVES/CONTAM. . <1%
- TOGETHER ..... **13%**



# CONCLUSSIONS

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- TOXICOLOGY IS DYNAMIC,  
EXCITATING SCIENCE
- TOXICOLOGY CAN DISCOVER MANY  
MYSTERIOUS THINGS IN LIFE
- TOXICOLOGY CAN REDUCE HUMAN  
CHEMOPHOBIA