



NIEHS Activities in Liver Disease Research



National Institute of Environmental Health Sciences





NIEHS



NIEHS Mission

- To reduce the burden of diseases and dysfunctions associated with the environment
- Chemical and Physical Agents
- Chemicals in manufacturing and byproducts, pesticides, heavy metals, air pollutants, biological toxins



DDT: Governmental Response to Public Concerns



- 1964 – Federal Insecticide, Fungicide, Rodenticide Act : Any economic poison or chemical pesticide must be registered before being marketed in interstate commerce
- 1970 – Environmental Protection Agency established to regulate air and water pollution, use of pesticides, and other affairs concerning the environment
- 1969 - NIEHS established within the National Institutes of Health





NIEHS: Mission Background

- 1976 – Toxic Substances Control Act
- Manufacturers must supply EPA information on environmental and health effects of chemical substances and mixtures 90 days prior to manufacture
- NIEHS : Research to support regulatory decisions, Training funds to develop manpower pool to support TOSCA





Priority Environmental Agents

- **Metals**
 - lead, cadmium, mercury, arsenic
- **Hormonally Active Agents (receptor-mediated toxicity)**
 - environmental estrogens, antiestrogens, antiandrogens
 - TCDD, PCBs, pesticides
- **Agricultural Chemicals**
 - pesticides, herbicides
- **Industrial Chemicals**
 - solvents, intermediates, alkylating agents, plasticizers
- **Botanicals/Nutrition – fungal and plant toxins**
- **Air Particulates**
- **Drugs/Lifestyle**





NIEHS Portfolio in Liver Disease

- \$25.5 million (FY2003 estimate)
- Drug and toxicant metabolism and the liver
- Mechanisms of drug- and toxicant induced liver disease
- Liver Cancer
 - Pathophysiology
 - Epidemiology





NIEHS Administrative Elements

- Extramural: Unsolicited and Solicited Grant Programs
- Intramural: Basic Research
- National Toxicology Program:
Intramural Research and Contracts
 - Toxicological Testing Programs
 - Develop Testing Methods
 - Report Toxicity Data



Numbers of Chemicals Associated with Site-Specific Neoplasia



Liver	146
Kidney	57
Lung	53
Mammary Gland	37
Hematopoietic System	36
Forestomach	34



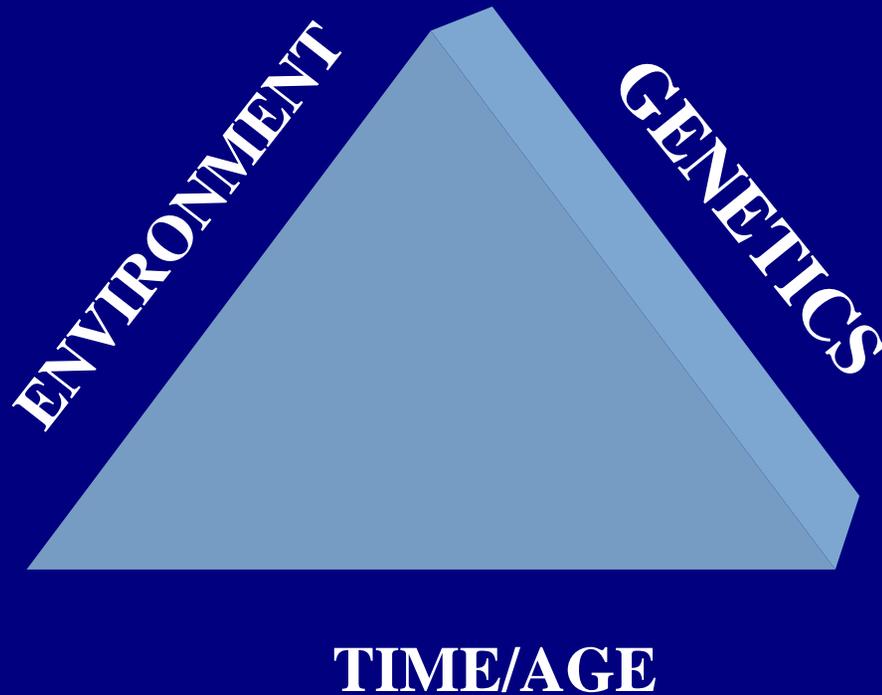


Types of Hepatic Injury

Injury type	Representative toxins
Fatty liver	CCl ₄ , valproic acid
Hepatocyte death	Acetaminophen, Cu, dimethylformamide, Fe, germander, microcystin
Canalicular cholestasis	Chlorpromazine, 1, 1, dichloroethylene, estrogens, Mn, phalloidin
Bile duct damage	ANIT, methylene dianiline, sporidesmin
Cirrhosis	Arsenic, pyrrolizidine alkaloids
Vascular disorders	Arsenic, dacarbazine, pyrrolizidine alkaloids, microcystin
Tumors	Aflatoxins, androgens, thorium dioxide, vinyl chloride



Susceptibility to Disease





Environmental Genome Project

- Mouse Genomics Centers Consortium: mouse models of functional human polymorphisms
- Re-sequencing and functional analysis of polymorphisms in human environmentally responsive genes
- Gene SNP's Database (Human and Mouse)
 - DNA repair
 - Cell cycle control and cell division
 - Cell signaling
 - Homeostasis





National Center for Toxicogenomics

- Application of gene and protein expression technology
- Understand relationship between exposures and human disease susceptibility
- Identify biomarkers of disease and exposure
- Improve computational methods
- Create a public database of environmental effects of toxic substances on biological systems



Toxicogenomics Research Consortium



- Goal: Identify and characterize sources of variation in gene expression experiments and establish standard protocols (“best practices”)
- Five Cooperative Research Grants (\$37 million, 5 years) plus NIEHS based microarray users group
- Both cooperative and independent projects
- Standardization experiments on liver array profiles after acetaminophen exposure





Conference on Translation of Animal Toxicity Findings to Clinical Pharmacology of Toxic Agents and Human Liver Disease



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