



# ***Developing Computational Tools for Applying Toxicogenomics to Risk Assessment and Regulatory Decision Making***

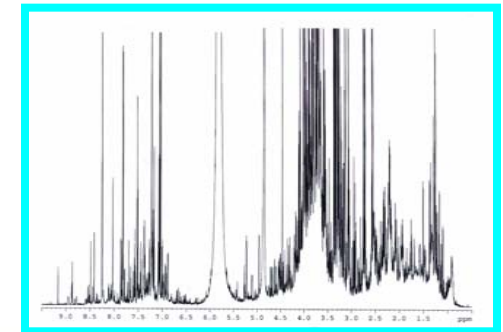
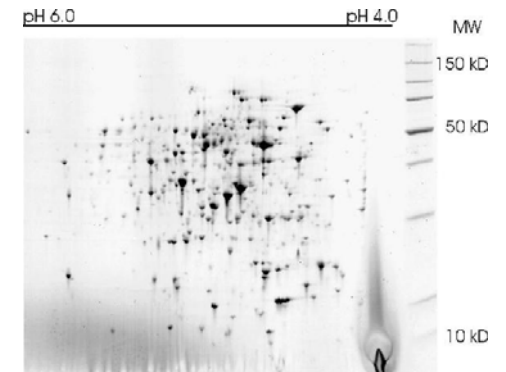
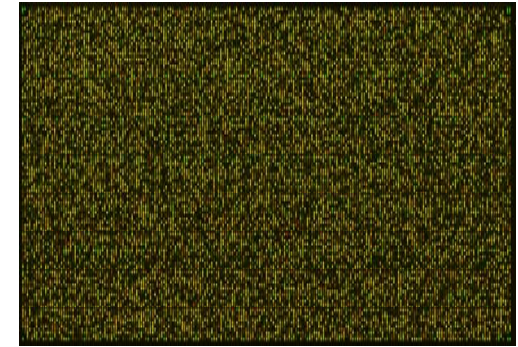
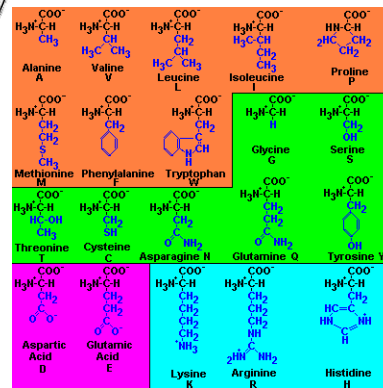
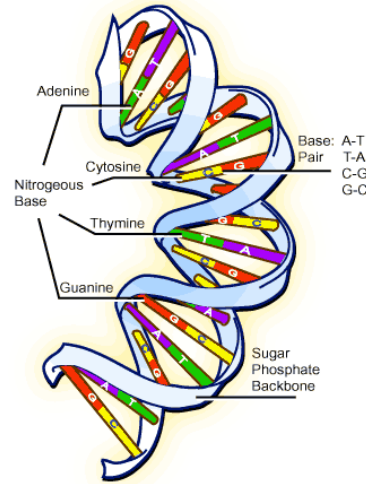
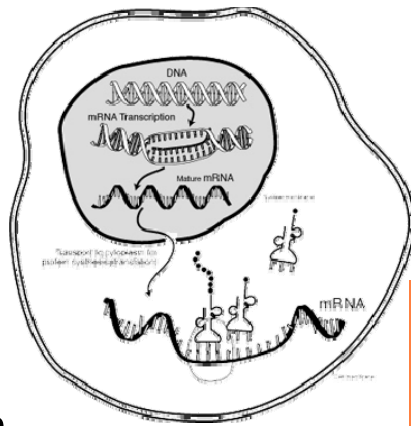
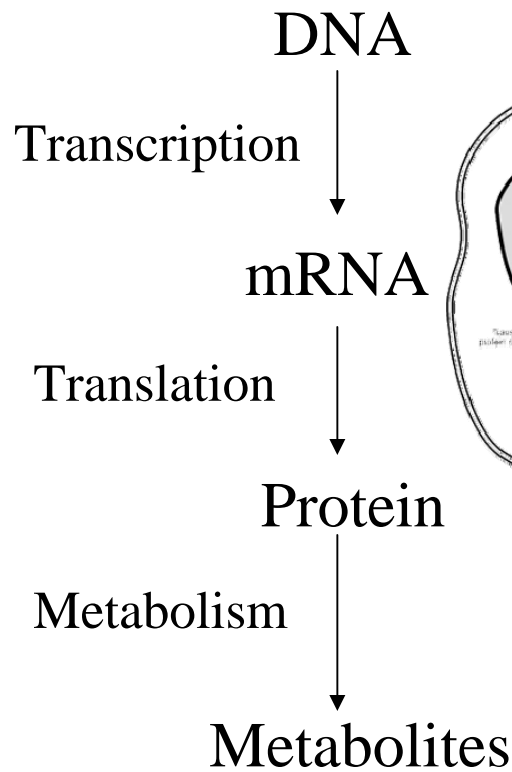
***NCCT BOSC Review  
June 19, 2006***

**David Dix**

*This work does not necessarily reflect official Agency policy.*

# Data from the Toxicogenomics Toolkit

## Molecular Biology

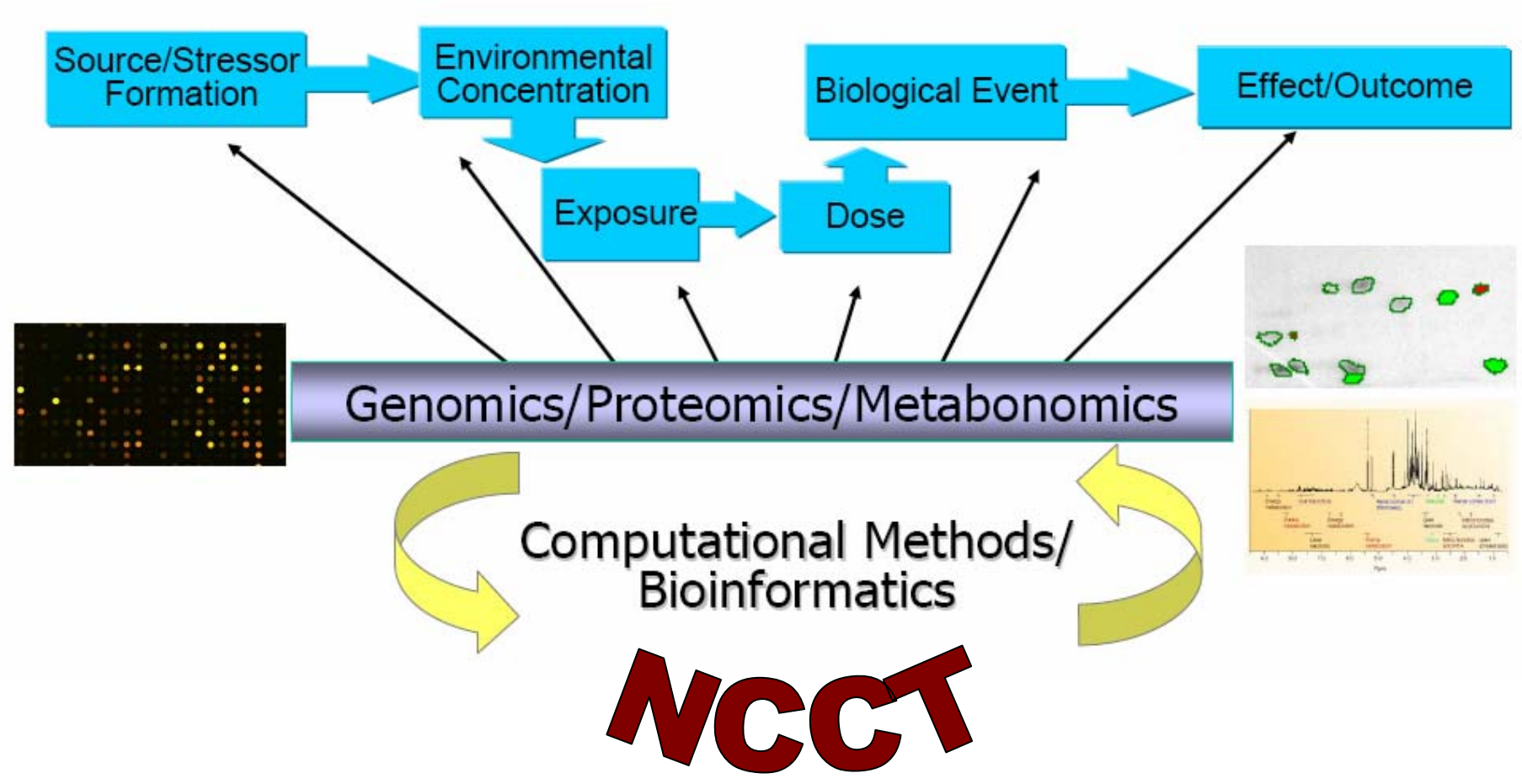


## 'omics Technologies

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# ***Incorporation of Toxicogenomics into Regulatory Toxicology***



## ***Milestones in Genomics Science Policy Underpinning Efforts in Computational Toxicology***

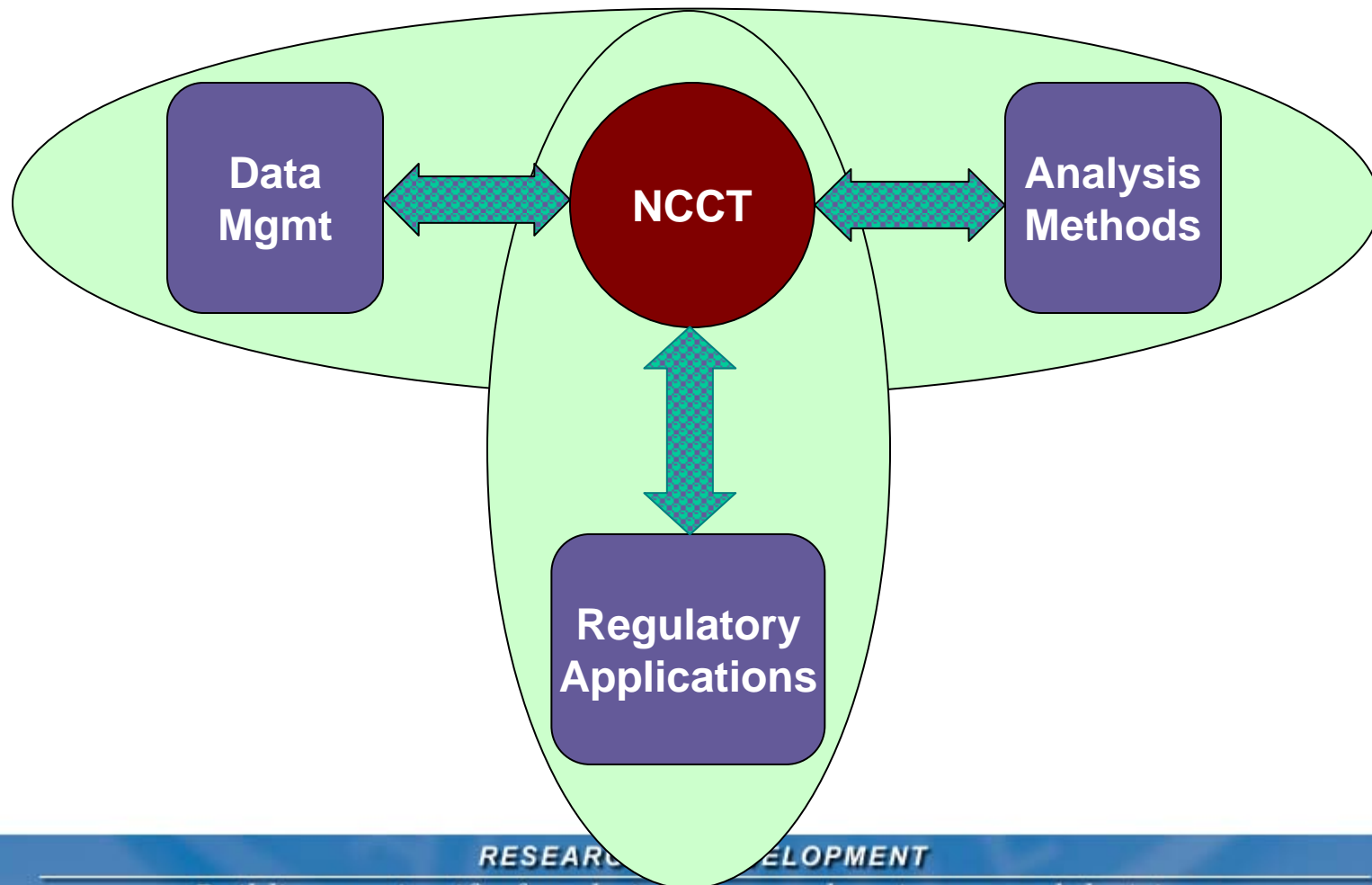
<b>Year</b>	<b>Publication</b>	<b>Purpose</b>	<b>Internet URL</b>
<b>2002</b>	<b>Interim Policy on Genomics</b>	<b>Defined Agency's initial approach to using genomics information in risk assessment and decision making</b>	<b><a href="http://www.epa.gov/osa/spc/genomics.htm">www.epa.gov/osa/spc/genomics.htm</a></b>
<b>2004</b>	<b>Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA</b>	<b>Identified impact genomics likely to have on: 1) prioritization of contaminants and contaminated sites; 2) monitoring; 3) reporting provisions; 4) risk assessment.</b>	<b><a href="http://www.epa.gov/osa/genomics.htm">www.epa.gov/osa/genomics.htm</a></b>
<b>pending internal review</b>	<b>Interim Guidance for Microarray-Based Assays: Regulatory and Risk Assessment Applications at EPA</b>	<b>Describes: 1) microarray data submission; 2) quality assessment parameters; 3) data management, analysis and evaluation; 4) training needs for risk assessors and decision makers.</b>	<b><a href="http://www.epa.gov/osa/index.htm">www.epa.gov/osa/index.htm</a></b>

## ***Recommendations from the Interim Guidance on Microarrays***

- Develop Agency-wide data management and analysis solutions
- Genomics training for Programs and Regions
- Toxicogenomics case studies

***NCCT is working across the Agency to accomplish these recommendations.***

# ***1<sup>st</sup> Recommendation: Development of Data Management and Analysis Tools for Toxicogenomics***



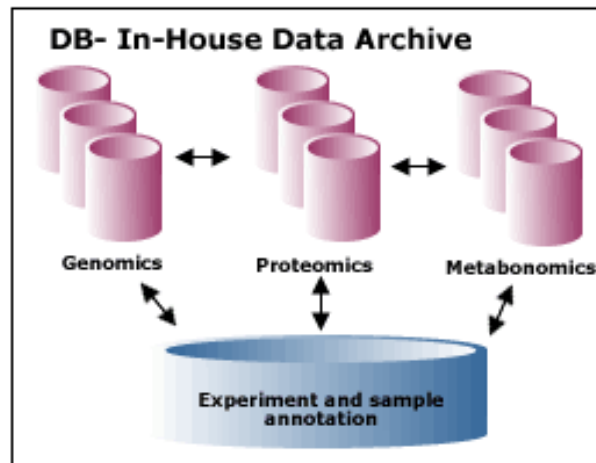
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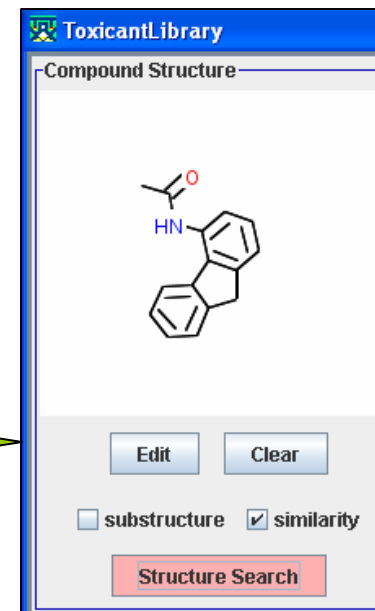
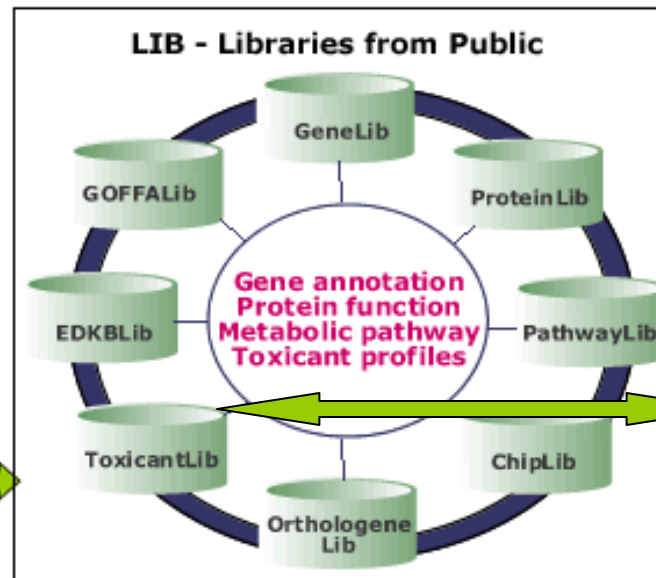
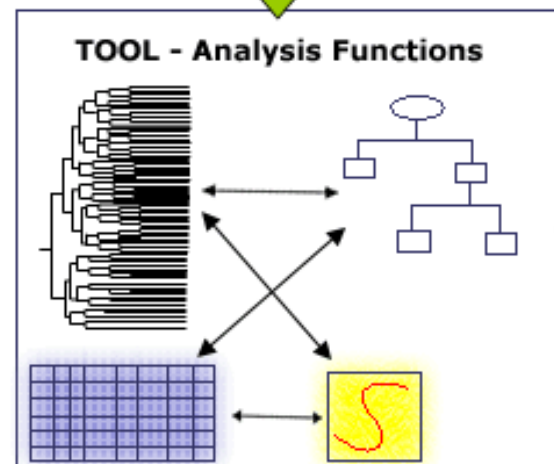
# ***The Environmental Bioinformatics Centers at NC and NJ are important partners in developing genomics database and analysis solutions***

- UMDNJ and FDA are developing ebTrack, building on ArrayTrack
- UNC is cooperating in developing RefToxDB, and genomics analysis tools

# ArrayTrack



**ArrayTrack v3.2.0** installed locally at EPA-RTP.  
Will update to v4.0.0



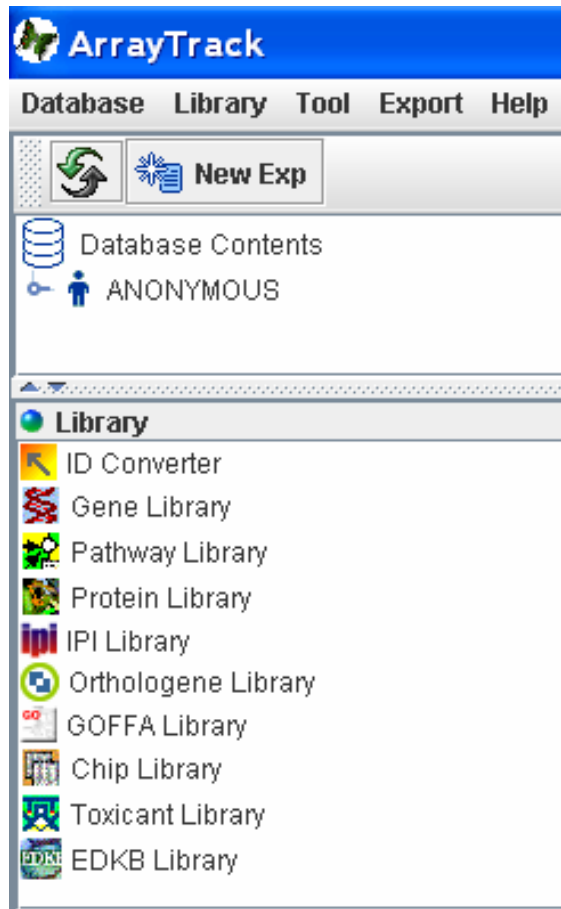
ArrayTrack is being integrated and further refined at the US FDA as a review tool for pharmacogenomics, and is freely available to public.

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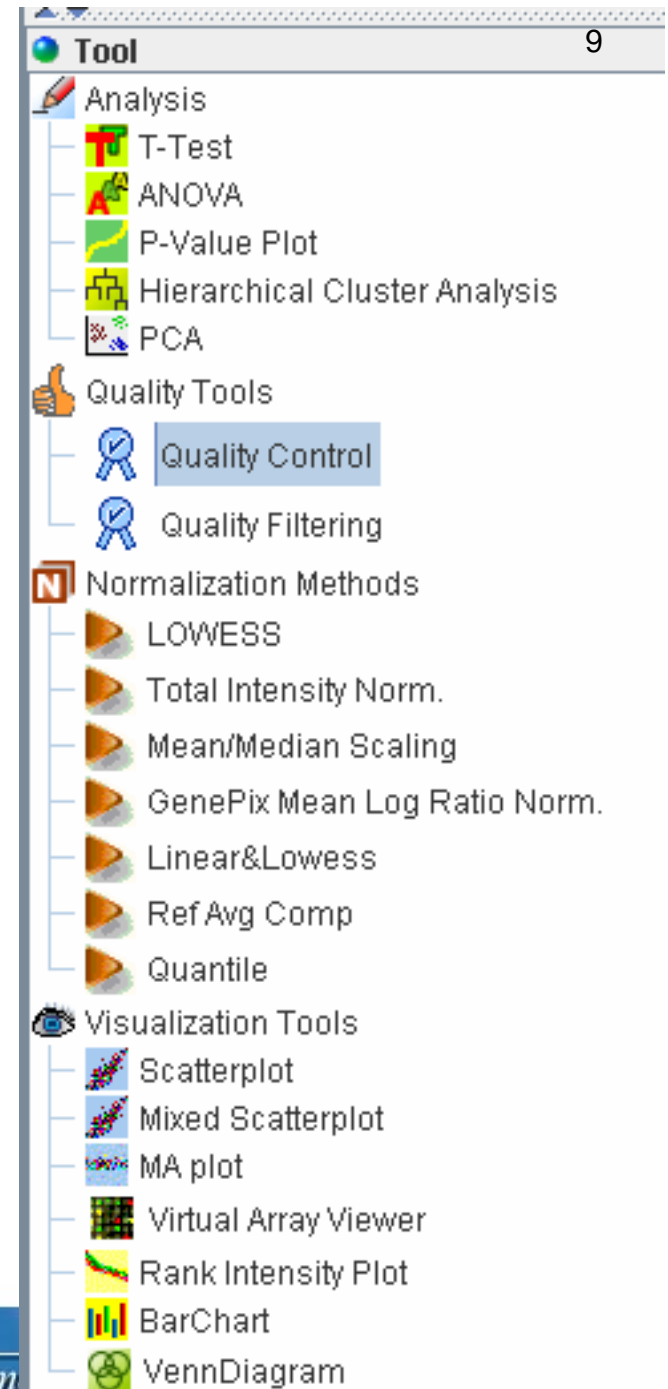
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# ArrayTrack

Besides the DB and libraries...



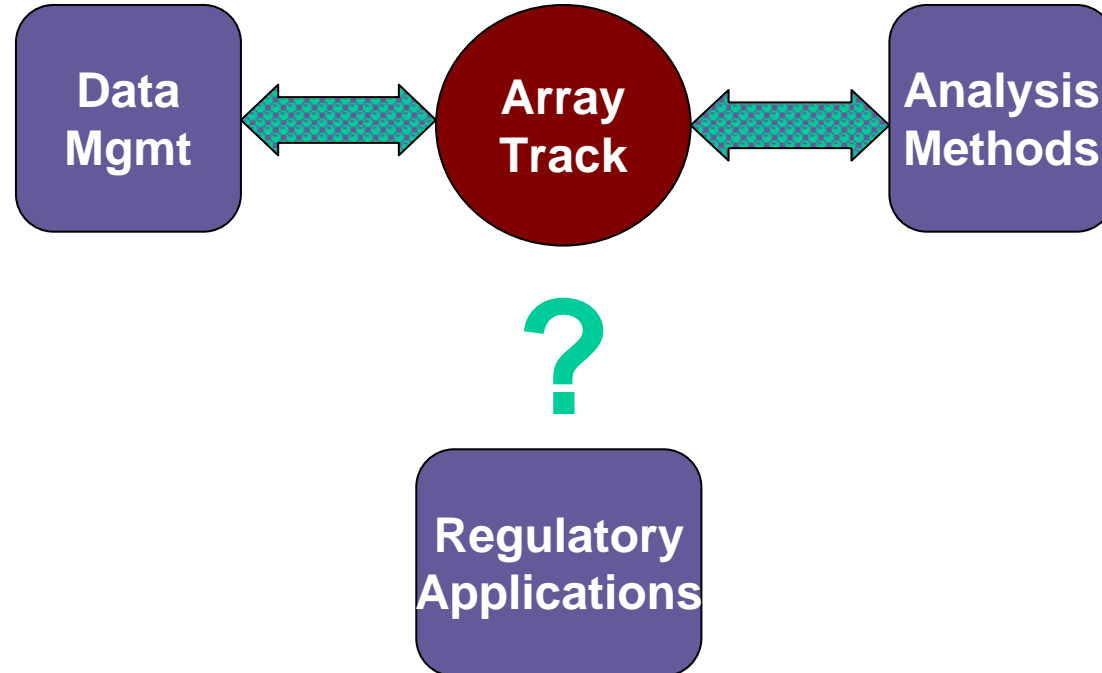
...ArrayTrack has a growing collection of analysis and QC tools for microarray data.



# ***Microarray Quality Control (MAQC) Project Is Adding Data, Analysis Tools and QC Metrics to ArrayTrack***

- Coordinated by FDA/NCTR
- FDA, NIH, NIST, and EPA participation
- EPA participants from NCCT, NHEERL, and the OSA (GTF leads)
- Collection of 14 papers submitted describing analysis methods and performance metrics
- MAQC data imported into ArrayTrack

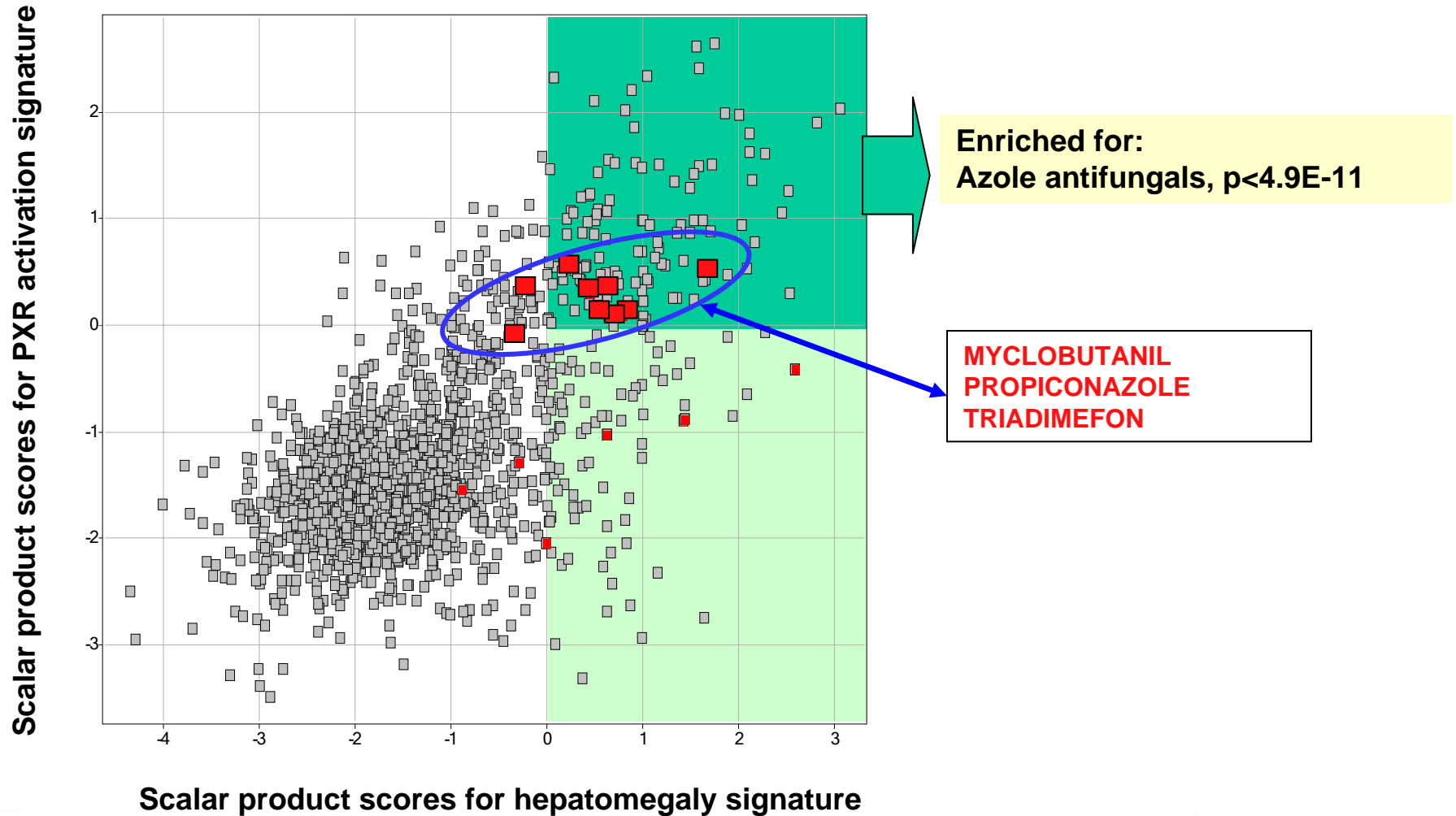
# ***ArrayTrack or ebTrack Can Provide Toxicogenomic Data Management and Analysis EPA Requires for Research***



***The solution for regulatory applications is unclear.***

***2<sup>nd</sup> Recommendation:  
Genomics Training for Risk  
Assessors and Senior  
Management in EPA Program and  
Regional Offices***

# Iconix genomics signatures combine with their reference database to correctly group EPA compounds with other conazole antifungals <sup>13</sup>



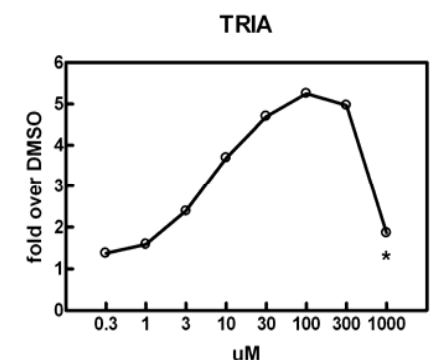
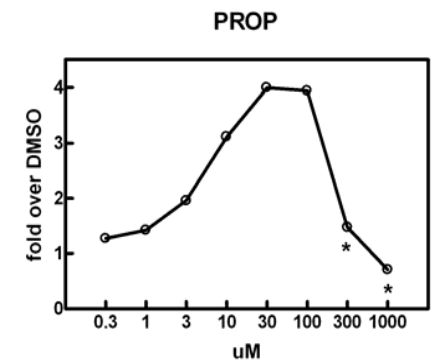
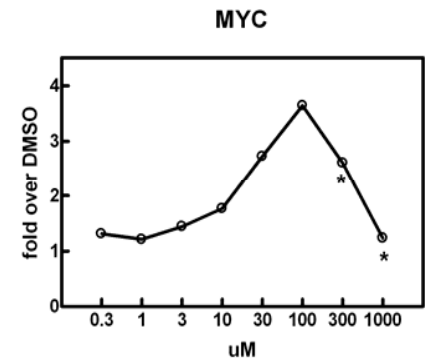
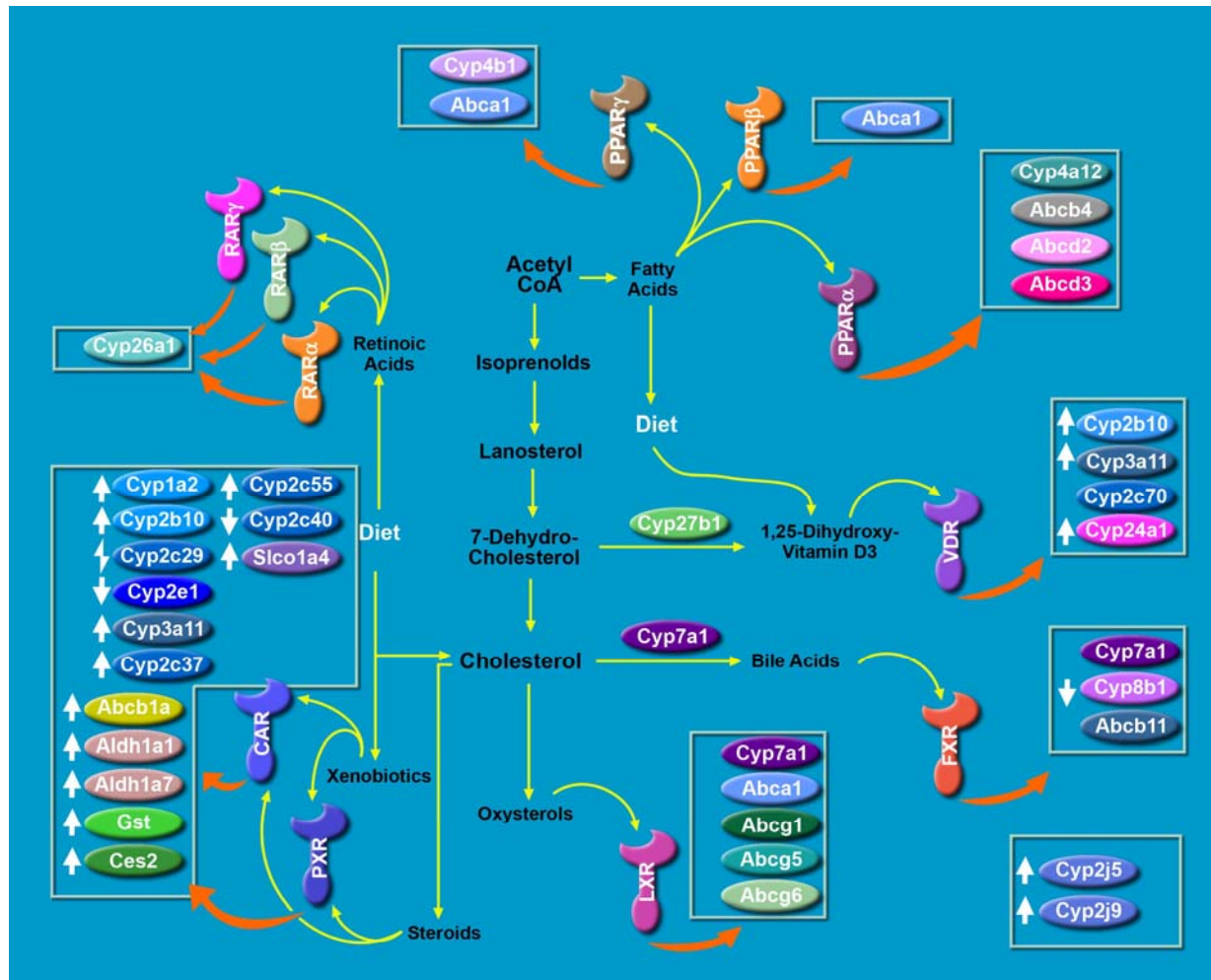
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## ***3<sup>rd</sup> Recommendation: Apply Guidance to Case Studies to Verify Utility in Risk Assessment***

- Conazole antifungals
- Dibutyl Phthalate
- Iconix and Gene Logic
- Primary Hepatocytes
- Small Fish
- ToxCast Genomics

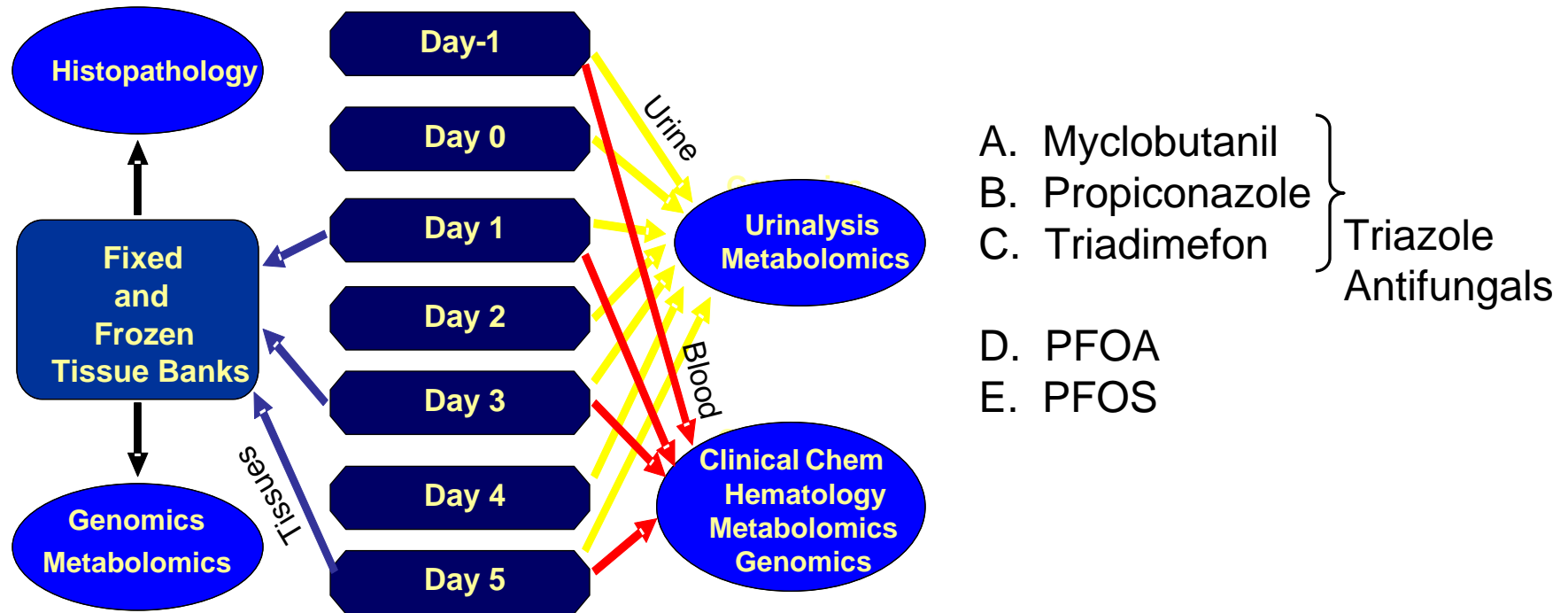
# Gene Expression Profiling to Characterize Conazole Modulation of Nuclear Receptors Significant to Toxicological Mechanisms



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# Integrated Genomics and Metabolomics Study with Iconix and ORD/NERL



Single dose, multiple timepoints.

Short-term in vivo rat study.  
Goal: predictive toxicology.

# ***In Vitro Toxicogenomics in Human and Rodent Primary Hepatocytes with 10 Environmental Chemicals***

## Pesticides

deltamethrin	1, 3, 10 uM
permethrin	1, 3, 10 uM
myclobutanil	10, 30, 100 uM
propiconazole	10, 30, 100 uM
triadimefon	10, 30, 100 uM

## Polychlorinated Biphenyls

PCB118	1, 3, 10 uM
PCB153	1, 3, 10 uM

## Flame Retardant

DE-71	1, 3, 10 uM
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## Plasticizers

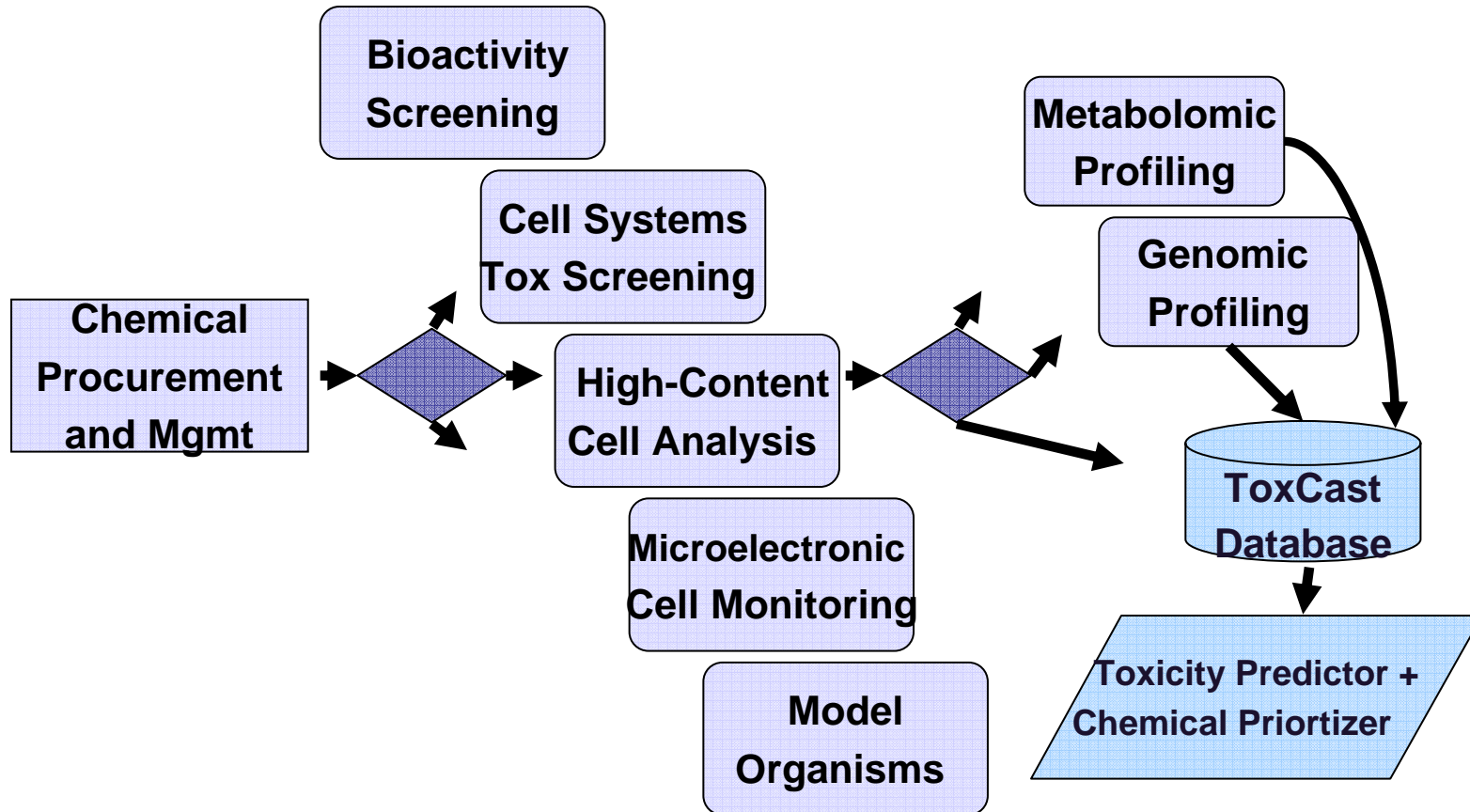
monoethylhexly phthalate	10, 30, 100uM
4-nonylphenol	10, 30, 100 uM

## Positive Controls

Phenobarbital	Rat	200 uM
	Human	1000 uM
Rifampicin	Humans	30 uM
PCN	Rats	30 uM

*NCCT/NHEERL collaboration, will also be analyzed using Iconix-Affymetrix arrays, and chemical list extended via ToxCast.*

# ToxCast Toxicogenomics

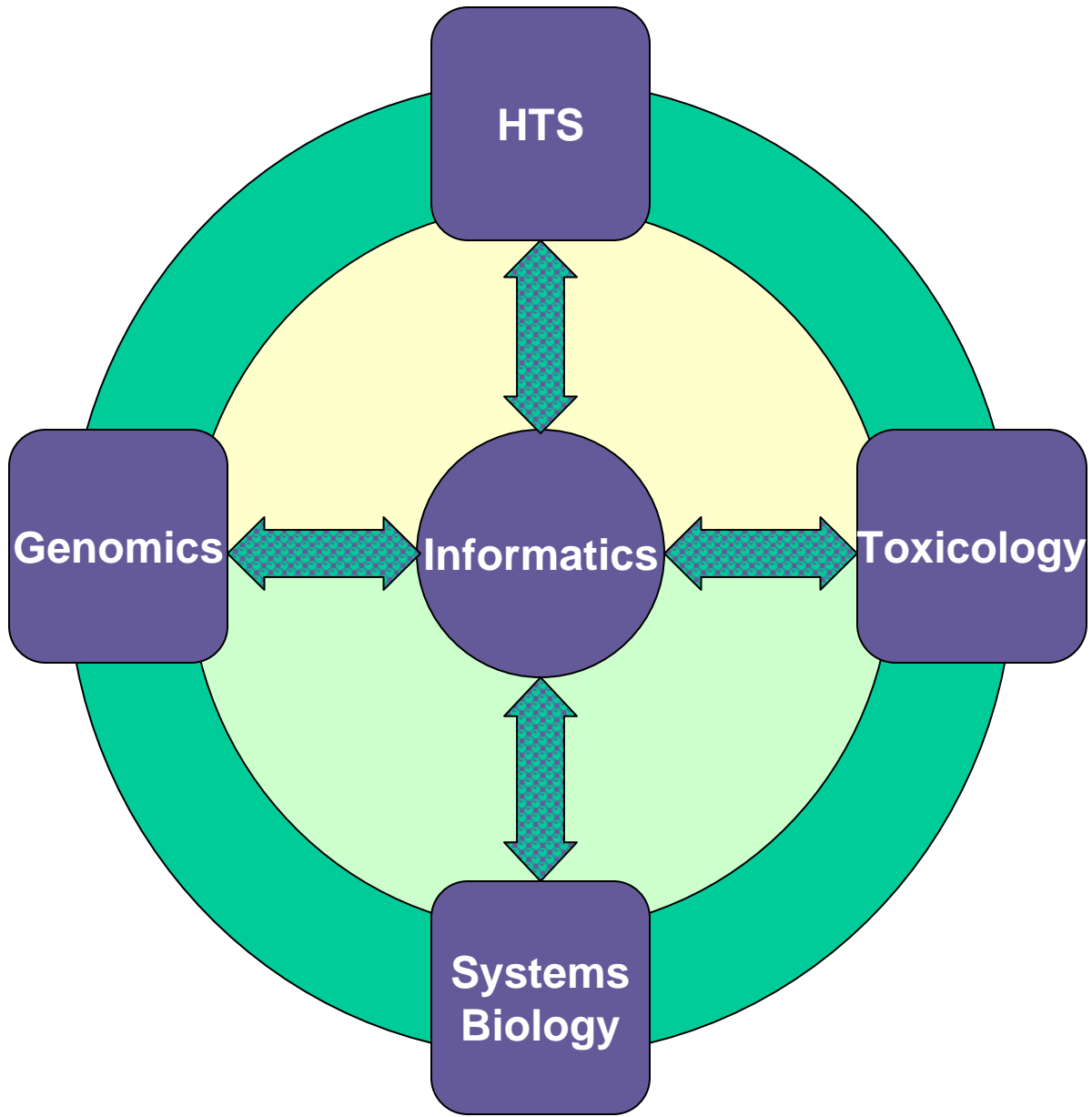


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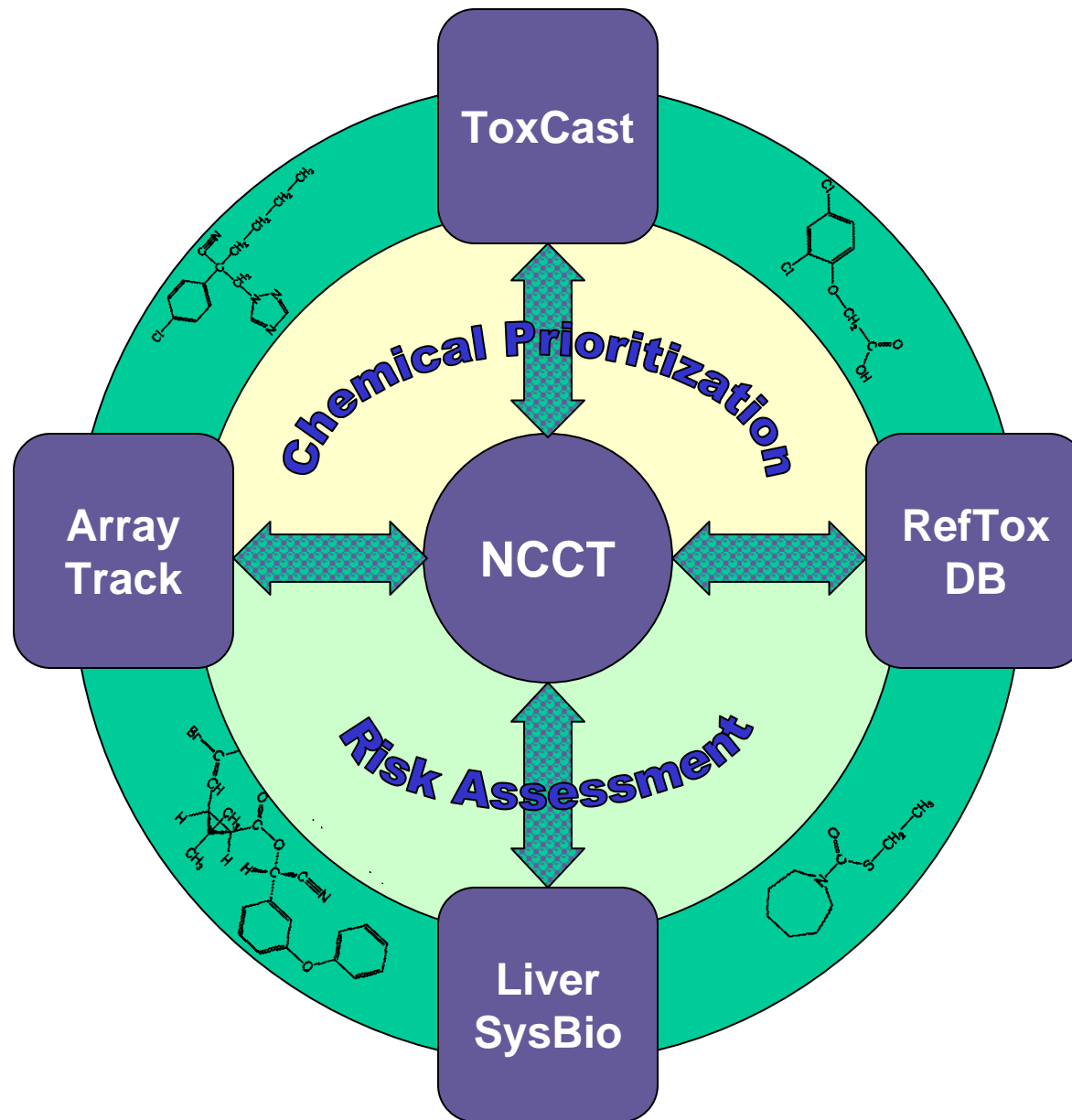
### ***3<sup>rd</sup> Recommendation: Apply Guidance to Case Studies to Verify Utility in Risk Assessment***

- 6 projects from the ORD Comp Tox research program are good candidates
- Need collaboration of Program, Regional and Policy Offices
- Stakeholder participation would be ideal



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# ***Acknowledgements***

## **EPA/ORD**

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