Perchlorate Risk Characterization: US EPA Technical Perspectives

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NRC Committee to Assess the
Health Implications of Perchlorate Ingestion
October 27, 2003
Washington, DC

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Research and Development at EPA

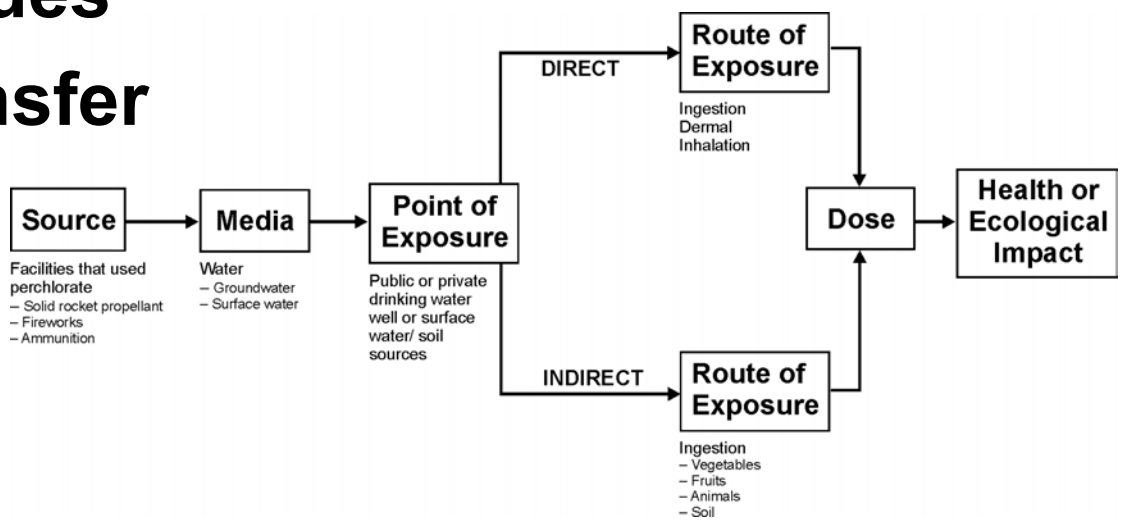
- 1,950 employees
- $700 million budget
- $100 million extramural research grant program
- 13 lab or research facilities across the U.S.
- Credible, relevant and timely research results and technical support that inform EPA policy decisions

Making decisions with sound science requires..

- **Relevant, high quality, cutting-edge research in human health, ecology, pollution control and prevention, and decision sciences**
- **Proper characterization of scientific findings**
- **Appropriate use of science in the decision process**

The Perchlorate Contamination Challenge: Comprehensive Characterization

- **Human health effects / toxicology**
- **Ecological impact / transport and transformation**
- **Analytical methods (detection in various media)**
- **Occurrence surveys**
- **Treatment technologies**
- **Stakeholder issues**
- **Technology transfer**



Pro-active Federal/Private Partnership and Public Participation

1997 Testing strategy and assessment development

- US EPA expertise to aid protocol development
- DOD and industry consortium (Perchlorate Study Group (PSG)) to contract and perform studies
- US EPA to address and expedite assessment

1998 Stakeholder meetings

- Early to identify issues and impact protocols
- Information to educate and empower

1998 Public peer review process

- Transparent process
- Iterative testing strategy
- Responsive to comments
- Continued refinement of risk assessment

Risk Assessment Development and External Peer Review Process

- December 1998: EPA publishes first external review draft (ERD) of health and ecotoxicological assessments
  - Used available literature and data developed by testing strategy
  - Proposed harmonized reference dose (RfD) for human health and screening level ecological risk assessment
- February 1999: Public external peer review workshop
  - Endorsed mode of action and conceptual model
  - Recommendations for additional studies
- Response to peer panel recommendations
  - New studies performed and submitted by defense industry contractors and the DOD
  - Pathology Working Group (PWG), NIEHS, and EPA analyses
- January 2002: EPA publishes second ERD

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Risk Assessment Development and External Peer Review Process

- **March 2002: Second public external peer review**
  - **Extended public comment period**
  - **17 external experts address ERD and receive public comments**
  - **Reinforced endorsement of mode of action and conceptual model; suggested analyses/revisions**
- **June 2002: Peer review report released to public**
- **June 2003: EPA, DOD, NASA and DOE request NAS review of scientific issues**
- **October 2003: EPA response to 2002 expert peer panel report and public comments developed**
  - **Analyses performed to address panel and public comments**
  - **New data in the literature considered**
  - **Revisions recommended**
- **NRC recommendations will be considered before finalization**

Summary: Development of Sound Scientific Foundation for Decision-making

- **Open and Participatory Process**
  - **Pro-active partnership to develop data**
  - **EPA, NIEHS and NIOSH collaboration on assessment**
  - **Iterative responses to public and peer review process**
- **State-of-the-Science Assessment**
  - **Assessment of both human and ecosystem health**
  - **Model motivated by data and mode of action**
  - **Harmonized approach to noncancer and cancer toxicity based on key biological event**
  - **Assessment reflects public health perspective**
    - **Point of Departure (POD) considers human and animal key events**
    - **Life stage sensitivity**
    - **Inference guidance/uncertainty factors ala NRC (1983 and 1994)**

Pro-Active Partnership

Department of Defense
AFRL
Perchlorate Study Group

PSG

ORD
OW
OSWER
Regions

NIEHS

National Institute for Occupational Safety and Health
NIOSH

Interagency
Perchlorate
Steering
Committee

I P S C

Perchlorate Guidance Status

- January 2003: EPA reaffirmed 1999 interim guidance for an RfD which converts to a level of 4-18 ppb in drinking water.
- This range is intended as a screening tool to see if site specific risk assessment is needed.
- This range is considered to be protective of sensitive subpopulations.
- Uncertainties still exist in the science in the 2002 ERD and 2003 Responses and Recommendations document.
- EPA has decided that the 4-18 ppb range should remain in effect as guidance pending the outcome of the NAS study.

2002 Risk Assessment / 2003 Response Authors

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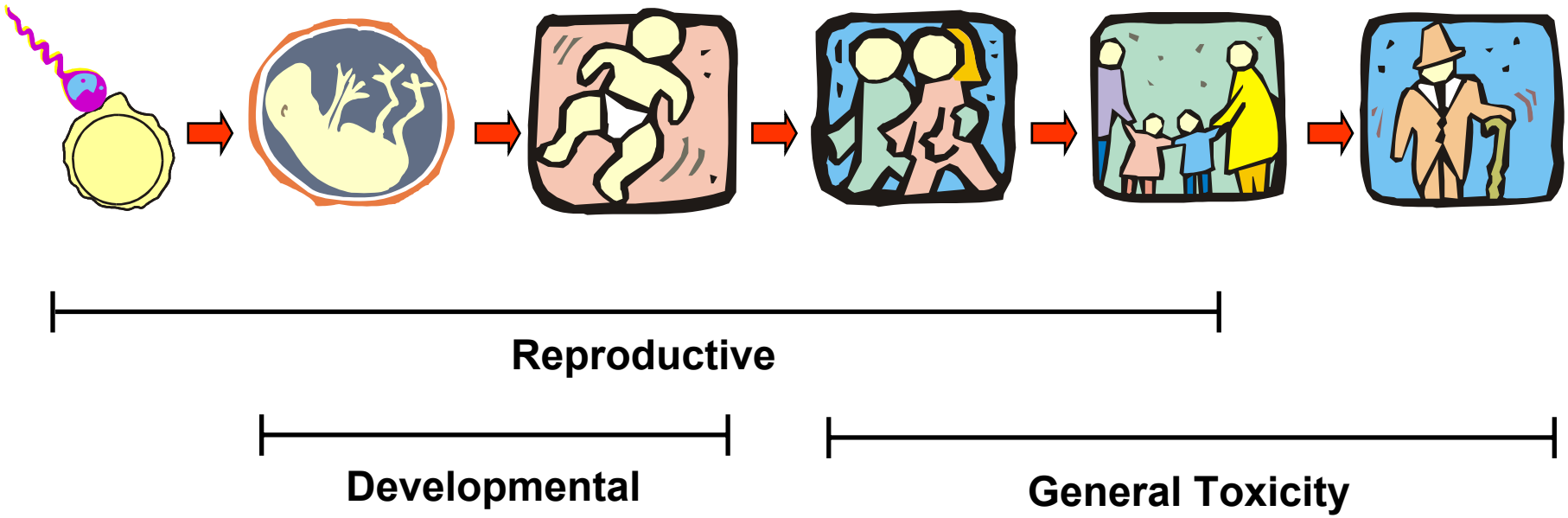
Overview of EPA Perspective

- Background
  - Typical reference dose (RfD) database
  - Perchlorate mode of action
  - Testing strategy and additional studies
  - Basis of 1999 and 2000 assessments
- 2003 EPA Responses and recommendations for revisions to 2002 EPA assessment external review draft (ERD)
  - General outline
  - Specific issues based on peer panel and public comments
- Summary

A Reference Dose (RfD) Addresses All Potentially Critical Life Stages



A reference dose is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime

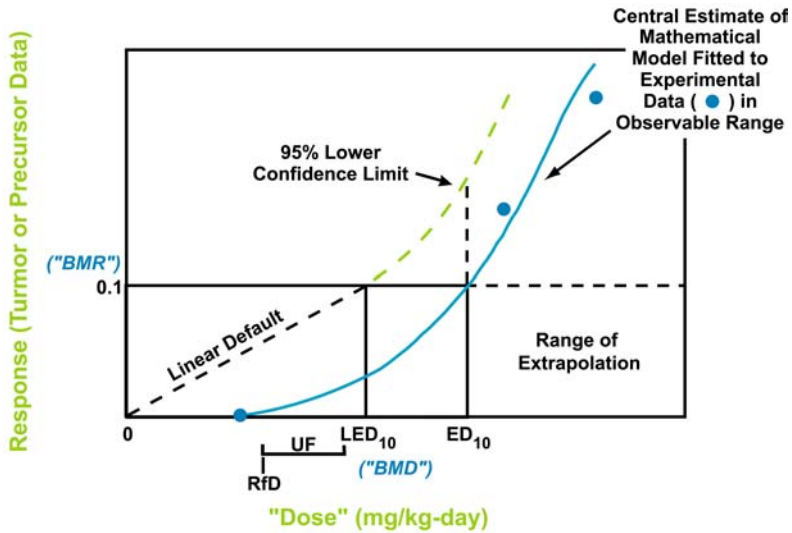
Standard Reference Dose (RfD) Derivation

$$\text{RfD} = \frac{\text{POD [HEE]}}{\text{UF}}$$

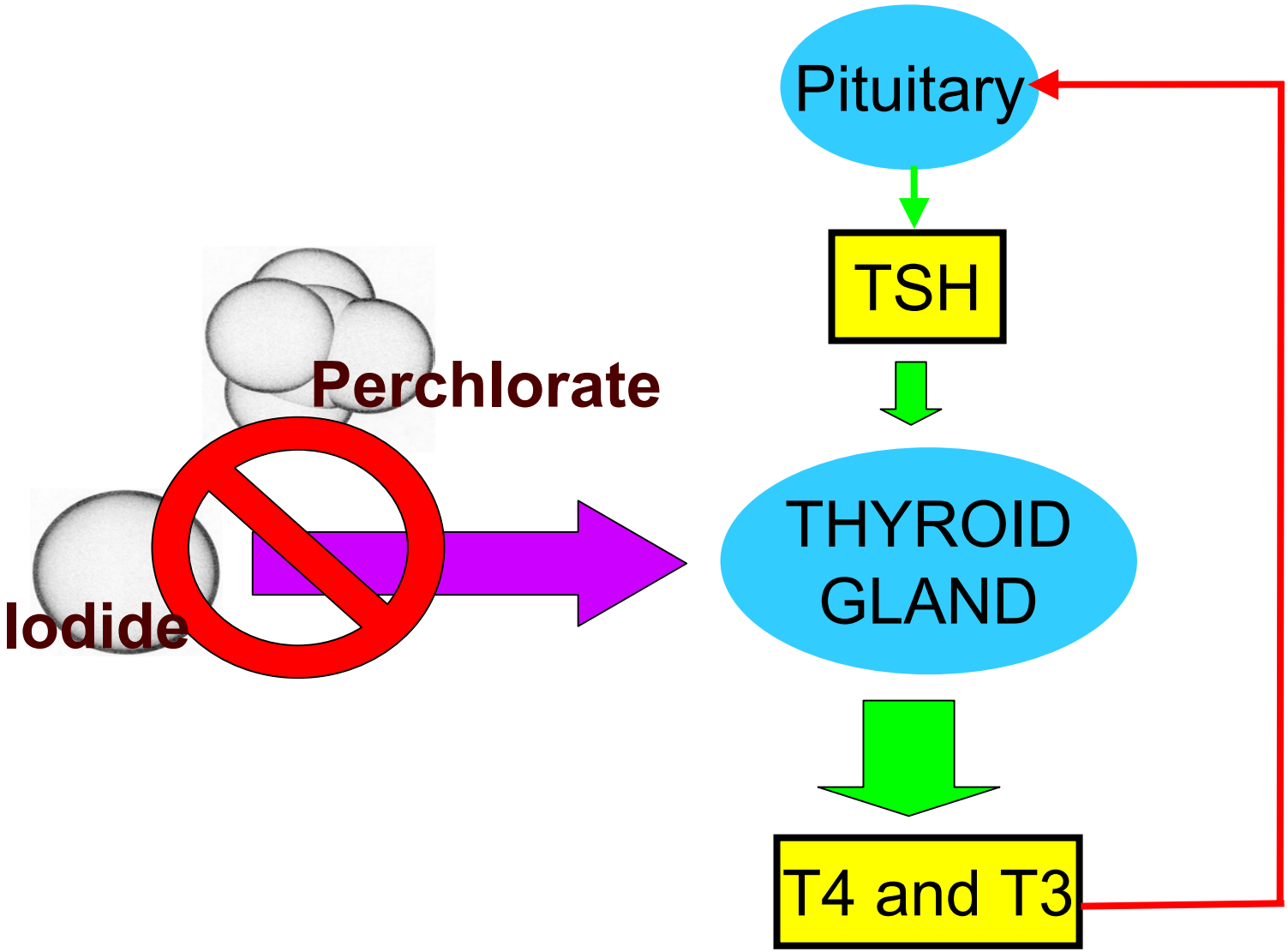
Where:

POD [HEE] = The point of departure or level of concern that is dosimetrically-adjusted to a human equivalent exposure [HEE]. Typically defined by a No-Observed-Adverse-Effect Level (NOAEL) / Lowest-Observed-Adverse-Effect Level (LOAEL) approach or benchmark dose model

UF = Uncertainty factor(s) applied to account for the extrapolation required from the characteristics of the experimental regimen to the assumed human scenario



Perchlorate Mode of Action



1997 DOD-sponsored Review Summary of Database Deficiencies

- Target tissue appeared to be the thyroid but available testing not comprehensive across endpoints
  - Limited clinical studies in adults with disease or other treatments
  - Laboratory animal studies dated with respect to assays and used a limited range of doses and endpoints
- Anti-thyroid effects would differ among adult versus developing fetus and children
- Anti-thyroid effects associated with benign neoplasia development in rats; likely a nonlinear process but genotoxicity not characterized

1997 Testing Strategy* Developed by Federal/State Agencies and Defense Contractors

- 90-Day subchronic oral bioassay (rats)
- Developmental neurotoxicity study (rats)
- Genotoxicity assays (Salmonella, MN, lymphoma)
- Mechanistic studies
- ADME - Absorption, Distribution, Metabolism and Elimination
- Developmental study (rabbits)
- 2-Generation reproductive toxicity study (rats)
- Immunotoxicity (mice)
- Set of screening studies to characterize eco risk

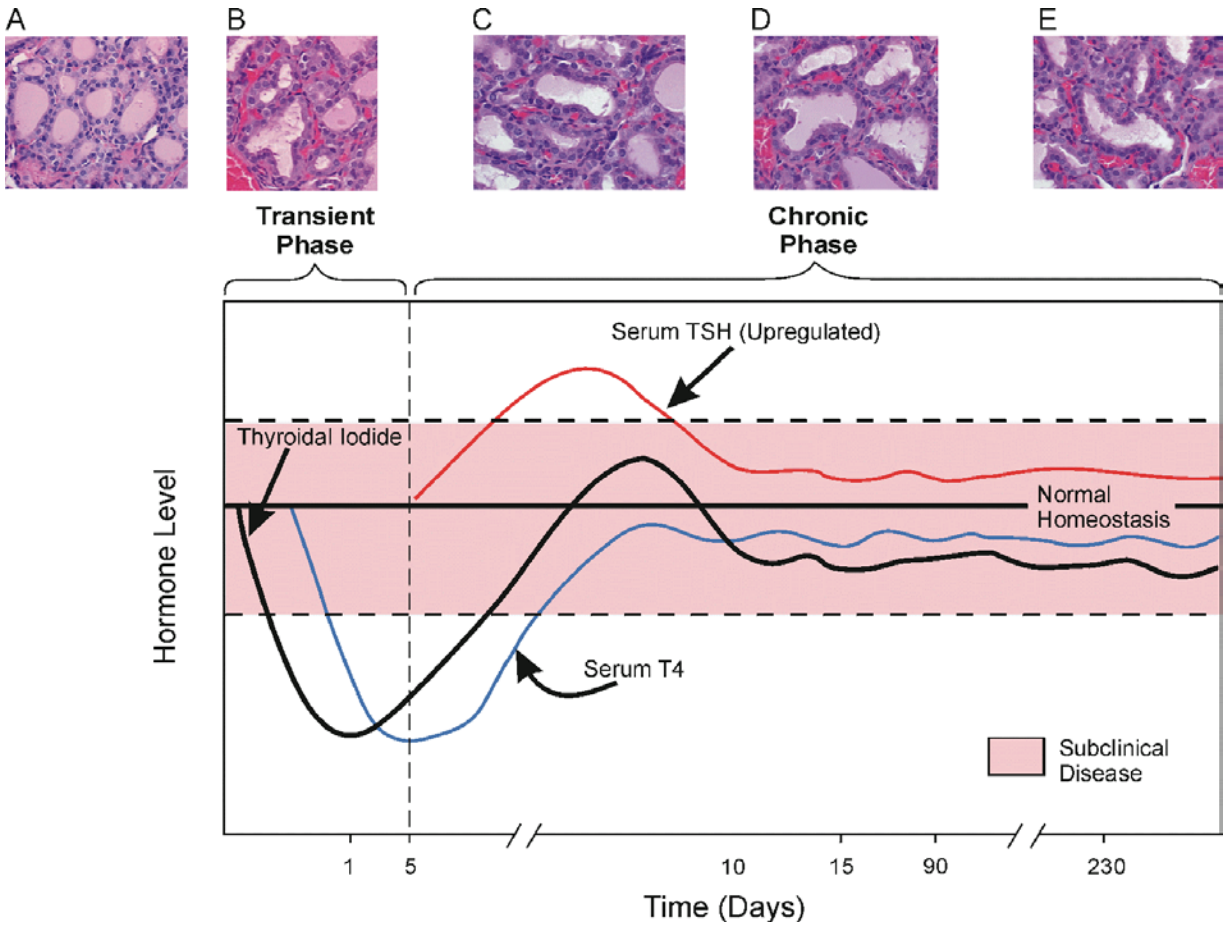
* Hormone analyses (T4, T3, and TSH), thyroid histopathology, and recovery satellites also added

1998 EPA Assessment External Review Draft (ERD) and 1999 Peer Review

- Basis of 1998 health assessment
  - Thyroid histopathology in PND5 rat pups
  - Histopathology in neonatal pup thyroid used as biomarker for adverse hormonal changes *in utero*
- Screening level ecotoxicological assessment
  - Agreed with characterization
  - Identified additional data gaps
- Scientific expert peer findings
  - Concurred with conceptual model and nonlinear approach
  - Supportive of concern for neurodevelopmental effects
  - Provided recommendations for additional studies

Challenge of Characterizing Dynamic System

- Histopathology is “freeze frame” at specific points
- Changes in gland acting as biomarker for perturbation of hypothalamic-pituitary-thyroid (HPT) axis



1999 Peer Review Recommendations

- Evaluate variability in radioimmunoassay (RIA) kits across laboratories
- Pathology Working Group of thyroid histopathology
- Additional brain morphometry if material available
- New developmental study in rats
- Repeat motor activity study in rats
- Repeat and additional immunotoxicity studies in mice
- Pharmacokinetic information in humans and rats
- Alternative statistical analyses for hormone data
- Chronic ecotoxicological studies
- Additional ecotoxicological receptors
- Data on transport and transformation

2002 EPA ERD and Expert Peer Review

- Basis of 2002 health assessment
  - Multiple lines of evidence to arrive at conclusions regarding neurodevelopmental toxicity
  - Point of departure based on thyroid hormone changes, brain morphometry, and thyroid histopathology
- Summary of scientific expert peer findings (peer panel report, June 2002)
  - Concurred with key event, conceptual model, and harmonized, nonlinear approach to RfD derivation
  - Uncertainty regarding nature of interaction of perchlorate with sodium (Na^+)-iodide (I^-) symporter (NIS) and concern over added impact at fetal and neonatal life stages
  - Suggested synthesis of human data to inform point of departure
  - Divergent opinions on brain morphometry – different options for clarifying how these data help to inform point of departure
  - Revisit uncertainty factors based on above

2002 EPA ERD and Expert Peer Review

- Basis of 2002 ecotoxicological screening-level assessment and findings
  - Agreed with conceptual approach and characterization
  - Recommended that new studies warranted revisit
- 2003 Response document used new data to arrive at full characterization of ecotoxicological risks
- New evidence for potential of indirect exposure via plant and other food commodities (e.g., milk)
  - Impact on relative source contribution (RSC) for derivation of drinking water standard but not on RfD
  - Purview of efforts by other agencies (USDA and FDA)

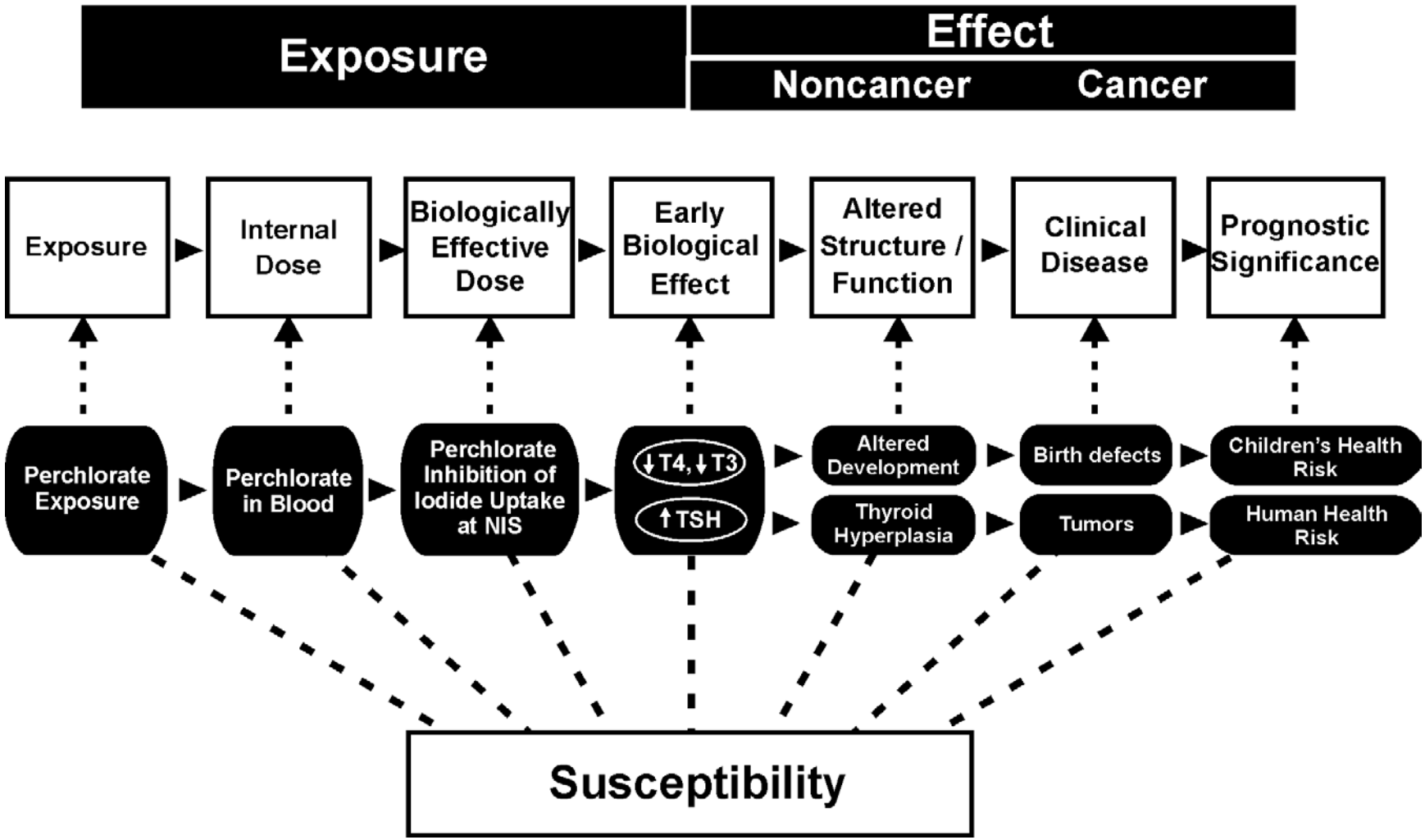
2003 EPA Response Document

- **General outline of EPA response document**
  - Peer panel report and public comments
  - EPA response
  - EPA recommended revisions as required
- **Specific issues in each area correspond to chapter topics**
  - Mode of action and PBPK models
  - Laboratory animal data
  - Human data
  - Human health risk assessment
- **Revised integration of data to identify point of departure**
  - Performed analyses to address panel and public comments
  - Incorporated new data from literature
  - Used established approaches to designate effect levels
  - Reconsidered UF based on above

Perchlorate and the Sodium (Na^+)-Iodide (I^-) Symporter (NIS)

- **Overall conceptual model and proposed sequelae**
  - Nonlinear low-dose extrapolation
  - Rat as model for neurodevelopmental effects versus neoplasia
- **NIS inhibition in other tissues affects dosimetry at different life stages**
  - Placental transfer impact on fetus
  - Lactational transfer impact on neonate
  - Uncertainty in parallelogram approach and use of area-under-the-curve in blood (AUCB) as dose metric
- **Interaction of perchlorate at the NIS**
  - Competitive or non-competitive
  - Translocation of parent or reduced forms
  - Choice of AUCB as dose metric
  - Comparison with other anions

Revised Mode of Action (MOA) Model



Perchlorate Sequelae

- Neoplasia
  - Consistent with existing Agency guidance on assessment of thyroid tumors (Assessment of thyroid follicular cell tumors, US EPA, 1998 EPA/630/R-97/002 available on-line @ www.epa.gov/ncea/thyroid.htm)
  - Carcinogen characterization takes into account
    - Thyroid tumors in laboratory animals
    - Relevance of mode of action
- Neurodevelopment
  - Shape of dose-response for neurodevelopment not established; some data suggest linear
  - Rat is appropriate animal model for neurodevelopmental effects
  - Uncertainty in dose metric for brain changes — serum hormones are external surrogate for target tissue
- Nonlinear approach is indicated and harmonized RfD is protective for both sequelae

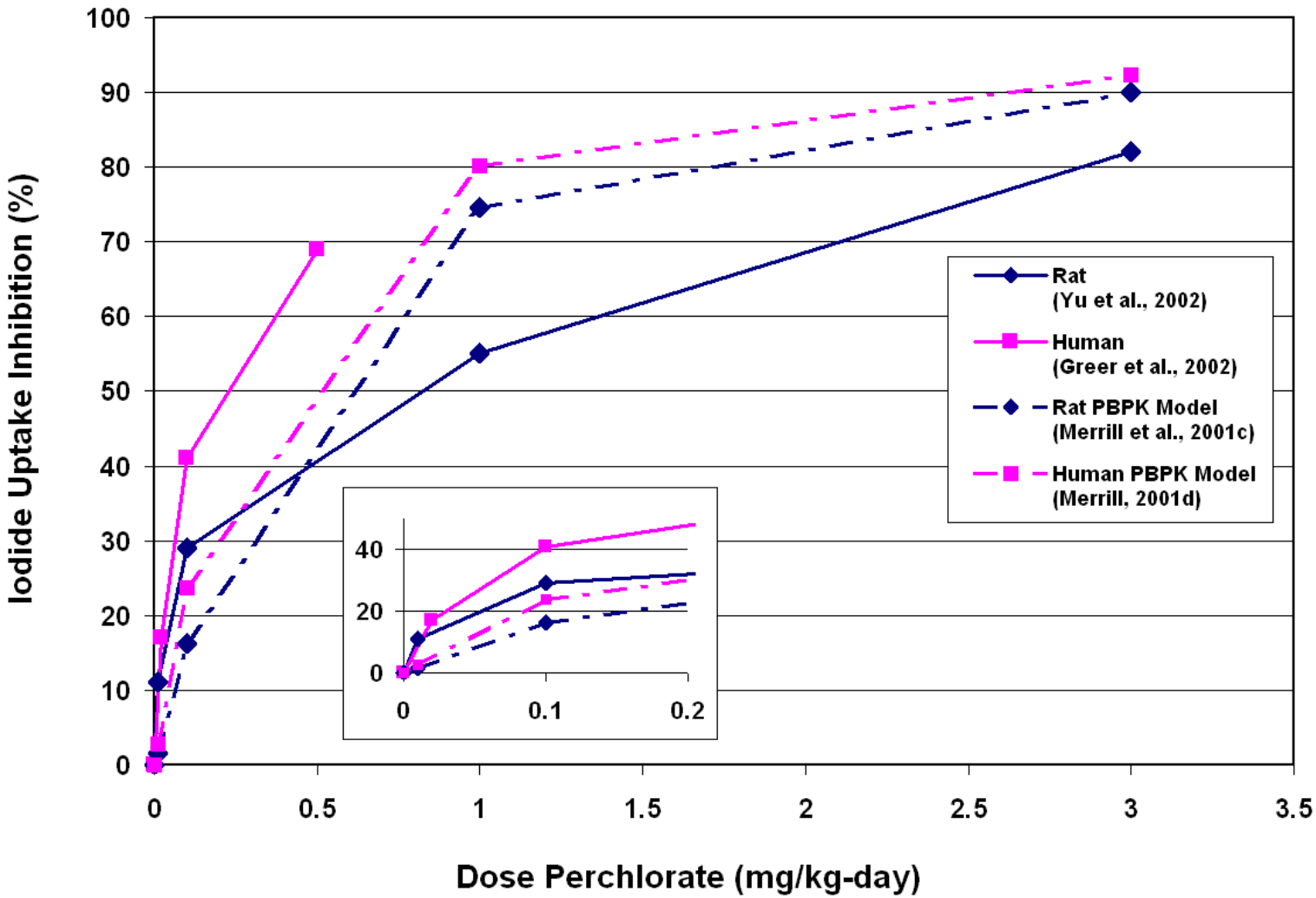
Rat Model of Neurodevelopment

- **Rat model is basis of most knowledge of thyroid hormone action and gene expression in brain**
- **Rat model is relevant to humans**
  - Analogous regulatory feedback system
  - TR expression and sequencing of genes in brain development
  - Similar disease hallmarks: growth rate, motor impairment, hearing loss, structural brain changes and cognitive dysfunctions
  - Replacement therapy can reduce deficits
- **Allows experimental evaluation of timing and impact on**
  - Life stages
    - TH maternal circulation reaches fetus
    - Fetus, neonate, reproductive and senescent adult
  - Critical endpoints
    - Brain structure and function
    - TH effects on fetal brain affect behavior in adulthood
- **US EPA and WHO assessment guidelines rely upon rat model to characterize risk of neurodevelopmental toxicity**

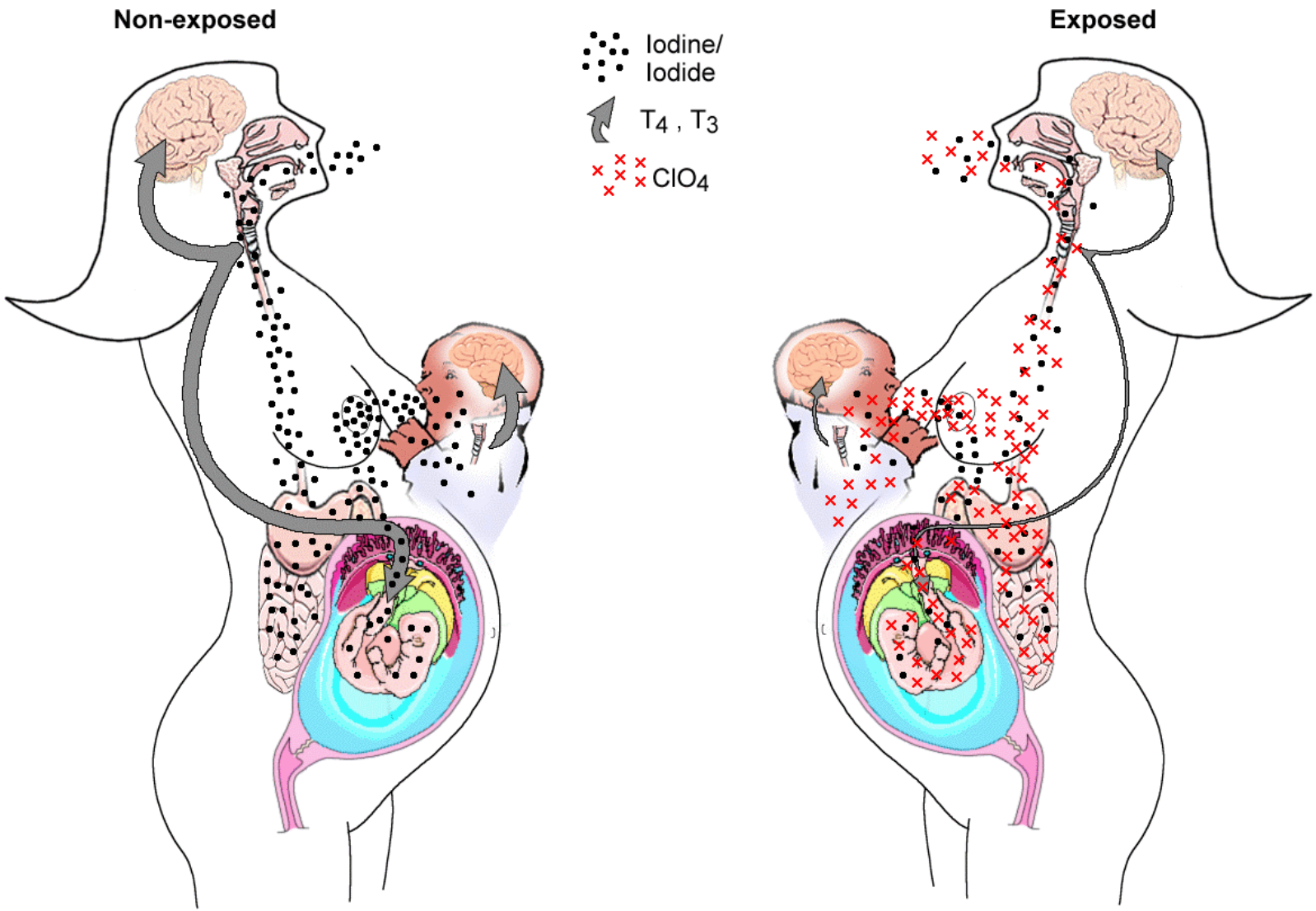
Sensitivity of Rat Model

- "Threshold" for altering gene expression has not been experimentally identified
  - Limited epidemiological data suggest subtle maternal hypothyroxinemia impairs neurodevelopment
  - Rat models to date have not studied more subtle forms of disease
  - Target tissue (brain) relationships to serum hormones not established in either dams or offspring
- Rat equal to or less sensitive than human for neurodevelopmental impairment

Interspecies Comparison of NIS Inhibition

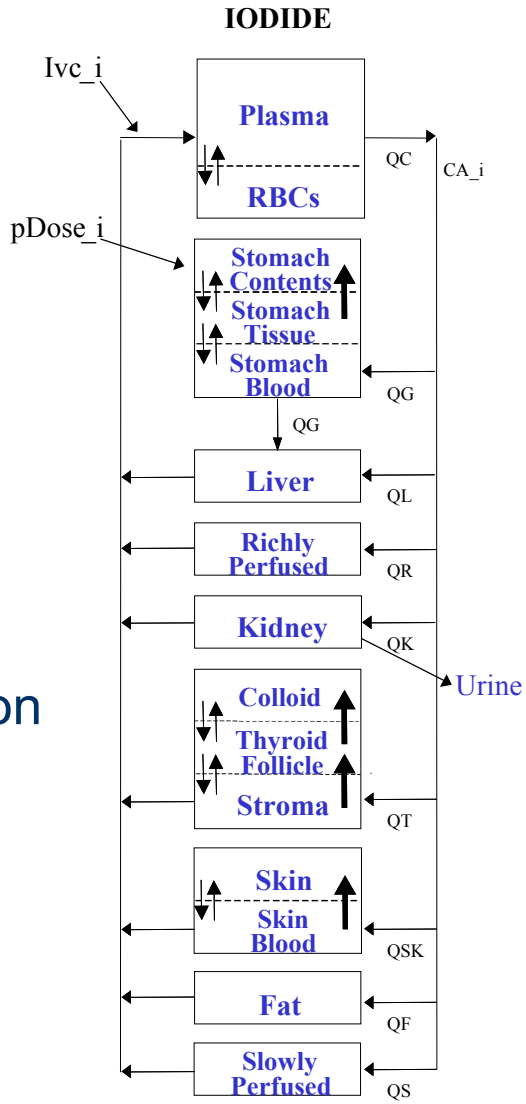


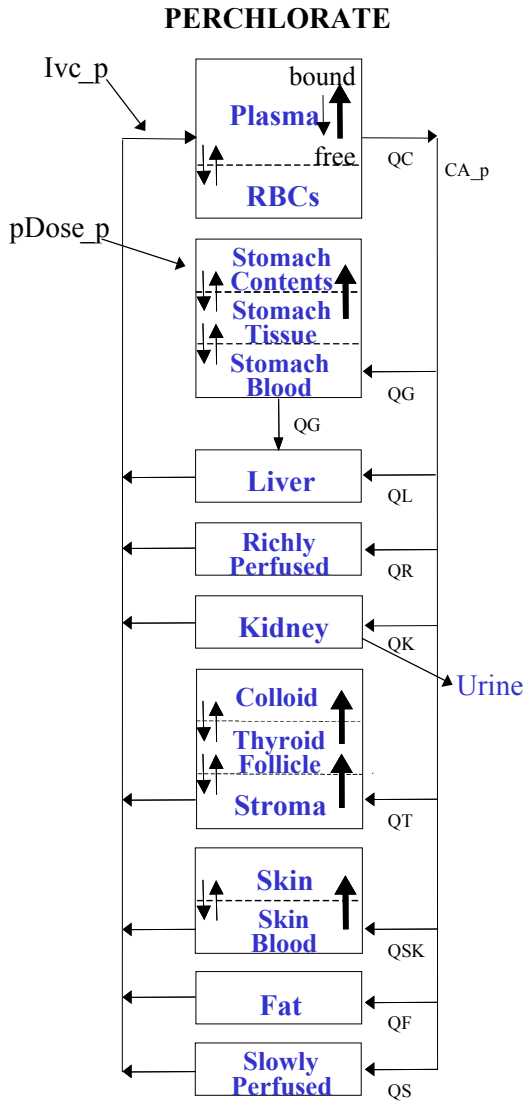
Life Stage Dosimetry Considerations
Perchlorate Exposure is Multifactorial



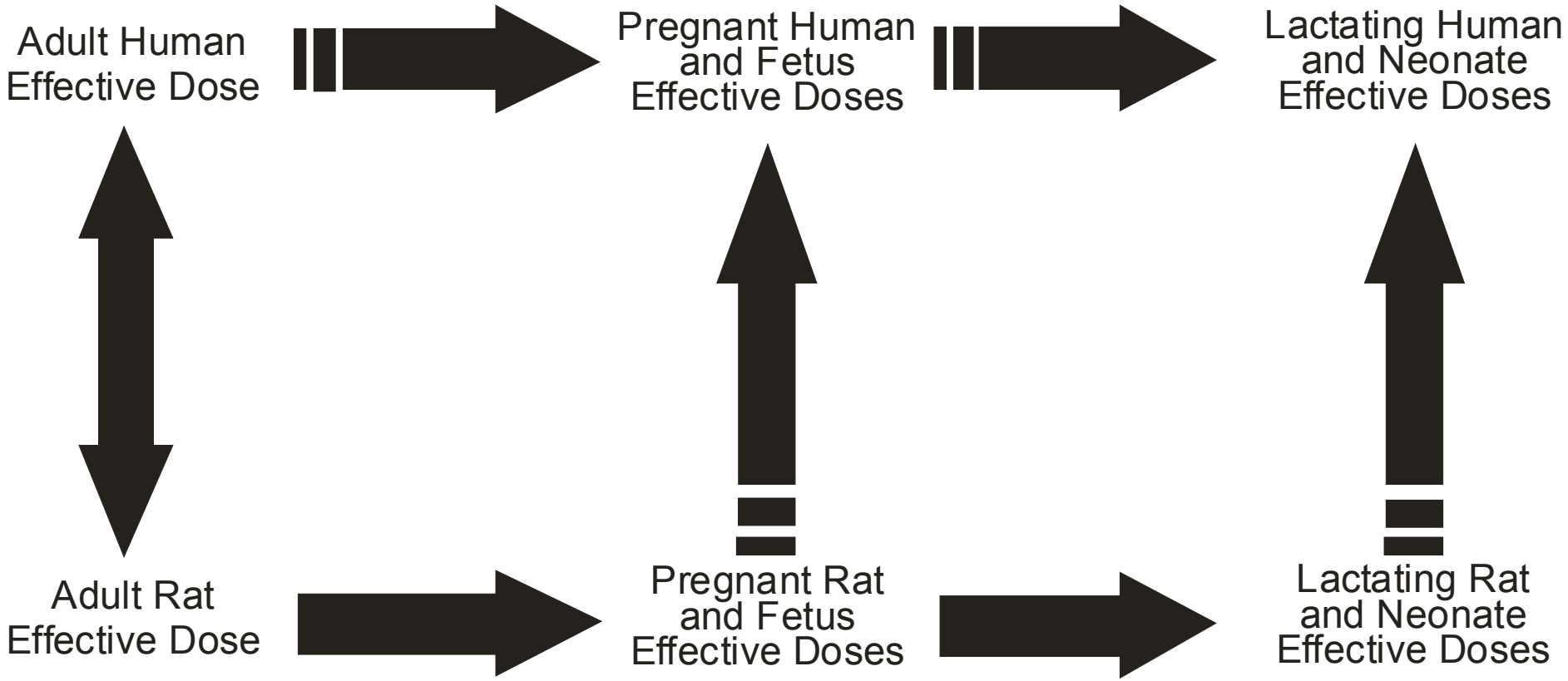
Air Force Research Laboratory Dosimetry Model Structures

- 4 Model structures
  - Adult male rat
  - Adult human
  - Pregnant rat & fetus
  - Lactating rat & fetus
- Compartments for key tissues
- Iodide and perchlorate disposition
  - Active uptake described Michaelis-Menten saturation
  - Permeability area cross products and partitions
  - Passive diffusion
  - Plasma binding
  - Urinary elimination
- Growth





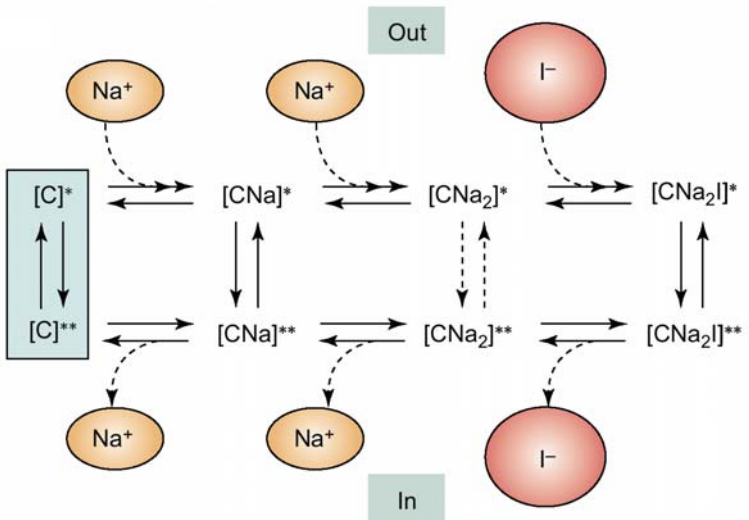
Uncertainty in Parallelogram Extrapolation



- Area-under-the-curve in blood (AUCB) chosen as dose metric

Uncertainty at NIS

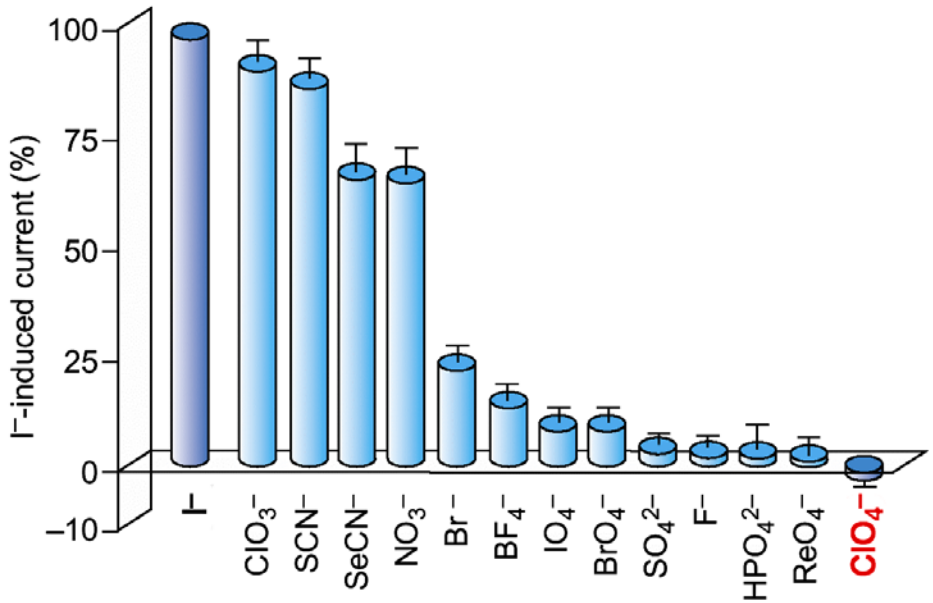
- Uncertainty exists regarding mechanism(s) of perchlorate interaction at NIS in thyroid and other tissues
- Not likely to affect area-under-the-curve in blood (AUCB) as dose metric because thyroid represents small volume
- Revised document to include more mechanistic description of NIS and update with any new data or conclusions



Electrophysiological model of NIS (Riedel et al., 2003)

Uncertainty at NIS

- Electrophysiological data also suggest perchlorate is not translocated into follicular cells but does not rule out a 1:1 exchange or reduced forms entering the cells
- Relative potency of anions for NIS interaction an important characterization for comparisons and consideration of background exposures



Considerations of Other Dietary Anions

- Agency recognizes the importance of background dietary exposure to anions, both as a potential cumulative burden of toxicity and as a basis for evaluating relative contributions
- Comparisons of perchlorate toxicity and proposed RfD to various dietary NIS inhibitors are nonproductive
  - Quantitative comparison precluded given disparity in database, endpoints, uncertainty factors and derivation date
  - Data on thiocyanate and nitrate are old and limited
  - Need comparable quantitative dose-response and pharmacokinetic data in life stages
  - Agency may need to revisit the other RfD estimates
- Mechanistic differences in potency of different anions at the NIS must be addressed

Challenges and Uncertainty Due to Dynamic System

- Concern for transient hormone changes
  - Clinical norms not necessarily appropriate for public health characterization and population studies
  - Controversy regarding adequacy during pregnancy
- Timing of critical developmental windows
  - Difficult to detect cognitive effects in humans
  - Laboratory animal models not refined
- Dosimetry in fetus
  - Dependent on maternal thyroid hormones for most of gestation
  - Perchlorate crosses placenta
- Dosimetry in neonate
  - Perchlorate inhibits iodide uptake in mammary glands
  - Perchlorate transferred in milk

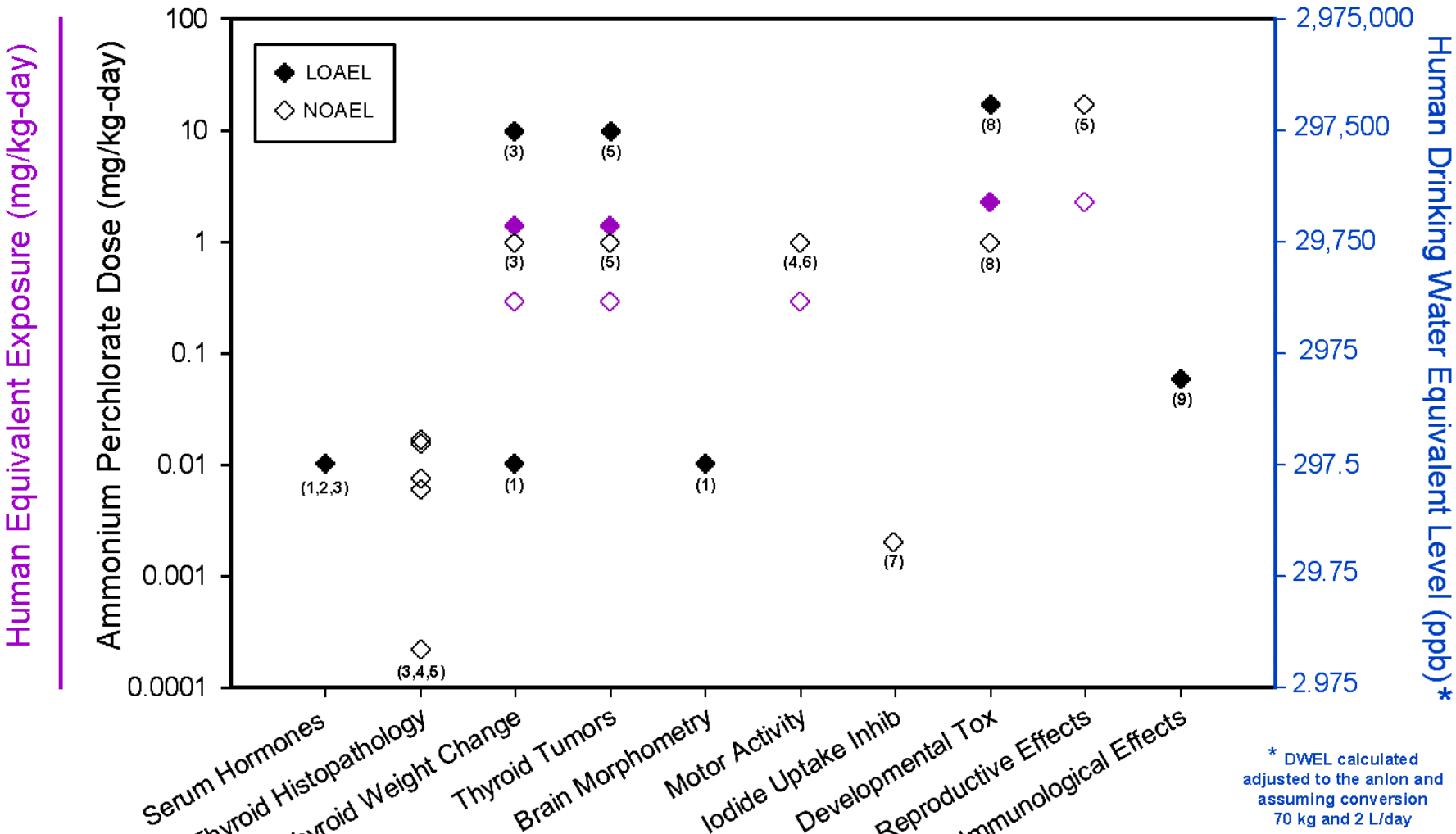
EPA Point of Departure Analysis

- Point of departure (POD) critical to RfD derivation
- POD is typically identified from No-Observed-Adverse-Effect Level (NOAEL) / Lowest-Observed-Adverse-Effect-Level (LOAEL) or Benchmark Dose (BMD) approach
- New analyses to designate effect levels
- Multiple effects in laboratory animal results observed at 0.01 mg/kg-day
- Human iodide uptake inhibition parallels rat results

EPA Point of Departure Analysis

- Integration of human and laboratory animal data
  - Consider reliability of study to characterize effect in different life stages
  - Weight of evidence for endpoints
  - Apply dosimetric adjustment

Revised Point of Departure Analysis



Point of Departure: Thyroid Histopathology

- Three indices (colloid depletion, hypertrophy, and hyperplasia) chosen by NIEHS Pathology Working Group (PWG) to represent changes indicative of an impact on HPT axis and thyroid function
- Benchmark dose approach with 10 % response level used to characterize dichotomous effects
- Overlap of indices within individual studies indicate that all three monitor feedback mechanism
- Inform point of departure in context with other endpoints
  - BMDL for colloid depletion in pups at 0.009 and in dams at 0.029 mg/kg-day in 1998 DNT study
  - BMDL for hyperplasia at 0.0004 mg/kg-day at 19 weeks in two-generation study
  - BMDL for colloid depletion and hypertrophy at 0.03 and 0.008 mg/kg-day in 90-day study
- EPA agrees with 2002 peer panel comment that it is unlikely experimental diet had any bearing on studies

Point of Departure: Serum Hormone Data

- ANOVA used to address shift in exposed versus control means
- Qualitative pattern consistent across entire data array
- Quantitative differences due to disparity in laboratories and experimental design (life stage, dosing, and sampling times)
- Variability also due to calibration of RIA kits
- LOAEL for hypothyroidism in dams at 0.01 mg/kg-day in 2001 effects study; and for T4 and TSH in male pups at PND21
- LOAEL for T4 and TSH at 14-day and 90-day time point as well

Point of Departure: Brain Morphometry

- Measurements recommended by EPA / OECD screening test guidelines — developmental neurotoxicity (DNT) study considered key in testing strategy
- Two studies funded by PSG / DOD show effects on brain
  - 1998 DNT study (Argus Research Laboratories)
  - Repeat morphometry with Argus 2001 "Effects Study"
- EPA performed profile analysis to address repeated measurements made in brains of individual animals
- Profile analysis indicated 0.01 mg/kg-day as a LOAEL
- Various methodological concerns brought to panel attention
- Difference of opinion on reliability — 2002 peer panel recommended that EPA needed to address these issues and / or rely on other endpoints to designate POD

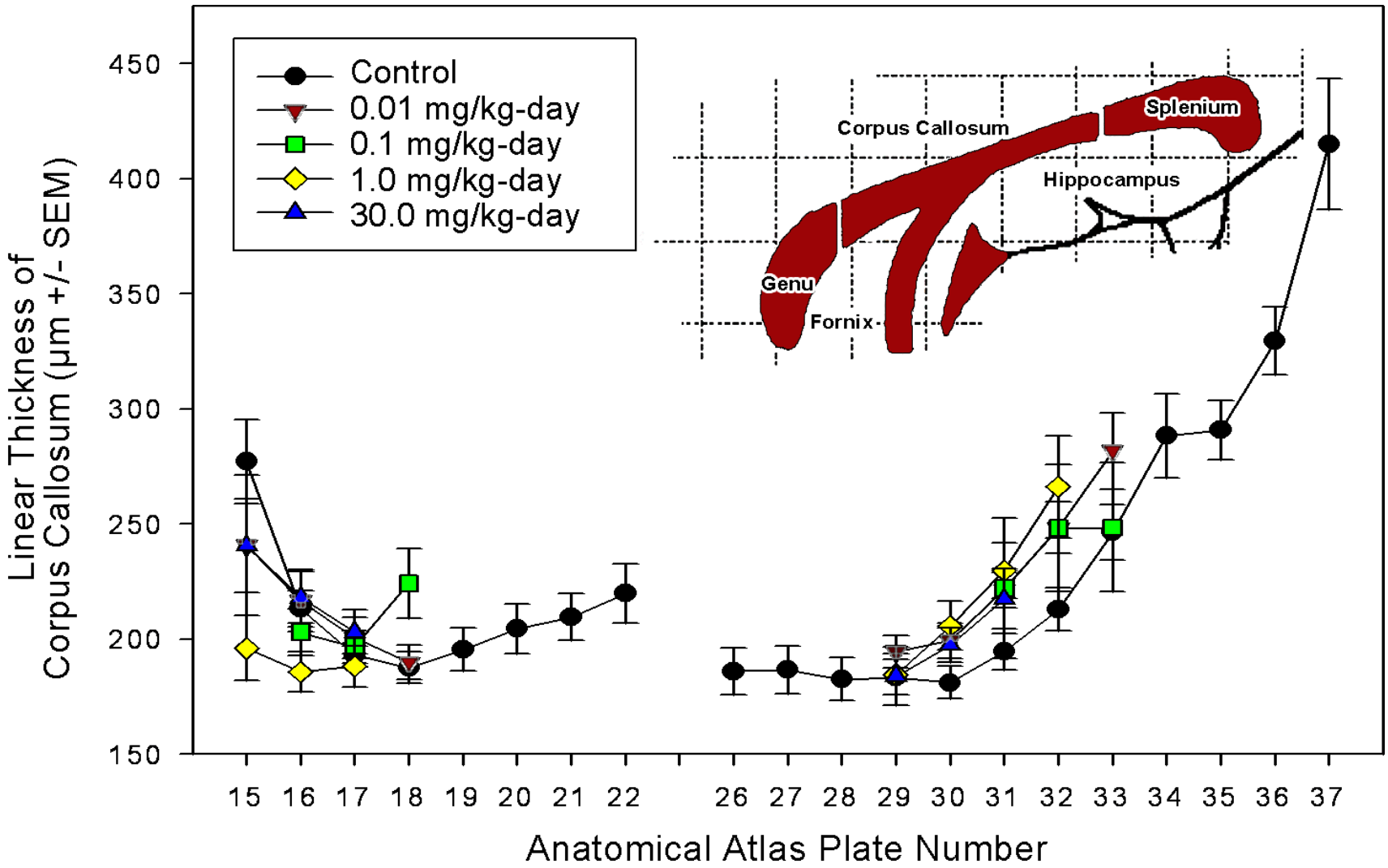
EPA Responses to Brain Morphometry Issues

- Sectioning and plane of cut
  - Protocol agreed upon by all parties *a priori*
  - Confirmed all tissues blocked and fixed at same time; sectioned by same pathologist
  - Coronal sectioning better for other brain regions affected; corpus callosum reliably evaluated
  - EPA focused on PND21 brains as suggested by NIEHS; same results if use PND9 brains
- Linear measurements and lack of blind reading
  - No data to suggest volumetric measures better
  - Society of Toxicologic Pathology does not suggest blind reading for measurements
- Variability in measurements
  - Evaluated through standard statistical approaches

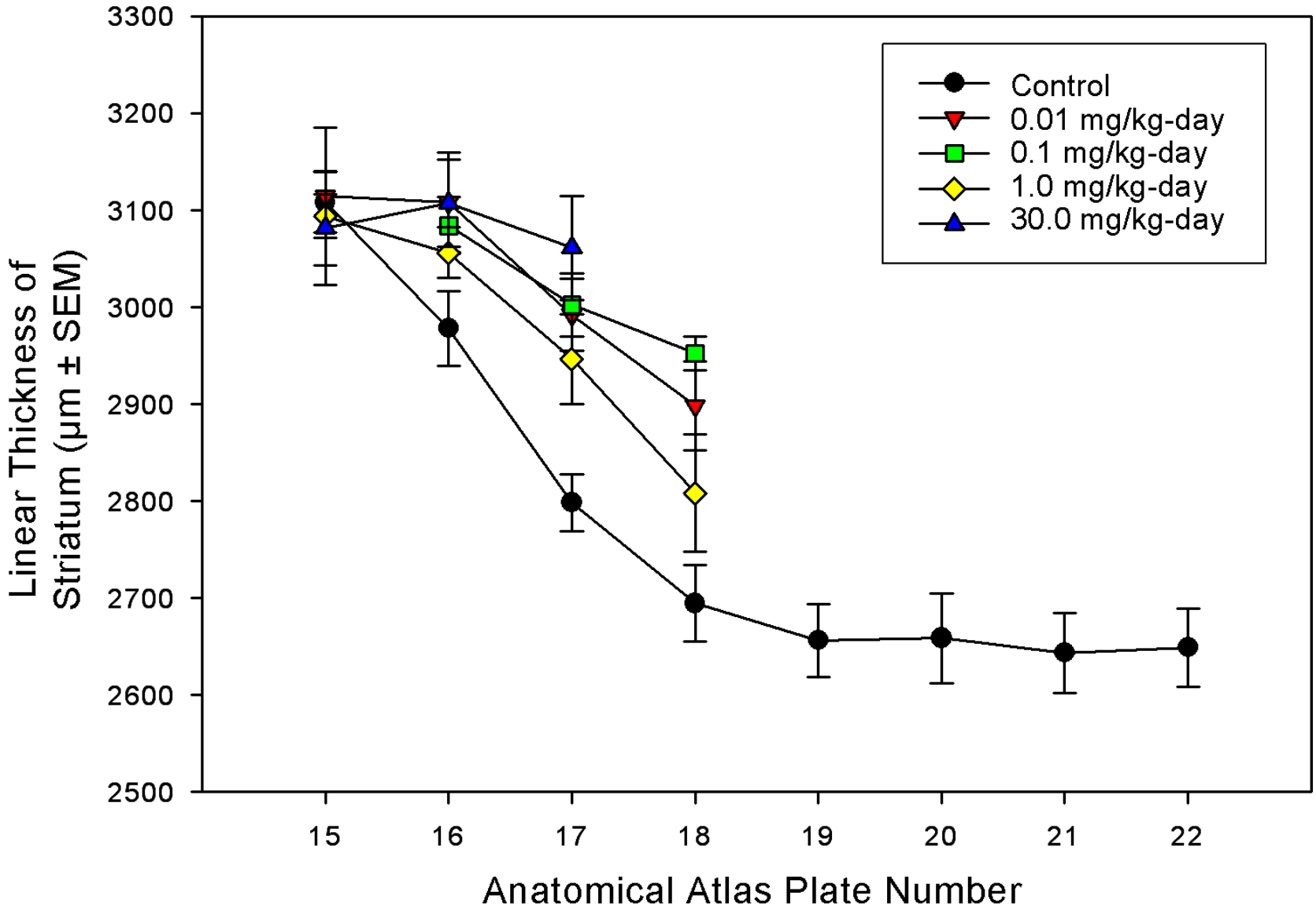
EPA Responses to Brain Morphometry Issues

- Systematic bias in sections of tissue block level II
  - 2002 Panel determined likely to be random rather than introduce an effect that is not there
  - Supported by restricted analyses limited to sections from tissue blocks not in question
  - EPA addressed further with analysis of new data that controlled for depth
  - EPA contracted with same pathologist as Argus studies
- Shape of the dose-response
  - U-shaped likely due to multiple mechanisms and brain regions with different trajectories

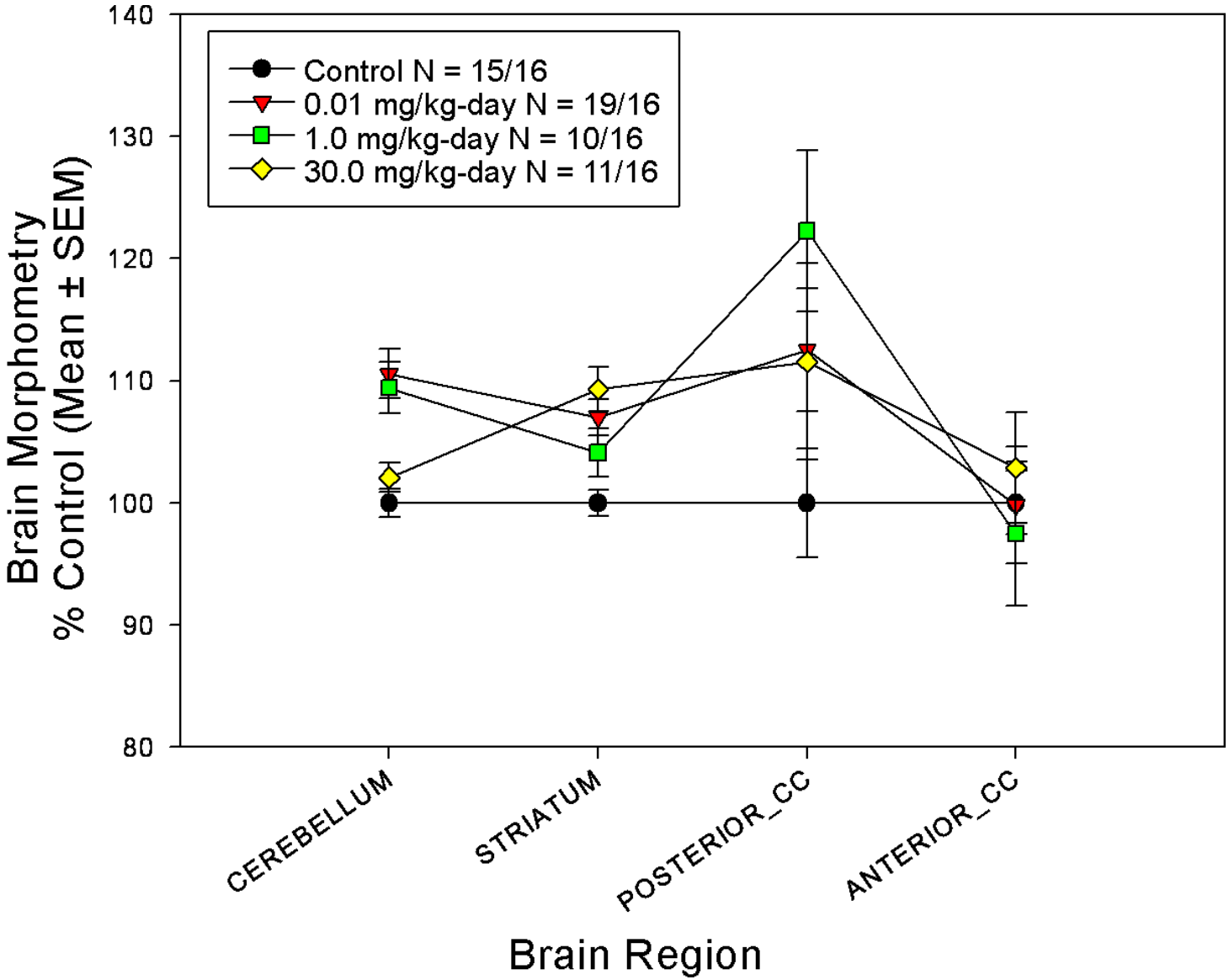
New Sections of Corpus Callosum



New Sections of Striatum



New Profile Analysis of Sections Controlled for Section Depth



Analysis of Motor Activity

- Data from two studies funded by PSG / DOD
  - 1998 DNT (Argus Research Laboratories, Inc. 1998a)
  - Repeat DNT performed by US Navy (Bekkedal et al., 2000)
- Infrared photocell fields used to measure number of movements, distance moved, time spent moving
- Bayesian approach to address statistical issues:
  - Univariate repeated measures ANOVA require adjustment for multiple comparisons
  - NIEHS used an animal and age-specific latent variable approach that tracks global effects and affords comparisons between studies
- 2002 Peer panel agreed that analyses indicate neurobehavior affected — NOAEL estimated at 1.0 mg/kg-day

Perchlorate Neurotoxicity

- Use contemporary principles (EPA and WHO) to integrate neuroendocrine impacts, neurobehavioral effects, and structural changes in brain across various studies
  - Perchlorate reduces serum thyroid hormones
  - Hypothyroxinemia alters neural development
  - Perchlorate alters size of brain structures
  - Perchlorate alters behavior of offspring
- Pattern of evidence combined with larger scientific knowledge regarding role of thyroid hormones is sufficient to conclude developmental exposure constitutes potential risk of adverse effects at 0.01 mg/kg-day

Thyroid Tumors

- Three adenomas observed at 19 weeks in two F1-generation pups (dams exposed to 10 mg/kg-day) with increased incidence (6.7%) and decreased latency
- Bayesian approach to compare against all 2-year bioassay data in same strain and sex of rats
  - Consistent with precursor lesions
  - Rare tumors — background incidence of 1.1%
- Indicates concern for *in utero* programming
  - Recalibration of HPT during fetal exposure enhances susceptibility for additional exposures throughout life
  - Reinforced by observations of duration dependence in 90-day study and human short-term study
  - Highlights uncertainty due to lack of chronic data

Other Endpoints in Data Array

- Developmental toxicity
  - Historical data limited in utility
  - Correction of LOAEL as 30 mg/kg-day
- Reproductive toxicity
  - EPA re-evaluated sperm motility data based on peer panel concern
  - EPA again concludes the NOAEL is 30 mg/kg-day
- Immunotoxicity
  - EPA concerned for hypersensitivity base on local lymph node assay (LLNA) results
  - 2002 peer panel did not recommend as sole basis of UF for database deficiency

2002 Peer Review Comments on Human Data

- Human data help inform point of departure
  - Clinical data more mechanistic
  - Ecological studies limited in utility
    - Poor exposure characterization
    - Lack of control for confounding
    - Small sample size
    - Limited outcome measures – no cognitive function
- Recommendations
  - Re-evaluate Greer et al. (2002) and Crump et al. (2000)
  - Perform new analyses to address specific concerns over aspects in each

Greer et al. (2002)

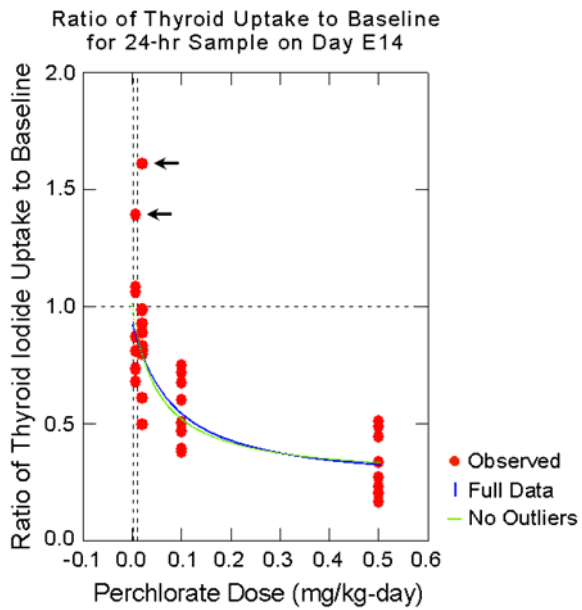
- PSG funded study was originally designed to provide pharmacokinetic data to AFRL human model development
- Fourteen-day exposure duration in 37 euthyroid adults
  - 24 in “main study” at doses of 0.5, 0.1 and 0.2 mg/kg-day
  - Limited “uptake study” in additional group of 7 subjects at 0.007 mg/kg-day and two more subjects at each previous dose group
- Radioactive iodide uptake (RAIU) and serum hormones measured after 1 and 14-days of exposure and 14-days post exposure
- Analyzed with linear-log regression model
  - 0 % inhibition substituted in equations for 1- and 14-day data to estimate “no effect” level range
  - No calculation of confidence intervals

EPA Reanalysis of Greer et al. (2002)

- RAIU and serum hormone data evaluated with alternative approaches
- Specific recommendations of 2002 peer panel addressed:
  - Influence of any apparent outlier(s)
  - Use of a more sophisticated model structure that allows for evaluation of the goodness of fit
  - Calculation of confidence intervals to address variability
  - Evaluation of the influence of age and gender with randomized block design
  - Evaluation of duration of the study exposure on resultant risk estimates
- Additional objective was to verify reported results

EPA Reanalysis of RAIU Data

- Alternative model structures explored
  - Allows extrapolation outside range of observation
  - Provides formal calculation of confidence limits
- Evaluation of outliers and goodness of fit



- Benchmark response level of 5% inhibition selected
  - Typical for continuous measure based on analysis of developmental data
  - Similar % inhibition in animals is associated with brain and serum hormone changes
- Evaluation of confounding including duration and age

Results of EPA RAIU Reanalysis

- Hill model chosen to fit individual data without outliers in observed range as well as the linear-log regression model used by Greer et al. (2002)
- A benchmark dose lower limit (BMDL) of 0.002 mg/kg-day estimated for the 24-hour sample on exposure day 14 — falls below “no effect” level calculated by regression because it is not a maximum likelihood estimate
- Consideration for uncertainty in extrapolation to general population include
  - Significant dependence on sample-time (8- or 24-hr) and dose-duration (after 1 or 13 days of exposure) demonstrated
  - Confounding by age also indicated
- Randomized block design not attempted due to limited sample size and lack of random assignment of subjects to dose groups

Greer et al. (2002) Serum Hormone Data

- Greer et al. (2002) used categorical variables in two-way ANOVA
  - Time of exposure (before, during, and after perchlorate)
  - Dose (low, mid, and high)
- Measured T4, fT4, T3 and TSH restricted to “main study” subjects (n=24)
- No significant dependence revealed but a mild decrease in TSH was observed at high (0.5 mg/kg-day) dose
- EPA analysis employed regression models using individual data and evaluated covariates of dose, sample times, exposure duration, circadian rhythm, and sex

Serum Hormone Data Results

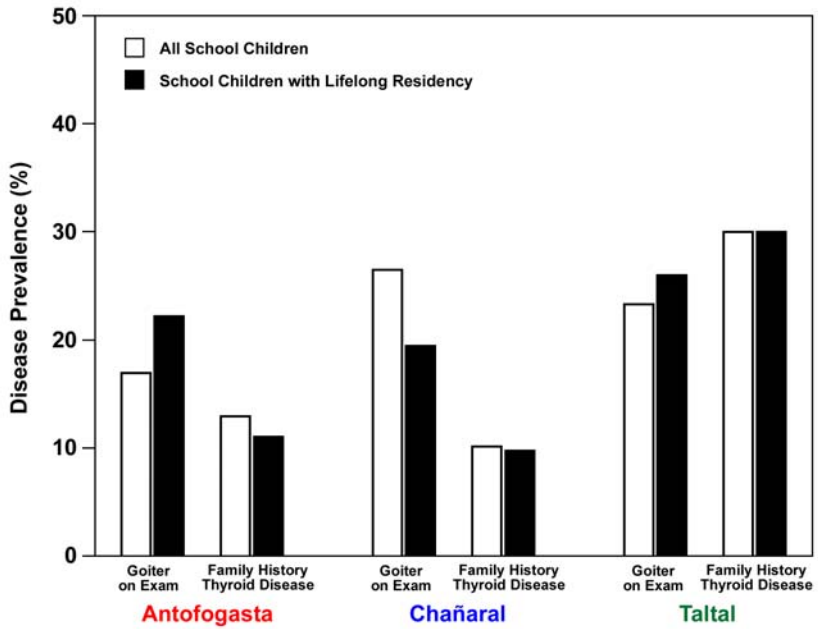
- EPA performed in-depth analysis using individual data
- Results suggest
  - Largest source of variability is individual baseline values
  - Duration of exposure is important — interaction products that included duration were more significant
  - Dose and duration of exposure produce shift in phase and amplitude of circadian rhythms of serum hormone levels

Crump et al. (2000)

- Ecological epidemiology study of three cities in Chile
  - 163 schoolchildren (ages 6 to 8 years)
  - 11,967 neonates (birth to 7+ days with 75% at age 3 days) in screening program
- Questionnaire and analysis of serum hormones
- Objectives of EPA reanalysis
  - Verify reported results
  - Consider study population
  - Evaluate exposure characterization
  - Analyze data with alternative approaches

EPA Reanalysis Results

- High background incidence of goiter and familial history of thyroid disease and elevated urinary iodine excretion levels suggest study population and location are inappropriate to study the effects of perchlorate
- Limited exposure characterization (mean of 25 samples) and use of indicator variable may not capture heterogeneity
- Arbitrary assignment of exposure values for concentrations below detection limits may exacerbate uncertainty
- Concern for comparability of demographic health characteristics compound that for sample size and variability of serum hormone analyses

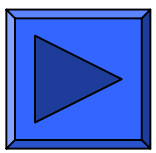


Use of Human Data

- Greer et al. (2002) supports point of departure
- Ecological studies funded by PSG are limited in utility
  - Occupational studies not appropriate route of exposure and did not adjust for dosimetry of particle size and distribution
  - Crump et al. (2000) population is not appropriate, lacks adequate exposure characterization, and failed to address covariates
- Two independent ecological studies [Brechner et al., (2000) and Schwartz (2001)] indicate effects of perchlorate on T4 in newborns in range of 1 to 5 ppb

Typical Factors for Uncertainties in Applied Extrapolations

H	Intrahuman variability
A	Interspecies extrapolation
S	Subchronic to chronic extrapolation
L	Lowest-Observed-Effect-Level (LOAEL) to No-Observed-Effect-Level (NOAEL)
D	Database deficiency



Magnitude of 1, 3 or 10 based on consideration of components within each factor

Data-derived and mechanistic insights may modify magnitude on case-specific basis

EPA Considering Revised Uncertainty Factors

- Intrahuman variability and interspecies extrapolation combined as a factor = 10
  - Uncertainty due to fetal and neonatal dosimetry
  - Uncertainty in AUCB as dose metric
- LOAEL to NOAEL extrapolation = 10
  - Brain morphometry, thyroid hormones, thyroid histopathology
  - Shallow dose-response curve
- Lack of chronic data and database deficiencies combined as a factor = 3
  - No two-year bioassay
  - Indications of *in utero* programming and duration-dependence of effects in 90-day rat study and in 14-day human study
  - Inadequate characterization of hypersensitivity

Operational Derivation

RfD (mg/kg-day) = 0.01 x 0.85 ÷ 300 = 0.00003

Where:

- 0.01 is the point of departure
- 0.85 adjusts to perchlorate anion alone
- 300 is the composite uncertainty factor

Hypothetical RfD Conversion

- Critical to distinguish the RfD from any guidance value that may result
- RfD (mg/kg-day) often confused with drinking water equivalent level (ppb)
- Conversion to drinking water equivalent level (DWEL) in ug/L (ppb):
  - Adjustment by 70 kg and 2 L
  - DWEL = 1 ug/L (ppb)

EPA Summary

- Studies provided to EPA by DOD / PSG represent state-of-the-science for risk assessment
  - According to test guidelines
  - Per strategy and in response to peer review recommendations
- Rigorous analyses performed by EPA
  - Formal statistics to address variability and designate effect levels
  - Mode of action superimposed on inferences
- Point of departure based on integration of human and lab animal data
- Harmonized approach protective of both neoplasia and neurodevelopmental effects
- EPA has benefited from previous peer reviews

NAS Review of the Science

- **EPA recognizes that an RfD determination is not a purely scientific matter.**
  - **Frequently a biological change or effect is observed, but there may exist uncertainty about what this effect means regarding an actual change in health status.**
  - **Science-policy judgments are often needed to determine the specific effects that should be presumed adverse for the purposes of determining an RfD.**
  - **Determining the appropriate uncertainty factor to apply to a believed adverse effect level also involves a science-policy judgment.**

- **EPA recognizes that scientific advice alone will not fully resolve this matter and that NAS is not a policy making body.**

- **EPA is requesting scientific advice from the NAS and is eager to consider whatever scientific insights NAS can provide.**