



Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures for the IRIS Program

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PAH Mixtures Review Panel
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Overview

- History of PAH mixtures risk assessment
- Available PAH data for consideration
- Development of the draft RPF approach for PAH mixtures
- Scientific questions and key issues to consider

Major 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's and USEPA Regulatory Activities

- PAH compounds fall within the Clean Air Act hazardous air pollutant (HAP) group, polycyclic organic matter (POM).
- PAH compounds constitute the major risk component of POM.
- Assessment of cumulative risk of PAHs (along with all HAPs) from source categories is conducted as part of the Residual Risk Program and as a part of the National-Scale Air Toxics Assessment.
- 16 PAH compounds are included on the Priority Pollutant List (1984) under the Clean Water Act
- These 16 PAH compounds are listed on the Contract Laboratory Program Target Compound List for the Superfund Program and are routinely sampled for in media at hazardous waste sites.

Available Guidance and PAH assessments on the IRIS database

- Provisional Guidance for Quantitative Risk Assessment of PAHs (1993) (Relative Potency Factor Approach).
- Current PAH assessments on the IRIS database include:
 - (1) 15 non-methylated PAHs with 3 or more rings (e.g., benzo[a]pyrene or BaP); 7 PAHs are considered B2 (probable) human carcinogens; BaP is the only single PAH with a oral slope factor (no inhalation unit risk).
 - (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.
- Ongoing PAH-related IRIS assessments: Reassessment of BaP health effects (anticipated completion date – summer 2011).

Approaches for Health Assessment of PAH Mixtures

- Use data from mixture of interest to derive toxicity values.
- Whole mixtures approaches:
 - Comparative potency approach (data on a group of similar mixtures used to estimate risk from mixture).
 - Surrogate approach (data on a sufficiently similar mixture used to estimate risk from mixture using surrogate PAH).
- Component approach:
 - Relative potency approach (data on the chemical components in a mixture used to estimate risk from mixture).

Relative Potency Factor Approach

- Component approach
- Estimate potency of component PAHs relative to index compound (BaP)
- Add scaled doses together to estimate PAH mixture risk
- Estimate response to total BaP equivalent doses, using the dose-response curve for BaP
- Requires bioassay data for the index PAH (e.g., BaP)
- Ideal situation:
 - Common mode of action among individual PAHs
 - Consistency in the dose-response of the individual PAHs
 - Dose additivity
 - Lack of toxicological interactions

General Recommendations from EPA's 2002 Peer Consultation Workshop

- EPA conducted a Peer Consultation Workshop on Approaches to PAH Health Assessment with 10 invited expert participants (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54787>).
- Workshop goal: To discuss the state of the science related to the health assessment of PAH mixtures.
- General recommendations:
 - Whole mixtures approaches preferred over component approaches
 - Surrogate approach --- preferred approach with the least uncertainty, providing the judgment of “sufficient similarity” has been well-defined.
 - RPF approach --- pointed out some advantages and disadvantages

Some specific recommendations for the RPF approach from the Peer Consultation Workshop

- (1) Additional carcinogenic PAHs should be added to the current set of PAHs for which relative potency factors are derived (EPA, 1993) (suggestions ranged from including all EPA “target” PAHs to adding only PAHs known to be potent and removing those known to be of low potency).
- (2) The entire database of available PAH studies should be examined for usefulness in an RPF approach, including both *in vitro* and *in vivo* studies.
- (3) EPA should re-evaluate the validity and usefulness of the relative potency factor approach, using all available data sets.
- (4) The oral cancer slope factor for BaP should be updated and an inhalation unit risk estimate should be derived.

Practical Advantages of the RPF Approach for PAH Mixtures

- On the basis of increased risks of lung cancer or skin cancer, occupational exposures to PAH mixtures during coal gasification, coke production, coal-tar distillation, paving and roofing, aluminum production, and chimney sweeping have been classified as carcinogenic to humans (IARC, 2005). However, very few PAH mixtures have cancer dose-response data.
- BaP is the only PAH with cancer dose-response data for oral and inhalation exposure --- oral data are now available for 7H-benzo[c]fluorene (Weyand et al., 2004).
- IARC (2005) indicated that “a few PAHs seem to be more potent carcinogens than BaP. Of particular concern is dibenzo(a,l)pyrene, which seems to be more than 10 times more potent than BaP. The Working Group recommended that this PAH be measured routinely in the workplace and the environment. Another highly potent PAH is dibenz(a,h)anthracene.”
- Large database of studies is available comparing potencies of individual PAHs to BaP for various endpoints.

EPA's Current RPF Approach for PAH Mixtures

- Most recent guidance: *Provisional Guidance for Quantitative Risk Assessment of PAHs (1993)*.
- RPFs were developed for 7 PAHs, each classified as a Probable Human Carcinogen (Group B2), including benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-cd]pyrene.
- RPFs were based on ratios of potencies of subject PAHs to potency of BaP in several mouse skin carcinogenesis bioassays.
- Assumed similar mode of action of carcinogenicity.
 - generation of genotoxic reactive metabolites
 - genotoxicity generally proportional to tumorigenicity
- Assumed additivity of PAH response.
- Recommended use for oral exposure only because only an oral slope factor was available for BaP.

Some limitations of estimating risk associated with exposure to PAH mixtures using current RPF approach

- Available guidance is limited in PAHs addressed.
- PAH mixtures exist as complex mixtures (composition unknown generally, includes metals, etc).
- Available guidance doesn't address more recent research findings on PAHs (e.g., certain PAHs may be more potent than those currently considered --- cyclo-penta and fjord-region PAHs).
- Lacking validation of available methods to human exposure and "real" mixtures.

Overview of topics in RPF document

- (1) A rationale for recommending an RPF approach (Chapter 2);
- (2) A summary of previous approaches for developing the RPF approach for PAHs (Chapter 3);
- (3) An evaluation of the carcinogenicity of individual PAHs (Chapter 4);
- (4) Methods for dose-response assessment and individual study RPF calculation (Chapter 5);
- (5) Selection of PAHs for inclusion in the RPF approach (Chapter 6);
- (6) Derivation of RPFs for selected PAHs (Chapter 7); and
- (7) Characterization of strengths, weaknesses, and uncertainties associated with the RPF approach to PAH cancer risk assessment (Chapter 8).

Data Available for Estimating RPFs

- 74 individual PAHs were identified (3 or more rings containing C and H only) that have comparison data with BaP and are environmentally relevant.
- Over 300 studies were found to contain dose-response information with comparisons to BaP.
- Available animal studies:
 - rodent cancer bioassays
 - newborn mouse bioassays
 - initiation/promotion bioassays
 - skin painting assays
- Available *in vivo* and *in vitro* assays of cancer-related endpoints:
 - mutagenicity
 - DNA adduct formation
 - clastogenicity
- 51 PAHs had dose-response information that was further evaluated.

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

Criteria for Selecting *In Vivo* or *In Vitro* Studies for RPF Development

- Included one PAH as well as BaP.
- Included concurrent control group.
- Quantitative dose-response data available.
- Statistically significant tumor/biological response at one dose, or significant trend observed.
- <90% tumor incidence at lowest dose of bioassay.

Determination of Proposed RPFs

- Weight of evidence evaluation used for determining carcinogenic potential.
- Development of relative potencies
 - point estimates
 - dose-response modeling (multistage models) to determine ED10s (or other)
- Average value used for determining final RPF (with range) for each PAH.
- Relative confidence rating (high, medium, low) given to each RPF based on the overall data base and other general criteria.

General Methods for RPF Calculations

$$\text{RPF} = \text{slope PAH}_i \div \text{slope BaP}$$

- For dichotomous variables, fit multistage model to data and calculate ED_{10} : Slope = $[0.1 / \text{ED}_{10}]$
- For continuous variables, fit linear model to data and calculate $\text{ED}_{1\text{SD}}$: Slope = $[1 \text{ SD change} / \text{ED}_{1\text{SD}}]$

Results of Data Evaluation and RPF Calculation

- 51 of the 74 PAHs with toxicological data relevant to cancer had adequate data to calculate at least one RPF.
- 16 PAHs had only 1 or 2 RPF values based on an *in vitro* genotoxic endpoint only
 - Due to limited data, these PAHs were not selected for inclusion in the RPF approach.
- The remaining 35 PAHs had at least one RPF based on *in vivo* data or more than two RPFs based on *in vitro* genotoxic endpoints.
- Finally, 24 PAHs had nonzero RPFs based on tumor data, plus RPF values based on genotoxic endpoints; 3 PAHs were determined to be noncarcinogenic.

Recommendations for Final RPFs for PAHs

- Preference for tumor bioassay RPFs over genotoxicity RPFs.
- Final RPFs were derived as an average (with range) from bioassay data for any PAH that had at least one RPF based on a tumor bioassay.
- For potentially carcinogenic PAHs without tumor bioassay data, final RPFs were calculated as an average (with range) of all genotoxicity RPFs (applies only to dibenz(a,c)anthracene).
- RPFs were assigned a relative confidence rating of *high, medium, or low confidence*. The relative confidence rating reflects the nature of the database.
- The current analysis represents a significant improvement upon the previous component-based approaches for PAH mixtures risk assessment.
- One of the most important improvements is the consideration of data from a comprehensive review of the scientific literature dating from the 1950s through 2009 on the carcinogenicity and genotoxicity of PAHs.

Assignment of Relative Confidence Ratings

Confidence rankings were based on the robustness of the database.

- availability of tumor bioassays
- availability of supporting data for cancer-related endpoints
- whether multiple exposure routes were represented
- availability of more than one in vivo study
- whether effects were evident in more than one sex or species

Application of Age-Dependent Adjustment Factors (ADAFs) for Increased Susceptibility from Early-life Exposure

- According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005), BaP is carcinogenic by a mutagenic mode of action.
- In this analysis, the PAH compounds for which a RPF value was derived are also considered to be carcinogenic by a mutagenic mode of action.
- Therefore, when assessing PAH cancer risks for life-stages under 16 years of age, or for lifetime exposures that include early-life exposures, the RPF values should be applied with specific exposure information to the BaP cancer risk estimates including an adjustment for early-life susceptibility, through the application of age-dependent adjustment factors.

Additional topics of interest

- Appendix B: Bibliography of studies without BaP as a reference compound.
- Table 8-3: Comparisons among average tumor bioassay RPF values by exposure route and target organ.
- Appendix F: Example calculation of RPF detection limit.
- Appendix G: Evaluation of alternatives for ranking RPFs.

Some uncertainties associated with using an RPF approach for PAH Mixtures

- The approach only considers a small subset of PAHs (unsubstituted PAHs only, no heterocyclic compounds or nitro- or alkyl-substituted PAHs included).
- Only the PAHs chosen for RPF estimation would be considered in a PAH mixtures risk assessment using this approach – may underestimate risk in this respect.
- There are no human toxicity data for any individual PAH – lack of “true” validation.
- There are issues associated with assumption of additivity – there may be interactions among PAHs or between PAHs and other components of a mixture (e.g., metals)
- There are issues associated with the assumption that PAHs generally have a common mode of action – multiple modes of action for PAH-induced carcinogenesis may exist.
- The use of the available data across routes of exposure is not straightforward.

Some issues associated with cross-route extrapolation

- Recommendation is to apply the proposed RPFs across all routes of exposure.
- Cross-route extrapolation would be contraindicated if there were convincing toxicokinetic evidence that absorption of PAHs does not occur by one or more exposure routes.
- Point of entry toxicity may be considered contrary evidence for cross-route extrapolation. The one inhalation bioassay of BaP identified the upper respiratory tract as the site of tumor formation.
- BaP-induced tumors are observed primarily at point of contact in oral studies, while MGP residue and coal tar produce tumors in lung, liver, forestomach and other organs.
- 7H-benzo[c]fluorene-induced tumors observed in lungs when administered as i.p. injection or when fed to mice in diet.

Selected Key Issues to Consider

- Scientific justification for RPF approach for estimating risk associated with PAH mixtures.
- Unidentified fraction of the PAH complex mixture not taken into consideration.
- Assumption of similar mode of carcinogenic action across PAHs.
- Assumption of additivity across PAHs.
- Inclusion of PAHs compared to BaP in the same experiment/publication only.
- Use of cancer-related endpoint data.
- Use of tumor multiplicity data to estimate individual study RPFs.
- Dose response methodology, including comparisons in some instances at high effect levels.
- Use of arithmetic mean, instead of other determination methods such as geometric mean, weighted average, or maximum value to estimate RPFs.
- Determination of situations for when to apply the RPF approach.

Next Steps

- 2010
 - EPA SAB peer review report
 - Address peer review and public comments
- 2011
 - Completed document loaded on IRIS database