Understanding the Integrated Risk Information System (IRIS)

SAMANTHA J. JONES, PHD

ASSOCIATE DIRECTOR FOR SCIENCE

IRIS PROGRAM

NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT

OFFICE OF RESEARCH AND DEVELOPMENT

U.S. ENVIRONMENTAL PROTECTION AGENCY

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Disclaimer

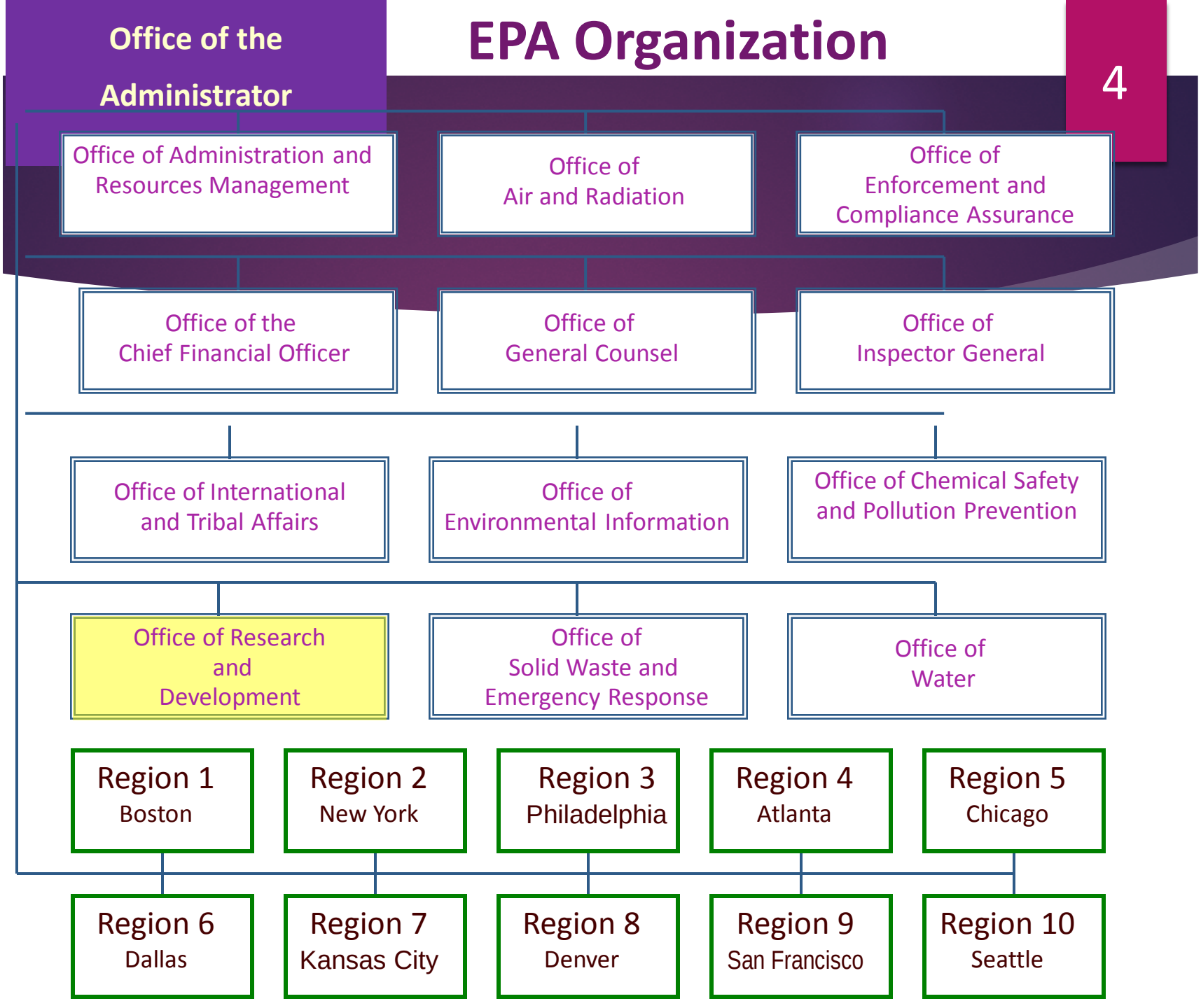
- The views expressed in this presentation are those of the author and do not necessarily represent the views and policies of the U.S. Environmental Protection Agency.

Overview

- Where is IRIS?
- Who makes up IRIS?
- What is IRIS?
- What are the components of an IRIS assessment?
- Uses of IRIS assessments
- Challenges and advances
- Engagement

Where is IRIS?

EPA Organization



ORD's National Labs and Centers

National Health and Environmental Effects Research Laboratory

Research on mechanisms and susceptibility to identify hazards and dose-response

National Exposure Research Laboratory

Research to measure, characterize and assess exposures and to support compliance with environmental regulations and policies

National Risk Management Research Laboratory

Research and technology transfer to prevent, mitigate and control pollution

National Center for Computational Toxicology

Application of computational tools and models to improve understanding of toxicity and risks posed by environmental agents.

National Center for Environmental Assessment

Development of human health assessments, research on risk assessment methods, and guidance development

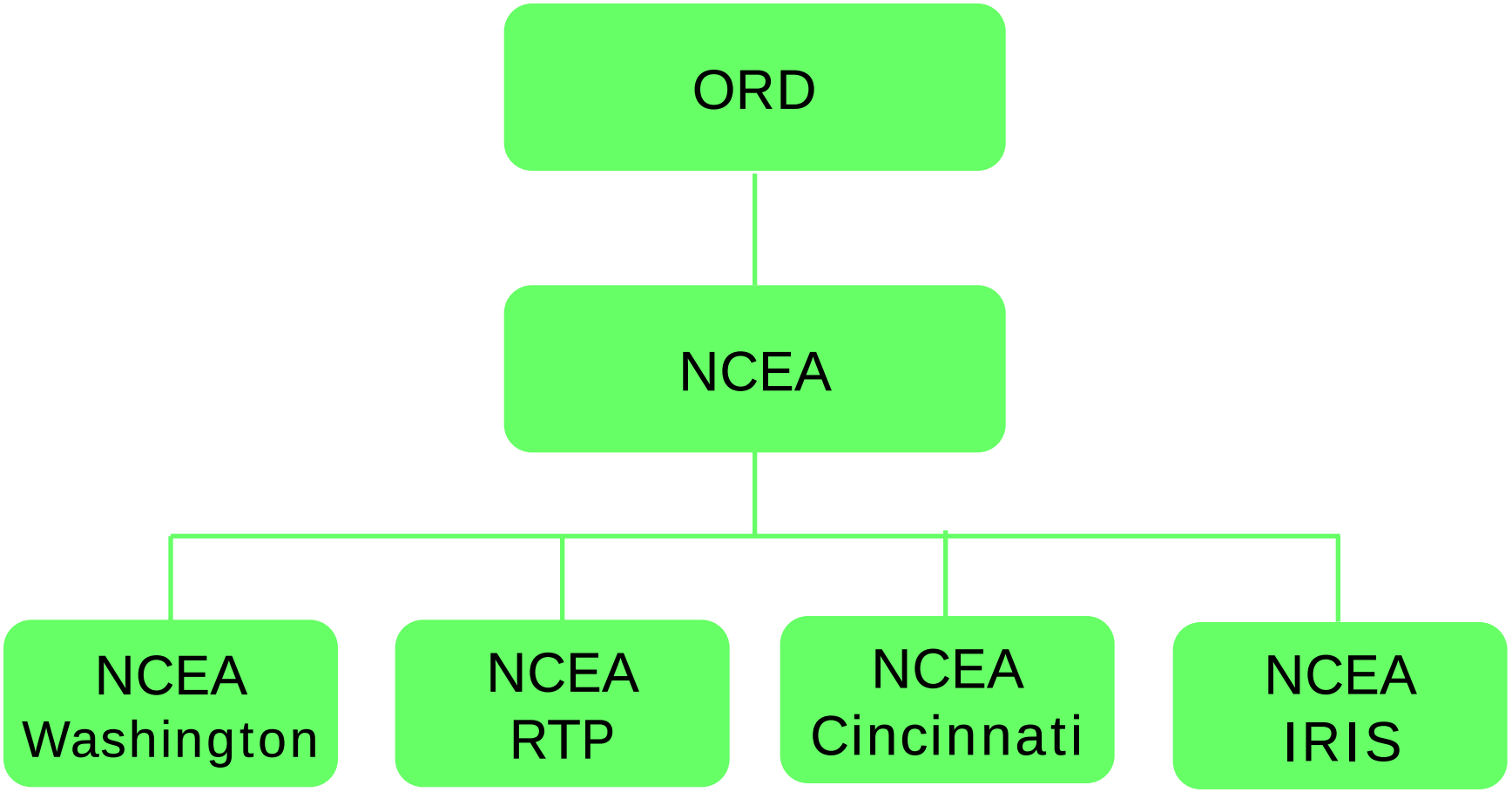
National Homeland Security Research Center

Research to help decision-makers prepare and respond to chemical and biological attacks

National Center for Environmental Research

Extramural program - grants, fellowships, and national centers of excellence - to complement ORD's in-house research program

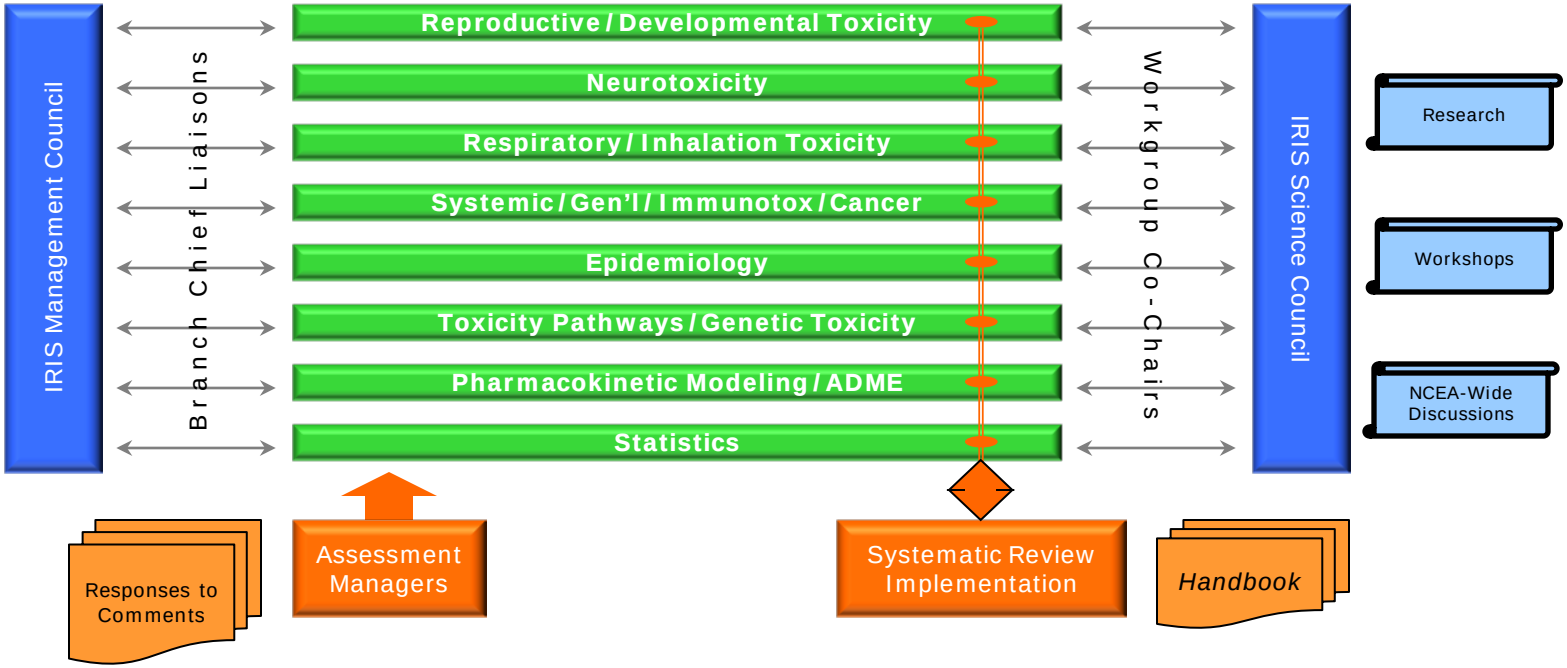
IRIS Program housed in National Center for Environmental Assessment



Who makes up IRIS?

IRIS Scientists

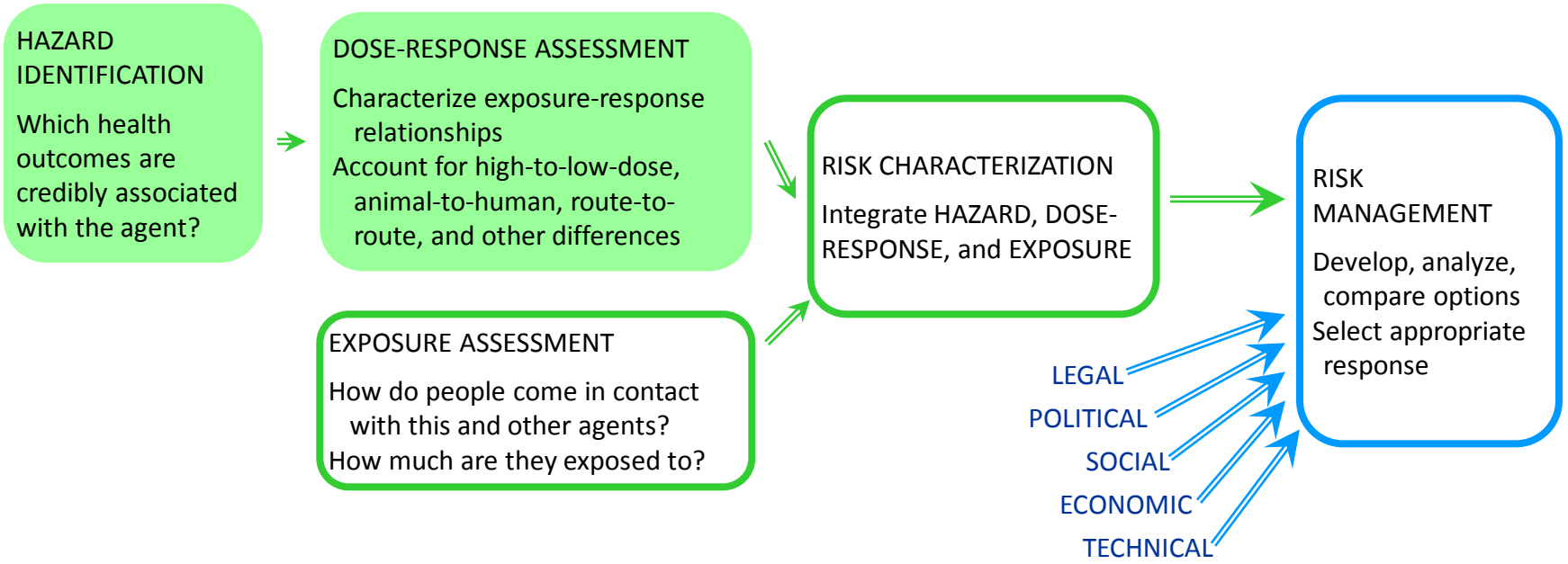
Staff comprised of toxicologists, epidemiologists, biologists, statisticians, and public health scientists.



What is IRIS?

Two steps of the Risk Assessment Process

- IRIS assessments critically review publicly-available peer-reviewed studies to
  - Identify adverse health outcomes
  - Characterize exposure-response relationships



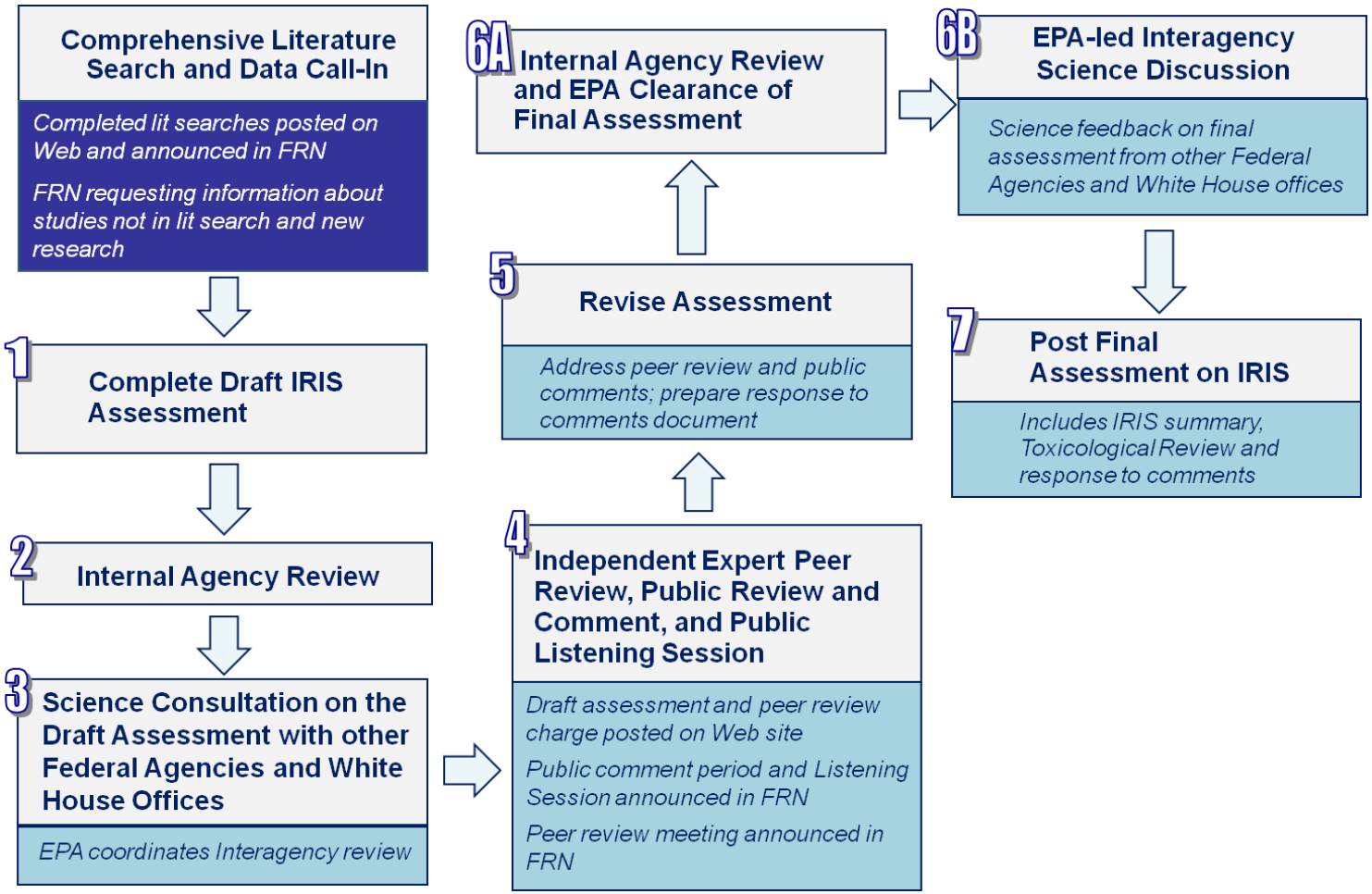
www.epa.gov/iris

- Provides scientific positions on potential adverse health effects that may result from exposure to substances found in the environment --> hazard assessments.
- Presented on the IRIS database in the form of an IRIS Summary and Supporting documents (i.e., Toxicological Reviews).
- Provides qualitative and quantitative health effects information on hundreds of substances.
- Toxicity values
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).

IRIS Program Overview

- Only federal public program that provides toxicity values for both cancer and noncancer effects.
- Focus is on estimating toxicity and cancer risk due to chronic exposure to environmental chemicals for purposes of protecting human health.
- Have no direct regulatory impact until they are combined with other information (extent of exposure to people, cost of cleanup, available technology, etc.) to inform actions and decisions.
- Used by:
  - EPA program and regional offices.
  - State and local health agencies.
  - Other federal agencies.
  - International health agencies.

IRIS Process



Components of the Assessment

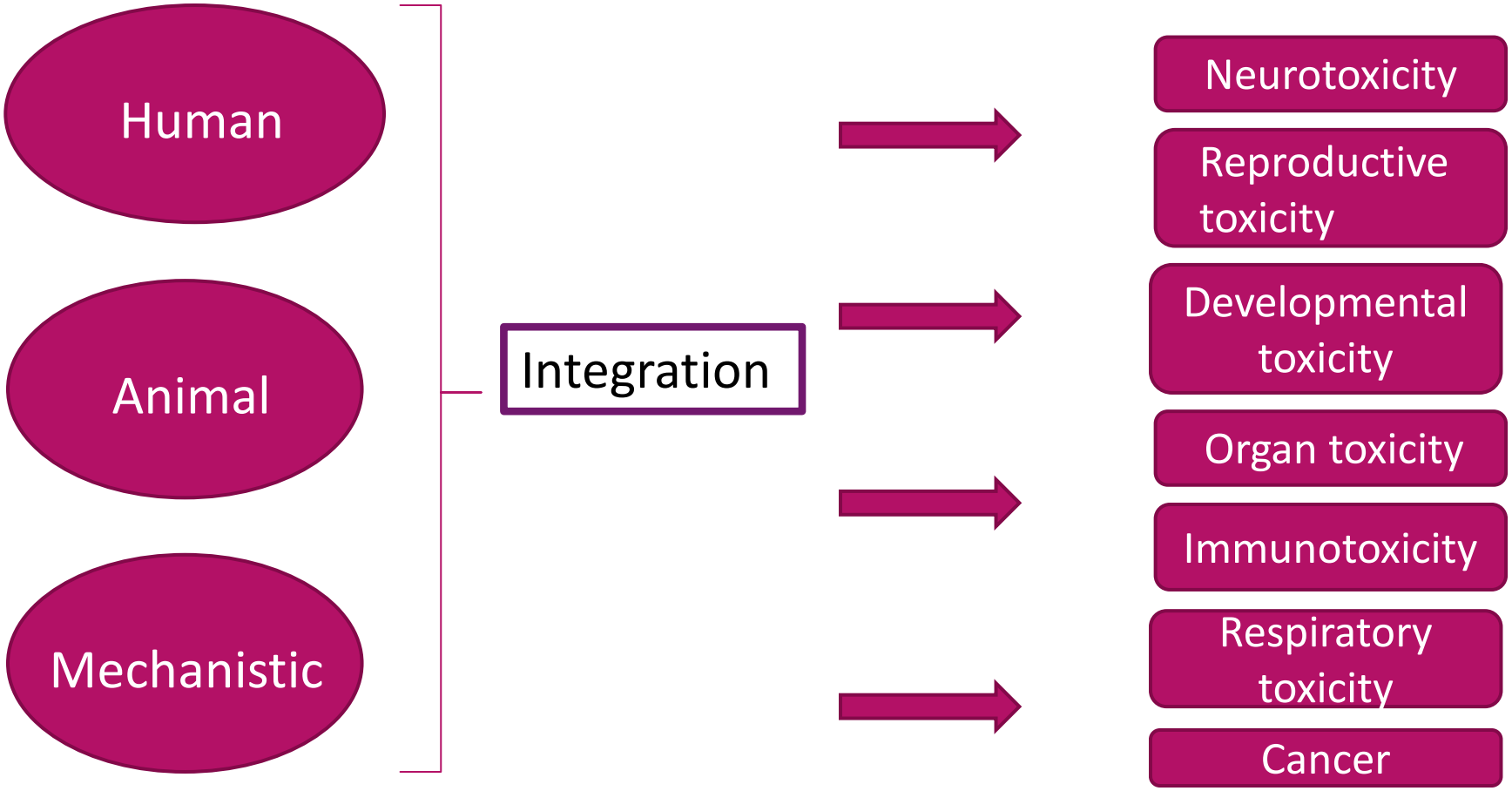
NONCANCER HAZARD STATEMENTS

CANCER DESCRIPTORS

IRIS Assessments seek to answer several questions…

- What health hazards are associated with Agent X?
- What can we say about toxicity pathways?
- What can we say about dose-response relationships?

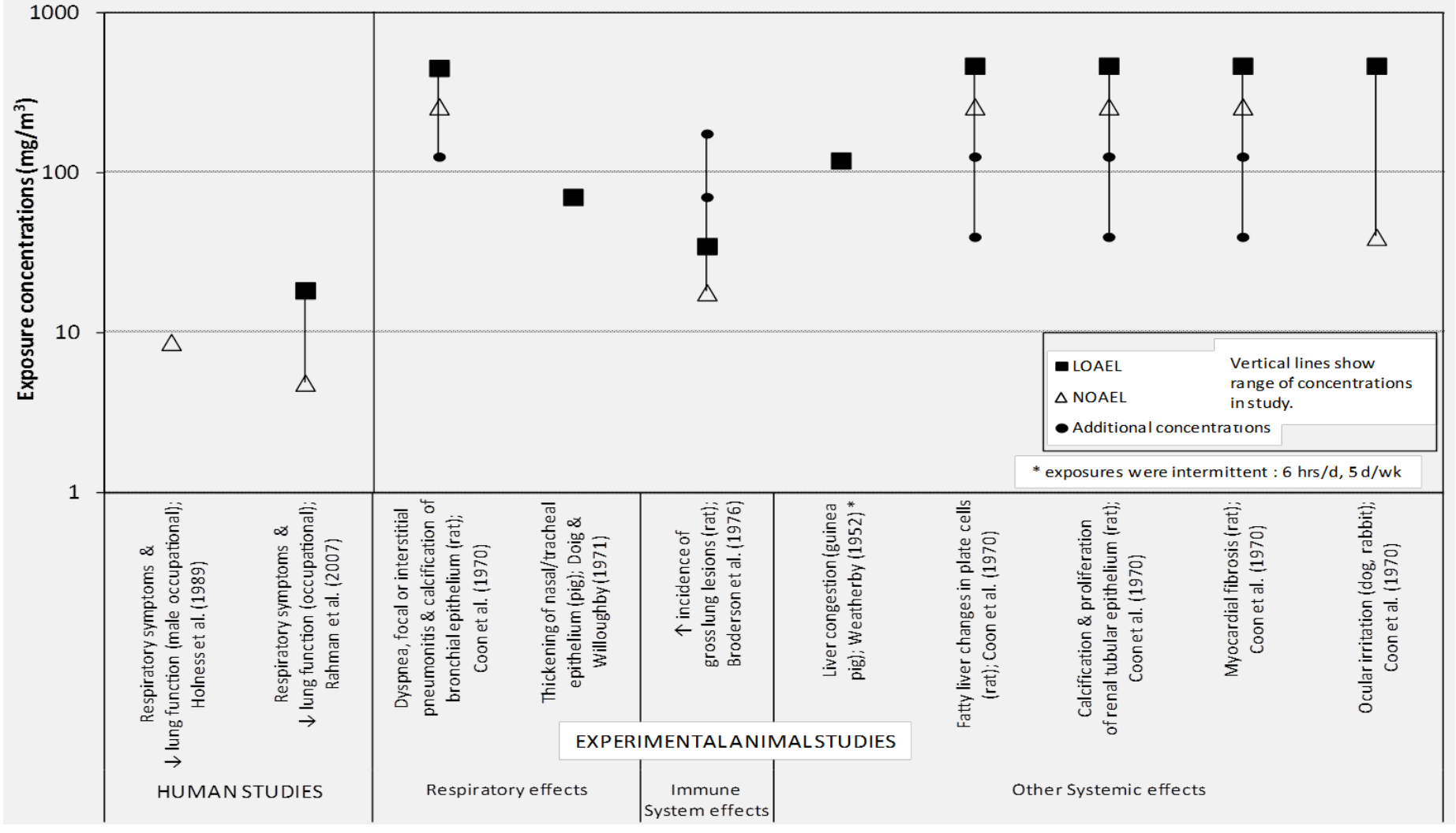
Hazard Identification



Standardized Presentation of Studies: Evidence Table

Study Design and Reference	Results
Birth outcomes and postnatal growth	
Mackenzie and Angevine (1981) CD-1 mice, 30 or 60 F0 females/ dose 0, 10, 40, or 160 mg/kg-d by gavage GDs 7–16	↓ number of F0 females with viable litters: 46/60, 21/30, 44/60, and 13/30* ↓ F1 body weight at PND 20: Response relative to control: 0, 4, -7*, and -13* ↓ F1 body weight at PND 42: Response relative to control: 0, -6*, -6*, and -10* (no difference in pup weight at PND 4)
Jules et al. (2012) Long-Evans rats, 6–17 F0 females/dose 0, 0.15, 0.3, 0.6, or 1.2 mg/kg-d by gavage GDs 14–17	No overt signs of toxicity in dams or offspring, differences in pup body weight, or number of pups/litter
McCallister et al. (2008) Long-Evans Hooded rats, 5–6/group 0 or 0.3 mg/kg-d by gavage GDs 14–17	No difference in number of pups/litter No overt maternal or pup toxicity No difference in liver:body weight Increased brain:body weight ratio at PNDs 15 and 30 (data not shown)
Reproductive effects in offspring	
Mackenzie and Angevine (1981) CD-1 mice, 30 or 60 F0 females/ dose 0, 10, 40, or 160 mg/kg-d by gavage GDs 7–16	↓ number of F1 females with viable litters: 35/35, 23/35*, 0/55*, and 0/20* ↓ F2 litter size from F1 dams (20%) at 10 mg/kg-d (no litters were produced at high doses) ↓ size or absence of F1 ovaries (weights not collected) hypoplastic ovaries with few or no follicles and corpora lutea (numerical data not reported)
Kristensen et al. (1995) NMRI mice, 9 F0 females/dose 0 or 10 mg/kg-d by gavage GDs 7–16	↓ number of F2 litters (63%) ↓ F2 litter size (30%) ↓ ovary weight (31%) in F1 females Few or no small, medium, or large follicles and corpora lutea

Exposure-Response Array for Several Hazards



EPA's Qualitative Descriptors of Carcinogenic Potential

- *Carcinogenic to humans*
  - Convincing human evidence of a causal association
  - Strong human evidence supported by other evidence

- *Likely to be carcinogenic to humans*
  - Plausible evidence in humans
  - Multiple positive results in animals
  - Positive animal results supported by other evidence

EPA's Qualitative Descriptors of Carcinogenic Potential

- *Suggestive evidence of carcinogenic potential*
  - Small increase in a tumor with a high background rate
  - Positive response in a study with design limitations
  - Positive response at one dose only, but no overall trend
- *Inadequate information to assess carcinogenic potential*
  - Little or no pertinent information, or conflicting evidence
- *Not likely to be carcinogenic to humans*
  - Negative studies in two animal species
  - Convincing evidence of a threshold

Carcinogenic to Humans	Libby Amphibole Asbestos (2014) Trichloroethylene (2011)
Likely to be Carcinogenic in Humans	1,4-Dioxane (2013) Carbon Tetrachloride (2010)
Suggestive Evidence of Carcinogenic Potential	Biphenyl (2013) Tetrahydrofuran (2012)
Inadequate Evidence to Assess Carcinogenic Potential	2-Hexanone (2009) Urea (2011)
Not Likely to be Carcinogenic	Ethylene glycol monobutyl ether (2010)

Dose-Response Assessment

Evaluate Data

Animal or human

Exposure route

Exposure duration

Age

Gender

Confounders

Species and strain

Characterize Dose-Response Relationship

Identify a critical effect(s) and level(s)
Conduct dose-response modeling

Conduct dose-response modeling

Identify point of departure

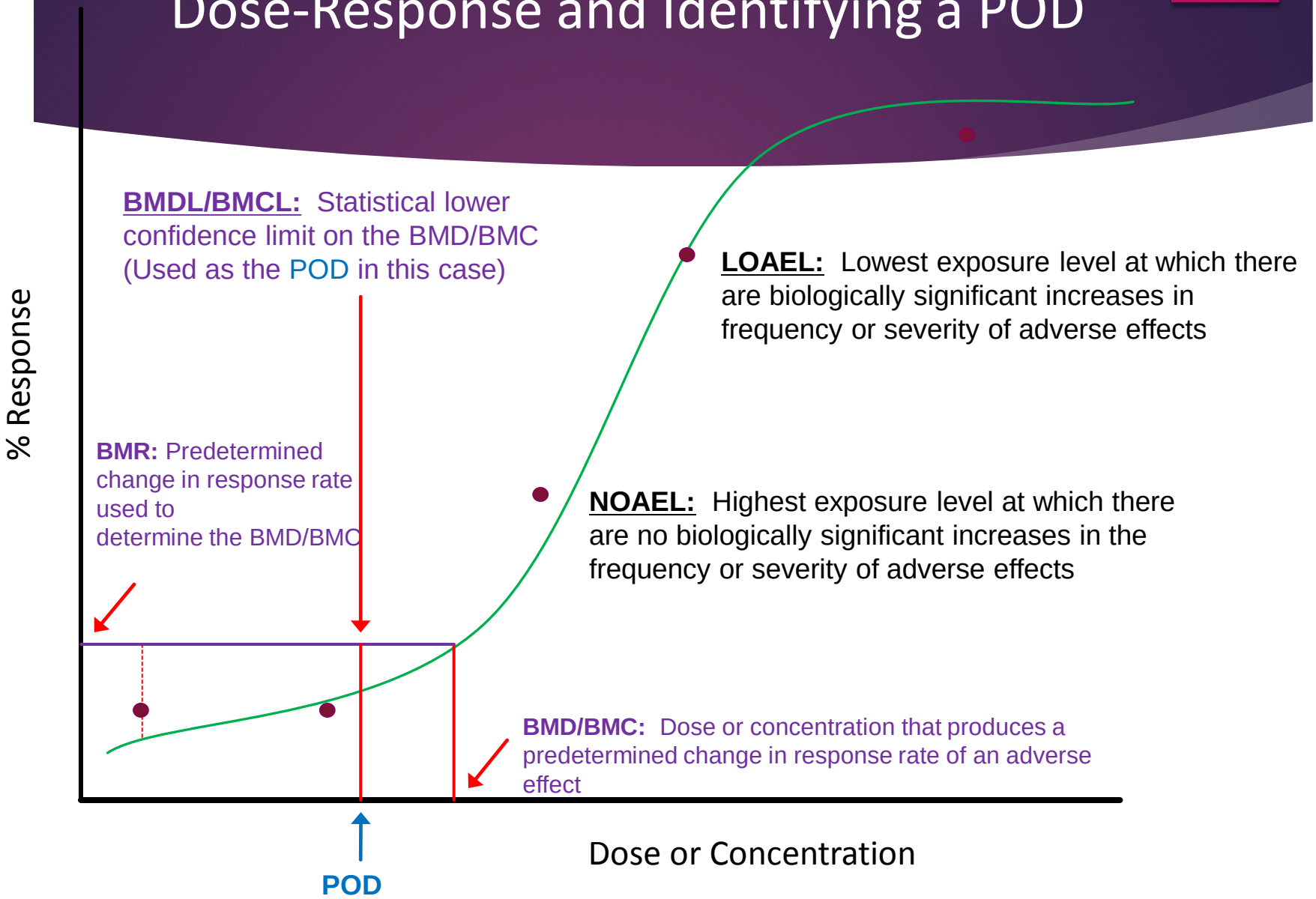
Apply Uncertainty Factors

Calculate Reference Value

RfD

RfC

Dose-Response and Identifying a POD



IRIS Uncertainty Factors

- UF_H – Human variability
- UF_A – Animal-to-human extrapolation
- UF_S – Subchronic-to-chronic extrapolation
- UF_L – LOAEL-to-NOAEL extrapolation
- UF_D – Database deficiencies
- UF_C – Composite uncertainty ($UF_H \times UF_A \times UF_S \times UF_L \times UF_D$)

Select a 1, 3, or 10

Deriving Noncancer Human Health Effect Reference Values

Reference Value = Dose ÷ Uncertainty

$RfD/RfC = POD \div UF_C$

- An **estimate of a daily exposure to the human population** (including sensitive subgroups) that is **likely to be without an appreciable risk of deleterious effects during a lifetime**.

Derivation of Quantitative Cancer Values

Cancer potency estimates

- A value that expresses the incremental increased risk of cancer incidence from a lifetime exposure to a substance per unit dose.
- Typically expressed in units that are the inverse of dose units.
- Can be multiplied by a given dose to quantify the lifetime cancer risk at that dose.

Inhalation Unit Risk

- The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/m^3 in air.
  - if unit risk = 2×10^{-6} per µg/m^3, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical per m^3 of air.

Calculation of Cancer Slope Factors and Inhalation Unit Risks

- The cancer value is derived from the POD ($BMDL_{10}$, the 95% lower bound on the exposure associated with an 10% extra cancer risk, by dividing the risk (as a fraction) by the $BMDL_{10}$, and represents an upper bound, continuous lifetime exposure risk estimate:

$$\text{Cancer slope factor/IUR} = 0.1 \text{ (extra risk)} \div BMDL_{10}$$

Uses of IRIS Assessments

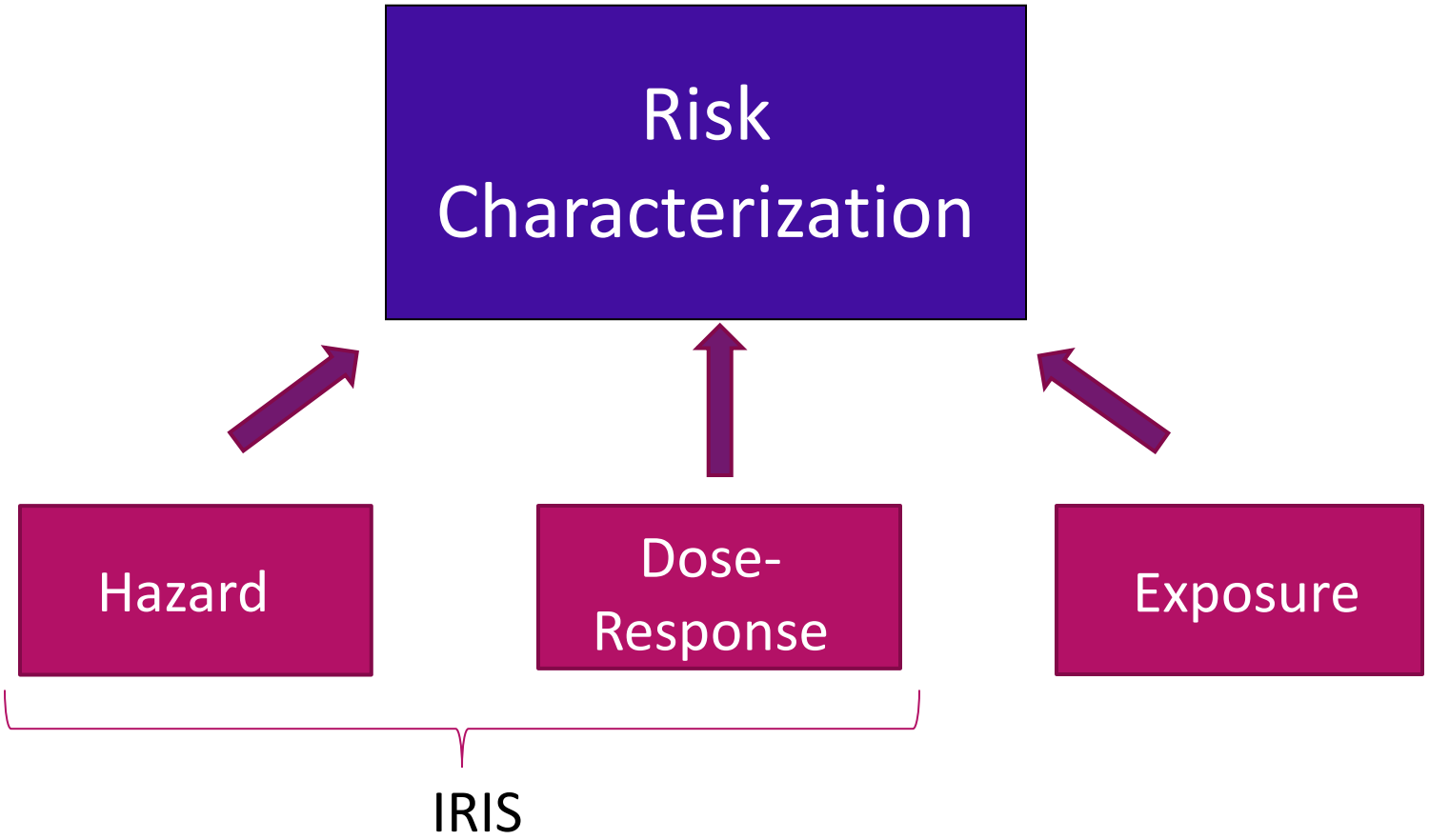
OFFICE OF AIR QUALITY PLANNING AND STANDARDS

OFFICE OF WATER

REGION 5

OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE/SUPERFUND

How Does EPA Assess Risk?



Risk Characterization Number

$$\textbf{Hazard Quotient (HQ)} = \frac{\textbf{Daily Intake}\left(\frac{mg}{kg-day}\right)}{\textbf{RfD}\left(\frac{mg}{kg-day}\right)}$$

$$\textbf{Cancer Risk} = \textbf{Lifetime Daily Intake}\left(\frac{mg}{kg-day}\right) \times \textbf{Cancer Slope Factor}\left(\frac{mg}{kg-day}\right)^{-1}$$

Risk Characterization is not just a number!

- Risk characterization is the integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.
- Risk characterization requires: transparency, clarity, consistency, and reasonableness.

- **Key Information**
- **Context**
- **Sensitive Populations**
- **Scientific Assumptions**
- **Policy Choices**
- **Key Conclusions**
- **Alternatives Considered**
- **Variability**
- **Uncertainty**
- **Bias and Perspective**
- **Strengths and Weaknesses**
- **Confidence Statements**
- **Research Needs**

EPA Programs and Regions Use IRIS Assessments in Various Ways…

OAQPS in the National Air Toxics Assessment

- Identify and prioritize mobile source air toxics for reduction strategies.

Office of Water

- Used for CCL contaminants to inform evaluations of health effects, occurrence at levels of health concern, and opportunity for health risk reductions for CCL Regulatory Determinations.
- Evaluate contaminants nominated for IRIS assessment to determine if there is sufficient health effects information to support including the contaminant on the next CCL.

Region 5

- Stack tests indicated emission levels at a company that produces resin-coated sand, violated Illinois' Clean Air Act. EPA's Air Enforcement and Compliance Assurance Branch modeled the emissions of formaldehyde and phenol from the plant. Based on predicted concentrations and using the IRIS IUR for formaldehyde, an elevated cancer risk of 365 in a million was calculated. This risk information was used in negotiations with the company, and a settlement was reached that required the company to reduce facility-wide VOC emissions by 92%.

IRIS – Used in Risk/Hazard Calculations

Office of Solid Water and Emergency Response

- To develop risk assessments that support rule-making efforts and site specific risk assessment conducted under CERCLA and RCRA. Goal is health protection under reasonable maximum exposure.
  - Calculate residential screening levels used in the selection of Chemicals of Potential Concern (761 RSL table values for residential soil, 399 based on IRIS).
  - Calculate Cancer Risks and Noncancer Health Hazards for Chemicals of Potential Concern in various site media (i.e., soil, groundwater, etc.) for land use.
  - Are cancer risks above the risk range of 10^{-4} (1 in ten thousand) to 10^{-6} (one in a million) to support site-specific decisions to take action or not.
  - Determine clean-up goal of protection for noncancer hazards; calculated if Hazard Quotient or Hazard Index exceeds 1 (i.e., there may be concern for potential noncancer effects).

Challenges and Advances

LIBBY AMPHIBOLE ASBESTOS

HEXAVALENT CHROMIUM

PHTHALATES

Libby Amphibole Asbestos and choice of critical effect

Critical effect: Localized pleural thickening (LPT) measured as thickening due to fibrosis and collagen deposits in the diaphragm (parietal pleura)

Several public commenters noted that LPT was:

- Not adverse
- Not associated with lung function
- Confused with diffuse pleural thickening (DPT)
- Measured with unreliable diagnostic methods (x-ray radiography which is prone to misdiagnosis vs well-accepted High Resolution Computed Tomography (HRCT).

EPA's Science Advisory Board (SAB) provided independent, expert peer review. concluding:

- an irreversible structural, pathological alteration of the pleura
- generally associated with reduced lung function
- an appropriate health endpoint for the derivation of RfC.
- Provide further support with additional literature and analysis

Libby Amphibole Asbestos and choice of critical effect

- EPA defines an adverse effect as a “biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge”
- EPA conducted a systematic review and meta-analysis of the influence of LPT on lung function and concluded there was an association.
  - associated with statistically significant decrease in lung function (forced vital capacity [FVC]) and forced expiratory volume in 1 second [FEV_1]).
  - decreases in lung function are unlikely to be due to other factors.
  - In a meta-analysis considered only groups that did not contain any DPT or parenchymal abnormalities, so that there would not be confusion of LPT with DPT
  - conducted meta-analyses of x-ray and HRCT studies and of HRCT studies separately; the summary estimate in the meta-analysis of HRCT studies showed similar or greater decreases in lung function associated with LPT.

External Expert Peer Review

- Review conducted by a multi-disciplinary (i.e., epidemiology, toxicology, biostatistics, asbestos, medicine, inhalation toxicity, etc) committee of 21 scientists.
- An authoritative body providing expert advice.
- Peer Review is very important to the IRIS Program
- A newly established SAB Chemical Assessment Advisory Committee (CAAC) will review IRIS assessments.
  - Consensus recommendations
  - Consistent recommendations
  - Scientific advice on cross-cutting issues

Oral Exposure to Hexavalent Chromium

- Generally accepted as inhalation toxicant and carcinogen, but less understood via oral exposure.
- NTP bioassay (2008) reported clear evidence of GI-related carcinogenicity in mice and rats following chronic oral exposure.
- Suggesting implications for human health if orally exposed to hexavalent chromium.
- An IRIS assessment is underway for hexavalent chromium.
- Assessment in draft development stage and preliminary materials (i.e., literature search, evidence tables) have been completed.

Oral Exposure to Hexavalent Chromium

A few considerations:

- Chromium is biologically prevalent in either the trivalent (CrIII) or hexavalent (CrVI) state.
- When ingested, Cr(VI) can be reduced to Cr(III) by a number of reducing agents within the GI tract, but oxidation of Cr(III) to Cr(VI) will not occur in the human body.
- Extracellular Cr(III) poorly absorbed by cells and thus poses little or no carcinogenic risk to humans
- Extracellular Cr(VI) can be readily absorbed by cells via nonspecific anionic transporters, then reduced intracellularly, potentially leading to toxic or carcinogenic effects.

State-of-the-Science Workshop

http://www.epa.gov/iris/irisworkshops/cr6/

- Need to better understand competing processes of reduction and absorption, the transit of chromium species through the GI tract prior to absorption, and how these processes differ between humans and rodents.
- Convened a workshop to discuss the toxicokinetic issues and the potential impact on evaluating carcinogenicity of oral exposure to Cr(VI).
- Facilitated discussion among experts from industry, academia, government, and the public – Panelists included principal investigators of Cr(VI) studies
- Discussions on gastrointestinal metabolism, physiology, and variability
  - Discussions emphasized many unknowns regarding Cr(VI) uptake and reduction.
  - Uncertainty in uptake transporters, variability of GI motility and gastric acid secretion.
  - Physiologically-based pharmacokinetic (PBPK) modeling is possible for the GI tract (although challenging).

Phthalates and human relevance of rat data

- Shown to cause effects in rats, more specifically the developing male fetus due, in large part, to inhibition of testosterone synthesis, i.e., anti-androgenicity.
- In rats, effects of reduced anogenital distance, retained areola/nipples, cryptorchidism, hypospadias are commonly referred to as the phthalate syndrome.
- Phthalate syndrome in rats resembles testicular dysgenesis syndrome (TDS) in humans (e.g. cryptorchidism, hypospadias, poor sperm quality).
- IRIS assessments are underway for several phthalates.
- Assessments are in the draft development stage and preliminary materials (i.e., literature search, evidence tables) have been completed.

Phthalates and human relevance of rat data

- Recent studies using human testicular tissue xenografts and ex-vivo tissue culture preparations comparing testosterone effects in human, mice, and rat fetal testes.
  - Studies conclude that human fetal testes are resistant to phthalate-induced changes in testosterone.
  - Raising questions about the human relevance of some of the testes-specific endpoints in rats.
- Reviews of these studies have suggested limitations in these studies, including variability in the human population, small sample size, and gestational age of the human tissues.
- Additionally, there is some evidence suggesting that phthalate-induced alterations in the development of the male reproductive system may be mediated through both androgen dependent and independent pathways.
  - For example, adverse effects on germ cell development have been observed and these responses are conserved in a majority of mammalian species (including humans) and life stages tested.

Public Science Discussions at Bimonthly IRIS Meetings

- Phthalates were discussed at an October public IRIS meeting.
  - Researchers shared their work.
  - Stakeholders provided their interpretations of the data.
  - EPA asked questions and all participated in the discussion.
- Discussion will continue at the February meeting.

Purpose of public science meeting is **to discuss key science issues.**

- study methods or quality
- scientific considerations to address in the upcoming draft assessment
- alternative interpretations of the evidence
- approaches to reconciling positive and negative results
- mode-of-action hypotheses

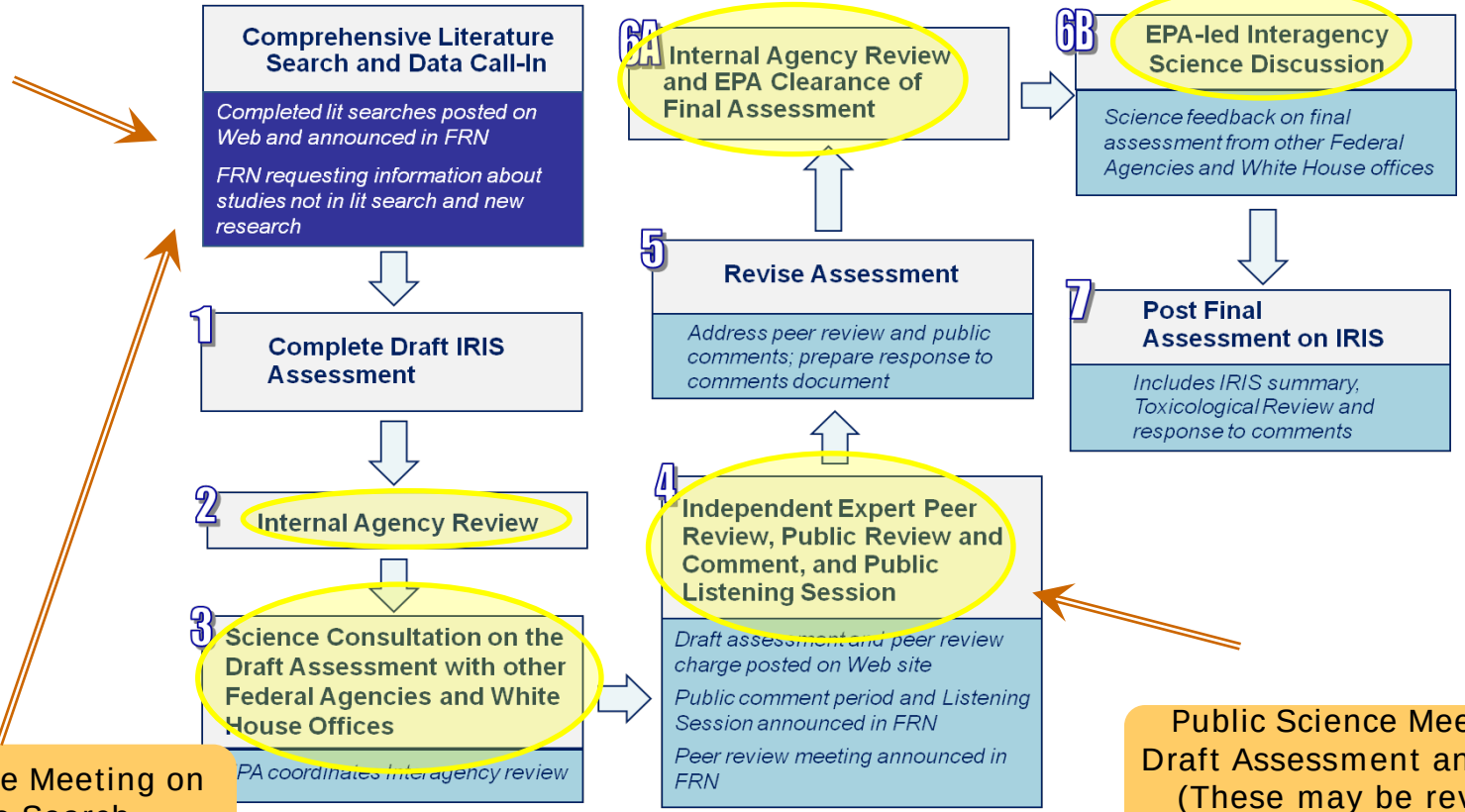
http://www.epa.gov/iris/publicmeeting/iris_bimonthly-feb2015/index.htm

How Can Someone Engage with IRIS on the Science?

- PUBLIC COMMENT PERIODS/DOCKETS
- PUBLIC SCIENCE MEETINGS
- WORKSHOPS

Enhanced IRIS: Public Engagement

Public Science Meeting on Problem Formulation



Public Science Meeting on Literature Search, Study Tables, Key Issues

Public Science Meeting on Draft Assessment and Charge (These may be revised in response to public comments)

Engaging with IRIS

- General comments docket
- Assessment-specific dockets
- Public science discussions during problem formulation stage, draft development, and prior to peer review
  - Broadly attended meetings are useful for discussing science issues where there are multiple points of view
- Ad-hoc meetings with external stakeholders
- Upcoming state-of-the-science and peer consultation workshops
  - Epigenetics
  - Less than lifetime
  - Systematic review
  - Analysis and communication of uncertainty

Thank you!

Questions?

Contact Information

- www.epa.gov/iris
- Jones.samantha@epa.gov
- http://www.epa.gov/iris/comments.htm
- http://www.epa.gov/iris/contact_hotline.htm