

Evaluation of the Carcinogenicity of PAHs

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Mixtures Review Panel

General Comments

- EPA's RPF Selection Criteria is Exclusionary and Reduces Reliability in RPF values.
- EPA RPF Calculation Ignore Differences in Cross-Route Relative Potency
- EPA should follow it's own Guidance for Weight of Evidence (WOE) Evaluation for Assessing the Carcinogenicity of Individual PAHs
- EPA has not validated the derived RPFs using cancer response data from real world complex mixtures.
- EPA Should Not Use the RPF Approach because it is not scientifically justified

PAH RPF WOE Evaluation

- EPA did not perform a WOE as called for in EPA's 2005 Cancer Guidelines*.
 - PAHs selected were based on an “evaluation of whether the available data were adequate to assess the carcinogenicity of each compound.”
- EPA considered *a single* positive result as adequate WOE for inclusion in the RPF approach and 10 RPFs are based on single results
- **One stand-alone positive result in a tumorigenicity test or one positive plus one or more negative results provides an inadequate WOE**

*Guidelines for Carcinogen Risk Assessment. Risk Assessment. EPA/630/P-03/001B. March. 2005

PAH Weight of Evidence

- RPF values should only be derived for chemicals with:
 - IARC Class Group 1 or Group 2A
 - EPA Class A or B1
- There is insufficient human evidence for the 27 PAHs included in EPA's RPF analysis when reviewed by EPA or IARC, with the exception of B(a)P .

Carcinogenic Classifications of Individual PAH

PAH	Proposed RPF	IARC Classification	EPA Classification
Anthanthrene	0.4	3	NC
Benzo[a]pyrene	1	1	B2
Benzo[b]fluoranthene	0.8	2B	B2
Benzo[c]fluorene	20	3	NC
Benz[j]aceanthrylene	60	2B	NC
Benz[l]aceanthrylene	5	3	NC
Dibenzo[a,e]fluoranthene	0.9	3	NC
Dibenzo[a,h]pyrene	0.9	2B	NC

Notes:

NC = not classified by Agency

IARC Classification: (Volume 92, 2010)

- Group 1: The agent is carcinogenic to humans
- Group 2A: The agent is probably carcinogenic to humans
- Group 2B: The agent is possibly carcinogenic to humans
- Group 3: The agent is not classifiable as to its carcinogenicity to humans

EPA Classification:

- A: Known human carcinogen
- B1: Probable human carcinogen - indicates sufficient evidence in animals and limited evidence in humans
- B2: Probable human carcinogen – indicates sufficient evidence in animals and inadequate or no evidence in humans
- C: Possible human carcinogen
- D: Not classified as to human carcinogenicity based on no human data and inadequate animal data

Mode of Action

- The RFP Approach assumed that all PAHs act via a mutagenic mode of action but scientific evidence does not support this:
 - There is considerable uncertainty with the molecular events involved with individual PAHs
 - Urano et al. (1995), Graem (1986), and Soballe et al. (1996) showed that mouse skin is sensitive to papilloma formation with a variety of treatments, including PAH treatments, while human xenografts are not.

Assumption of Dose Additivity

- EPA provided little information in support of the “dose additivity assumption”
 - On the contrary, EPA ignored a great deal of scientific data on antagonistic interaction of PAHs
- Validation exercises (see Appendix B) show the EPA’s RPFs approach overestimate carcinogenic risk.
- EPA did not adequately validate the derived RPFs using cancer response data from real world complex mixtures (EPA 2000)*
- The PAH RPF Approach does not address how the proposed RPF methodology will be applied in real mixtures
 - The accuracy of most analytical methods is insufficient to differentiate similar, single compounds especially at low concentrations of PAH mixtures.

* EPA’s The Supplemental Guidance for Conducting Health Risk Assessment of Chemical Mixtures

Summary

- EPA did not provide sufficient scientific evidence or quantitative data to support a similar toxicological action of PAH components in the mixture
- EPA's RPF approach does not follow EPA guidelines for cancer risk assessment
- API Supports the oral comments presented by the Association of American Railroads and the Pavement Coatings Technology Council