Toxicology Updates

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Declaration of Interests

- I have no conflicts of interest to declare.
- I am a member of the US EPA's Clean Air Scientific Advisory Committee (CASAC). CASAC reviews documents pertaining to the National Ambient Air Quality Standards (NAAQS). This presentation is not being made on behalf of US EPA or the CASAC, and is not intended to communicate any policy position about the NAAQS or the NAAQS pollutants.

Outline

- Background about the TCEQ Toxicology, Risk Assessment, and Research Division
- Toxicity factor derivation
  - PFAs
  - Ethylene oxide
- Committee updates

TCEQ Toxicology, Risk Assessment, and Research Division

TCEQ Mission Statement:

The Texas Commission on Environmental Quality strives to protect our state's public health and natural resources consistent with sustainable economic development. Our goal is clean air, clean water, and the safe management of waste.

- 15 Toxicologists (soon to be 17)
- Our Division supports different offices at the TCEQ
  - Air Monitoring
  - Air Permitting
  - Remediation
  - Water issues
- Research
  - Diverse topics of importance to Texas, as well as the larger community. For example, research on criteria pollutants, remediation site cleanup levels, potential public exposure to oil and gas production, risk assessment & toxicity factor development methodologies
- Other
  - Review of toxicological assessments from other agencies; emergency response; risk communication; communication with the public, press, regulatory community, regulated community, legislators, etc.
- Toxicity Factor development

Recent Division Changes

- Name change from Toxicology Division to Toxicology, Risk Assessment, and Research Division

- Greater focus on, and resources for, research on topics that are important to the State of Texas, and to the advancement of regulatory toxicology and risk assessment

Toxicity Factors

PFAs

Ethylene Oxide

Toxicity Factor Derivation

- Toxicity factors are concentrations or doses of a chemical that are considered to be safe or to cause very low risk in a particular population

- Primer on toxicity factor derivation
  - Uncertainty factors
  - PFAs
  - Low-dose extrapolation
  - Ethylene oxide

Steps of Toxicity Factor Derivation: Non-Cancer

Chemical of Concern
consider route of exposure

↓

Review the Literature
identify studies that investigate health effects after exposure to chemical

↓

Most Sensitive Health Effect
occurs at the lowest chemical concentration – preferably a mild, reversible effect

↓

Uncertainty Factors
divide chemical concentration by modeling or uncertainty factors

↓

Toxicity Factor
protective of public health with an ample margin of safety

Steps of Toxicity Factor Derivation: Non-Cancer Default Uncertainty Factors

	E.g. Animal Study	E.g. Human Study
Highest No Effect Concentration		
↓	10 ppm	2 ppm
Animal-to-human uncertainty factors: 3.3 – kinetics (how long the chemical stays in the body) 3.3 – dynamics (how sensitive the body's tissues are to the chemical)		
↓	1 ppm	2 ppm
Intra-Human uncertainty factors: 10 – sensitive subpopulations		
↓		
Final Toxicity Factor	100 ppb	200 ppb

Non-Default Uncertainty Factors: PFAs

- Per- and polyfluoroalkyl substances (PFAs): not found naturally in the environment, have been used extensively as surface protection agents in consumer products, and in fire-fighting foams

- PFAs persist for long periods of time in the human body (half-life of 1-4 years), much longer than in laboratory animals (half-life of days to weeks) – reason for difference is poorly understood

- PFAs can cause liver and developmental effects in laboratory animals

Non-Default Uncertainty Factors: PFAs

Perfluorooctanoic acid (PFOA)

	ATSDR	USEPA	TCEQ
Lowest effect concentration (mg/kg/day)	0.3	1	0.3
Kinetics adjustment factor	365	189	81
Other UFs	300	300	300
Final Toxicity Factor (mg/kg/day)	0.3×10^{-5}	2×10^{-5}	1.2×10^{-5}

Perfluorooctanoic sulfonate (PFOS)

	ATSDR	USEPA	TCEQ
Highest no-effect concentration (mg/kg/day)	0.1	0.1	-
Lowest effect concentration (mg/kg/day)	-	-	0.6
Kinetics adjustment factor	194	196	263
Other UFs	300	30	100
Final Toxicity Factor (mg/kg/day)	0.2×10^{-5}	2×10^{-5}	2.3×10^{-5}

TCEQ Toxicity Factors for Per- and Polyfluoroalkyl Substances (PFAs)

- Derived in 2011 for use at remediation sites, reviewed numbers in 2016 https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf
- No immediate plans for updating numbers

CASRN	PFC [1]	Acronym	Formula	RfD (mg/kg-day)	RfC (mg/m^3)
375-22-4	**Perfluorobutyric acid**	PFBA	$C_4HF_7O_2$	2.9E-03	1.0E-02
375-73-5	**Perfluorobutane sulfonate** (Perfluorobutane sulfonic acid)	PFBuS	$C_4HF_9O_3S$	1.4E-03	4.9E-03
2706-90-3	Perfluoropentanoic acid	PFPeA	$C_5HF_9O_2$	3.8E-06	NA
355-46-4	**Perfluorohexane sulfonate** (Perfluorohexane sulfonic acid)	PFHxS	$C_6HF_{13}O_3S$	3.8E-06	1.3E-05
307-24-4	Perfluorohexanoic acid	PFHxA	$C_6HF_{11}O_2$	3.8E-06	NA
375-85-9	Perfluoroheptanoic acid	PFHpA	$C_7HF_{13}O_2$	2.3E-05	NA
1763-23-1	**Perfluorooctanoic sulfonate** (Perfluorooctane sulfonic acid)	PFOS	$C_8HF_{17}O_3S$	2.3E-05	8.1E-05
335-67-1	**Perfluorooctanoic acid** (Perfluorooctanoate)	PFOA	$C_8HF_{15}O_2$	1.2E-05	4.1E-06
754-91-6	**Perfluorooctane sulfonamide**	PFOSA	$C_8H_2F_{17}NO_2S$	1.2E-05	4.1E-06
375-95-1	**Perfluorononanoic acid**	PFNA	$C_9HF_{17}O_2$	1.2E-05	2.8E-05
335-76-2	**Perfluorodecanoic acid**	PFDeA	$C_{10}HF_{19}O_2$	1.5E-05	5.3E-05
67906-42-7	Perfluorodecane sulfonate	PFDS	$C_{10}F_{21}SO_3$	1.2E-05	NA
2058-94-8	Perfluoroundecanoic acid	PFUA	$C_{11}HF_{21}O_2$	1.2E-05	NA
307-55-1	**Perfluorododecanoic acid**	PFDoA	$C_{12}HF_{23}O_2$	1.2E-05	4.2E-05
72629-94-8	Perfluorotridecanoic acid	PFTrDA	$C_{13}HF_{25}O_2$	1.2E-05	NA
376-06-7	Perfluorotetradecanoic acid	PFTeDA	$C_{14}HF_{27}O_2$	1.2E-05	NA

[1] Bolded PFCs had at least some chemical-specific data (e.g., PFOSA had an LD_{50}).

Steps of Toxicity Factor Derivation: Cancer

Chemical of Concern
consider route of exposure

↓

Review the Literature
identify studies that investigate health effects after exposure to chemical

↓

Cancer Mode of Action
if chemical acts by damaging DNA → Non-threshold extrapolation

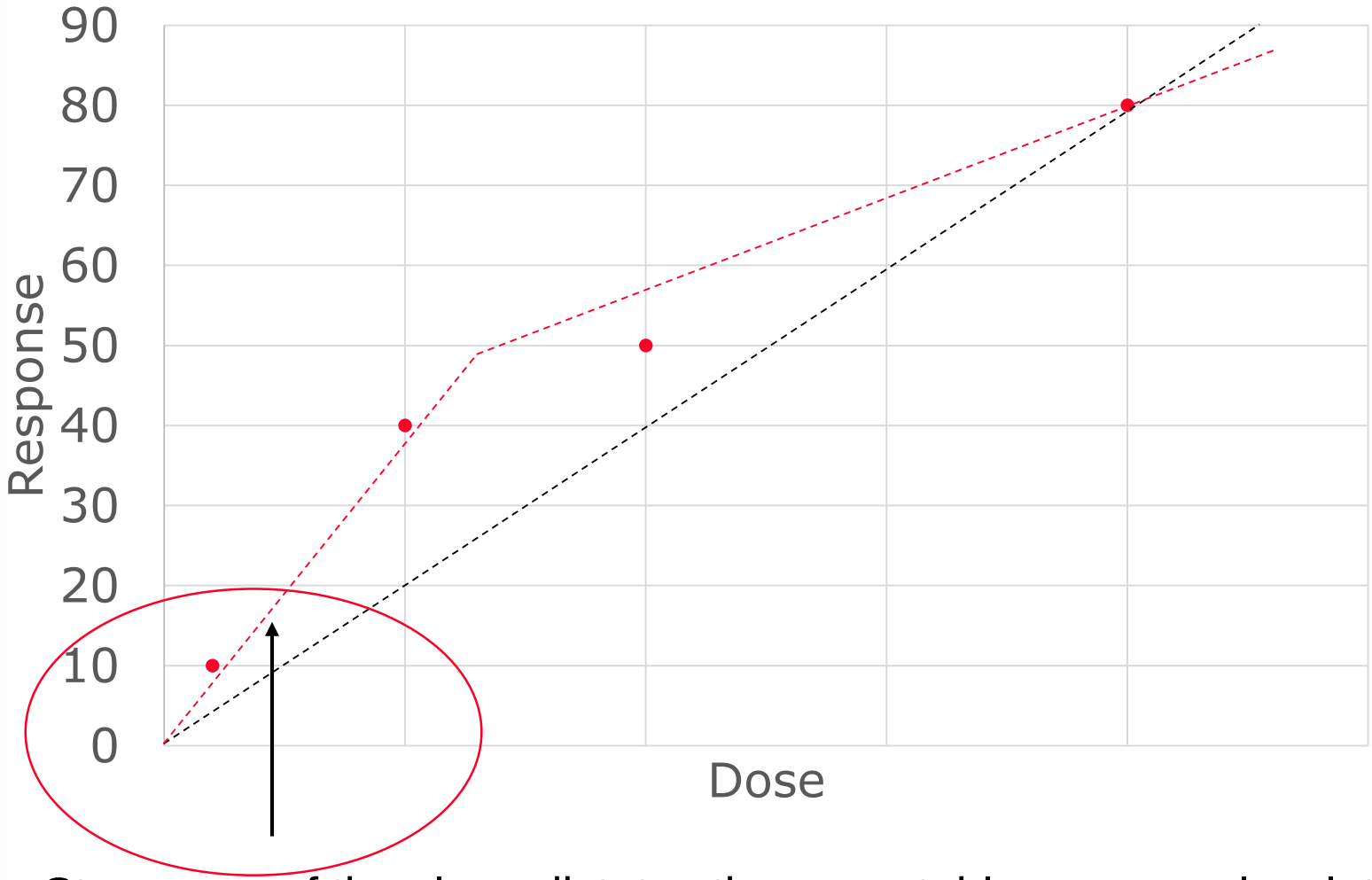
↓

Non-Threshold Extrapolation & Risk Level
extrapolate dose-response curve to zero, choose cancer risk level
(from 1×10^{-6} to 1×10^{-4})

↓

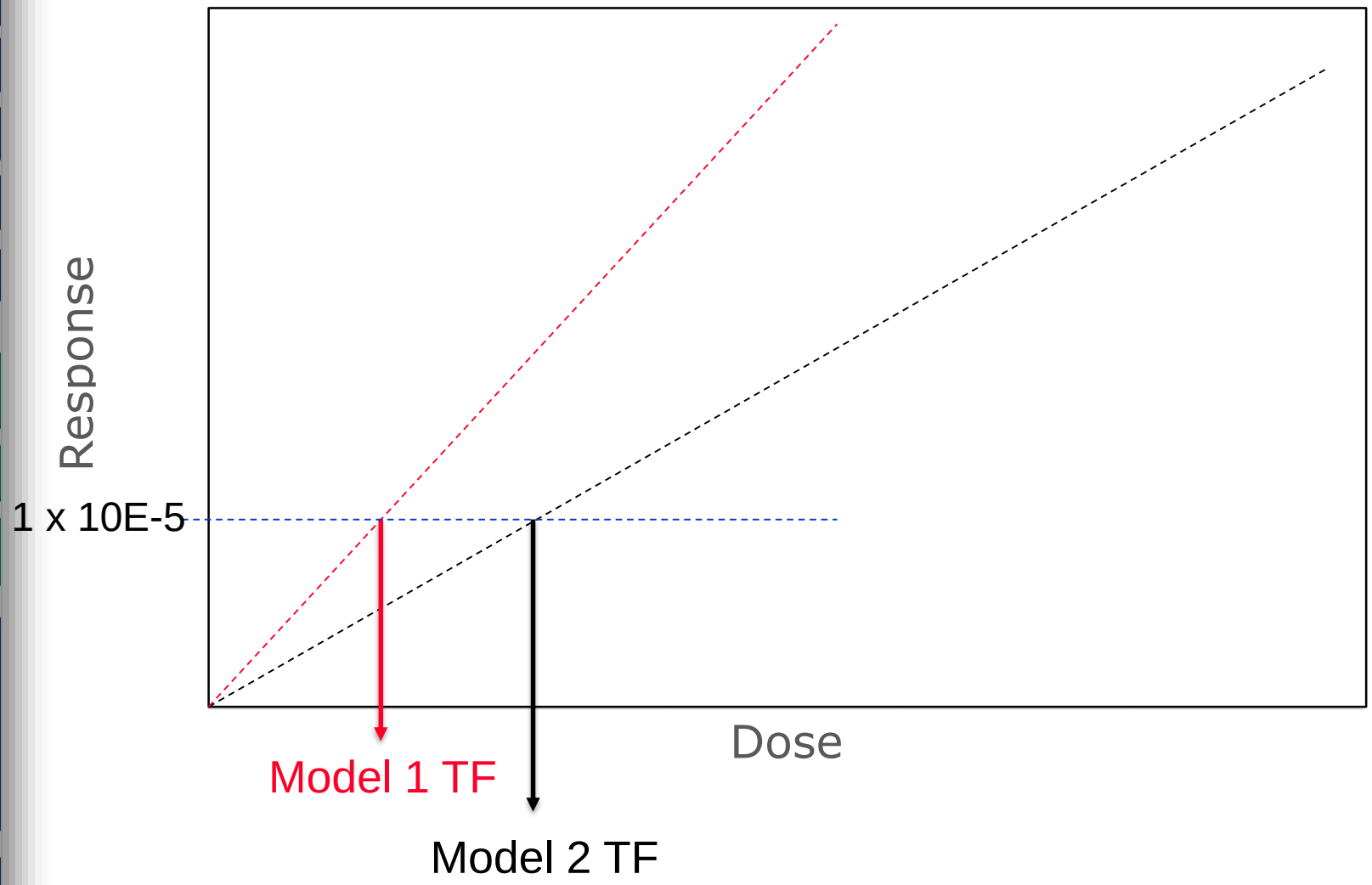
Toxicity Factor
protective of public health with an ample margin of safety

Low-Dose Extrapolation



Steepness of the slope dictates the acceptable exposure level: the steeper the slope, the lower the acceptable chemical concentration

Low-Dose Extrapolation



Low-Dose Extrapolation: Ethylene Oxide

- EtOx is a high production volume chemical. It is used as a raw material and an intermediate in the production of many materials
- EtOx is used to sterilize medical equipment
- EtOx is a direct-acting alkylating agent that can damage DNA, and it is a low potency carcinogen in animal models
- There are several occupational cohorts that show possible lymphopoietic and breast tumors in exposed workers

Low-Dose Extrapolation: Ethylene Oxide

- US EPA's 2016 IRIS assessment of EtOx used a two-piece linear spline model, with the slope of the steeper lower-dose line used to calculate the acceptable air concentration

- TCEQ is in the process of deriving a toxicity factor for EtOx and will carefully consider the low-dose extrapolation method

Committee Updates

Science Advisory Board

Clean Air Scientific Advisory Committee

USEPA's Chartered Science Advisory Board

- Our Division Director, Michael Honeycutt, is the Chairman of the EPA's Science Advisory Board (SAB)

- The SAB is required to "provide such scientific advice as may be requested by the Administrator" to the EPA administrator as well as Congressional committees of jurisdiction
  - Ensure EPA is using the best science and data available
  - Review EPA's semi-annual regulatory agenda
  - Review work of standing committees (e.g. Chemical Assessment Advisory Committee) and ad hoc committees and panels (e.g. Risk and Technology Review Methods Panel)
  - Conduct projects identified by the Administrator or Congressional Committees
  - Self-initiate activities

SAB Updates

- EPA Administrator Wheeler has appointed 8 new SAB members and has reappointed 6 members for a second term
- SAB completed the quality review of the SAB Chemical Assessment Advisory Committee (CAAC) reviews of Ethyl t-Butyl Ether (ETBE) and t-Butyl Alcohol (TBA) - posted to the SAB website February 27, 2019
- SAB completed a quality review of EPA's Assessment Framework for Biogenic Carbon Dioxide Emissions from Stationary Sources – will be posted very soon
- US EPA is seeking nominations for an ad hoc review panel for EPA's ORD new All-Ages Lead Model. A list of candidates and their biosketches were posted on the SAB website on March 1, 2019 and comments are due March 22, 2019

USEPA's Chartered Clean Air Scientific Advisory Committee (CASAC)

- Advise EPA Administrator on the National Ambient Air Quality Standards (NAAQS); one term on the committee is 3 years (can serve up to two terms consecutively)

- 7 members - 1 must represent states, 1 must be a member of the National Academy of Sciences, Engineering, & Medicine, 1 must be a medical doctor

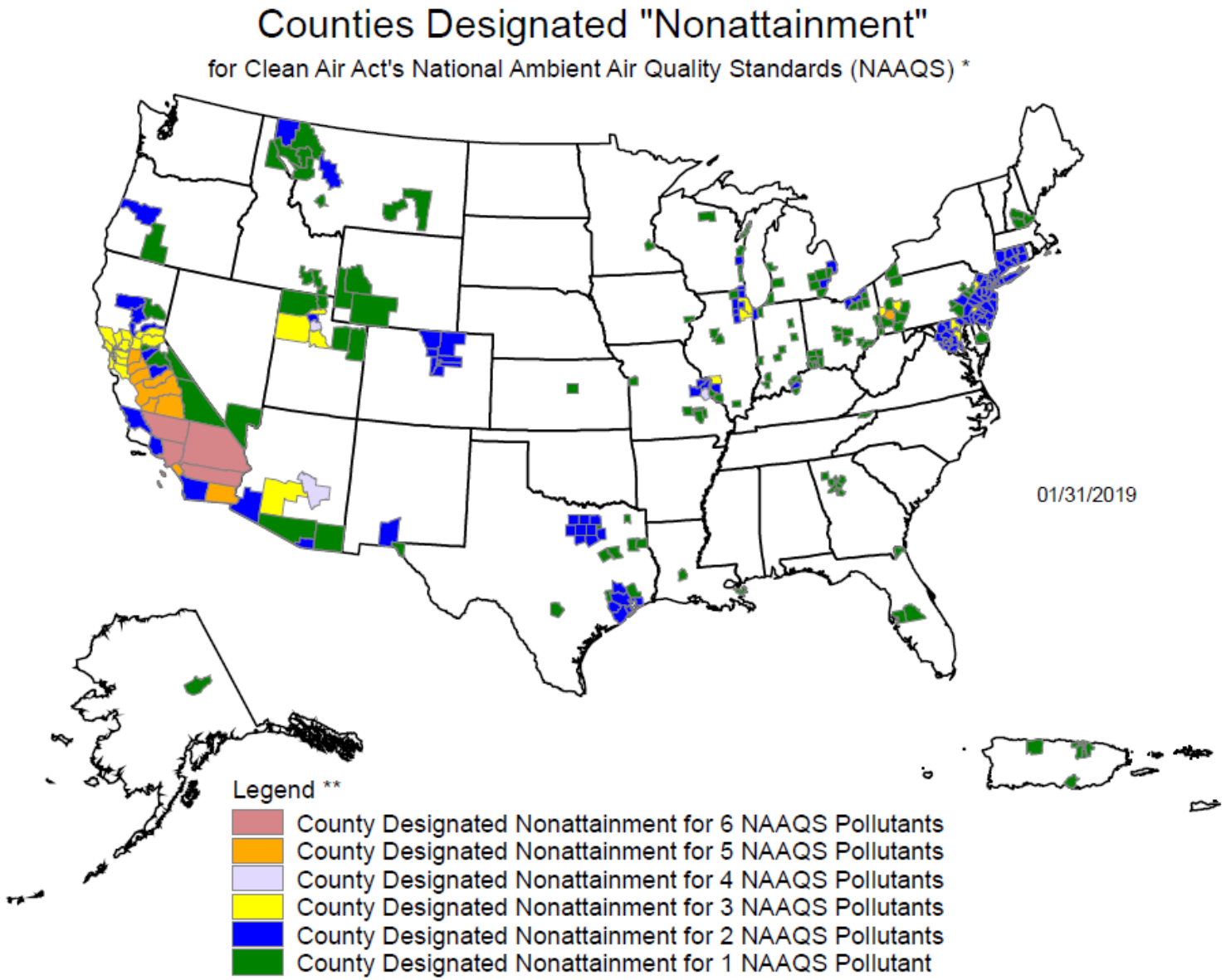
- Current committee members:
  - Dr. Tony Cox, Cox Associates (Chair)
  - Dr. James Boylan, Georgia Dept of Natural Resources
  - Dr. Mark Frampton, University of Rochester Medical Center
  - Dr. Sabine Lange, Texas Commission on Environmental Quality
  - *Dr. Timothy Lewis, US Army Corps of Engineers**
  - Dr. Corey Masuca, Jefferson County Dept of Health
  - Dr. Steven Packham, Utah Dept of Environmental Quality

**Dr. Lewis is retiring – EPA is accepting nominations for an ecological expert until April 1, 2019*

National Ambient Air Quality Standards (NAAQS)

- EPA must set NAAQS for six "criteria" air pollutants
  - Ground level ozone (O_3)
  - Nitrogen dioxide (NO_2)
  - Particulate matter (PM_{10} and $PM_{2.5}$)
  - Sulfur dioxide (SO_2)
  - Carbon monoxide (CO)
  - Lead (Pb)
- EPA must review these standards every five years
  - Currently actively reviewing the PM and ozone NAAQS
- Counties that do not meet the NAAQS for these pollutants are designated as non-attainment, and States must make plans and take actions to reduce the levels of these pollutants

Nonattainment Map



Expedited NAAQS Review

- Former NAAQS review process:
  - Integrated review plan
  - Integrated science assessment (multiple drafts)
  - Risk and exposure assessment (multiple drafts)
  - Policy assessment (multiple drafts)
  - Proposed rule
  - Final rule
- May 2018 memo from EPA Administrator:
  - Directed an expedited review of the NAAQS to meet statutory deadlines (review every 5 years)
  - Identified ways to streamline the process – more focus on policy-relevant information, avoiding multiple drafts of document
- New NAAQS review process:
  - Integrated review plan
  - Integrated science assessment (one draft)
  - Policy assessment, to include risk and exposure assessment (one draft)
  - Proposed rule
  - Final rule

Former PM NAAQS Review Schedule

Table 1-3. Anticipated schedule for the review of the PM NAAQS.

Stage of Review	Major Milestone	Actual or Target Date
Planning	Literature Search	Ongoing
	Federal Register Call for Information	December 3, 2014
	Workshop on Science/Policy Issues	February 9-11, 2015
	Release Draft IRP for CASAC/public review	April 2016
	CASAC Review Meeting for Draft IRP	May 23, 2016
	Release Final IRP	December 2016
Science Assessment	Release First Draft ISA for CASAC/public review	Fall 2017
	CASAC Review Meeting for First Draft ISA	Winter 2018
	Release Second Draft ISA for CASC/public review	Fall 2018
	CASAC Review Meeting for Second Draft ISA	Winter 2019
	Release Final ISA	Fall 2019
Risk/Exposure Assessments	Release REA Planning Document(s) for CASAC/public review	Fall 2017
	CASAC Review Meeting for REA Planning Document(s)	Winter 2018
	Release First Draft REA(s) for CASAC/Public Review	Fall 2018
	CASAC Review Meeting for First Draft REA(s)	Winter 2019
	Release Second Draft REA(s) for CASAC/Public Review	Fall 2019
	CASAC Review Meeting for Second Draft REA(s)	Winter 2020
	Release Final REA(s)	Fall 2020
Policy Assessment/ Rulemaking	Release First Draft PA for CASAC/public review	Fall 2018
	CASAC Review Meeting on First Draft PA	Winter 2019
	Release Second Draft PA	Fall 2019
	CASAC Review/Public Comment on Second Draft PA	Winter 2020
	Release Final PA	Fall 2020
	Proposed Rulemaking	2021
	Final Rulemaking	2022

Final PM IRP Dec 2016

PM NAAQS Review

EPA United States Environmental Protection Agency

Timeline and CASAC Role in the Current Review

Date	EPA	CASAC
Dec 2014	Call for Information	
Feb 2015	Kickoff Workshop	
April 2016	Draft IRP	**Reviewed** the draft IRP, which presented the plan for reviewing the air quality criteria and the NAAQS for PM
Dec 2016	Final IRP	
Oct-Dec 2018	**Draft ISA**	**Review** draft ISA, which provides an assessment of the currently available scientific information on public health and welfare effects of PM and is the science foundation for the review *(the air quality criteria)*
Summer 2019	**Draft PA** (with REA analyses)	**Review** draft PA, which presents an evaluation of the policy-relevant aspects of the current scientific evidence and quantitative risk and air quality analyses, focusing on implications with regard to the adequacy of the current standards and, as appropriate, potential alternatives
~~2019-2020~~	**Final ISA**	
	Final PA	
Spring 2020	**Proposed decision**	
Dec 2020	**Final decision**	

EPA Presentation at PM ISA CASAC Meeting, Dec 2018

Ozone NAAQS Review

EPA United States Environmental Protection Agency

Timeline and CASAC Role

Key Milestones in the Ozone NAAQS Review		
Date	**EPA**	**CASAC**
June 2018	Call for Information	
Fall 2018	Draft IRP	**Consultation** on plans for the review, including plans for ISA, REA analyses and PA
Early 2019	Final IRP	
Spring 2019	**Draft ISA**	**Review** of draft ISA, which provides an assessment of the currently available scientific information on public health and welfare effects of ozone and is the science foundation for the review *(the air quality criteria)*
Fall 2019	**Draft PA** (with REA analyses)	**Review** of draft PA, which presents an evaluation of the policy-relevant aspects of the current scientific evidence and quantitative exposure, risk and air quality analyses, focusing on implications with regard to the adequacy of the current standards and, as appropriate, potential alternatives
	Final ISA	
	Final PA	
Spring 2020	**Proposed decision**	
Late 2020	**Final decision**	

EPA Presentation at O3 IRP CASAC Meeting, Nov 2018

CASAC NAAQS Review

- Particulate Matter:
  - Reviewing the PM ISA (public meeting on Dec. 12-13)
  - Drafting responses to EPA's charge questions – public meeting to discuss draft responses ~ end of March
- Ozone:
  - Reviewed Ozone IRP November 2018
  - Plan to review Ozone ISA Spring 2019

Conclusions and Upcoming

- Differences in toxicity factors between agencies are often a function of choices made in areas of uncertainty (e.g. toxicokinetic considerations, low-dose extrapolation)
- TCEQ is working on a systematic review of our EtOx cancer toxicity factor and will carefully consider those areas of uncertainty
- SAB meeting in May or June, just finalized reviews of ETBE & TBA, and biogenic carbon emissions, gathering experts for new EPA blood lead model
- Accelerated NAAQS review, expect drafts of documents for both PM and ozone reviews in the next few months

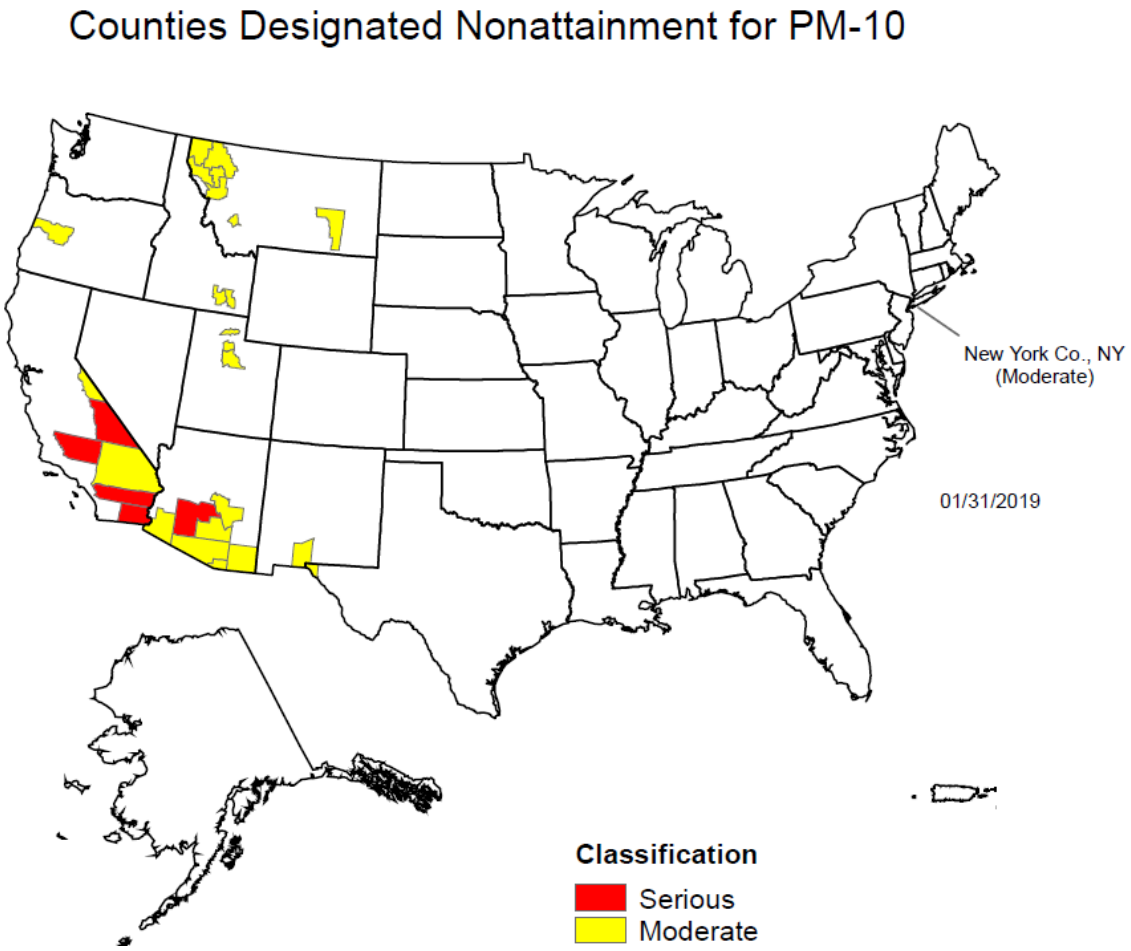
Extra Slides

Particulate Matter

- There are two particulate matter standards: particulate matter less than 10 µm (PM_{10}), and less than 2.5 µm ($PM_{2.5}$)
- $PM_{2.5}$ is 10-times smaller than the width of a human hair
- PM is emitted directly from many sources (major sources are combustion for $PM_{2.5}$, and dust for PM_{10})
- PM is generated as a secondary pollutant from chemicals such as nitrogen oxides (NO_x) and sulfur oxides (SO_x)
- Unlike other pollutants (e.g. ozone, mercury, hydrogen sulfide), PM regulation is not based on a specific chemical, but on the ***size*** of the particle (heavy metals and small particles of soil are treated as equally toxic)

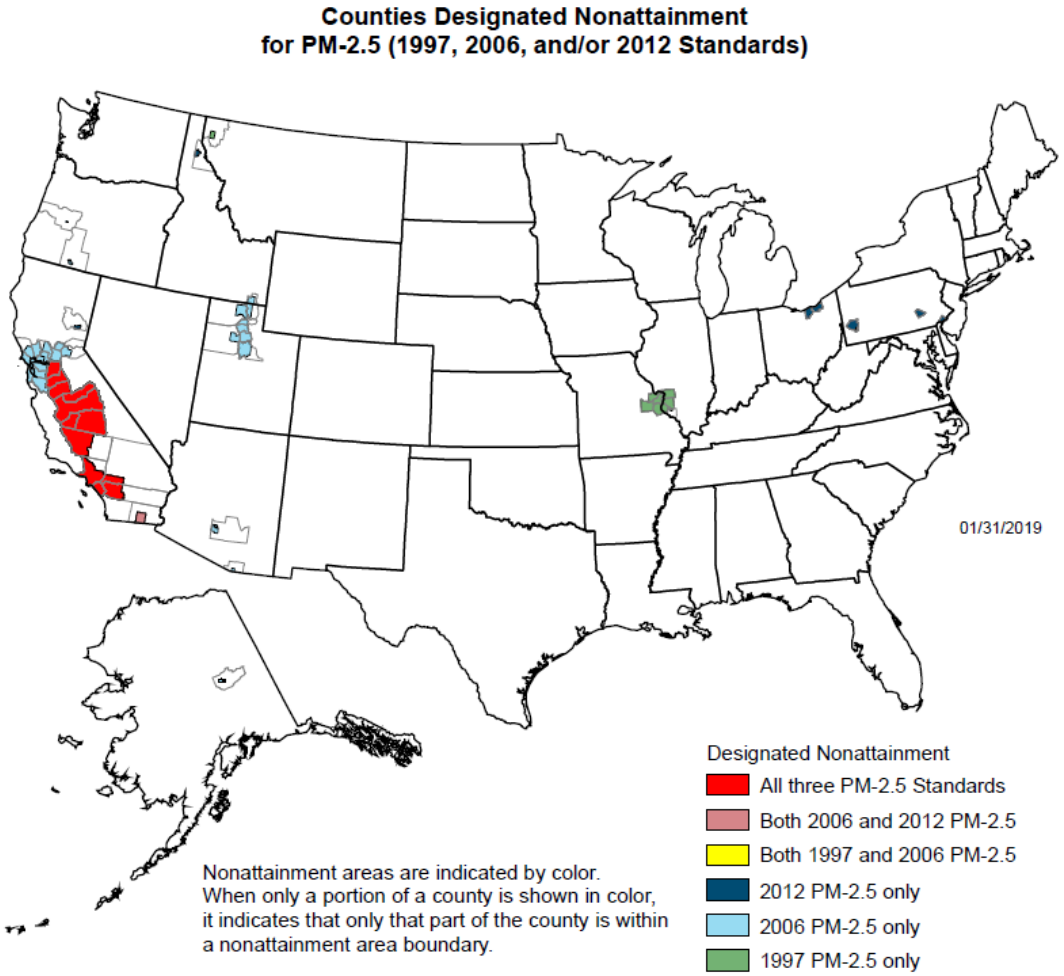
PM_{10} Standard

150 µg/m^3, 24-hr average not to be exceeded more than once per year on average over 3 years



$PM_{2.5}$ Standard

35 µg/m^3, 24-hr average 98th percentile, averaged over 3 years
12 µg/m^3, annual mean, averaged over 3 years

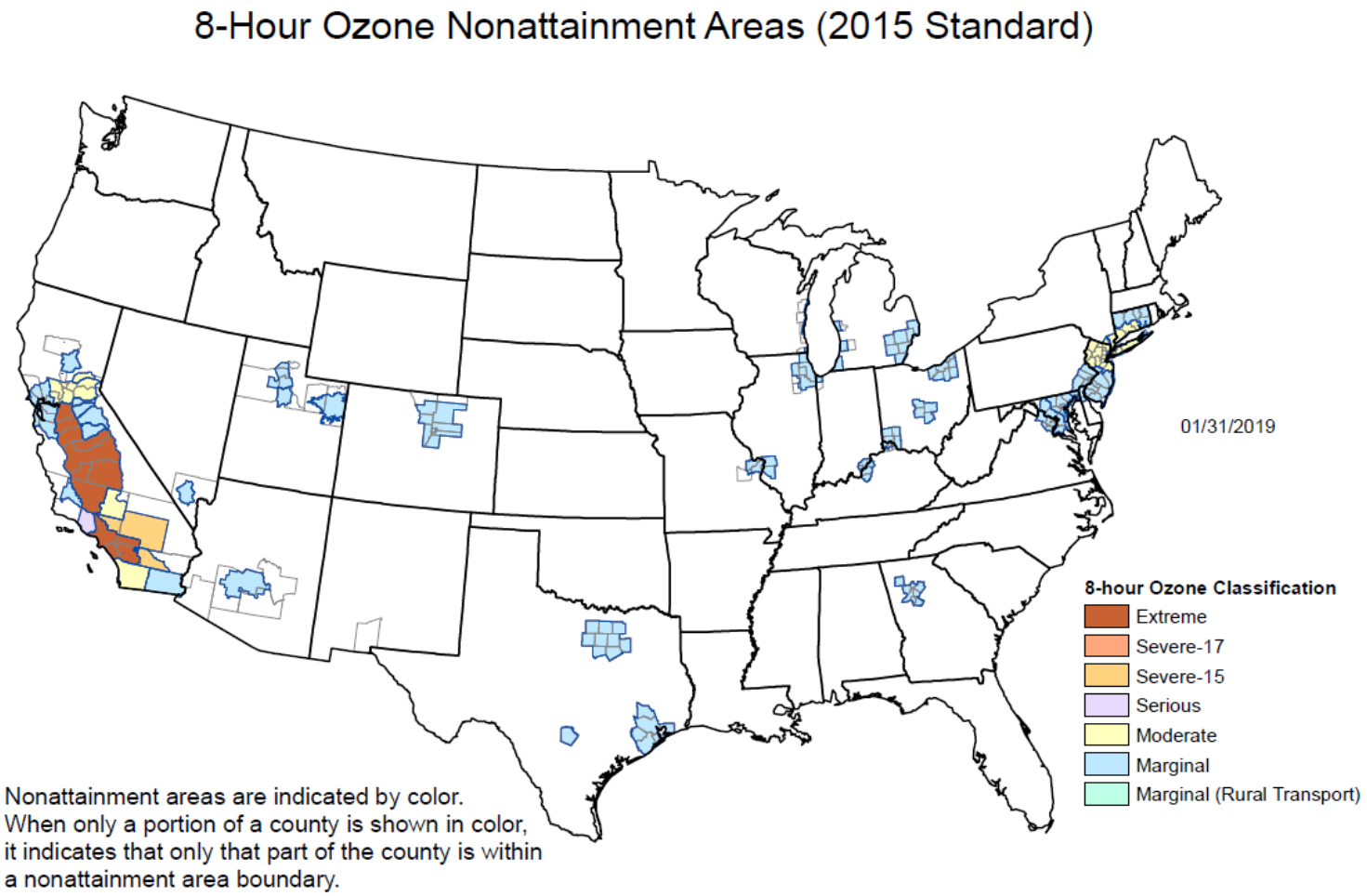


Ozone

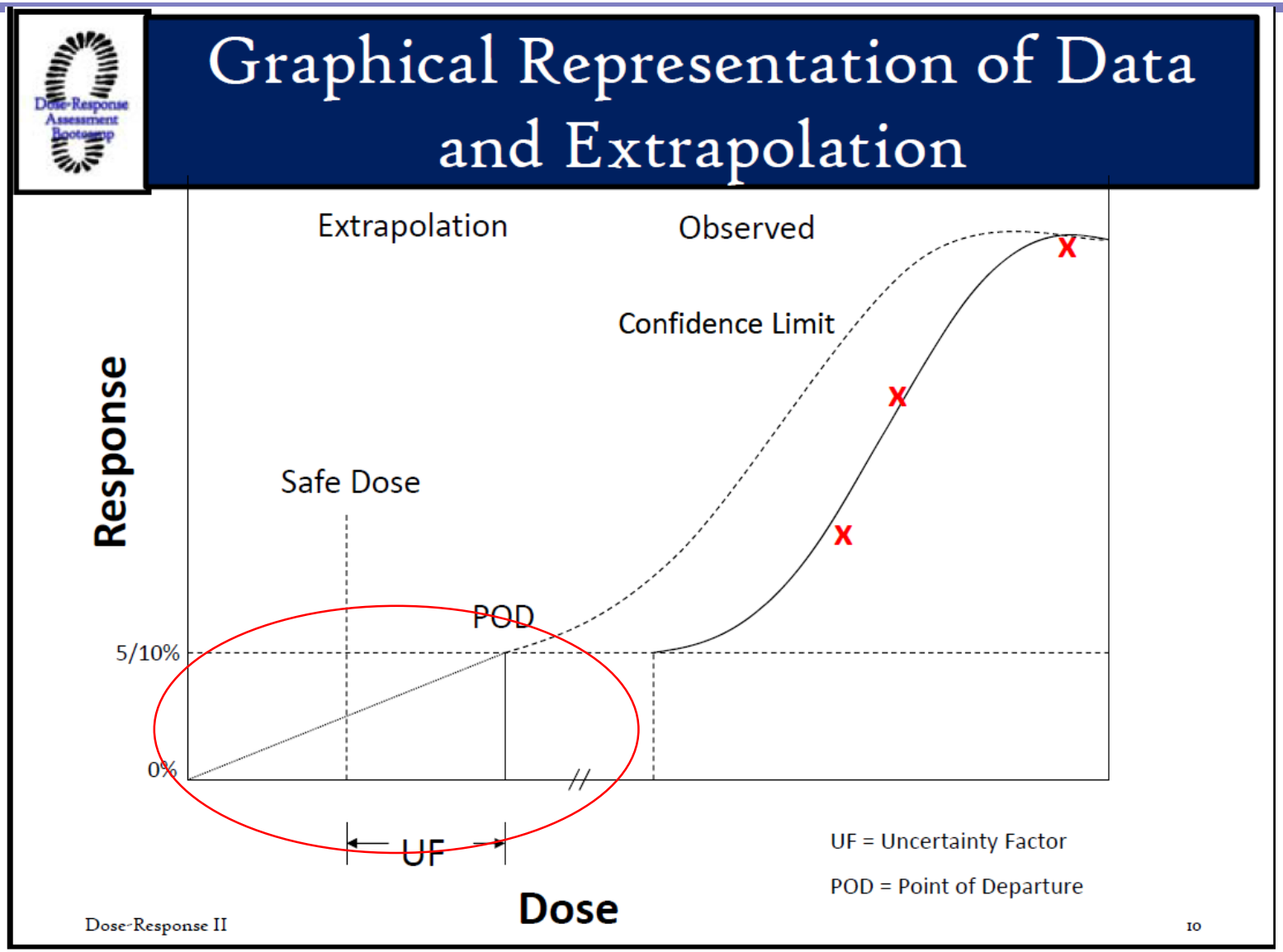
- Ozone is a secondary air pollutant, formed when nitrogen oxides (NO_x) and volatile organic compounds (VOCs) react with ultraviolet radiation from sunlight
- NO_x is responsible for both formation and scavenging of ozone
- Ozone reacts with indoor surfaces and ventilation, scavenging it from indoor air – ozone is effectively an outdoor air pollutant
- Ozone is a highly reactive gas that causes inflammation and irritation of the respiratory tract

Ozone Standard (2015)

70 ppb, annual 4th highest daily maximum 8-hr concentration, averaged over 3 years

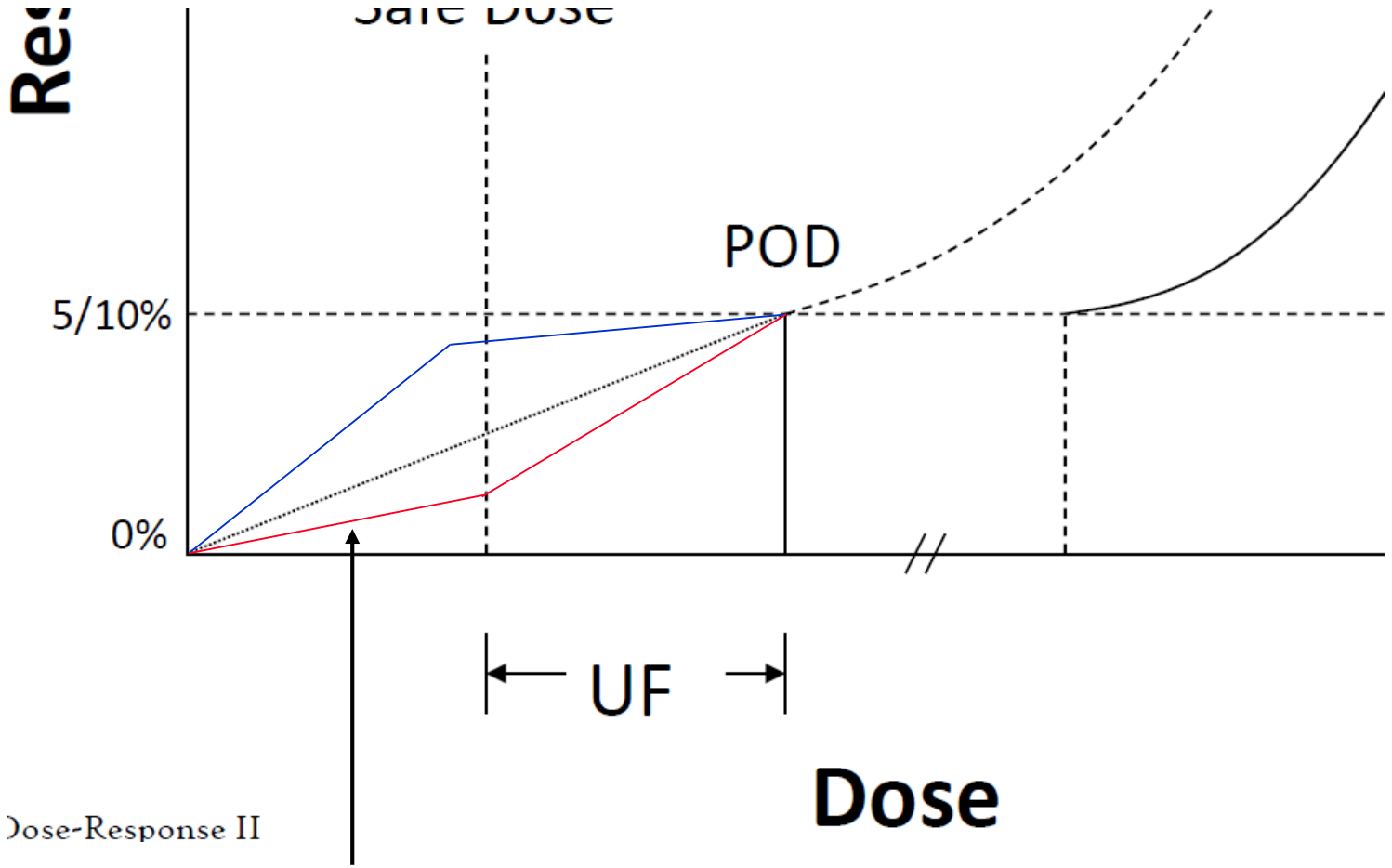


Low-Dose Extrapolation



Toxicology Excellence for Risk Assessment

Low-Dose Extrapolation



Steepness of the slope dictates the acceptable exposure level: the steeper the slope, the lower the acceptable chemical concentration