Toxicology of Polycyclic Aromatic Hydrocarbon Mixtures

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OVERVIEW OF PRESENTATION

- Introduction
- Approaches for PAH mixtures risk assessment
- Current guidance on the RPF approach for PAH mixtures
- New toxicology data
- Next steps

USEPA's Integrated Risk Information System (IRIS)

- A database containing Agency scientific positions on potential adverse health effects that may result from chronic (or lifetime) exposure to chemical substances found in the environment.
- ~540 chemical files on IRIS.
- Originally developed in the mid-1980s to promote use of consistent risk assessment information within the Agency.
- Widely used to support risk-based decision making at local, state, national and international levels.

US EPA Office of Research and Development

EPA United States Environmental Protection Agency

Sources of PAH Mixtures in the Environment

- Coke oven emissions
- Coal tar and coal tar pitch
- Creosotes (coal tar)
- Petroleum derived asphalts (bitumens)
- Coal and gas liquefaction
- Iron and steel foundries
- Printing inks
- Carbon black
- Mineral oils (excluding food and medicinally derived oils)
- Aluminum production
- Power plants (oil- and coal-fired)
- Wood derived source mixtures (emissions)
- Tobacco smoke
- Residential heating and cooking
- Motor vehicle emissions
- Fires and volcanoes

PAH Mixtures: Regulatory Implications

- *Office of Air and Radiation (OAR)*
  - PAH compounds fall within the Clean Air Act listed hazardous air pollutant group, polycyclic organic matter (POM)
  - PAH compounds constitute the major risk component of POM

- *Office of Superfund Remediation Technology Innovation (OSRTI)*
  - 16 PAH compounds were included on the Priority Pollutant List generated in the 1970s under the Clean Water Act
  - These 16 PAH compounds are now listed on the Contract Laboratory Program Target Compound List for the Superfund Program and are routinely sampled for in media at hazardous waste sites

EPA guidance and IRIS assessments on PAHs

- Current PAH assessments on IRIS include:

  (1) 15 non-methylated PAHs with 3 or more rings (e.g., benzo[*a*]pyrene); 7 PAHs are considered B2 (probable) human carcinogens

  (2) PAH-containing mixtures (coke oven emissions, creosote, diesel emissions)
- With the exception of diesel emissions, the assessments are from the late 1980s and early 1990s.
- Provisional Guidance for Quantitative Risk Assessment of PAHs (1993) (Relative Potency Factor Approach)

Limitations of the available guidance and IRIS assessments

- EPA does not have a general framework or guidance addressing PAH mixtures
- IRIS assessments do not address the environmental occurrence of PAHs as complex mixtures
- The individual assessments on IRIS and the Provisional Guidance don't reflect the most recent research findings on PAHs and PAH mixtures
- IRIS and the Provisional Guidance don't consider a number of additional PAHs with carcinogenic potential (e.g., cyclo-penta and fjord-region PAHs)

Goals of the PAH Mixtures Health Assessment

- The goal of the PAH mixtures health assessment is to recommend procedures that can be used in combination with exposure assessment information to evaluate the potential health risk of PAH mixtures when mixture-specific data are not available or are not sufficient for quantitation of risk
- Data for the mixture of interest should be used if available
- One approach will not fit all situations
- Focus on carcinogenicity and non-methylated PAHs

Available Guidance for Mixtures Health Assessment

- Guidance for the Health Risk Assessment of Chemical Mixtures (US EPA, 1986)
- Supplemental Guidance for Conducting Health Risk Assessment of Chemical Mixtures (US EPA, 2000)
- Framework for Cumulative Risk Assessment (US EPA, 2003)
- Draft Final Report on the Peer Consultation Workshop on Approaches to PAH Health Assessment (US EPA, 2002)

Approaches to Health Assessment of PAH Mixtures

- Whole Mixtures Approaches
  - Comparative Potency Approach (data on a group of similar mixtures)
  - Surrogate Approach (data on a sufficiently similar mixture)

- Component Approach
  - Relative Potency Approach (data on the chemical components in a mixture)

Comparative Potency Approach

- Whole mixture approach
- Human epidemiological data and bioassay data used to derive a scaling factor for one mixture
- Scaling factor applied to bioassay data for second mixture
- Sufficient similarity of two mixtures needed

Surrogate Approach

- Whole mixture approach
- Assume that the risk associated with the PAH component of a complex mixture is proportional to the level of an indicator or index chemical (typically BaP) in the mixture
- Estimates the PAH component only of the whole mixture
- Need to determine sufficiently similarity of various mixtures

Issues related to the implementation of the surrogate approach for PAH health assessment

- Defining a sufficiently similar mixture
- Selection of indicator PAH
- Availability of dose response data on PAH mixtures
- Interactions and additivity of individual PAHs in mixtures implicitly handled

Defining sufficient similarity of PAH mixtures

- Are the components of the mixtures similar and present in similar proportions?
- Do similarities exist in the toxicokinetics and toxicodynamics of the mixtures (or components)?

Relative Potency Factor Approach

- Component approach
- Estimates the potency of the mixture by adding only the PAHs with RPFs
- Requires bioassay data for the index PAH (e.g., BaP)
- Ideal situation:
  - Common mode of action among individual PAHs
  - Consistency in the relative toxicity of the individual PAHs
  - Dose additivity
  - Lack of toxicological interactions

EPA PROVISIONAL GUIDANCE FOR QUANTITATIVE RISK ASSESSMENT OF PAHs (1993) (RPF APPROACH)

- Benzo[a]pyrene used as the index PAH compound
- "Estimated orders of potential potency" or RPFs for 6 PAH compounds were determined relative to BaP
- Rankings based on data from complete carcinogenesis assays in mouse skin
- Assumed similar toxicity
  - generation of reactive metabolites
  - genotoxicity generally proportional to tumorigenicity
- Assumed additivity of PAH response
- Assumption that RPFs are applicable to oral exposure only

Relative Potency Factors (US EPA, 1993)

PAH	RPF
Benzo[a]pyrene	1
Benz[a]anthracene	0.1
Benzo[b]fluoranthene	0.1
Benzo[k]fluoranthene	0.01
Chrysene	0.001
Dibenz[ah]anthracene	1
Indeno[123-cd]pyrene	0.1

Mode of Carcinogenic Action of PAHs

- Oxidative metabolism to reactive intermediates that covalently bind to DNA, RNA, and proteins
- Formation of DNA adducts
- Tumor initiation due to genotoxicity and mutations in specific oncogenes
- Tumor promotion related to aryl hydrocarbon (Ah) receptor affinity and upregulation of genes related to biotransformation, growth, and differentiation

Data available for determining RPFs

- 62 individual PAHs identified (3 or more rings containing C and H only)
- Animal studies:
  - rodent cancer bioassays
  - newborn mouse bioassays
  - initiation/promotion bioassays
  - skin painting assays
- In vivo and in vitro assays of cancer-related endpoints:
  - mutagenicity
  - DNA adducts
  - clastogenicity

Overview of PAH studies that include BaP for comparison

Type of study	Number of available studies
Bioassay	79
In vivo genotoxicity	53
In vitro genotoxicity	171

Evaluation of data

- dose-response assessment
- data quality criteria
- determination of statistical significance for a positive response
- development of relative potencies
  - point estimates
  - dose-response modeling (multistage models) to determine ED10s

Issues related to the assessment

- Recommendations for whole mixtures approaches versus the component based RPF approach
- Determination of the degree of similarity between PAH mixtures
- Extrapolation between oral, dermal and inhalation data for the RPF approach
- Inclusion of new PAHs in the RPF approach
- Appropriateness of BaP as an index compound
- Use of in vivo or in vitro data for determining RPFs

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