

# Setting the stage: Issues in Defining Susceptible Populations for Chemicals

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# Overview

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- Background
- Legal framework (EPA perspective)
- Types of susceptibility
- Issues going forward
- Charge questions

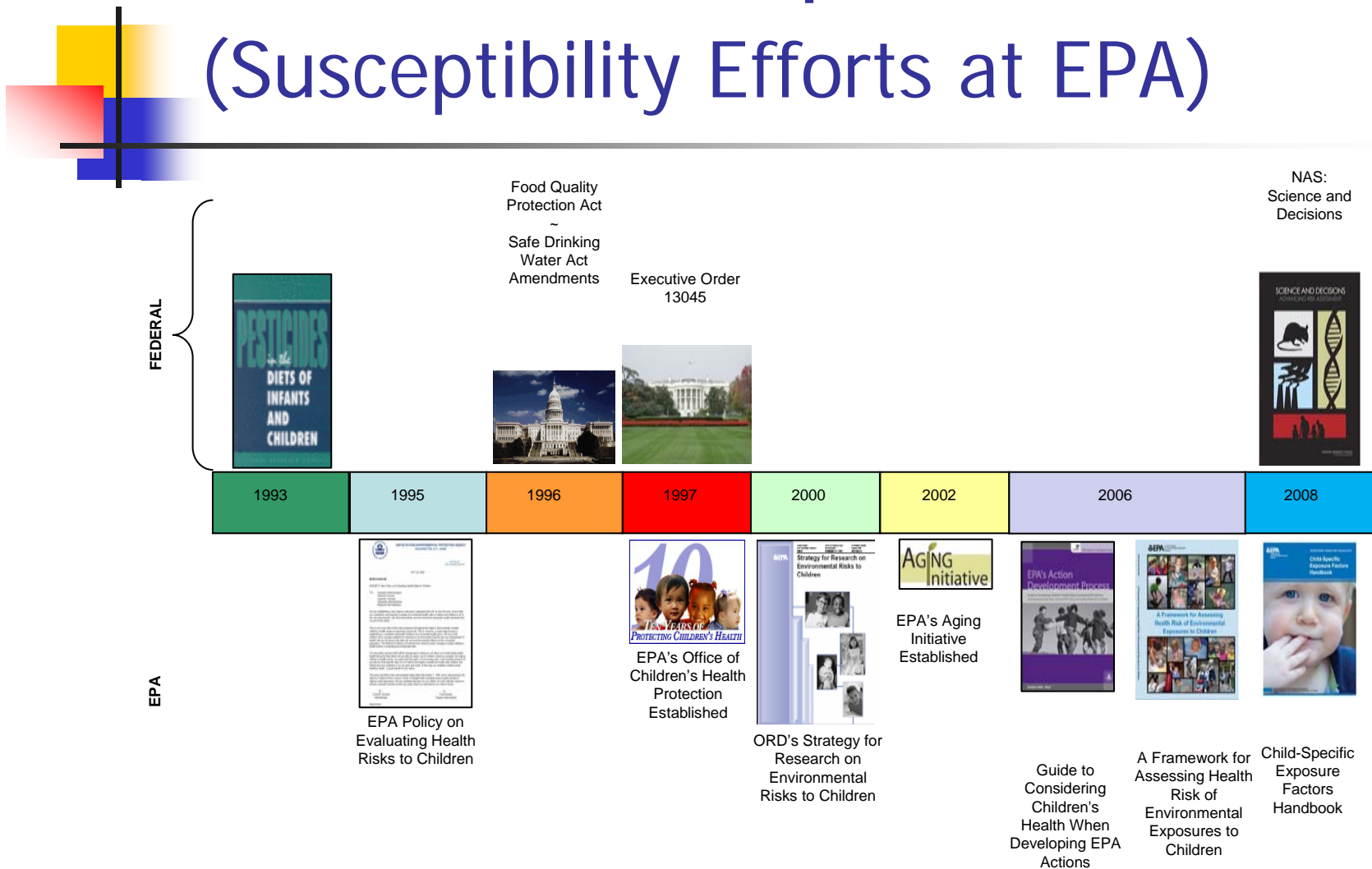


# Background

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- Why are risk assessors concerned about susceptibility?
  - Increased biological understanding
    - Developmental biology
    - Genetics
    - Exposure science
  - Increased public concern
    - NRC Reports
    - High visibility media coverage (e.g., endocrine disruptors)
  - EPA Initiatives
    - Children's health protection
    - Environmental justice
    - Etc.
  - Legal mandates
    - Food Quality Protection Act (1996)
    - Safe Drinking Water Act Amendments (1996)
    - Etc.

# Historical Perspective (Susceptibility Efforts at EPA)





# Legal Framework

(EPA examples)

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- Food Quality Protection Act (FQPA)
  - Focus on ensuring protection for infants and children
- Safe Drinking Water Act (SDWA) Amendments
  - Broader focus on at-risk subpopulations
- Clean Air Act
  - Legislative history of focus on protection of asthmatic individuals



# Types of Susceptibility

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- Lifestage
- Genetic
- Disease status
- Exposure-related



# Lifestage Susceptibility

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- Early lifestages
  - Prenatal
  - Postnatal
  - Youth
  - Adolescent
- Adult
- Aging



# Lifestage Susceptibility - Issues

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- Critical windows of development
  - Increased sensitivity of developing organism during discrete vulnerable periods
- Metabolic differences across lifespan
  - Ontological patterns during development
  - Changes in older adults due to health, nutritional status, or age-related changes
- Physiological differences across lifespan
  - Body size
  - Activity patterns
  - Ventilation rates, heart rate, etc.





# Pharmacokinetic Differences Across Lifestages (Relative to Adults)

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	Children	"Aged"
Absorption		
ventilation	higher	lower
gastric pH	lower	lower
Distribution		
plasma protein binding	lower	lower
$V_d$ (body water)	higher	lower
Metabolism		
phase I	immature (ontogeny)	basically unchanged
phase II	immature (ontogeny)	basically unchanged
Elimination		
renal elimination	immature	decreased



# Lifestage Susceptibility – Risk Assessment Issues/Needs

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- Methods to measure or model differences in response, to determine most sensitive population group
- Increased understanding of critical developmental pathways
- Improved estimates for the range of response variability
- Appropriate use of safety/uncertainty factors to account for differences

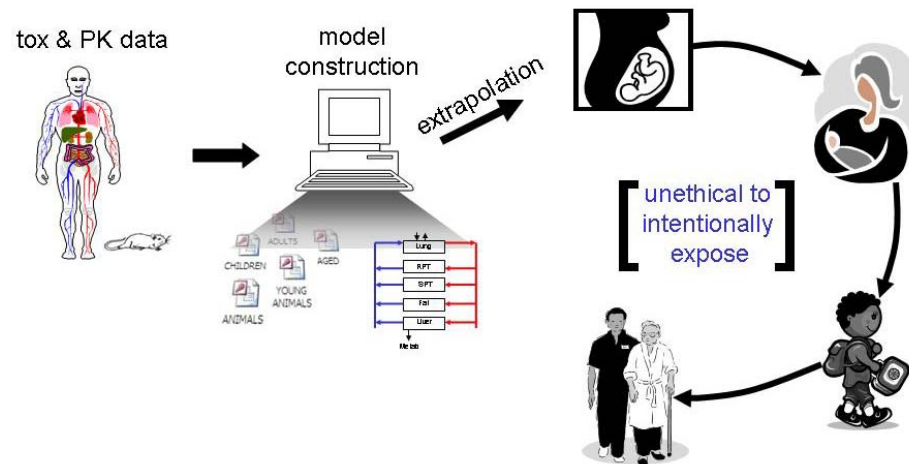


## Lifestage Susceptibility – Resources (examples)

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- Databases of enzyme ontogeny
- Databases of age-related physiological differences
- Children's Exposure Factors Handbook
- Framework for Assessing Health Risks of Environmental Exposures to Children

# Databases for Lifestage Physiological Information for Humans and Animals



Developmental lifestage:

Developing rodents <http://www.epa.gov/comptox/parameters.html>

Childhood [http://rsi.ilsilsi.org/Projects/Physio\\_Parameters\\_db.htm](http://rsi.ilsilsi.org/Projects/Physio_Parameters_db.htm)

Adult lifestage for both humans and laboratory animals (not yet released)

Aging lifestage

<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=188288>



# Genetic Susceptibility

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- Gender
- Polymorphism



# Genetic Susceptibility - Issues

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- Gender-based differences in response
  - Endocrine disrupting chemicals
  - Physiological differences
- Genetic polymorphisms
  - Toxicokinetic differences: variability in metabolic rates and/or metabolites leading to differences in exposure at target tissue
  - Toxicodynamic differences: polymorphisms in (e.g.) transporter proteins or DNA repair enzymes lead to differences in response at critical targets



# Genetic Susceptibility – Risk Assessment Issues/Needs

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- Methods to estimate range of population variability
- Identification of genetically susceptible populations
  - Source of susceptibility
  - Incidence rate in population
  - Mitigating/confounding factors
- Improved understanding of interaction among different genetic susceptibility factors



# Genetic Susceptibility – Resources

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- Databases of genetic polymorphisms and their implications
  - Range of metabolic outcomes
  - Proportion of population with various enzyme forms
- Databases identifying genetic differences associated with human disease
- Peer-reviewed literature





# Disease-related Susceptibility

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- Acute
- Chronic
- Nutritional status



# Disease-related Susceptibility - Issues

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- Increased sensitivity of affected individuals, e.g.,
  - Response of asthmatic individuals to air pollutants
  - Compromised immune function
- Coexposure to pharmaceuticals, e.g.,
  - Interactions between drugs and environmental chemicals
  - Changes in response thresholds due to physiological or other drug-related responses
- Changes in metabolizing enzymes due to diet or nutritional status



# Disease-related Susceptibility Risk Assessment Issues/Needs

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- Identify critical health factors related to increased susceptibility
- Improved understanding of vulnerable populations
  - Duration of vulnerable period
  - Interactions of vulnerability factors
    - Co-exposures
    - Lifestyle factors
    - Critical windows
- Methods for incorporation of health-related susceptibility information into risk assessments



## Disease-related Susceptibility - Resources

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- Population databases regarding
  - Disease incidence
  - Nutritional status
- Medical data regarding drug interactions



# Exposure-related Susceptibility

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- Racial/ethnic
  - Genetic susceptibility, socio-economic status, dietary exposure
- Lifestage
  - Critical windows
- Environmental
  - Occupational exposure, co-exposure to other compounds, geographic residence
- Lifestyle factors
  - Smoking, diet, health status, activity patterns



# Exposure-related Susceptibility – Risk Assessment Issues/Needs

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- Identification of factors influencing differential exposure
- Methodology for incorporating exposure across multiple sources and time frames
- Incorporation of susceptibility information into exposure models



# Exposure Resources

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- Population dietary surveys
- Toxics release inventory
- Water monitoring data
- Occupational survey data
- Census data
- NHANES and other health survey data
- Lifecycle analyses
- Methods and models for exposure estimation
- Etc.



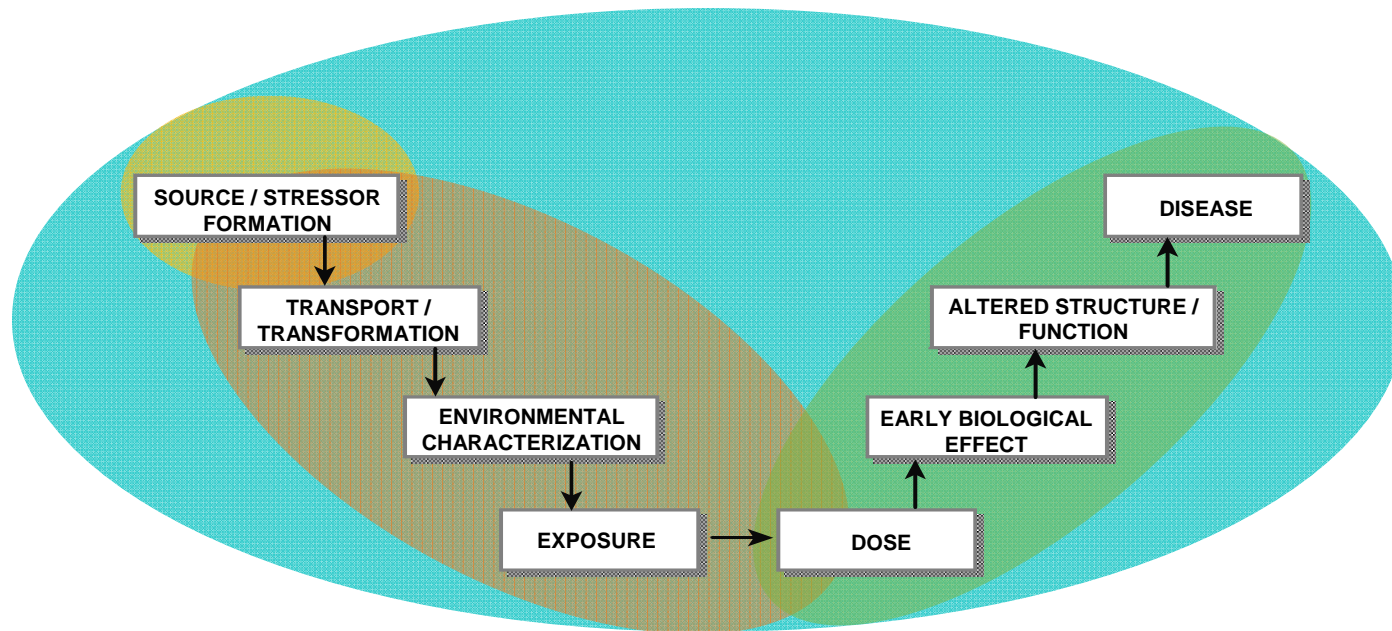
# Issues Going Forward

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- Susceptible populations in a risk assessment context
  - Life stage susceptibility
  - Other susceptibility considerations
    - Genetic
    - Disease status
    - Exposure-related
- Research Needs
  - Risk assessment tools
  - Basic and applied research regarding characteristics of susceptible populations
  - Incorporation of susceptibility considerations into new toxicology testing paradigms as they evolve



# Considerations in Conducting Chemical Risk Assessments for Susceptible Populations



- Where are individuals living and working? What are the important exposure sources in those locations?
- What activities are individuals engaged in that bring them into contact with these chemicals? Where do they spend their time? How does that activity affect physiological processes?
- What happens to those chemicals inside the body? What are the target tissues? What are the determinants of tissue dose and clearance?
- What are the critical adverse health effects and adverse outcomes?
- How do we integrate information across this continuum, across biological scales and targets?



# Some EPA Susceptibility Resources

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## **Childhood Susceptibility:**

*Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (2005)  
*Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (2005)  
*A Framework for Assessing Health Risk of Environmental Exposures to Children* (2006)  
*Child-Specific Exposure Factors Handbook* (External Review Draft) (2007)  
Database of Physiological Parameters for Early Life Rats and Mice (2007)  
Database of Physiological Parameters for Early Life Stages for humans (2007)  
Report on Dosimetric Adjustments Across Lifestages (in progress)

## **Elderly Susceptibility:**

*Aging and Toxic Response: Issues Relevant for Risk Assessment* (2005)  
*Summary Report of a Peer Involvement Workshop on the Development of an Exposure Factors Handbook for the Aging* (2007)  
Database of Physiological Parameters for Aging Population and Disease States (2007)

## **Disease Status:**

Database of Physiological Parameters for Aging Population and Disease States (2007)

## **Genetic Polymorphisms:**

Genetic polymorphisms in principal xenobiotic metabolizing enzymes relevant to characterizing variability in human toxic response (in progress)

## **EPA Research Program on Susceptible Populations:**

Details at <http://www.epa.gov/hhrp/research-goal3.html>



# Charge Questions

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## Question 1

- Is the concept of what constitutes a susceptible population clear for this group of hazards?
- Can you provide a description or definition of the concept that you think should be generally used by risk assessors and risk managers and in multiple public health contexts?
- Is the definition sufficiently concrete that it can be applied when extracting data from the literature or resource databases?
- For example, is it possible to actually use the concept of being “immunocompromised” or “elderly” for data mining?
  - If not, are there other more functional terms that should be used?
- Does it make sense to consider the probability of an adverse outcome separately from the severity of outcomes when thinking about susceptible populations?



# Charge Questions

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## Question 2

- What currently available data resources can be used to characterize susceptible populations in terms of their size, demographics, and exposures?
- Is it possible to “mash up” data from multiple resources to provide more detailed descriptions of specific susceptible populations?
- Is there significant heterogeneity in the quality and quantity of data available for different susceptible populations or types of susceptibility (e.g., lifestage versus genetic)?



# Charge Questions

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## Question 3

- What currently available data resources and tools can be used to characterize the relative susceptibility for different populations?
- Can the available data sources and tools be used to characterize both the probability of adverse events and the relative severity of the events in susceptible populations?
- Are data resources available for some populations but not others, or for some hazards and exposure but not others?
- To what extent can data from different populations or about different hazards be used to fill data gaps?
- Do we have tools that will allow us to differentiate variability and uncertainty when considering differential susceptibility in risk assessments?



# Charge Questions

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## Question 4

- Are there untapped data resources and tools that were developed for other purposes that might be used to identify and measure susceptible populations? (For example, medical treatment records or public health records assembled to monitor other issues).



# Charge Questions

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## Question 5

- What important questions were not included in this charge?



# Charge Questions

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## Question 6

- Considering the answers to the previous questions, what are the most critical data gaps and needs?
- Which of these data needs can be addressed in the short term and which require long term solutions?