Centro de Investigación y de Estudios Avanzados del IPN

30th International Congress on Occupational Health

"Occupational Health for all: from research to practice"

"Biological monitoring for occupational and environmental health risk assessment"

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Can Cun, QR., Mexico, March 2

Content

1. **General concepts**
2. **Biological monitoring in occupational settings**
3. **Molecular biology contributions to occupational health**
4. **"Omics" data for risk assessment in occupational settings**
5. **Perspectives of biology techniques in the occupational environment**

Introduction

- Workers represent **half** the world's population
- Workers health is **the task force** that maintain world´s production
- Workers' health might be affected by **environmental contaminants**

GLOBAL PLAN OF ACTION ON WORKERS' HEALTH 2008–2017. WHO

Introduction…

- Therefore, the aim of the biological monitoring is **to provide reliable data** to perform accurate human risk assessments based on the **most sensitive chemical** and biological methods, thus
- **New** chemical and biological methods need to be developed

Introduction….

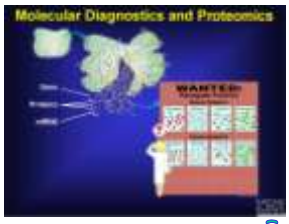
Then, it is required:

- **Innovation** in chemical and biological analytical techniques to monitor both the occupational environment (chemical monitoring) and workers health effects (biological monitoring)
- Up to date methods provide reliable data necessary to devise **effective** and **efficient** solutions to and/or prevent occupational health risks

GLOBAL PLAN OF ACTION ON WORKERS' HEALTH 2008–2017. WHO.

Introduction…

- Molecular biology techniques are **new tool**s potentially useful to evaluate health effects caused by chemical exposure in occupational settings.



General Concepts

- Any industry whose operations handle toxic materials must **identify, assess and monitor** employees exposure and the effect of these hazards
- A **sanitary strategy** to guaranty health conditions in the workplace has to be implemented
- An **effective biological monitoring program** includes: relevant issues of the health and safety legislation, identification of relevant issues appropriate for biological monitoring and, full technical supervision

Monitoring Strategy

1. **Identification** of all hazardous chemicals in the workplace
2. Estimate the potential and actual **exposure** of workers that may come in contact with the hazardous chemical
3. Hazardous chemicals should be **constantly tested** throughout the process
4. Consider all **routes of exposure**

Factors influencing the extent of contamination exposure

1. **Physical and chemical** characteristics of the contaminants
2. **Occupational environmental conditions**
3. **Status of the workers protection equipment**
4. **Routes of exposure**
5. **Workers individuality**

Workers Individuality

- **Hygiene habits**
- **Age**
- **Gender**
- **Fitnes level**
- **Genotype**

Properties of a useful "biomarker"

A good **biomarker** useful for an specific chemical class or an specific mechanism should be:

- The "biomarker should be **inducible** or repress by external agents,
- The response should be **specific** for a chemical family ,
- The response should be **sensitive** enough to the aggression in order to be detected routinarily
- The biomarker should be precise and reproducible among experiments in a laboratory and in different laboratories and study or experimental models,
- The biomarker quantitation should be useful to estimate the risk level

Benninghoff AD, (2007) Tox Sci., 95: 1-4

BIOLOGICAL MONITORING

- **Measurement and assessment** of chemicals or their metabolites (substances the body converts into) in exposed workers
- Measurements are performed in **body samples**
- Biological monitoring measurements **reflect the total uptake** of a chemical by an individual through all routes (inhalation, ingestion, skin absorption or combinations)

http://www.dmp.wa.gov.au/documents/MS_BiologicalMonitor(1).pdf

"OMICS'"

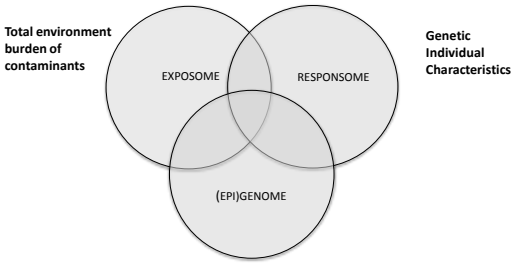
THE SCIENCE OF INTEGRATION

"Omics"

- **"Omics" simultaneusly** detects changes in gene expression, proteins content and activitiy, as well as metabolites' content by applying high performance technologies

Benninghoff AD, (2007) Tox Sci., 95: 1-4

ENVIRONMENT "OMICS" AND HEALTH



Effect of the environment in the workers genome

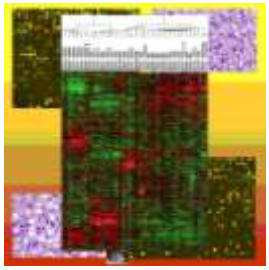
Modified from: Vlaanderen, et al. (2010) Occup. Environ. Med. 67:136-143

Gene Expression

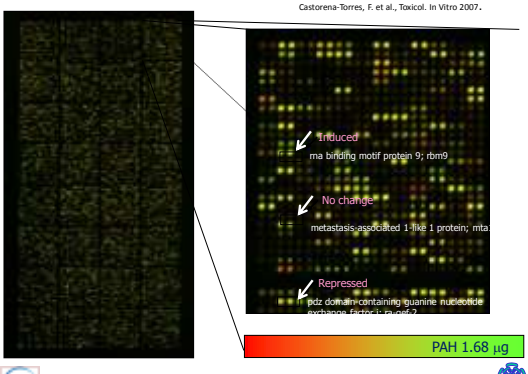
- There are several routine techniques such as:
  - PCR and microarrays, to evaluate gene SNPs or their expression by measuring mRNA, or
  - ELISA, to assess protein levels

Microarrays

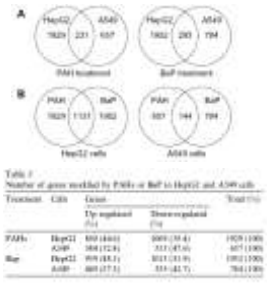
- Recently, the use of microarrays has several **applications** in chemical exposure evaluation



Castorena-Torres, F. et al., Toxicol. In Vitro 2007.



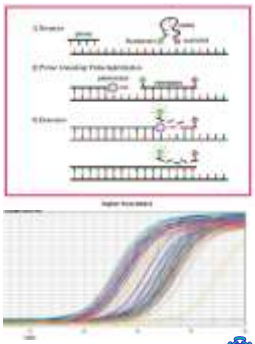
Use of microarrays to analyze exposure to toxicants



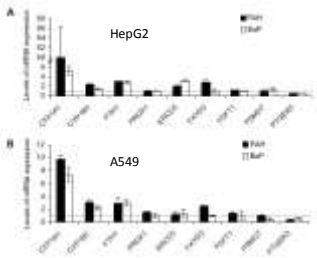
Castorena-Torres, F. et al., Toxicol. In Vitro 2007.

Real time PCR

- **PCR applications** to genetic and molecular toxicology assessment:
  - detection of genetic polymorphisms
  - quantification of chromosomal DNA deletions, and
  - quantification of gene expression

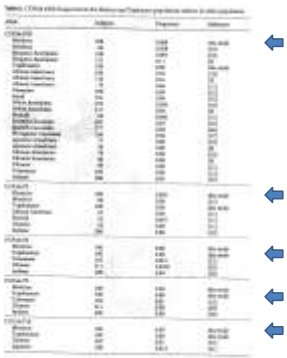


Real time qPCR for gene expression analysis



Real-time PCR analysis of differential expression of genes modulated by PAH (obtained from a coke oven factory) or BaP treatments in HepG2 (A) and A549 (B) cells.

Castorena-Torres, F. et al., Toxicol. In Vitro, 2007.



Genotype frequencies in a *Tepehuanes* population

There is an enormous variation in allele frequencies among human populations

Reyes-Hernandez (2008) 81, 97-103

METABOLOMICS

Metabolomics (Oliver, 1998) "the set of metabolites synthesized by a biological system"

- Takes into account all the **small molecules** present in in an organism, tissue, cell, or body fluid
- **Metabolites** are the smallest molecules and primary actors in the life processes. Therefore, changes in their estructure and/or concentrations might reflect relevant biological changes for the organism health

Johnson CH et al., Ann. Rev. Pharmacol. Toxicol. 2012, 52: 37-56.

Genomic, exposomic and personal variations on individual metabotypes and metabolomes

Johnson CH et al., Ann. Rev. Pharmacol. Toxicol. 2012, 52: 37-56.

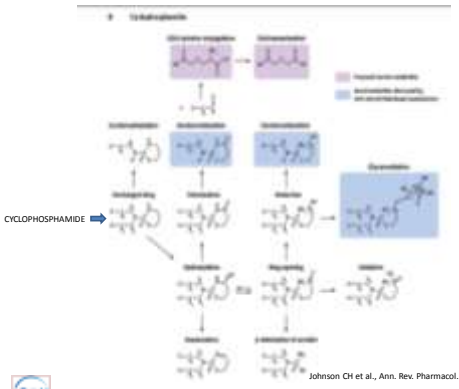
METABOLOMICS (2)

METABOTYPE

- **Includes all genome, environmental and individual microflora modifications that participate in the metabolic transformations that undergo chemicals internilized in an individual**

Metabolomics and Xenobiotics

Through **METABOLOMICS** it is possible to identify **new intermediate compounds,** product of their biotransformation, and establish **novel mechanism** of toxicity



TOXICO-METABOLOMICS

Toxico-metabolomics is useful for:

- Producing data that ,by using mathematical models, are useful to foresee the fate and effects caused by a contaminant.
- Helps to foresee the hazardous outcome and secondary effects produced by a chemical
- The metabolome is difficult to study due to diversity in genomes and environmental factors to which an individual is exposed
- Metabolome studies in human populations should ensure: a) a sufficient statistical power; b) genomic and metabolomic tools had the capacity to detect changes in biological systems

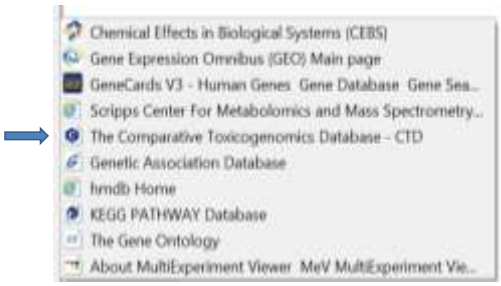
Typical difficulties of meabolome studies in human

- There are considerable variations in phase I and phase II drug metabolims enzymes that affect xenobiotics pharmacokinetics, pharmacodinamics and elimination
- Limited usefulness of animal models in the human situation
- Usefulness of transgenic animal models

Other *Omics* complications

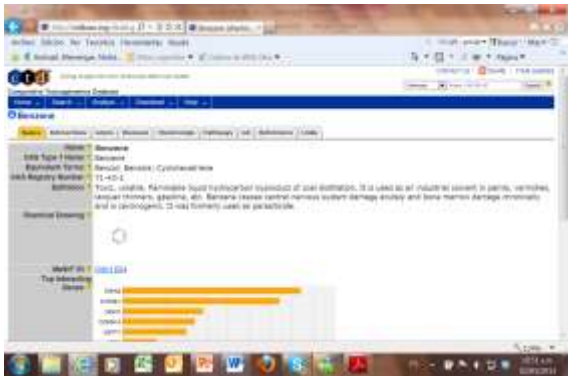
- Profile effects of chemical contaminants differ among species
- Molecules with diverse chemical structure may produce similar responses
- An “omic study” is an punstual image of effects caused by a chemical contaminant
- In fact, effects observed in human populations result for exposure to chemical mixtures, thus their study are extremely complex
- Chemical exposure is just one factor in the work environment

OTHER DATABASE USEFUL IN BIOMARKERS DEVELOPMENT FOR OCCUPATIONAL HEALTH



DATABASE URL USEFUL FOR BIOMARKERS DEVELOPMENT IN OCCUPATIONAL HEALTH

- http://www.niehs.nih.gov/research/resources/databases/cebs/index.cfm
- http://www.ncbi.nlm.nih.gov/geo/
- http://www.genecards.org/
- http://metlin.scripps.edu/
- http://ctdbase.org/
- http://geneticassociationdb.nih.gov/cgi-bin/index.cgi
- http://www.hmdb.ca/
- http://www.genome.jp/kegg/pathway.html
- http://geneontology.org/
- http://www.tm4.org/mev/about

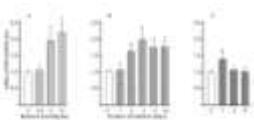


VOC´s in the Environment:

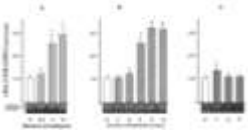
- **Benzene and toluene**

VOC´S effects on CYP2E1 mRNA in rats

Liver



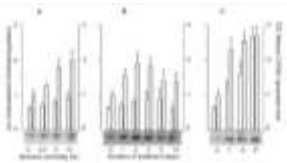
Lymphocytes



Benzene and toluene induce CYP2E1 mRNA but not acetone or pyridine

Gonzalez-Jasso, et al., (2003) Tox. Lett. 155: 55-67

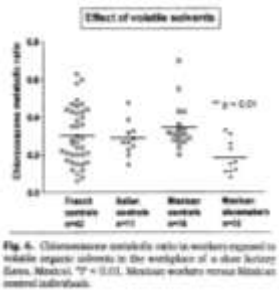
VOC´S effects on CYP2E1 mRNA in rats



Benzene and toluene induce CYP2E1 mRNA, protein and enzyme activity, but acetone or pyridine

Gonzalez-Jasso, et al., (2003) Tox. Lett. 155: 55-67

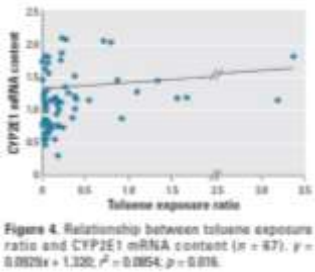
CYP2E1 activity in toluene exposed workers



Chlorzoxazone metabolisms is inhibited in toluene exposed workers

Lucas et al., (1999) Pharmacogenetics 9: 377-388

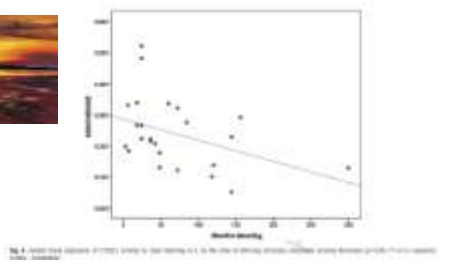
CYP2E1 mRNA in toluene exposed workers



Toluene Exposure Ratio = environmental exposure levels/ hyppuric acid excretion

Mendoza-Cantú (2006) Environ. Health Perspect. 114: 494-499.

Effects of chronic toluene exposure on CYP2E1 activity



Jiménez-Garza, O. et al. (2012) Tox. Lett. doi:10.1016/j.toxlet.2012.01.021

The *Vanishing Zero Paradigm* in Occupational Health

- **Ever increasing sensitivity** of analytical techniques
  - Adequation of **NON-DETECTABLE** definition to FEMTO or ATTOMOLE levels.
- Genomics is able **to assess global cell response** to exposure as a function of dose.
- Transcription allows damage detection at **doses** much lower than those necessary to observe histopathology changes.
- Omics provides **mechanistically based data** to risk assessment and dose response data, providing the non-transcriptional effect level (NOTEL) which is linked to **receptors.**

Zarbl H, et al. (2010) Chem-Biol- Interact. 273-278

Future Issues in Omics Research

Rosalind Franklin
The Lady of DNA

- **Construction** of "omics" data bases
- **Development** of mathematical tools to integate human population data (including inter-individual variation) and environmental characteristics
- **Identify and solve** specific problems applying "omics" criteria

Ethical Issues in Molecular Biology Studies in Occupational Health

Respect to the autonomy of the participant:

- Written informed consent and withdrawal at any time
- Access to personal information (wright to know and right to not know the study result
- Securing proper managing data (data protection to avoid misuse in employment, insurance, loading and learning opportunities)