CTRP Implementation Plan

BOSC Computational Toxicology
Sub-committee Meeting

June 19 – 20, 2006

Implementation for the CTRP Framework

- Framework developed by ORD in 2003
- Computational toxicology
  - Integration of modern computing and information technology with molecular biology and chemistry

ORDs Computational Toxicology Program

ORD's

Computational Toxicology

Research Program

Implementation Plan

(FY 2006 – 2008)

April 2006

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The Plan

- Overview of research program theme and organization for three years and beyond
- Three year plans of specific projects to accomplish the first phase of the program
- Expected products and outcomes over the three years
- Outreach and networks

Components of the CTRP

- Projects of the national center
- Other ORD intramural efforts
- STAR environmental Bioinformatic centers

Research Program Organization

- Three long term goals
  - Five research tracks
    - 21 main projects
- Three communities of practice (fourth under consideration)
- STAR bioinformatics centers

Three LTGs and Five Research Tracks

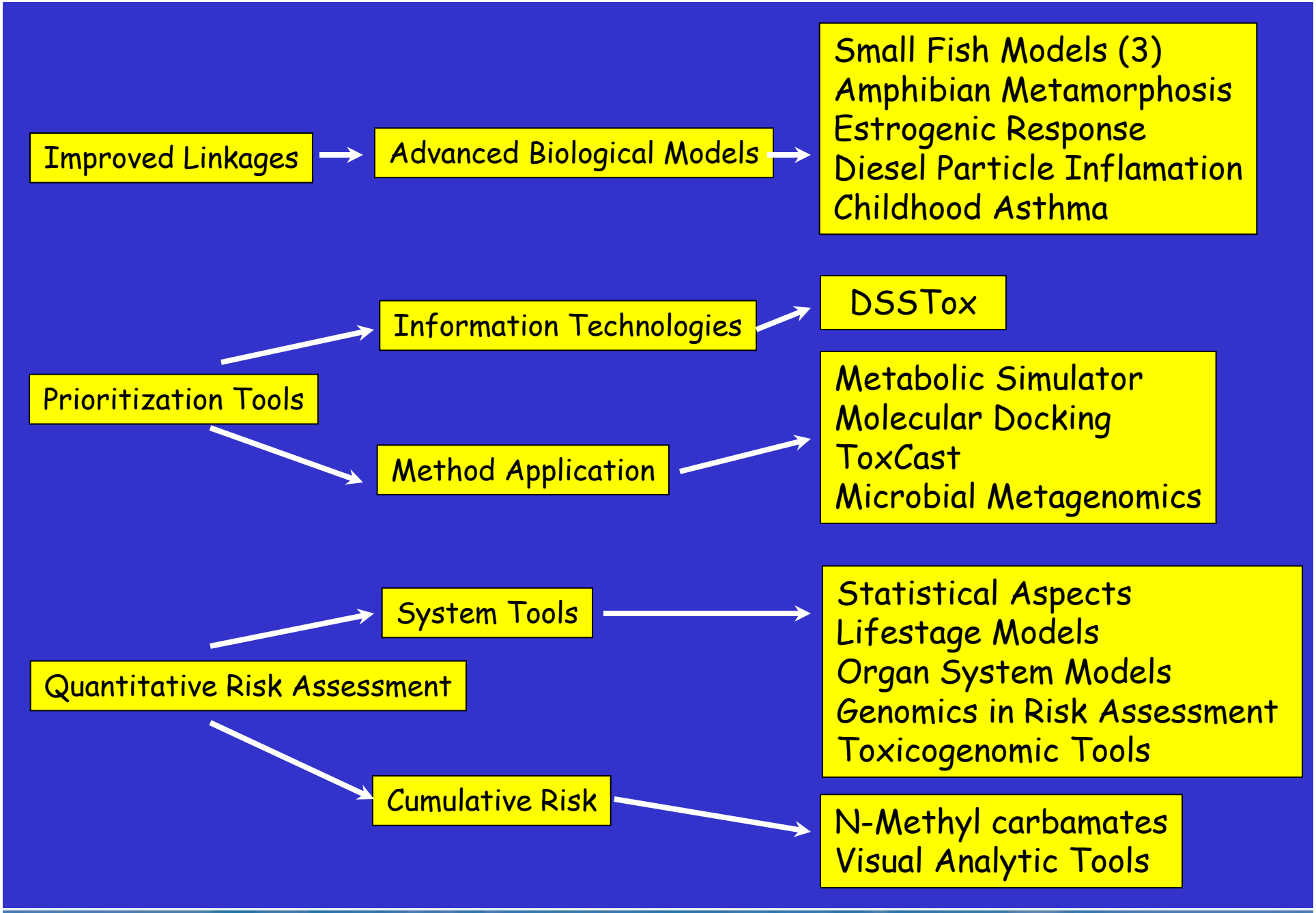
A. Development of Data for Advanced Biological Models

B. Information Technologies Development and Application

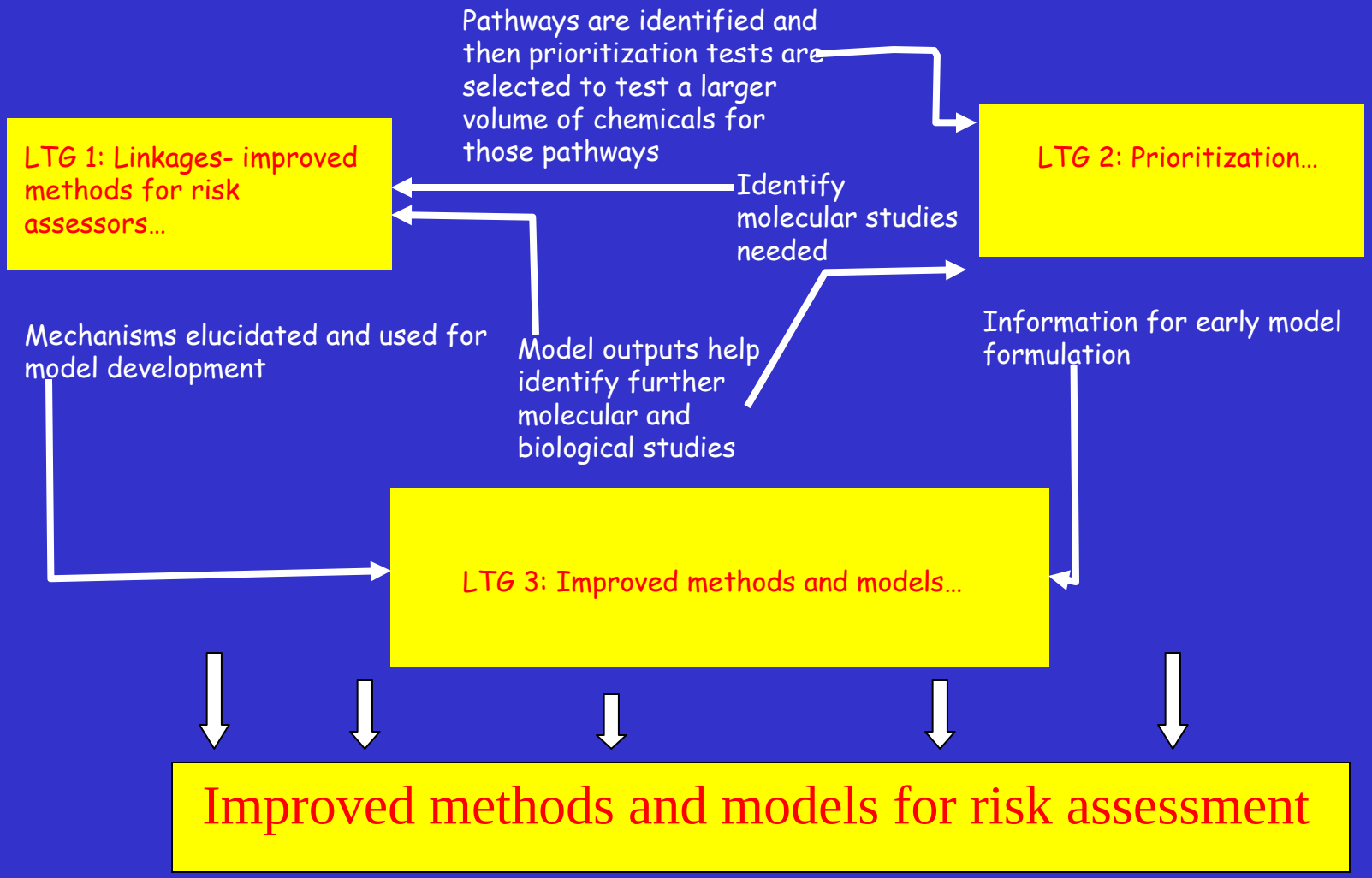
C. Prioritization Method Development and Application

D. Providing Tools and System
Models for Extrapolation across
Dose, Life Stages, and Species

E. Advanced Computational Toxicology Approaches to Improve Cumulative Risk Predictions


Improved Linkages
Advanced Biological Models
Small Fish Models (3)
Amphibian Metamorphosis
Estrogenic Response
Diesel Particle Inflamation
Childhood Asthma
Prioritization Tools
Information Technologies
DSSTox
Method Application
Metabolic Simulator
Molecular Docking
ToxCast
Microbial Metagenomics
Quantitative Risk Assessment
System Tools
Statistical Aspects
Lifestage Models
Organ System Models
Genomics in Risk Assessment
Toxicogenomic Tools
Cumulative Risk
N-Methyl carbamates
Visual Analytic Tools

How LTGs Interact



How the Work is Done by LTG

LTG 1 Data generation: mostly laboratory based biological studies: Outside of NCCT but with ORD Laboratories

LTG 3 Data use: in house computational and modeling

LTG 2: Combination of NCCT computation and contract laboratories to generate necessary data

Computational Toxicology Research Program Design

Research Program

Inputs and Resources

- Strategic guidance
- Research Plans:

client needs, research questions, research priorities, outcomes, multi-year plans (EDC, SP2, DW, HH), Research Strategies

- Partnerships
- ORD Intramural Research Resources
- ORD Extramural (STAR) Research Resources
- Program-level funding & FTE

Research Topics & Activities

ORD conducts research to:

- Develop improved methods and tools to better understand and describe the linkages of the source to outcome paradigm
- Develop advanced hazard characterization tools to prioritize and screen chemicals for toxicological evaluation
- Develop new and improved methods and models based on the latest science for enhanced quantitative risk assessment

Research Outputs

Research Outputs

ORD research provides:

- Prioritization and screening tools with abbreviated testing protocols to improve inter-species extrapolation and identify potential toxicities
- New and innovative ways to assimilate, evaluate, and use molecular and chemical information
- In-silico means to predict complex interations of pollutants with important endogenous proteins
- Modeling systems that represent comprehensive descriptions of the underlying biology of adverse impacts caused by environmental pollutants

Outreach & Transfer

- Scientific conferences and workshops
- Peer-reviewed publications
- Technical and decision support
- Publicly available data bases and models

Clients

- EPA (OPPTS, OW, OCHP, OEI, OAR, Regions
- Risk assessors (IRIS, RAF)
- Other Federal agencies (FDA, ATSDR, NIH, NTP, DOE)
- States
- Tribes
- International health organizations and universities (WHO)
- Regulated community
- Academic community
- Targeted communities
- American Public

Outcomes

Short-Term Outcomes

Independent experts, risk assessors, or others in the field:

- Use ORD's Screening and prioritization tools
- Use ORD's Advanced data base systems to study the relationships between exposure, chemical properties, molecular interactions and toxicity
- Use ORD's methods and models to better characterize the mechanistic basis at molecular level for risk Assessment purposes
- Use ORD's methods and models to characterize effectiveness of risk management decisions

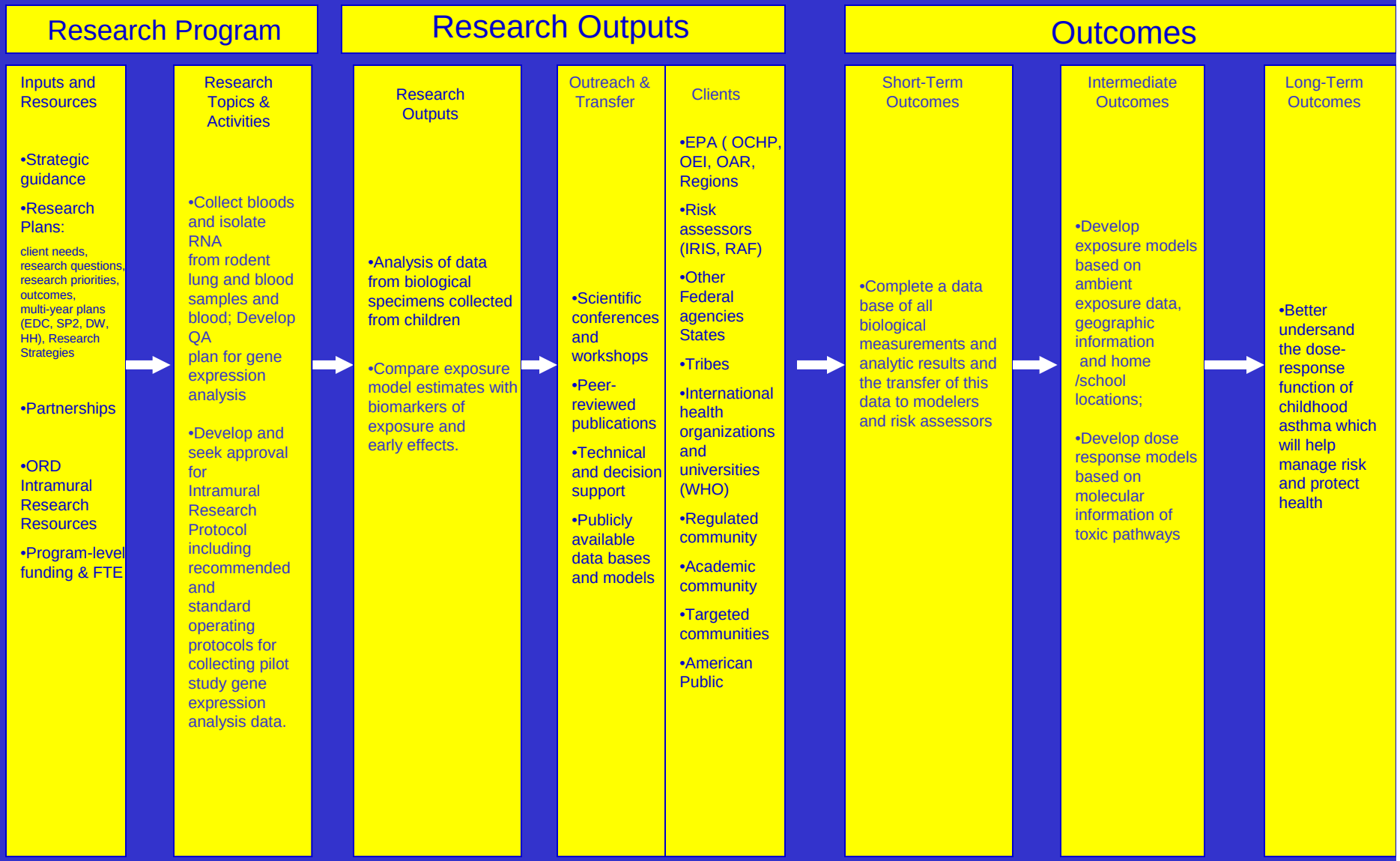
Intermediate Outcomes

- Large number of compounds or compound classes of HPV, pesticides, and others that may pose greatest risk and warrant further testing are more quickly identified
- Reduction on use and reliance of animal tests.
- Exposure to compounds expected to produce greatest risk is reduced
- Dose-response models based on latest sound science are used in making risk management decisions thereby improving the effectiveness and cost effectiveness of risk management decisions

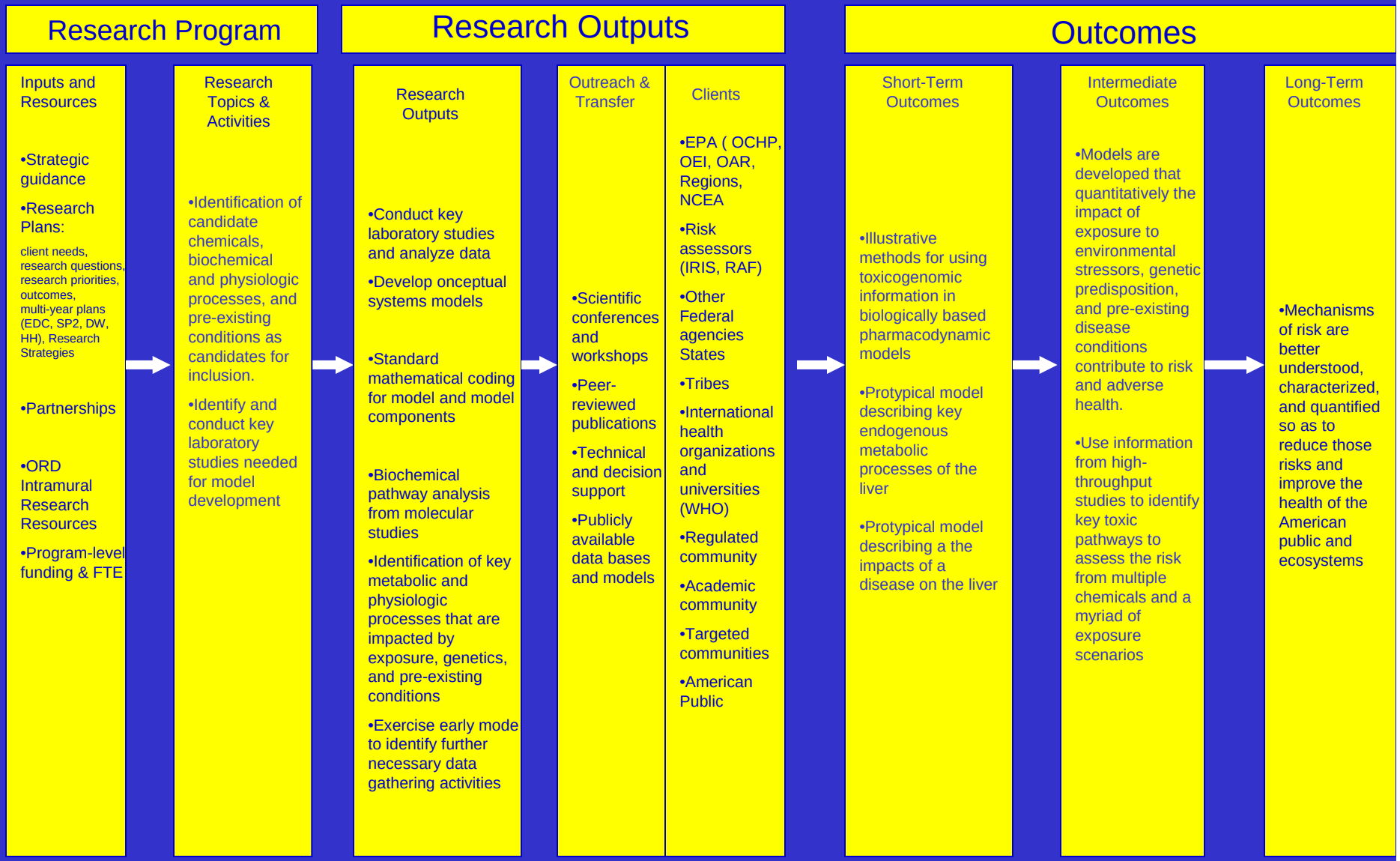
Long-Term Outcomes

- Risk to humans and the environment from environmental stressors is reduced or prevented

Example: Mechanistic Indicators of Childhood Asthma



Example: Systems Biology Model Development and Application



Communities of Practice

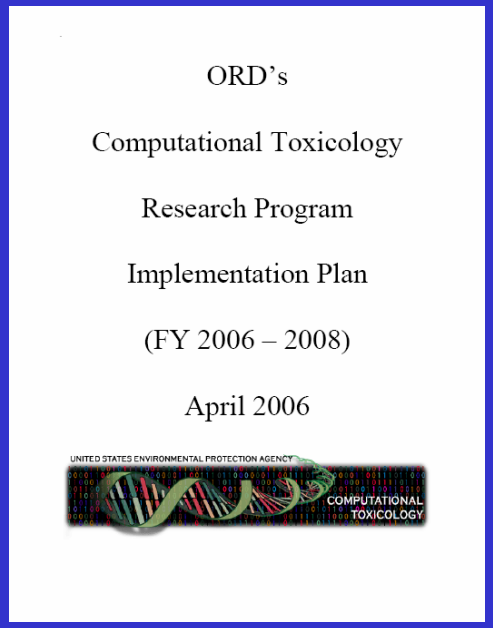
- Chemoinformatics
- Biological modeling
- Chemical prioritization
- Cumulative risk (under consideration)

Updating

- Three year plan
- Each year
  - Report progress
  - Update outputs and outcomes for new year
  - Introduce new projects
- Every third year revamp main part of plan

ORD's Computational Toxicology Program

2003



2006

OUTCOMES

2008

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Questions for the Committee

- Does implementation plan present a logical program?
- Are we making good progress?
- Is the research program responsive to agency needs?
- Will the outcomes be reasonable and useful?