

Risk Characterization

FACILITY CORE

Providing guidance on study design and data analysis

Developing statistical methods for characterizing risks to children

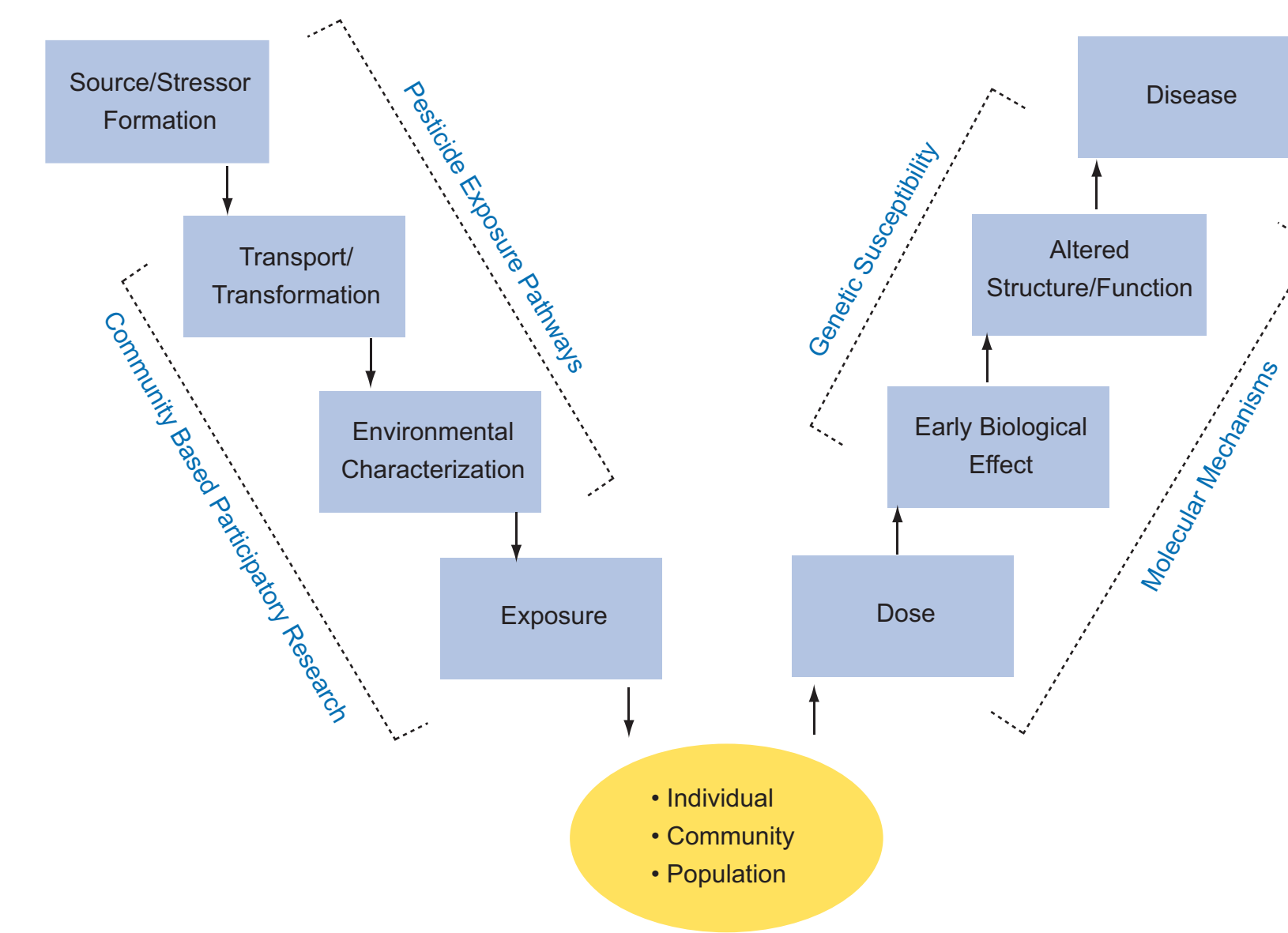
Building mathematical models to describe how pesticides affect the developing brain before and after birth

PROJECT OVERVIEW

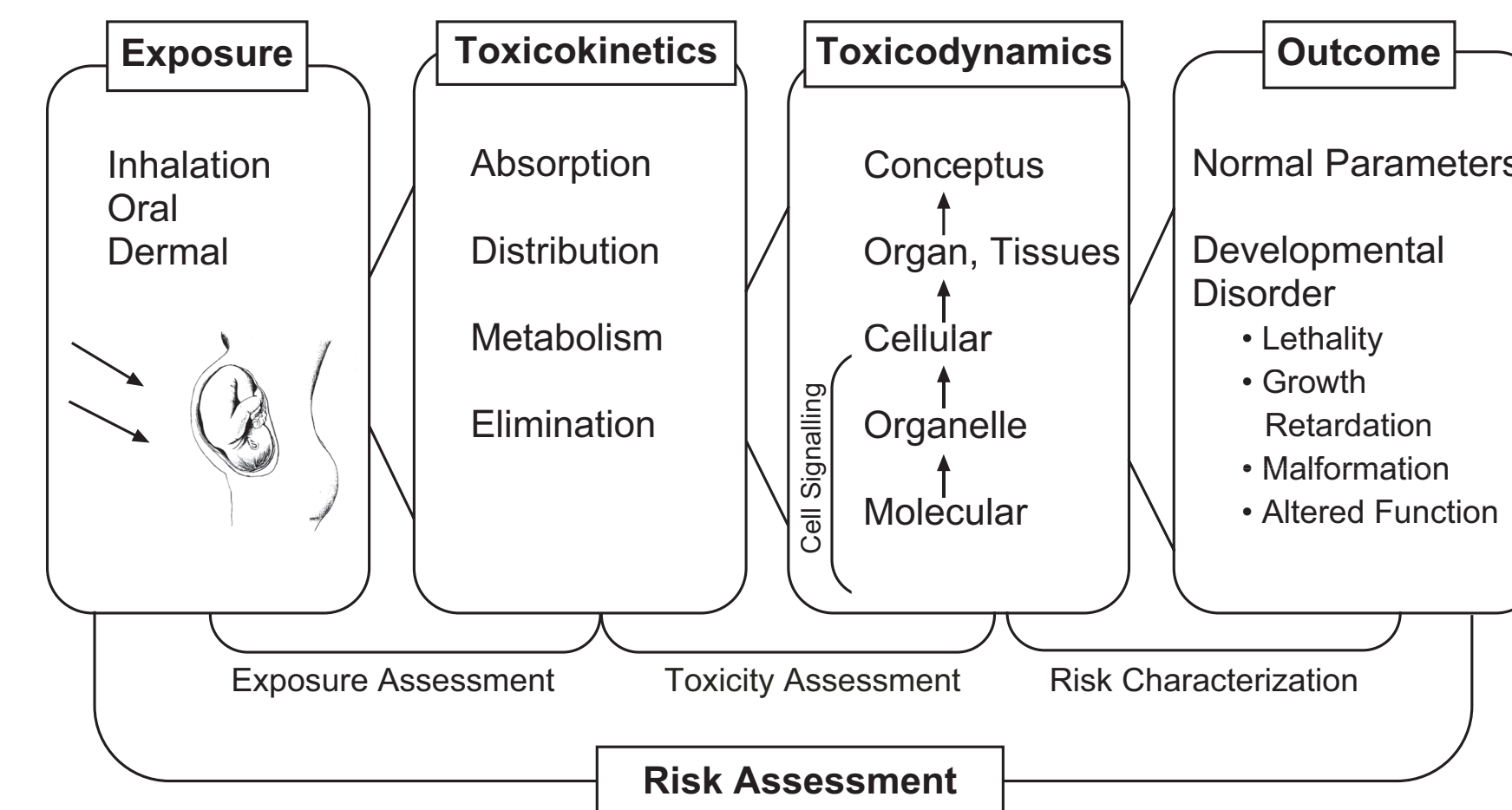
The Risk Characterization Core is building models that help us understand how pesticides affect neurobehavioral development before and after birth by altering the dynamic relationship of cell proliferation and differentiation during early brain development. Because the Center is built around a risk assessment framework, we are able to link findings on pesticide exposure and kinetics to improve our ability to predict outcomes using innovative modeling techniques.

The Risk Characterization Core has developed biologically-based dose response models (BBDR) that effectively describe dynamic processes such as early brain development. Table 1 shows how the methods and techniques used by the Risk Characterization Facility Core support the research projects of the Center. As single activities each of these studies provides important information regarding the kinetics and mechanisms of pesticide toxicity. Additionally, the Center structure allows us to link this data to develop powerful tools for assessing risk and improving protective measures for children's environmental health.

The Risk Characterization Facility Core is a group with expertise in biostatistics and risk evaluation that is an essential part of the Center. This facility core will continue to provide innovative, state of the art biostatistical support for the Center and research community.



Models facilitate understanding the relationships in the Environmental Public Health Continuum.



The Risk Characterization Facility Core uses the NRC's developmental toxicity and risk assessment modeling framework (NRC 2000) to describe the effects of pesticides on development.

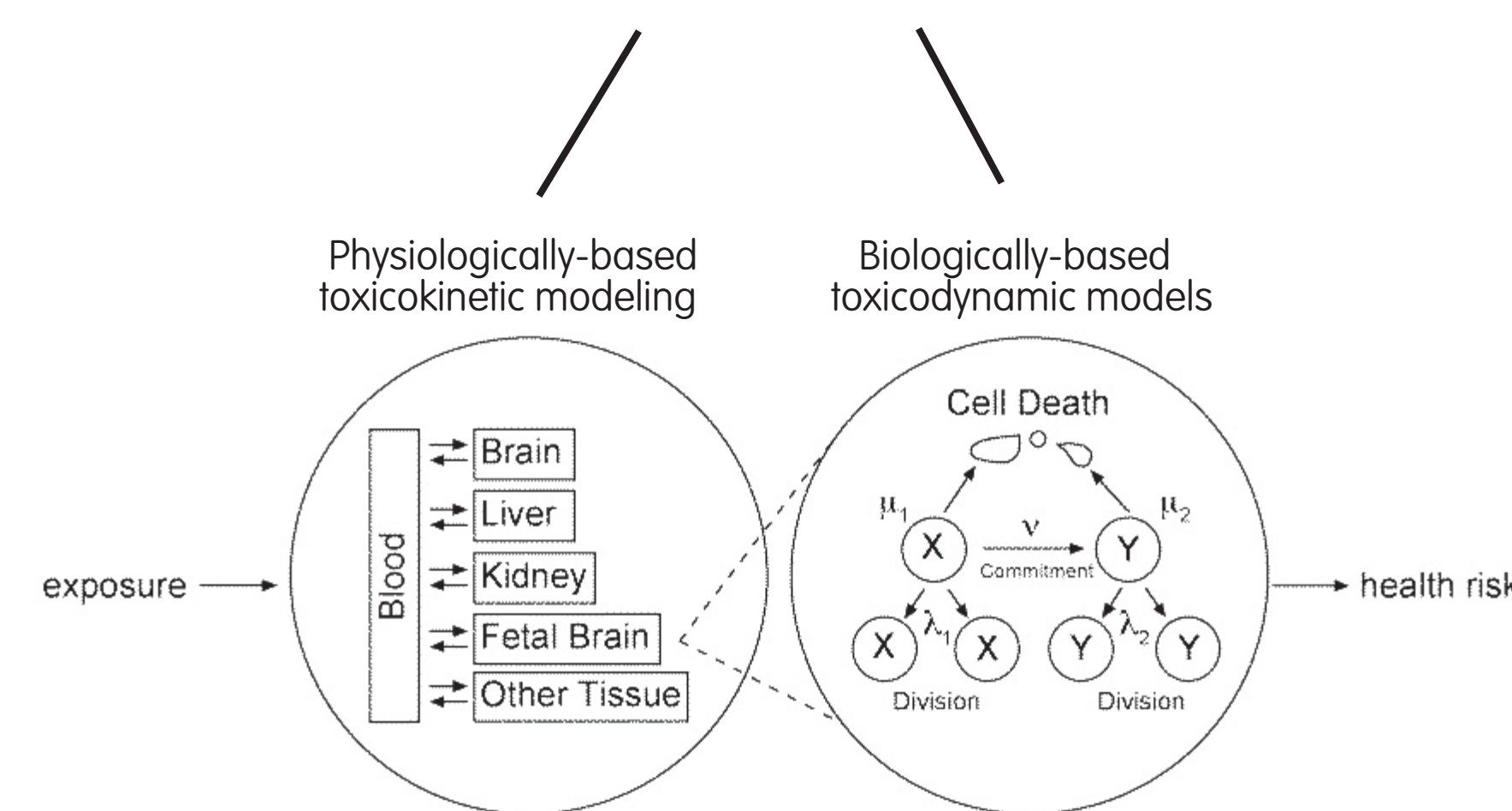


Figure 1. The Risk Characterization Facility Core will build models that will link exposure and outcome. This will be done using methods and techniques listed in Table 1 and relationships established in the figures above. A key emphasis of these models will be identifying both environmental and genetic factors that affect children's susceptibility to pesticides.

Table 1. Risk Characterization Core Methods and Techniques — Center Linkages.

Methods	Description	Linkages to Projects/Cores	CHC Applications
Dose-Response Assessment:			
Physiologically-based Pharmacokinetic Modeling (PBPK)	Models rate of movement of a chemical in the body to determine target dose	Pesticide Exposure Pathways, Community-based Participatory Research (CBPR), Exposure Assessment.	Estimate dose reaching the conceptus
Biologically-based Dose-response Modeling (BBDR)	Uses physiological data to inform dose-response modeling; Models effects of compound on the body (sometimes at cellular level) to inform dose response	Molecular Mechanisms, Genetic Susceptibility, Neurobehavioral Assessment	Model effects on neurodevelopment at the cellular level
Linking PBPK and BBDR Models	Uses dose estimate from PBPK model as input for BBDR model	All projects and cores	Linkage of models to more accurately assess health effects
Risk Characterization:			
Biostatistical Evaluation	Study design, biostatistical methods development, data analysis, assist with PBPK/BBDR modeling	All projects and cores; CBPR, Molecular Mechanisms, and Pesticide Exposure Pathways in particular	Provide biostatistical expertise in study design and evaluation
Methods Development:			
Statistical Analysis of Low Level Samples	Statistical methods for evaluating data when a high % of the samples have non-detectable levels; Evaluation of risk significance of non-detect data	Pesticide Exposure Pathways, CBPR, Molecular Mechanisms, and Exposure Assessment Core in particular	Supports data analyses; assess analytical sensitivity of residue testing
Uncertainty Analysis	Tools to capture uncertainty in quantitative models	All projects and cores	Supports modeling activities
Value of Information Approaches	Assess the disease and cost reduction potential of additional data for decision making	All projects and cores, particularly Community Outreach and Translation	Supports and informs analyses; Examine VOI cholinesterase monitoring programs
Risk Management:			
Translation of Risk Characterization Information	Risk-benefit analyses; quantification of child health impacts	All projects and cores, particularly Community Outreach and Translation.	Supports quantitative risk estimation of child health impacts

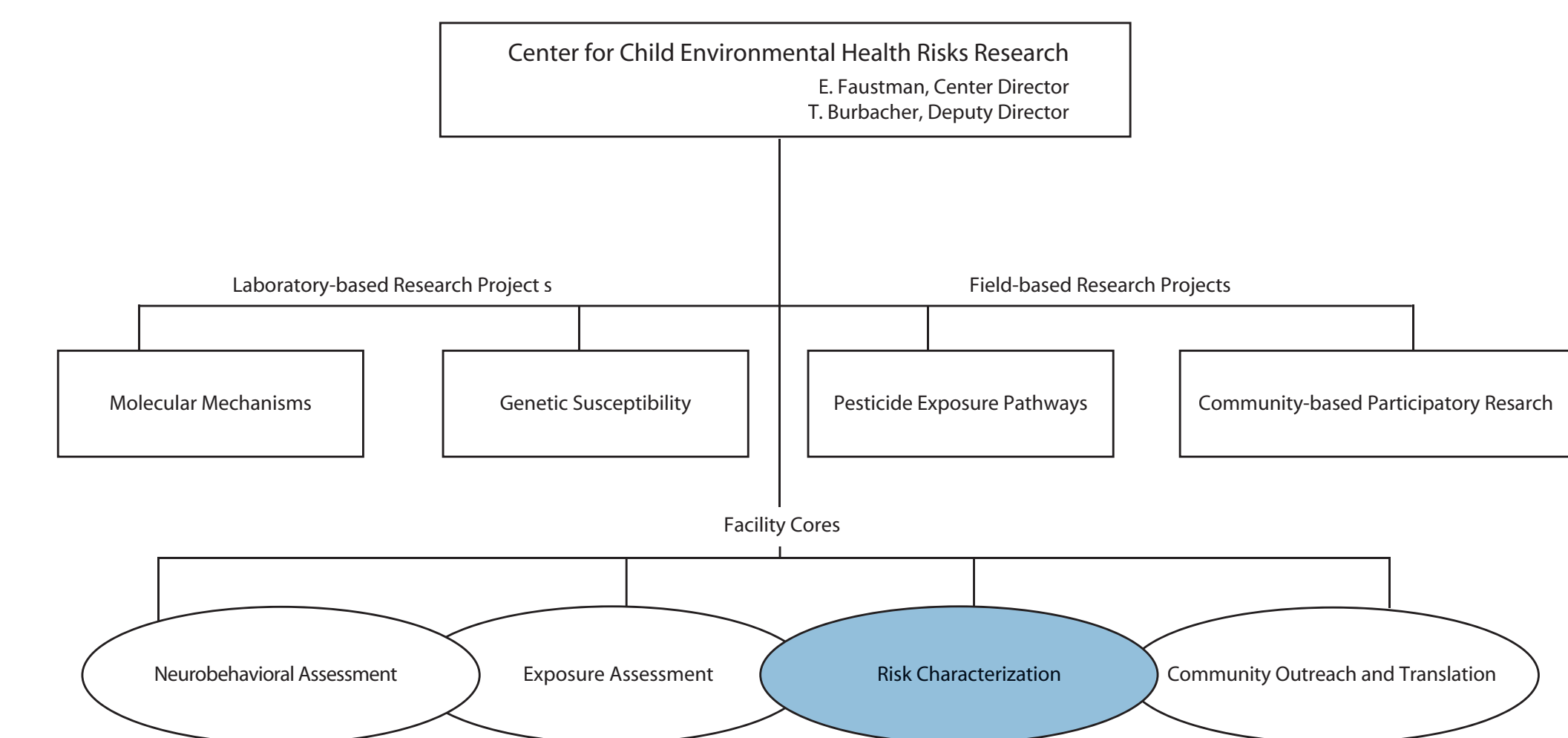
SPECIFIC AIMS

1. Provide outreach and translation of risk characterization information.
2. Develop new methods for biostatistical evaluation of Center studies;
 - a. Develop dose-response assessment methods to improve risk characterization, and
 - b. Develop new risk characterization methods to better inform risk management.
3. Provide statistical collaboration and consultation on study design, data analysis, manuscript writing, and interpretation of results for their impacts on children.

ANTICIPATED OUTCOMES

Collaboration with investigators on statistical designs and analysis has resulted in improved power of the studies to detect statistically significant results. The BBDR models under development improve our ability to evaluate the potential for neurodevelopmental impacts by better understanding how to interpret cell cycle data in terms of basic biological mechanisms of the developing and differentiation neurons. The models also improve our understanding of basic biological mechanisms on a more complex level by linking exposures to toxic substances to actual tissue concentrations of the substances and their toxic effects on neurodevelopment. The work on temporal fallacies in evaluating biomarkers of exposures assists in development of better risk assessment methods for children's environmental exposures and in the identification of susceptible time points for chemical impacts during neurodevelopment.

RESEARCHERS



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