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Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment

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**Peer Consultation Workshop on Approaches to Polycyclic Aromatic
Hydrocarbon (PAH) Health Assessment**

National Center for Environmental Assessment
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Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment

EXECUTIVE SUMMARY

The National Center for Environmental Assessment (NCEA) of the U.S. Environmental Protection Agency (EPA) sponsored a two-day peer consultation workshop, entitled “Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment” on October 24-25, 2001, in Arlington, Virginia. The objectives of the workshop were to: (1) evaluate the extent to which each of the three available approaches to PAH health risk assessment is supported by the current scientific literature; and (2) assess how well each approach addresses the range of exposure situations and monitoring data encompassed by EPA program offices. The workshop focused on the extensive carcinogenicity literature for PAHs. Ten experts in polycyclic aromatic hydrocarbon (PAH) toxicology and chemistry, and risk assessment of chemical mixtures, provided their individual opinions on existing approaches and recommended additional analyses and research; consensus was not required. Dr. Joe Mauderly served as chairperson and moderator. Versar, Inc., provided logistic support and prepared a summary report of the proceedings.

Representatives from EPA’s Office of Air and Radiation (OAR) and Office of Solid Waste and Emergency Response (OSWER) briefly described how their respective program offices handle PAH risk assessment. EPA scientists from the Office of Research and Development (ORD) provided background summaries on three available approaches to PAH health risk assessment: (1) surrogate approach; (2) comparative potency approach; and (3) relative potency factor approach. Following these opening presentations, the experts discussed the strengths and weaknesses of each approach, noting the scientific and practical considerations as well as future data needs. Summarized below is a brief description of the approaches that were discussed and the main comments and suggestions provided by the participants.

Surrogate Approach

The surrogate approach was described as a whole mixture approach based on the assumption that any mixture of PAHs in the atmosphere (or mixture of concern) is merely a dilution of a “surrogate” mixture of PAHs, the “surrogate” being a potent PAH-containing mixture that has been well characterized both chemically and toxicologically. Under this assumption, the risk from any PAH mixture of concern is directly related to the extent of this dilution. The extent of dilution is based on examining the ratios of several PAHs common to both the mixture of concern and the surrogate mixture. The surrogate approach is based on the Agency’s mixtures’ guideline which recognizes and endorses whole mixture approaches. Fundamental difficulties of this approach include the appropriate choice of a “surrogate” whole mixture and evaluation of “sufficient similarity” to the mixture of concern, based on EPA’s mixtures’ guidelines. Major advantages to the surrogate approach include: (1) a mixture (as compared to single components) is used as the reference compound, and (2) the composition and toxicity of the surrogate mixture as a whole is known. Several experts stated that the surrogate approach exhibits considerably less uncertainty than the other approaches, mainly because the surrogate is a mixture whose individual components are known and potential interactions among components are included in

toxicity characterization. As long as the chosen “surrogate” mixture is more potent than the mixture actually being evaluated, this approach would also be more conservative. For this reason, some experts considered it to be the preferred approach. The key assumption underlying the use of this approach is a judgment of “sufficient similarity” of the mixture of interest to the surrogate mixture. It was recommended that analysis be conducted on a range of complex mixtures to determine composition and the degree of similarity/difference among mixtures.

Some, but not all, participants considered a limitation of this approach to be the choice and use of only one reference mixture, i.e., “surrogate.” One participant considered the principal limitation of the approach, in its present form, to be that it is only intended to account for the PAH fraction of a complex mixture, specifically the unsubstituted PAH fraction, and other components of the mixture (including nitro and other substituted PAHs) are not accounted for. It was also noted in the example given for this approach that the animal bioassay data are for inhalation exposure only, and the approach might not be currently useful (at least without further refinement) for assessments in which ingestion and dermal routes of exposure are important. Some participants recommended that other reference mixtures be identified and characterized, and that the use of additional indicator compounds for estimation of potency be explored. Suggestions for other indicator compounds included: (1) the group of 7 PAHs classified as probable human carcinogens currently utilized in the relative potency factor approach; (2) the 4- to 7-ring PAH fraction; (3) total organic carbon (TOC); and (4) total PAH mass.

Comparative Potency Approach

The comparative potency approach was initially developed by EPA to evaluate the adverse health effects of diesel fuels in the 1980's, when it was assumed that the entire automobile fleet would eventually be dieselized and that there would be widespread human exposure to diesel emissions. The underlying assumption of the comparative potency method is that similar mixtures in a data set (e.g., combustion mixtures) act in a similar manner toxicologically, and that the relative potency of two such mixtures in an *in vivo* or *in vitro* bioassay is directly proportional to the relative potency in humans, represented by k , a scaling factor. For a mixture of interest of unknown potency considered to be a member of this group of similar mixtures, human cancer potency can be estimated by applying the scaling factor to short-term bioassay data. This assumption was examined for three complex organic emission products (from cigarette smoke, coke oven emissions, and roofing tar) that had previously been shown to be associated with the induction of respiratory cancer in exposed human populations. For these three emission products, data from the Sencar mouse skin tumor initiation assay was most highly correlated with unit risk estimates for lung cancer. Inhalation unit risk estimates derived from occupational epidemiology studies on coke oven emissions, roofing tar, and cigarette smoke were used to rank these three mixtures, normalizing to coke oven emissions, and these rankings coincided with the animal bioassay data. The human cancer potency for diesel emissions was subsequently determined by using cancer data from a rat inhalation study, multiplied by the scaling factor. Using this approach, the relative potency of diesel emissions was less than roofing tar but more than cigarette smoke.

The strength of this approach is based on the concept that the potency of a PAH-containing mixture can be estimated without having to either identify or quantify individual PAH components. To use this approach, a simple and low-cost animal assay would be performed with

the mixture of interest and the results extrapolated to humans, using a scaling factor determined from a set of similar mixtures. However, there must be sufficient evidence to determine that the mixture of interest is: (1) a potential human carcinogen and (2) sufficiently similar to the set of mixtures used to develop the scaling factors.

The participants acknowledged that the advantage to this approach is that the toxicity for the whole mixture is characterized, whether or not the composition of the mixture is known. The key assumption underlying this approach is that the ratio between the potency for the same mixture in an animal bioassay and the human cancer risk is constant for different PAH-containing mixtures. Major issues associated with the approach include: (1) it cannot be used with mixtures from multiple or unknown sources; (2) there is considerable uncertainty about the reliability and validity of the lung cancer epidemiology studies which are available to derive scaling factors, because of the confounding effects of smoking; and (3) this approach is currently based on inhalation exposure data and might only be applicable to the inhalation route because no human oral exposure studies are available. Most participants were skeptical about the use of physiologically-based pharmacokinetic (PBPK) models for route-to-route extrapolation because of the difficulty of characterizing the toxicokinetics of a complex mixture containing numerous compounds. Route-to-route extrapolation of data was not recommended, based on the current state of the science.

Relative Potency Factor Approach

The relative potency factor approach is a component approach in which the carcinogenic potencies of selected PAHs relative to an index compound (e.g., benzo(*a*)pyrene (BaP)) are determined, and individual PAH risks are summed to yield a cancer risk estimate for the whole mixture. Current EPA provisional guidance (EPA, 1993) utilizes this approach to assess the risk associated with PAH mixtures. The key assumptions underlying the use of this approach are that individual PAH risks are additive and that the sum of the risks of selected PAHs adequately characterizes the risk for the entire PAH component of the mixture. The advantage of this approach is that it is practical for exposure situations in which the source and the composition of the mixture are unknown. However, many participants agreed that this was the least scientifically-defensible approach, and that any approach that utilizes the toxicity of a mixture as a whole is preferable to the use of the relative potency factor approach. The major issues associated with this approach are that it is not based on a reference PAH mixture with known toxicity (animal or human), that there are no human toxicity data on any of the individual PAHs, and that the assumption of additivity of individual PAH toxicity may not be accurate.

Cross-Cutting Issues

While much of the experts' discussion focused on the three approaches, there were many issues raised that pertained to all three methods and the challenges facing PAH risk assessment in general. It was noted frequently that most data on the carcinogenicity of PAHs comes from mouse skin tumor initiation studies. Some participants recommended that chronic exposure studies be conducted on key PAHs and PAH mixtures, and that oral potency should be based on oral studies, and inhalation potency on inhalation studies. Evaluation of the dermal carcinogenicity of PAHs was suggested, using all available data; additional dermal carcinogenicity studies might also be useful. Some participants did not recommend direct route-

to-route extrapolation for any of the approaches, and many participants were skeptical about the utility and validity of the currently available pharmacokinetic modeling for mixtures. Uncertainty associated with extrapolation of bioassay data to humans was also noted.

The lack of human toxicity data on any of the individual PAHs was a recurring concern; several participants observed that without human data, the relevance of the animal data to human exposure situations is questionable. One participant suggested that re-examination of the effects of coke oven emissions in animals and humans might be useful in back-calculating a human potency estimate for BaP, and noted that this approach has been adopted by the World Health Organization (WHO). It was also noted that the WHO has concluded that the scientific basis for the relative potency factor approach is lacking; currently, WHO recommends the surrogate approach, with BaP as the surrogate indicator compound.

The use of additional indicator compounds to characterize the composition and toxicity of PAH mixtures was recommended for all approaches. Currently, BaP is the only PAH for which chronic exposure bioassay data are available, and thus by default, it remains the index compound or “gold standard.” Research exploring the utility and validity of using additional indicator compounds or PAH fractions was suggested. It was noted that tumors in target organs other than the skin have not been considered in developing relative potency estimates; a number of published and unpublished studies have examined tumors in other organs. It was recommended that these data be located and evaluated in conjunction with skin tumor data.

In general, participants concluded that the relative potency factor approach should be employed only “as a last resort,” when the mixture of interest was judged not to be “sufficiently similar” to either the surrogate mixture or the specific mixtures used in developing the comparative potency approach. A major concern was that the relative potency approach may not provide a valid estimate of the toxic potency of the mixture as a whole and thus may not be protective of public health. Some participants recommended that the relative potency factor approach not be used, and that a mixtures approach be employed even if the mixture of interest has only been partially characterized and biological activity data are scanty. Several participants noted that existing studies comparing the composition of PAH-containing mixtures suggested that most such mixtures were similar, irrespective of source or age. However, other participants did not think that mixtures from different sources (e.g., combustion versus noncombustion) or with different weathering patterns could be similar. Participants agreed that both the composition and toxicity of PAH mixtures should be better characterized. Although there was some concern about general similarities among mixtures, most of the discussion focused on the difficulties of judging whether mixtures were “sufficiently similar” to each other to justify the use of a mixtures approach.

Action Items: Future Research and Research Needs

Throughout the discussion many recommendations were provided on information that is needed to improve the risk assessment approaches for PAHs. Some of these comments addressed evaluating existing data sets while others called for new research or assessments.

Recommendations for future information and research needs included: (1) EPA should convene a panel to re-evaluate the validity and usefulness of the relative potency factor approach, using all available data sets; (2) the oral cancer slope factor of BaP should be updated, using the data from the recent chronic feeding study (Culp et al., 1998); (3) EPA should develop an inhalation unit risk estimate for BaP, using available data; (4) EPA should commission a new inhalation study, preferably with two species and two sexes per species, conducted by NTP; (5) the validity of using BaP as the indicator compound should be re-evaluated; (6) 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); and (7) existing dermal carcinogenicity studies should be evaluated to obtain information on the absorption and distribution of PAHs and PAH-containing mixtures, and data on the systemic tumorigenicity of exposure via this route.

Information needs are numerous and need to be prioritized. Recommendations for additional specific testing were considered to be beyond the scope of the charge for this peer consultation. Participants recommended that EPA convene another peer review to review the literature and to develop a priority list of PAH compounds and PAH-containing mixtures to be tested, as well as exposure routes for testing (particularly oral and inhalation). Additional epidemiologic data are also needed. Existing data sets should be re-evaluated to determine the degree of similarity/difference among complex mixtures. Other suggestions included research on: (1) the development of markers for characterizing the degree of transformation that occurs between source emissions and the point of exposure; (2) the development of markers for identifying sources of mixtures of unknown origins; and (3) the use of urinary metabolites of PAH compounds, such as 1-hydroxypyrene (a metabolite of pyrene), as biological markers of exposure.

Particularly for the relative potency factor approach, the following testing should be prioritized: (1) whether BaP is still the most suitable compound to test and to use as a reference standard or whether there were other PAHs that might be more toxic/more prevalent in PAH mixtures, and thus more appropriate for testing and use as a reference; (2) what chemicals should be presented to NTP for testing; (3) whether recommendations for testing should be for individual PAHs or for complex mixtures (e.g., diesel fuel, coke oven emissions, and others). In addition, the list of relevant PAHs should be revisited — better data and a longer list of compounds are needed. It was recommended that a group of scientists/regulators review the literature and develop a priority list of compounds to be tested at a later date, including recommendations of route of exposure.

It was generally agreed that data on PAHs in different media, from different sources, and from different exposure routes are all important information needs. Media play a role in terms of PAH bioavailability. Information on the source of the mixture influences the selection of the approach

used for PAH assessment. Additional data on different exposure routes, particularly dermal and dermal absorption, are needed. The National Institute for Environmental Health Sciences (NIEHS) is examining the bioavailability of a range of compounds via different routes; for skin, isolated human skin cultures are being used. With regard to individual PAHs, there are some data showing that BaP and dibenz(*a,h*)anthracene are absorbed through the skin; the degree of absorption in general depends on the molecular weight of the compound.

1.0 INTRODUCTION

1.1 Workshop Purpose

The U.S. Environmental Protection Agency (EPA) sponsored a two-day peer consultation workshop, inviting ten experts in polycyclic aromatic hydrocarbon (PAH) toxicology and chemistry, and risk assessment of chemical mixtures, to examine approaches to the health assessment of PAH mixtures. This workshop was held on October 24-25, 2001, at the Key Bridge Marriott Hotel, in Arlington, Virginia.

Specifically, the purpose of the workshop, entitled “Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment” was to (1) evaluate the extent to which each of the three available approaches to PAH health risk assessment is supported by the current scientific literature and (2) assess how well each approach addresses the range of exposure situations and monitoring data encompassed by EPA program offices. The expert opinions and recommendations emanating from this workshop will be considered by EPA in the development of an appropriate and scientifically defensible health assessment procedure for PAH mixtures. The workshop focused on the extensive carcinogenicity literature for PAHs, as information needed to support the development of a mixtures approach for assessing the noncancer effects of PAHs is limited or lacking.

1.2 Workshop Participants

The workshop was sponsored by EPA's National Center for Environmental Assessment (NCEA), Office of Research and Development. Versar, Inc., an EPA contractor, provided logistical support for the workshop. Ten experts were invited to present their views and recommendations. Dr. Joe Mauderly served as chairperson for the two-day meeting. During the first day of the workshop, EPA scientists presented overviews of PAH risk assessment practices in two program offices, Office of Air and Radiation (OAR) and Office of Solid Waste and Emergency Response (OSWER), and summaries of the three available approaches for assessment of PAH mixtures. Discussion followed each of the presentations. During the second day, Dr. Mauderly presented a summary of the major themes of discussion from the previous day and guided the discussion that followed. A list of the ten participants can be found in Appendix A. The meeting was attended by approximately 30 observers, who are listed in Appendix B. The meeting agenda is shown in Appendix C.

The remainder of this workshop report includes summaries of the opening presentations by EPA scientists (Section 2) and summaries of the major recommendations and conclusions provided by the experts (Section 3). Section 4 provides more detailed proceedings and Section 5 presents brief summaries of comments from observers. Section 6 summarizes recommendations from the participants for future research and information needs. The appendices contain materials handed out at the meeting.

2.0 SUMMARY OF OPENING REMARKS AND PRESENTATIONS

Dr. Mauderly introduced the EPA presenters who included: (1) two scientists from EPA program offices that have regulatory mandates requiring risk assessments for PAHs; and (2) four scientists from EPA's ORD who are leading this effort to develop PAH health risk assessment approaches. Slides used in these presentations are presented in Appendix D.

2.1 Welcome: Introduction and Background

Susan Rieth, ORD, Chair of the PAH Workshop Steering Committee, provided a background introduction on the Integrated Risk Information System (IRIS) Program and the purpose of the workshop. The IRIS Program develops EPA consensus scientific positions on potential human health effects that may result from chronic exposure to chemical substances found in the environment. Currently, there are health assessments for 15 non-methylated PAHs with 3 or more rings that are on EPA's Priority Pollutant List, and assessments for 3 PAH-containing mixtures: coke oven emissions, diesel engine emissions, and creosote. EPA recognizes, however, that the current scope of PAH assessments is insufficient, given the complexity of PAH mixtures. Although a relative potency factor (RPF) approach has been used to assess the carcinogenicity of 7 PAHs classified as probable human carcinogens, this process has not undergone consensus review. Three approaches, including the RPF approach, have been employed by government and nongovernment agencies and by investigators to evaluate the carcinogenic potency of PAHs. A discussion document, describing the three available approaches, was prepared by EPA and distributed to the participants in advance of the meeting (Appendix E). EPA has also published recent supplementary guidance for conducting health risk assessments for chemical mixtures.

The experts were asked to provide: (1) input to EPA on the extent to which each approach is supported by current scientific literature, and on the applicability of the available approaches to different exposure situations of interest to EPA; (2) recommendations for revising existing approaches or developing new approaches consistent with the toxicology literature; and (3) ideas for analyses and additional research that might be undertaken by EPA to resolve some of the more problematic issues associated with the current approaches to PAH risk assessment.

2.2 Overview of PAH Risk Assessment Practices in EPA Program Offices

2.2.1 Office of Air and Radiation (OAR)

Dr. Roy Smith, OAR, briefly discussed how OAR assesses PAH risks. The statutory basis for PAH assessment is the Clean Air Act of 1990, which identifies 189 hazardous air pollutants (HAPs), including 19 categories or groups of chemicals, one of which is a category for particulate organic matter (POM), defined by Congress as consisting of organic compounds with "two or more benzene rings, and a boiling point greater than 100⁰ C." PAH compounds fall into the POM category and, therefore, are considered to be HAPs. The assessment of POM was discussed in the context of two OAR programs: (1) the national-scale assessment, which is intended to guide the air toxics programs in prioritizing HAPs and emission sources, provide baseline data for assessing progress, and assist in scoping more refined assessments; and (2) the residual risk assessment (local scale), which evaluates the health risks remaining after imposition

of control technologies. The most recent national scale assessment considered only inhalation exposure, whereas the residual risk assessments evaluate both oral and inhalation exposures, as appropriate.

The national-scale assessment activity begins with the national emissions inventory for individual sources of POM and uses dispersion modeling on a census tract level to estimate ambient air concentrations. Human exposures are subsequently modeled and dose-response assessment and cancer risk characterization conducted. These analyses identify those pollutants (and sources) that are driving excess lifetime cancer risks. The residual risk assessment program uses the best available emissions data for PAH sources of interest, speciated wherever possible. Ambient air concentrations are estimated using dispersion models, and as relevant, other media concentrations are estimated using multi-media models. PAH oral and inhalation unit risk estimates for cancer and noncancer toxicity endpoints are used to assess dose-response, and estimated cancer and noncancer risks are aggregated.

Dr. Smith noted that the vast majority of POM emission estimates are engineering estimates, and for PAHs, there is currently no “reality-check” (i.e., examining the correlation between modeled and measured exposure data). Speciation data for individual emissions sources are currently very limited. PAH assessments are conducted by summing the cancer risk estimates developed for individual compounds. Both OAR programs characterize excess risks from inhalation exposure; however, EPA has not yet come to a consensus on the derivation of an inhalation unit risk estimate for quantitative dose-response cancer assessment of PAH mixtures in general or of an index compound, such as BaP. OAR uses the inhalation unit risk for BaP developed by California Environmental Protection Agency (Cal EPA), as a default (Collins et al., 1998), and applies the RPF approach to estimate PAH risks.

In response to a question by Dr. Mauderly, Dr. Smith stated that from OAR’s perspective, it would be most useful if the participants would recommend to EPA that a consensus inhalation unit risk estimate for PAHs be derived. It would also be helpful if the participants could suggest refinements to approaches to PAH assessment that are more technologically and quantitatively advanced than those now in use, so that: (1) the approaches to PAH assessment can be extended to other compounds, including heterocyclic POMs; and (2) a more convincing argument for measuring and speciating additional PAHs at their sources can be made.

2.2.2 Office of Solid Waste and Emergency Response (OSWER)

Dr. Lee Hofmann, OSWER, briefly discussed how OSWER currently handles PAH risk assessment. The statutory bases for regulating PAHs are the “Superfund” and hazardous waste legislation (i.e., CERCLA and RCRA); in general, emphasis is on site-specific risk assessments for hazardous waste sites including incinerators and other combustion facilities. PAH risk assessments focus on the seven PAHs classified as probable human carcinogens, using the relative potency factor approach, as outlined in EPA’s 1993 provisional guidance (EPA, 1993). PAHs contribute significantly to calculated human cancer risks at uncontrolled Superfund sites: in a ranking of the 50 major compounds contributing to excess lifetime cancer risk, BaP, benzo(*b*)fluoranthene, and benz(*a*)anthracene ranked 7th, 10th, and 11th, respectively.

In response to a question by Dr. Mauderly, Dr. Hofmann stated that from OSWER's perspective, it would be most useful for the participants to recommend approaches to PAH risk assessment that OSWER can use on a site-specific basis, which would include guidance for evaluating the most important PAHs given the current state-of-the science, guidance for dealing with PAH mixtures, and recommendation of methods to address assessment of risks from dermal exposure.

2.3 Background on Current Approaches to PAH Health Risk Assessment

EPA scientists provided background summaries on three available approaches to PAH health risk assessment: (1) the surrogate approach; (2) the comparative potency approach; and (3) the relative potency factor approach.

2.3.1 Surrogate Approach

Dr. Gary Foureman presented an overview of the surrogate approach. This approach assumes that an established mixture whose chemical content and carcinogenic potency are reasonably well known from animal or human studies can be used to assess the excess lifetime cancer risks of a new mixture of interest having limited animal or human data. The character and content of the established mixture is employed as a "surrogate" for the character and content of the new mixture of interest. The underlying assumption of this approach is that the surrogate mixture is "sufficiently similar" to the mixture of interest. Sufficiently similar mixtures may be mixtures that are similar on the basis of: (1) the presence of specific potent compounds (e.g., BaP); (2) the proportions or ratios of certain key PAHs; (3) the presence/absence of other contributory components (e.g., nitro- or alkyl-PAHs); (4) source; and/or (5) mode of toxic action. Other considerations in characterizing "sufficient similarity" include the nature of the monitoring and toxicologic data bases, such as whether components of the PAH surrogate mixture are monitored in environmental samples and whether components are carcinogenic, and the nature of toxicologic interactions among components.

Dr. Foureman recognized that the major issue in the use of this approach is the definition of "sufficiently similar." An informed scientific judgment must be made on the relevancy of the PAH surrogate mixture to the mixture of interest. Various criteria have been developed for evaluating the similarity of mixtures. For example, Dr. Foureman and his colleagues have utilized the criteria described in the previous paragraph to suggest that coal tar pitch (CTP) is an adequate and "sufficiently similar" mixture that could be used as a surrogate for other PAH "mixtures of interest". CTP has been analyzed to identify both PAHs and other chemical components that might be contributing to its toxicity. CTP contains the PAHs of regulatory concern that are routinely monitored and detected in environmental samples. Some exposure data were presented which gave support to the assumption that all PAH mixtures are similar to CTP with respect to the PAHs present and the relative mass ratios of one PAH to another. Further, CTP has been tested in chronic animal studies and its toxicity, including carcinogenicity and dose-response has been characterized. If one assumes proportionality in PAH composition between CTP and the mixture of interest, one can also assume proportionality in the health risks associated with exposure to any "mixture of interest" as long as it is judged to be "sufficiently similar." If, however, the mixture of interest is judged not to meet the criteria for being "sufficiently similar" to the surrogate, then the risk analysis would default to the relative potency factor approach.

In the case study presented, a risk was calculated from a hypothetical “mixture of concern” based on a comparison to the surrogate CTP. The hypothetical “mixture of concern” consisted only of measured air levels of BaP and chrysene. As a first step, the BaP/chrysene ratio in the hypothetical mixture was compared with that of the surrogate CTP, to judge whether the mixture of concern could be considered to be sufficiently similar to CTP. The ratios were quite different: 1.2 / 5 in the mixture of concern but only 1 / 0.8 in CTP. Based on these differences, a judgment could be made that the mixture of concern was not “sufficiently similar” to the surrogate CTP either because BaP was too low or chrysene was too high. However, based on other additional considerations, the decision was made that the mixture of concern could be prudently assumed to be a dilution of CTP and that a risk calculation could be made. These considerations included that (1) BaP is much more potent than chrysene and reliable risk estimates could be made based upon the amount of BaP present in the surrogate mixture, (2) actual measured BaP concentration should be used (i.e., the amount of BaP should not be extrapolated), and (3) the risk estimate resulting from the assumption that the hypothetical mixture of concern was a dilution of CTP is conservative (i.e., greater than it probably is). Calculation of the risk then proceeded using a simple proportional procedure based on the amount of BaP in CTP.

2.3.2 Comparative Potency Approach

Dr. Stephen Nesnow presented an overview of the comparative potency approach to assessment of PAH cancer risks from complex mixtures. This approach was initially developed by EPA to evaluate the adverse health effects of diesel fuels in the 1980's, when it was assumed that the entire automobile fleet would eventually be dieselized and that there would be widespread human exposure to diesel emissions. Because human epidemiologic data are not available for new combustion technologies, and lifetime animal carcinogenicity studies are both costly and time-consuming, EPA explored a comparative potency method for predicting human risk based on short-term bioassay data.

The underlying assumption of the comparative potency method is that similar mixtures in a set (e.g., combustion mixtures) act in a similar manner toxicologically, and that the relative potency of two such mixtures in an *in vivo* or *in vitro* bioassay is directly proportional to the relative potency in humans, as follows:

$$\frac{\text{Human cancer potency}_{\text{mixture 1}}}{\text{Human cancer potency}_{\text{mixture 2}}} = k \times \frac{\text{Bioassay potency}_{\text{mixture 1}}}{\text{Bioassay potency}_{\text{mixture 2}}}$$

For a mixture of interest of unknown potency considered to be a member of this group of similar mixtures, human cancer potency can be estimated from bioassay data by rearranging the above equation:

$$\text{Human cancer potency}_{\text{mixture x}} = \text{Bioassay potency}_{\text{mixture x}} \times k$$

This assumption was examined for three complex organic emission products (from cigarette smoke, coke oven emissions, and roofing tar) that had previously been shown to be associated with the induction of respiratory cancer in exposed human populations. Emission products were tested in various *in vitro* bioassay systems and in mouse skin tumor initiation assays with several strains of mice. For these three emission products, data from the Sencar mouse skin tumor

initiation assay was most highly correlated with unit risk estimates for lung cancer. In the Sencar mouse skin tumor initiation assay, mice were given a single treatment with the test agent applied to shaved skin; one week later, they were exposed to daily applications of a potent promoting agent (phorbol ester). Animals were scored for tumors every week; most had developed skin papillomas by weeks 20-26 and skin carcinomas were observed by 60 weeks. The different combustion mixtures were ranked by tumor multiplicity (number of papillomas per mouse per 1 mg organics) and tumorigenic dose₂₅ (TD₂₅ = the dose that induces a 25% increased incidence of tumors relative to background), and responses were normalized to coke oven emissions. The potency rankings coincided for both tumorigenic end points (coke oven emissions > roofing tar > cigarette smoke). Inhalation unit risk estimates derived from occupational epidemiology studies on coke oven emissions, roofing tar, and cigarette smoke were used to rank these three mixtures, again normalizing to coke oven emissions. These rankings also coincided with the animal bioassay data.

For the combustion mixtures data set, the k factors varied by a factor of 16 (ranging from 0.25 to 4.0) depending on which mixture pairs were used to determine k (e.g., coke oven emissions versus roofing tar; roofing tar versus cigarette smoke). The human cancer potency for diesel emissions was determined by using cancer data from a rat inhalation study and multiplying it by k. Using this approach, the relative potency of diesel emissions was less than roofing tar but more than cigarette smoke.

The strength of this approach is based on the concept that the potency of a PAH-containing mixture can be estimated without having to either identify or quantify individual PAH components. To use this approach, a simple and low-cost animal assay would be performed with the mixture of interest and the results extrapolated to humans, using a scaling factor determined from a set of similar mixtures. However, there must be sufficient evidence to determine that the mixture of interest is: (1) a potential human carcinogen, and (2) sufficiently similar to the set of mixtures used to develop the scaling factors.

2.3.3 Relative Potency Factor Approach

Dr. Lynn Flowers presented an overview of the relative potency approach for the assessment of PAH cancer risks from complex mixtures. One application of this approach (EPA, 1993) is used for health risk assessments at Superfund and RCRA sites within OSWER, where the sources of mixtures of interest are usually abandoned hazardous waste sites, such as coke ovens, manufactured gas plants, and steel mills, or active industrial chemical facilities. Many of these sites have existed for decades and the PAH contamination has been altered over time by numerous aging/weathering processes, including environmental fate and transport. The relative potency factor approach provides provisional/interim guidance (EPA, 1993) for assessment of PAH risks at these sites, as well as for other program purposes. This approach is based on the toxicity of select individual components of mixtures, and assumes additivity. Thus, it avoids the issues pertaining to complex differences among PAH mixtures and is considered to represent a compromise approach. However, the toxicity of other key mixture components and interactive effects are not considered. Excess lifetime risk is estimated by assigning relative potency values to a set of individual PAHs which are known to play a role in toxicity and for which toxicity data are available.

BaP is utilized as the standard or “index” PAH with the highest ranking, and is assigned a relative potency value of 1.0. The “estimated order of potential potency (EOPP)” of 6 additional carcinogenic PAHs (i.e., those classified as probable human carcinogens) is determined relative to BaP. The EOPPs are based on data from complete carcinogenesis assays using mouse skin, assumes additivity of PAH responses, and is considered to be appropriate for oral exposures only. For each PAH, the oral cancer slope factor of BaP is multiplied by the relative potency factor to yield a relative estimate of potency. The estimated risks associated with individual PAHs are summed to yield a cumulative PAH risk estimate. Cal EPA, Ontario Ministry of the Environment (OMOE), and various program and regional offices within EPA also utilize this approach for inhalation exposures.

The oral cancer slope factor for BaP is based on a composite analysis of the results from two chronic dietary exposure studies in rats and mice which produced forestomach papillomas and tumors.

3.0 SUMMARY OF KEY COMMENTS AND RECOMMENDATIONS

A summary of the key comments and recommendations over the course of the two-day workshop is presented in this section. A more detailed discussion is presented in Section 4.0.

3.1 Surrogate Approach

The surrogate approach is based on mixtures in which the PAH content of unknown “mixtures of interest” are considered to be dilutions of a surrogate PAH-mixture. The approach assumes that the risks due to an unknown PAH mixture vary proportionately to the risks from a surrogate mixture. The major advantage to the surrogate approach is that it is based upon a whole mixture and that the composition and toxicity of the surrogate mixture as a whole is known. The use of toxicity data from a whole mixture permits consideration of toxicological interactions, which toxicity data derived from single components are unable to assess. Consideration of interactions reduces the uncertainty about such interactions. Several participants stated that the surrogate approach thus exhibits notably less uncertainty than do the other approaches, and is also more conservative; therefore, it is the preferred approach. It was observed that data from OMOE suggest that the composition of most mixtures, irrespective of sources, environmental media, or weathering, is reasonably similar. It was recommended that further analysis be conducted on a range of complex mixtures to determine composition and the degree of similarity/difference among mixtures.

The principal issue associated with this approach is the reliance on the finding of “sufficient similarity” between the mixture of interest and the surrogate mixture. Further, “sufficient similarity” implies similarity in biological activity, and only a limited number of complex mixtures have been evaluated for toxicity in either animals or humans. Some participants considered this approach to be limited by the criteria used for selection of a surrogate or reference mixture. Other participants recognized that this determination may be a subjective judgement. One participant observed that the principal limitation of this approach, in its present form, was that it only accounted for the PAH fraction of a complex mixture (specifically the unsubstituted PAH fraction) and that the toxicity from other components of the mixture (including nitro and other substituted PAHs) was not addressed. It was also noted that, in the example given for this approach, the animal bioassay data were only for inhalation exposure, and that the approach might not be currently useful (at least without further refinements) for assessments in which ingestion and dermal routes of exposure are important. Some participants recommended that other reference mixtures be identified and characterized, and that the use of additional indicator compounds for estimation of potency be explored. Suggestions for other indicator compounds included: (1) the group of 7 PAHs classified as probable human carcinogens and currently utilized in the relative potency factor approach; (2) the 4- to 7-ring PAH fraction; (3) total organic carbon (TOC); and (4) total PAH mass. It was also suggested that the data from the diesel emissions study might be utilized to identify additional surrogate indicator compounds and evaluate their usefulness for characterizing whole mixtures.

3.2 Comparative Potency Approach

The comparative potency approach is another whole mixtures approach, in which human and animal toxicity data for a group of mixtures considered to be “sufficiently similar” are used to

derive a scaling factor which can be applied to other mixtures to estimate human cancer potency from animal bioassay data. A major advantage to this approach is that the toxicity for the whole mixture is characterized, whether or not the composition of the mixture is known. The key assumption underlying this approach is that the ratio between the potency of a mixture in an animal bioassay and the human cancer risk is constant for different PAH-containing mixtures. The mouse skin tumor initiation assay has been considered to be a reasonably good predictor of the relative potency of carcinogenic mixtures, assuming that mechanisms of tumorigenic action are similar in both humans and animals. Major issues associated with this approach include: (1) it cannot be used with mixtures from multiple or unknown sources; (2) there is considerable uncertainty about the reliability and validity of the lung cancer epidemiology studies which are available to derive scaling factors, because of the confounding effects of smoking; and (3) this approach is currently based on inhalation exposure data and might only be applicable to the inhalation route because no human oral exposure studies are available. The approach also assumes that the composition and toxicity of different samples from the same source category (e.g., diesel emissions) are similar; however, testing of diesel emissions suggests this assumption may not be valid. Most participants were skeptical about the use of PBPK models for route-to-route extrapolation because of the difficulty of characterizing the toxicokinetics of a complex mixture containing numerous compounds. Route-to-route extrapolation of data was not recommended based on the current state-of-the science. Although the mouse skin tumor initiation assay is a good predictor of the potency ranking of complex mixtures with regard to human lung cancer, the relative potency ranking needs to be demonstrated for other routes of exposure. Other assays should be considered.

3.3 Relative Potency Factor Approach

The relative potency factor approach is a component approach, in which the carcinogenic potencies of selected PAHs relative to an index compound (e.g., BaP) are determined, and individual PAH risks are summed to yield a cancer risk estimate for the whole mixture. Current EPA provisional guidance for assessing PAH risks (EPA, 1993) utilized this approach. BaP is the recommended standard. The key assumptions underlying the use of this approach are that (1) individual PAH risks are additive and (2) the sum of the risks of selected PAHs adequately characterizes the risk for the entire PAH component of the mixture. The advantage of this approach is that it is practical for exposure situations in which the source and the composition of the mixture are not fully known. However, participants were in general agreement that this was the least scientifically-defensible approach, and that any approach that utilizes the toxicity of a mixture as a whole is preferable to the use of the relative potency factor approach.

The major issues associated with this approach are that (1) it is not based on a reference PAH mixture with known toxicity (animal or human), (2) there are no human toxicity data on any of the individual PAHs, and (3) the assumption of additivity of individual PAH toxicity may not be valid. Other issues associated with the current provisional guidance (EPA, 1993) include: (1) the use of too few, and possibly the wrong, PAHs, (2) the reliance on BaP as the index compound (several studies have shown that BaP as an indicator compound may not accurately predict the carcinogenic potency of whole mixture, and may underestimate potency); (3) the lack of consideration of interactions among PAHs, and between PAHs and other mixture components such as metals; and (4) the applicability of this approach to oral exposure only. There were also questions raised regarding the adequacy of mouse skin tumor initiation studies for developing

relative potency factors. It was recommended that the database of *in vitro* carcinogenicity studies be evaluated for potential use in developing RPFs. It was recommended that, ideally, these factors be derived from low-dose chronic exposure studies.

3.4 Cross-Cutting Issues

While much of the experts' discussion focused on the three approaches, there were many issues raised that pertained to all three methods and the challenges facing PAH risk assessment in general. It was noted frequently that most data on the carcinogenicity of PAHs comes from mouse skin tumor initiation studies. Some participants recommended that chronic exposure studies be conducted on key PAHs and PAH mixtures, and that oral potency should be based on oral studies, and inhalation potency on inhalation studies. Evaluation of the dermal carcinogenicity of PAHs was suggested, using all available data; additional dermal carcinogenicity studies might also be useful. Some participants did not recommend direct route-to-route extrapolation for any of the approaches, and many participants were skeptical about the utility and validity of the currently available pharmacokinetic modeling for mixtures. Uncertainty associated with extrapolation of bioassay data to humans was also noted.

The lack of human toxicity data on any of the individual PAHs was a recurring concern; several participants observed that without human data, the relevance of the animal data to human exposure situations is questionable. One participant suggested that re-examination of the effects of coke oven emissions in animals and humans might be useful in back-calculating a human potency estimate for BaP, and noted that this approach has been adopted by the World Health Organization (WHO). It was also noted that the WHO has concluded that the scientific basis for the relative potency factor approach is lacking; currently, WHO recommends the surrogate approach, with BaP as the surrogate indicator compound.

The use of additional indicator compounds to characterize the composition and toxicity of PAH mixtures was recommended for all approaches. Currently, BaP is the only PAH for which chronic exposure bioassay data are available, and thus by default, it remains the index compound or "gold standard." Research exploring the utility and validity of using additional indicator compounds or PAH fractions was suggested. It was noted that tumors in target organs other than the skin have not been considered in developing relative potency estimates; a number of published and unpublished studies have examined tumors in other organs. It was recommended that these data be located and evaluated in conjunction with skin tumor data.

In general, participants concluded that the relative potency factor approach should be employed only "as a last resort," when the mixture of interest was judged not to be "sufficiently similar" to either the surrogate mixture or the specific mixtures used in developing the comparative potency approach. A major concern was that the relative potency approach may not provide a valid estimate of the toxic potency of the mixture as a whole and thus may not be protective of public health. Some participants recommended that the relative potency factor approach not be used, and that a mixtures approach be employed even if the mixture of interest has only been partially characterized and biological activity data are scanty. Several participants noted that existing studies comparing the composition of PAH-containing mixtures suggested that most such mixtures were similar, irrespective of source or age. However, other participants did not think that mixtures from different sources (e.g., combustion versus noncombustion) or with different

weathering patterns could be similar. Participants agreed that both the composition and toxicity of PAH mixtures should be better characterized. Although there was some concern about general similarities among mixtures, most of the discussion focused on the difficulties of judging whether mixtures were “sufficiently similar” to each other to justify the use of a mixtures approach.

4.0 DETAILED PRESENTATION OF INDIVIDUAL DISCUSSION TOPICS

This section provides detailed discussion among the participants on the three available approaches. Each approach is presented individually, noting the strengths and weaknesses of the approach as well as other issues raised by the participants.

4.1 Surrogate Approach

The participants provided comments and recommendations on issues relevant to the use of the surrogate approach. The major issues raised were: (1) strengths of the approach, (2) limitations of the approach, (3) defining sufficiently similar mixtures, (4) addition of reference mixtures, (5) modifications to the surrogate approach, (6) BaP as the indicator, (7) interactions/additivity, and (8) route-to-route extrapolation.

Strengths of the Surrogate Approach

Dr. Nesnow stated that in his judgment, the surrogate approach is an improvement over the relative potency factor approach, mainly because it utilizes inhalation bioassay data on the reference mixture as a whole. However, this approach is limited to the inhalation route of exposure and to mixtures for which human inhalation data are available.

Limitations of the Surrogate Approach

Dr. Nesnow noted that one weakness of this approach is the use of a single PAH (e.g., BaP) as the indicator compound, and the assumption that BaP tracks the activity of the PAH component of the mixture. Dr. Nesnow's studies have demonstrated that the activity of BaP in a mixture does not explain the activity of the mixture as a whole. In mouse-skin tumor initiation assays, Dr. Nesnow evaluated the dose-response for BaP as an indicator of the carcinogenic potency of combustion mixtures. The results showed that BaP in these combustion mixtures did not adequately characterize the potency of these whole mixtures.

Defining Sufficiently Similar Mixtures

A major issue concerning the use of the surrogate approach involves a judgment of "sufficient similarity" between the surrogate mixture and the mixture of interest. One issue concerns the chemical characterization of the mixture found in environmental media, which may differ from the original source mixture. Dr. DiGiovanni added that the ratio of individual constituent concentrations in the mixture was much more important than the concentration of specific compounds. Dr. Donnelly also questioned whether weathering (e.g., microbial oxidation) and transport would not greatly alter the downstream components of environmental mixtures, especially those distant from sources. If this occurs, the ratios/concentrations of PAHs in a mixture at the source may differ from those at the point of exposure, and thus characterization of the mixture at its source might not adequately represent the composition of the environmental mixture. Dr. Goldstein noted that in his judgment, a definition of sufficient similarity would be based on legal, not scientific, considerations. Dr. Nesnow disagreed, noting that sufficient similarity is based on a scientific weight-of-evidence approach for toxicologic similarity as well as similarity of chemical composition.

A concern of some participants was the lack of good epidemiologic data on mixtures, showing similarity in biological activity across different mixtures. It was noted that a designation of “sufficiently similar” includes similarity in toxicity or health outcome, in addition to similarity in composition. Dr. DiGiovanni commented that the range of biological activity is broad with animal data and that it would be even broader with epidemiologic data; he suggested that if the partial composition of a mixture of interest is known, it would be useful to use several surrogate mixtures. A number of participants agreed that there was no good substitute for testing the biological activity of whole mixtures but that such testing was not usually practical in terms of time and resources. However, Dr. Goldstein noted that the cost estimates for cleaning up hazardous waste sites ranged in the trillions of dollars. Based on these estimates, it would be worthwhile to spend some resources on refining the surrogate method, and other appropriate methods for assessing the risks of complex environmental mixtures.

Dr. Muller noted that he and his colleagues at OMOE have evaluated the use of the surrogate approach and concluded that the complex mixtures containing PAHs cannot be assessed as a whole. Instead, Dr. Muller defined a PAH-rich fraction as consisting only of unsubstituted PAHs. Mixtures were judged to be similar, if at the same concentration of BaP, the risk estimated from the predicted composition of the mixture and that estimated from the actual composition of the mixture (for the unsubstituted PAH fraction) did not differ by more than one order of magnitude. Dr. Muller noted that this standard for judging the similarity between mixtures is appropriate, because risk assessment is always associated with a degree of uncertainty. In general, few dose-response assessments are associated with uncertainty of less than one order of magnitude, and thus potency predictions within one order of magnitude are considered to be acceptable. In the OMOE evaluation, the differences were much smaller, suggesting that the surrogate approach is suitable for assessing the potency of the unsubstituted PAH-rich fraction of mixtures. Risks from other components of complex mixtures need to be estimated separately.

Addition of Reference Mixtures

Dr. Foureman noted that the surrogate method is currently tied to one specific mixture (i.e., CTP) and an animal bioassay assessing the inhalation toxicity of that mixture. One issue raised with the current application of the surrogate approach is the use of a single reference mixture, considered by some experts to be a weakness of this approach. It was suggested that the use of several reference mixtures and a range of reference indicators would significantly improve the approach. Additional mixtures that might be useful as reference mixtures include coke oven emissions, creosote, and Chinese smoky coal. Dr. Foureman asked for guidance from the participants as to how to include other mixtures in the surrogate approach, based on a judgment of “sufficiently similar.” One suggestion was to examine several different mixtures and evaluate the relationship between BaP activity and that of the mixture as whole, taking several samples of each mixture. This analysis would determine whether differences in the risks between two or more complex mixtures were proportional to differences in BaP concentrations in each of the mixtures. Dr. Muller noted that the unsubstituted PAH fractions for complex mixtures are sufficiently similar for dose-response purposes. The experts discussed the possibility of developing a better surrogate method by using more PAH indicators and more reference mixtures.

Two alternate approaches to the use of several reference mixtures were discussed. Dr. Mauderly noted that if a number of different reference mixtures were available, the one most similar to the mixture of interest could be selected as a surrogate. Dr. Nesnow stated that it would be more appropriate to estimate a range of potencies for the mixture of interest, using all reference mixtures; in his judgment, there was too much uncertainty associated with characterizing the similarities and differences of complex mixtures to be able to select the “most similar” reference mixture.

Modifications to the Surrogate Approach

Dr. Mauderly questioned whether it was reasonable to merge the surrogate and RPF approaches and use a group of PAHs as indicators of potency. Dr. Wise noted that the validity of this approach (i.e., the use of multiple PAH indicators) depended on the relative proportion of PAHs in the mixture. He stated that PAHs account for approximately 20% of the total mass of coal tar, with the remaining 80% usually not being characterized. Therefore, the more complex the mixture (in terms of presence of other compounds), the less useful this approach. However, this is true for all mixtures and all approaches to PAH risk assessment. Dr. Goldstein noted that there are data on refinery streams which demonstrate that the best correlation with potency occurs with the use of 4- to 7-ring PAHs as indicators; BaP does not correlate as well with potency as this group of PAHs. According to Dr. Wise, to measure 4- to 7-ring PAHs one must measure each of the relevant constituent compounds separately; it is not possible to measure this group as a whole.

Dr. Goldstein noted that the majority of PAH toxicity data come from mouse skin-painting studies. To obtain better toxicity data, other biological data should be evaluated, including mode of action information and data from other exposure routes.

To account for variability, Dr. Nesnow suggested that a range of indicator compounds be used; the risk of each indicator could be calculated, yielding a range of risks from which the upper and lower bounds could be estimated. Dr. Goldstein added that toxicity data should be characterized similarly; that is, a range of potency estimates should be calculated rather than using a single point estimate for the dose-response assessment of biological data.

BaP as the Indicator

Dr. DiGiovanni noted that although BaP may be useful as an indicator, it may not give a good representation of the mixture potency. Some participants stated that the use of more than one indicator compound would be useful. Several participants contemplated what additional indicator chemicals might be proposed. In comments submitted following the workshop, Dr. Muller noted that he did not share the view that multiple indicators would improve application of the surrogate approach. In his experience, using multiple unsubstituted PAHs in the 4- to 6-ring range would yield results similar to those with BaP and, furthermore, would make the assessment more complex. Drs. Nesnow and Baird suggested looking at total organic carbon (TOC), or total PAH mass for characterization of “sufficiently similar” in terms of composition; in their judgment, it was not necessary to use an indicator that has been tested in animal studies. Mixtures should be characterized as “sufficiently similar” not only in terms of PAHs but also in terms of other constituents such as nitroaromatics or phenols. It was suggested that the mixture

of interest, as well as the reference mixture(s), should be better characterized. Although the surrogate approach addresses the PAH fraction, the risk for other mixture constituents (e.g., metals, other organic compounds) must be estimated separately, and the presence of other non-PAH constituents may affect the potency of PAHs. Thus, differences in composition may alter mixture toxicity; however, the extent of these interactions is not known. Drs. Nesnow and Albert suggested that the data set for diesel emissions might be further evaluated to explore additional surrogate indicators and to assess whether these indicators would be useful.

Interactions/Additivity

A discussion followed of interactions among PAH compounds in a mixture. There was concern among some participants that the use of a single indicator compound, or even several, would not adequately characterize the potency of the whole mixture because of interactions. Dr. Baird noted that small amounts of some PAHs (e.g., benz(*a*)anthracene) may greatly affect the carcinogenicity of other PAHs (e.g., BaP); benz(*a*)anthracene appears to be an activating compound even though its relative potency is considered to be low. Dr. Thorslund added that PAH interactions in mixtures are concentration-dependent, and thus low environmental levels of PAHs may not exhibit the same kind of interactions observed at higher concentrations in the laboratory. Dr. Nesnow stated that elevated concentrations of pyrene in a complex mixture appear to obliterate the ability of BaP to induce tumor-forming cell masses and that pyrene is usually present at high levels in environmental samples.

Data evaluating the assumption of additivity of biological activity among PAHs were presented by Dr. Nesnow, who has studied interactions among 5 key PAHs in strain A/J mice. Predicted responses (lung tumors following a single intraperitoneal injection), based on individual dose-response studies, were compared with actual responses, based on mixtures containing environmental ratios of PAHs. Dose-dependent interactions were observed with the mixtures: more tumors occurred than predicted at low doses, and fewer tumors occurred at high doses. However, the extent of these dose-dependent differences in additivity for the 5 PAHs was approximately 2-fold, which is generally considered to be within acceptable bounds for a risk assessment. However, if pyrene was added to the mixture, the tumorigenic activity of the carcinogenic PAHs was inhibited, demonstrating the complexity of mixtures containing other PAHs. Other compounds in a PAH-containing mixture might also modulate the carcinogenic effects of individual compounds (e.g., in the mouse skin assay, tobacco smoke inhibits the tumorigenic activity of BaP whereas roofing tar enhances it. Nonetheless, Dr. Muller pointed out that the variability was, at most, within one order of magnitude, and that the interactions in actual mixtures would likely go both ways (i.e., inhibition and enhancement). Drs. Albert and Mauderly suggested that the literature be examined and summarized to determine the extent to which additivity occurs, and whether the range of estimates based on summing individual dose-response data is within acceptable limits for a regulatory risk assessment. It was noted that genetic variability and other factors may increase the variability.

Route-to-Route Extrapolation

Route-to-route extrapolation of tumor findings in animal studies was discussed. Dr. Goldstein noted that no lung tumors were observed in a recent two-year feeding bioassay with BaP, although forestomach tumors were observed at the site of contact. However, DNA adducts in the

lung were observed., suggesting that orally-ingested BaP reaches the lungs. Dr. Nesnow stated recent work has questioned the sole use of stable adducts to define dose-response curves; the formation of stable adducts are not necessary for tumor formation, as there are other processes or mechanisms which can be involved in tumorigenesis (e.g., formation of reactive oxygen species).

4.2 Comparative Potency Approach

The major issues raised during the discussion of the comparative potency approach were the following: (1) strengths of the approach, (2) limitations of the approach, (3) additional reference mixtures, (4) human relevance, and (5) route-to-route extrapolation.

Strengths of the Comparative Potency Approach

This approach is based on the availability of toxicity data for a group of similar mixtures. The advantage to this approach is that the toxicity for the whole mixture has been characterized, whether or not the composition of the mixture is known. Dr. DiGiovanni noted that, in his judgment, the comparative potency approach appeared to be the most accurate and had the most confidence as compared with the other approaches. Several participants agreed.

Dr. Muller noted that the assumption of sufficient similarity applied to both the surrogate approach and the comparative potency approach. He and his colleagues have looked at both models and have shown that there is a good relationship between the two: using an intact animal model, the relative potency of mixtures are similar for both approaches.

Limitations of the Comparative Potency Approach

The comparative potency approach was judged by some experts to have limited applicability. Dr. Mauderly noted that there were two types of uncertainties in this approach: (1) the relevance of the animal bioassay; and (2) the quality of the epidemiologic data. Dr. Donnelly observed that the assessment of the carcinogenic potency of complex mixtures in the range of environmentally-relevant concentrations is difficult because animal carcinogenicity experiments are conducted with very high concentrations, and dose-response information in the range of human exposures is usually not available. He questioned whether the comparative potency approach has validity without environmentally-relevant dose-response data.

Dr. Muller commented that he thought the comparative potency approach was limited in its application to environmental mixtures. For example, in Hamilton, Ontario, mixtures to which humans are exposed are complex and come from a variety of sources: steel industry coke ovens, diesel/gasoline engines, home heating (wood and oil), and others. In landfills, environmental mixtures are atypical and also come from a variety of sources. Each of these mixtures are likely to have different characteristics and one would have to do dispersal modeling and fingerprinting to identify sources. The comparative potency approach would not be applicable to any of these mixtures. Dr. Nesnow agreed that the comparative potency approach was not useful for sites with contaminants from a lot of different sources, and suggested instead that this approach might be utilized to assess relative risk reduction resulting from implementation of improved technology controls.

Dr. Muller noted that the biggest problem with the comparative potency approach was practical: it cannot handle mixtures from multiple or unknown sources. He also noted that an implicit assumption of the approach, that mixtures from a source category are “sufficiently similar,” may not always hold. Data from Dr. Nesnow’s laboratory for diesel exhaust showed that samples collected from different diesel engines had different biological potencies and different proportions of PAHs in the organic fractions.

Dr. Goldstein noted that this approach would be based on inhalation exposure data because no human data are available for the oral and dermal routes of exposure. At many hazardous waste sites, the overall risk for inhalation exposure was very small compared to the risks from ingestion and dermal exposures. Thus, the application of the comparative potency approach was only valid in exposure situations where the risk from inhalation drives the overall risk. For exposure situations in which ingestion and dermal routes are important, this method would not be appropriate. Further, the epidemiologic data for roofing tar and coke oven emissions might be limited by the failure to address the confounding effects of cigarette smoke. Dr. Albert noted that this approach may be limited to combustion mixtures for which the major route of exposure is via inhalation and the relevant health outcome is lung cancer. For internal consistency, the results from whatever animal bioassay is used should give the same relative potencies for the standard mixtures (i.e., coke oven, roofing tar, cigarette smoke) as the epidemiologic data. Dr. Albert suggested that the toxicologic data base should be updated and that this approach be re-evaluated using data from the most recent coke oven emissions study.

Additional Reference Mixtures

Dr. Mauderly questioned how data from other complex mixtures would be handled using this approach and whether the current standard mixtures were adequate for evaluating the range of complex mixtures occurring in the environment. He suggested that a new set of standard mixtures might be developed, or the database on the current standard mixtures might be updated. Dr. Nesnow agreed that more standards for different kinds of mixtures are needed, and that rodent inhalation studies for other mixtures were available that might be useful in expanding the list of standard mixtures.

Human Relevance

A limitation of this method is that only animal bioassay data would be available for mixtures of interest, and thus, it would not be known whether the animal results were relevant to the health outcome of interest in human populations. The choice of animal test is important. Dr. Nesnow noted, however, that EPA’s default procedure for regulatory risk assessment is to extrapolate findings in animal bioassays to humans; therefore, data from epidemiologic studies are not necessary to estimate human risks from animal studies.

Dr. Mauderly asked whether the mouse skin-painting bioassay was still considered to be the “gold standard” for comparing findings across mixtures. This assay could provide the animal data used for the comparative potency approach. Dr. Albert noted that a number of short-term tests have been evaluated for their usefulness in predicting lung cancer; however, the mouse skin-painting assay still gives the best correlation with epidemiologic data. Dr. Nesnow noted that the Chinese hamster ovary (CHO) test gave good results but agreed that an *in vivo* assay

(e.g., from mouse skin studies) was likely to be more widely accepted than *in vitro* testing. At this time, there are no new genetic approaches that might be better.

Dr. Mauderly noted that the mouse skin-painting assay was not used to predict human risk directly but was used to extrapolate risk from animals to humans, based on a scaling factor derived from the standard mixtures for which the relationship between the results in the mouse assay and those in human studies was known. However, an underlying assumption was that the mechanisms of tumorigenic action were similar in both humans and animals. Dr. DiGiovanni added that the mouse skin assay did not assess compounds that were mainly promoters; if a mixture had a strong promoting ability, a complete carcinogenesis model might be more appropriate. Dr. Albert noted that several investigators have postulated that promotion does not occur at low doses. Dr. DiGiovanni suggested that promotion might occur at low doses with some mixtures, depending on the composition of the mixture. Thus, low-dose chronic exposure studies were important for the assessment of the biological activity of complex mixtures, and should be conducted for at least some mixtures. Dr. Nesnow noted that the use of the Sencar mouse model shortened the length of the experiment by 6 months, and that the ranking of potency in low-dose chronic exposure studies and in Sencar mouse skin-painting assays was the same. Dr. Goldstein suggested that more than a single *in vivo* animal bioassay should be used for developing the correlation between animal and epidemiologic studies, incorporating more target organ systems and additional routes of exposure. A weight-of-evidence should encompass more than one bioassay and all available data should be re-evaluated. Other participants suggested that one assay might be sufficient, or that more than one assay might be used, if available.

Dr. Albert questioned whether skin tumors in mice were relevant to the development of lung tumors in humans. Dr. Nesnow replied that the relative potencies for human lung tumors were reliably predicted on the basis of mouse skin tumor responses. The induction of lung tumors in inhalation studies, in which animals are exposed to aerosols of organic matter, are difficult to interpret; no tumors are induced until the lungs are overloaded with particulates. Dr. Mauderly added that although rats exposed experimentally to high concentrations of diesel particulates for a lifetime did develop lung tumors, organic constituents did not appear to be the causal agent because particles without organic matter (e.g., carbon black) also induced a similar yield of lung tumors. In this case, inhalation exposures of rats did not reflect carcinogenicity of the organic portion of diesel soot, even at high doses. Dr. Thorslund questioned the reliability and validity of human lung cancer studies, noting that they are all confounded by smoking status and the length of time of smoking. Therefore, the observed lung tumor effects in epidemiology studies were likely due to an interaction between cigarette smoke and combustion mixtures.

Discussion followed on which animal assays to use to generate data that would be useful for the application of the comparative potency approach. A number of assays were briefly reviewed, including the transgenic mouse model, transgenic systems using both initiating and promoting test agents, oncogene expression profiling for classes of compounds to develop molecular signatures for cancer-causing chemical agents, DNA damage-repair, and other genotoxicity systems. It was generally agreed that these new models were in their infancy phase and would not be useful for regulatory purposes for some time.

Several participants were also skeptical about the human relevance of the results from skin-painting tumor-initiation assays in Sencar mice, stating that it was questionable to extrapolate to humans the results from an experimental protocol developed in a sensitive mouse strain for the purpose of “creating tumors.” Dr. Nesnow noted that the tumor processes may have a lot of similarities even though they are not the same: for example, both lung and skin tumors are epithelial in origin. Dr. DiGiovanni noted, however, that in lieu of other data, the mouse skin-painting assay is the best predictor of potency ranking of complex mixtures and that there are multiple epidemiologic data sets that validate the utility of this model. Thus, the mouse skin model has relevance for human potency ranking.

Route-to-Route Extrapolation

The issue was raised on whether this approach can be extrapolated to other routes of exposure. Both Drs. Nesnow and Goldstein agreed that oral exposure should be investigated using oral bioassay data. It was generally agreed that the exposure situations for which this approach would be applicable were all those with sufficient exposure/health outcome data. Dr. Muller noted that an issue of concern was being able to match the bioassay data with the human health outcome of interest. Dr. Goldstein suggested that the relative potency ranking needed to be demonstrated for other routes of exposure. Dr. Muller pointed to data from Grimmer and colleagues who found good correlations between relative potencies in mouse skin carcinogenicity assays and lung implantation studies for the same PAHs and PAH mixtures. Dr. Goldstein noted that the use of only inhalation data to assess cancer risk was considered by many investigators to be a default approach, utilized when data from other routes of exposure were lacking.

The use of PBPK modeling for route-to-route extrapolation was discussed. Several participants (Drs. Nesnow, DiGiovanni, Albert, Donnelly) were skeptical regarding the use of PBPK for extrapolation of the effects of skin painting to systemic effects induced by exposure via other routes. Skin painting causes local effects which result from topical application, and the relevance of PBPK extrapolation was likely to be limited. Dr. Donnelly noted that skin painting studies may overestimate the systemic toxicity, based on studies showing a higher rate of adduct formation following dermal as compared with oral exposures. Dr. Goldstein disagreed, noting that the distribution of adducts differed, depending on whether administration was dermal or oral. Several participants also felt that it would be extremely difficult to get reliable PBPK data on complex mixtures. For example, it is not clear what responses could be measured that would be considered representative of a complex mixture with numerous constituents.

4.3 Relative Potency Factor Approach

The major issues raised during the discussion of the relative potency factor approach were the following: (1) limitations of the approach, (2) use of the approach; (3) comparison with other approaches; (4) adequacy of animal data sets; (5) human relevance of animal data; (6) assumption of additivity; and (7) use of additional/other reference compounds; and (8) route-to-route extrapolation.

Limitations of Relative Potency Factor Approach

Overall, the major limitations of this approach are (1) the use of only 7 PAHs, expressed in terms of BaP equivalents; and (2) assumption of additivity of effects. Drs. Nesnow and Muller agreed that the relative potency factor approach does not adequately characterize mixtures and preferred any approach that tests the whole mixture. In addition, too few PAHs are used and there is too little empirical information on the mixture. Therefore, the mixture potency is likely to be underestimated. Further, the toxicity characterization uses old data from the 1970's and mode of action information is not examined.

Dr. Albert noted that there were discrepancies in the relative potency factor for dibenz(*a,h*)anthracene. Some papers indicate that it should be 5.0, not 1.0, which is currently the default RPF according to EPA's 1993 provisional guidelines. There are about 3-4 data sets from which differing values can be derived, and considerable uncertainty exists regarding the shape of the dose-response curve for high-to-low-dose extrapolation. Dibenz(*a,h*)anthracene appears to be more nonlinear than BaP.

Use of Relative Potency Factor Approach

Given the major limitations of this approach, the issue was raised as to whether participants should recommend either continued use of the relative potency factor approach or suggest that a different approach be employed. Dr. Nesnow commented that if EPA continues to use this approach, routine analysis should be conducted on other heterocyclic and methylated compounds that are not currently on EPA's target compound list (TCL). Dr. Nesnow further suggested that EPA convene a panel to re-evaluate the relative potency factor approach; a number of different data sets should be examined and consensus reached about how to use all available data. Otherwise, the relative potency factor approach will continue to underrepresent the potency of complex PAH-containing mixtures.

Dr. Muller did not recommend the use of the relative potency factor approach on the basis that it consistently underestimates the risk from the PAH fraction of the mixture. He felt that the surrogate approach was applicable to most real world situations. Dr. Goldstein added that if the relative potency approach were to be used, two factors needed to be considered: (1) the relevance of the tumor outcome in animal experiments to the tumor outcome of concern in humans; and (2) whether the potency of the indicator PAH (i.e., BaP) has been adequately characterized for the estimation of reliable and valid relative potency factors for other PAHs in the mixture. He noted that the oral cancer slope factor for BaP derived from a recent chronic feeding bioassay was 1.2 per mg/kg/day (Culp et al., 1998), as compared with the cancer slope factor of 7.3 per mg/kg/day currently being used by EPA. If the more recent cancer slope factor were used, the risks associated with all PAHs using the relative potency factor approach would change.

Dr. Albert commented that the relative potency factor approach was both usable and practical, especially in exposure situations where the source and composition of the mixture were unknown. The validity of this approach, however, was questioned by other participants. Dr. DiGiovanni noted that this approach lacks biological activity data and thus is likely to underestimate mixture potency. Dr. Nesnow noted that the carcinogenic potency of the index PAH (BaP) is based on animal, not human, data, and agreed that the validity of these data has

never been satisfactorily established. Several participants suggested that there were data in the literature, as well as in reports and other documents, that might be used to re-assess the carcinogenic potency of BaP. Dr. Muller noted that a comparative analysis of the potency of the PAH fraction (as determined in skin painting and lung implant studies) and the potency of the sum of the 7 individual carcinogenic PAHs showed a fairly sizable and consistent difference between the two; the 7 PAHs underpredicted the carcinogenic potency of the PAH mixture by greater than one order of magnitude. A comparison of the risk estimates from coke oven emissions with the risk of the sum of the individual PAHs also yielded a difference of similar magnitude.

It was again noted that the ratios of the individual constituent concentrations might be as important as the absolute concentrations. Further, the presence of additional PAHs might affect the health outcome. The problem with the relative potency factor method, according to Dr. DiGiovanni, is that this approach is not based on a reference material with known biologic activity data, and there are no human toxicity data on individual PAHs.

Dr. Albert also noted there was no EPA consensus on the inhalation unit risk estimate for BaP for evaluation of the risks associated with inhalation exposure. The inhalation unit risk value used by Cal EPA and some EPA regions and program offices is based on a Syrian golden hamster study by Thyssen and colleagues; however, this value has not been verified by IRIS. Further, only seven carcinogenic PAHs are sampled, and the source of the environmental mixture is generally unknown.

Comparison with Other Approaches

Drs. Baird and Nesnow noted that, in their judgment, the surrogate approach method was preferable to the relative potency factor approach. Several other participants agreed that the relative potency approach would always underestimate potency and human risk, because it measured only a few compounds in the mixture. Dr. Nesnow stated that he could not think of a single reason why one would prefer to use the relative potency approach for the risk assessment of a complex mixture. The surrogate approach would be more useful if the mixture of interest had been analytically measured for constituent compounds. Even if the mixture of interest was a mixture of mixtures, the surrogate approach might still be used with a core group of 4- to -7 ring PAHs. Dr. Muller added that because the relative potency factor method consistently underestimated public health risk, its use was not consistent with regulatory mandates to protect public health. The surrogate approach was preferred if the mixture of interest could be judged to be sufficiently similar to the surrogate mixture. If this could not be ascertained, then the use of the relative potency factor approach was the only realistic alternative.

Drs. Nesnow and DiGiovanni agreed that any approach that at some level relates back to a whole mixture was preferable to the relative potency factor approach. The strength of the surrogate approach is that it related the toxicity of a mixture of interest to a reference mixture whose toxicity as a mixture has been characterized. The strength of the comparative potency approach was that the toxicity of whole mixtures could be characterized without specifically identifying and quantifying the individual components. Both these approaches accounted for interactions. Dr. Nesnow stated that the relative potency factor approach should only be used as a last resort. Dr. Muller further noted that the WHO has concluded that there is no scientific basis for the

relative potency factor approach; WHO recommends the surrogate approach, with BaP as the surrogate indicator compound.

Dr. Muller again emphasized that the basis for regulation was protection of public health. An assessment based on a method known to under estimate risk did not protect public health, nor did it err on the side of caution. When approaches were compared with regard to associated uncertainties, the conclusion was that the surrogate approach exhibited considerably less uncertainty than the other approaches, and was also more conservative. Dr. Mauderly questioned whether the surrogate approach was appropriate with mixtures which were not judged to be sufficiently similar to a reference mixture. Dr. Albert noted that there were no good data available that compared approaches in a systematic manner and recommended that the three different approaches be compared and evaluated systematically.

Dr. Nesnow suggested that if the mixtures were simple, containing mainly PAHs, then the relative potency factor approach might be used, although at a minimum, the inclusion of additional PAH species, with associated exposures and toxicities was necessary. However, Dr. DiGiovanni commented that in his judgment, the use of the relative potency factor approach was inappropriate as compared with the use of a mixtures approach for which biological activity data on the whole mixture were available. Although the use of the relative potency factor approach might be considered for very simple PAH mixtures, simple PAH mixtures are unlikely to occur frequently in the environment. Intuitively, he would rather base risk factor analysis on some data available for a composite mixture and some biological data for that mixture. This approach would be more accurate and make more sense.

Sufficient similarity is based on strength of evidence. If the confidence is low regarding similarity of mixtures, Dr. Nesnow suggested that one might want to use the relative potency factor approach and assume additivity. If there is greater confidence regarding similarity of mixtures, the surrogate approach is preferred. Dr. Nesnow noted that the use of either approach involved trading one set of uncertainties for another. For example, the relative potency factor approach would not be appropriate for cigarette smoke. Dr. Nesnow also expressed dissatisfaction with the use of coke oven emissions as a surrogate, stating that these emissions were not similar to combustion mixtures. Dr. Muller noted, however, that when one looked at different mixtures in terms of composition and potency, the differences were not as large as might be assumed.

Dr. DiGiovanni emphasized that he is not a proponent of the relative potency factor method for the following reasons: (1) the basic assumption of the approach is additivity, which is unlikely to occur; and (3) a common mode of action among all PAHs is inferred by the use of this method, which is debatable. Thus, the assumptions underlying the relative potency factor approach may not be valid, and therefore, the method itself may not be valid. Dr. Mauderly questioned what the experts would do if the choice were to estimate toxic potency of a complex mixture by using the relative potency factor approach or not to estimate toxic potency at all. Dr. DiGiovanni replied that he would rather have a toxic potency/risk estimate based on some biological data for a mixture even if the mixture of interest were not very similar to the standard/reference mixture. Biological data for a whole mixture included data on interactions, and thus were more relevant and reliable. If the toxic potency/risk estimate were to be based on a reference mixture, there would then be some degree of confidence that the biological activity represented the sum of the

interactions. Dr. DiGiovanni further added that even if all available data were used, this approach would still be limited because interactions among PAHs and other compounds in the mixture are not considered. There may be other mixture constituents with different modes of action which may affect the carcinogenic potency of the whole mixture.

Dr. Thorslund observed that even if additional PAHs or other constituents of a mixture were monitored, a components approach still does not provide information on the toxicity characteristics of the whole mixture. If exposure is low, the probability is low that significant component interaction occurs. However, the potential for interactions increases if exposure is large; for example, with simultaneous exposure to cigarette smoke and a complex PAH mixture.

Dr. Nesnow stated that perhaps this approach should be used only when the mixture of interest comes from many sources and there is no reference mixture to enable another approach to be used (i.e., comparative potency or surrogate approach).

Adequacy of Animal Data Sets

The adequacy of the PAH animal data sets was discussed. Dr. Goldstein suggested that the toxicity data sets used should be based on chronic exposure. Dr. Nesnow noted that in the case of dioxin, toxicity equivalent factors were derived from short-term studies, and in his judgment, chronic exposure studies were not necessary for relative potency estimation. Dr. DiGiovanni stated that his major concern with the use of chronic studies is that they are conducted with very high doses whereas tumor initiation/promotion studies are conducted at much lower doses and thus are more relevant to environmental exposures. He agreed with Dr. Nesnow that mouse skin painting studies were adequate for the development of relative potency or toxicity equivalent factors.

Human Relevance of Animal Data

Dr. Goldstein added that the Electric Power Research Institute (EPRI) has estimated toxicity equivalents for a number of environmental coal tar containing PAHs. BaP, with the highest IRIS cancer slope factor, dominated the calculations, and accounted for approximately 70% of the biologic activity in the mixtures. The difficulty was extrapolating from animals to humans; the toxic potency for BaP was estimated from an oral cancer slope factor derived from a composite of two oral animal studies. There are no data relating the animal response to responses in humans; thus, the use of these animal data does not have scientific relevance for human exposure situations. Dr. Muller suggested that by looking at the effects of coke oven emissions in animals and humans, the human potency of BaP might be estimated, using back calculations. WHO also compared the ratios of the toxicity of BaP and the toxicity of a range of whole mixtures, and showed that these ratios ranged from 1.8 to 8.5. The largest ratio was for cigarette smoke in which the influence of BaP was relatively small. The range reflected the different contributions of PAH exposure/toxicity to the exposure/toxicity of mixtures. When WHO used coke oven emissions as the basis of the comparative analysis, the risk associated with the 4- to 7-ring PAH fraction overestimated the risk associated with the whole mixture. However, this overestimation might not have been toxicologically significant because of the modulating presence of other substances in the mixture. Dr. Muller again noted that this method only predicted the potency/risk of the PAH fraction of the mixture (i.e., 4- to 7-ring PAH fraction). Additional

analyses are generally conducted separately on other compounds in the mixture such as nickel, 1,3-butadiene, benzene and others, and all the risks are summed. Thus, interactions are not assessed by this method.

Assumption of Additivity

It is not clear at this time whether all PAHs act via a single mode of action. Different modes of action for different PAHs would limit the suitability of the relative potency factor approach for PAH-containing mixtures. Dr. Nesnow noted that the basic theoretical assumption underlying the relative potency factor approach is additivity, which can only occur if the mechanism(s) of action is (are) similar. Most participants agreed that the relative potency factor approach would only be appropriate if there was a single mode of action for all PAHs of interest. If they are different, then the potential for synergism exists. It was noted that after 100 years of research, scientists still do not understand how PAHs induce cancer. All PAHs appear to form DNA adducts; however, the type of adduct produced may differ among PAHs. At this time, there is controversy among PAH researchers over the significance of the formation of stable versus unstable DNA adducts. Also, the role of quinone and other reactive oxygen species in PAH carcinogenicity is not clear, and there is no current consensus.

The current scientific data are mixed regarding the default assumption of dose additivity. In studies by Dr. Nesnow which compared the effects of individual mixture constituents with those of the mixture as a whole, additivity was somewhat dose-dependent; depending on the concentrations, effects were either additive, greater than additive, or less than additive. However, the extent of the departure from additivity (greater or less than) was only about 2-fold, which fell within background noise. Nonetheless, several participants noted that the current science did not support the assumption of additivity; further, there was concern that other components of complex mixtures, such as metals, might have antagonistic effects on PAH toxicity.

Use of Additional/Other Reference Compounds

The use of additional PAHs as reference compounds for the relative potency factor approach was discussed. Dr. Nesnow noted that, by default, BaP was the only reasonable index compound for use in this approach because it was the only PAH tested in chronic animal bioassays. It was recommended that the oral cancer slope factor for BaP be derived *de novo* from the recent chronic feeding study in the mouse and that a second chronic feeding study with rats be conducted. For the inhalation route of exposure, it was recommended that a new chronic inhalation study be performed according to GLP procedures, and preferably with two species and two sexes per species. It was suggested that NTP be asked to conduct this study.

Discussion followed about which additional PAH compounds should be measured in a complex mixture. When toxicity equivalents are calculated, BaP accounts for approximately 70% of the total cancer risk among the currently-measured PAHs. Other BaP compounds (e.g., thiol BaP) are very potent but not very prevalent, whereas other compounds are prevalent but not potent. For example, cyclopenta(*c,d*)pyrene is present at about ten times the mass of BaP but has only 1/10th the biologic activity. Some compounds are present as artefacts in laboratory samples but are not observed in environmental mixtures. There are numerous uncertainties with regard to

PAH speciation and the biological importance of speciated compounds. Dr. Goldstein suggested that from a public health perspective, all putative PAHs should be included. Dr. DiGiovanni suggested that the list be re-evaluated and that compounds known to be potent be added. Other compounds known to be of low potency should be removed; the list should not be open-ended.

It was agreed that better toxicity data on more PAHs were needed, and a greater number of PAH compounds should be included in the toxicity analysis of whole mixtures. Several participants noted that, at the very least, the approximately 13 PAH compounds with environmental monitoring data and estimates of carcinogenic potency should be considered. Dr. Albert noted that the data used to develop the relative potency factors were almost two decades old. It was recommended that the current literature should be reviewed; the relative activity of each PAH in various model systems should be re-evaluated, and the relative potency factor approach expanded to include more PAHs.

Dr. Muller suggested that for a new mixture, one could assess the 4- to 7-ring PAH fraction; diverse mixtures have been shown to be very similar with regard to this PAH fraction.

Route-to-Route Extrapolation

Dr. Muller noted that both dermal and oral exposure routes should be considered when exposure was from soil; however, one could not extrapolate dermal potency from oral potency data, as per EPA's current guidelines. The current relative potency factors are based only on oral data; inhalation data are needed to derive an inhalation cancer slope factor and to extend the exposure characterization to the inhalation route. A multi-route analysis of exposure should also be conducted – one which includes inhalation and dermal routes of exposure.

With regard to dermal exposure, there are no toxicity values for dermal exposures, and this constitutes a significant data gap. It was noted that there were very few long-term dermal exposure studies addressing systemic carcinogenicity, and that these are very old (many conducted in the 1920's). The mouse-skin tumor initiation studies examine initiation/promotion in the skin but do not consider systemic toxicity/carcinogenicity. There is a need for animal data on systemic dermal carcinogenicity; there may be useful data in the current literature, such as skin penetration studies which describe dermally absorbed doses and rate constants for skin permeability. Exxon has a data set for which tumors in target organs other than the skin have been examined in a number of mouse skin-painting studies, and lung tumors have been observed; these data are either in the open literature or in trade association publications. It was recommended that all existing data sets relevant to the potential for dermal carcinogenicity in systemic organs be located and evaluated.

It is not known whether the relative oral potency rankings of the 7 PAHs used in the relative potency approach would be the same if exposure were via the inhalation route. Dr. Nesnow noted that there were multiple data sets that might be re-evaluated, including studies which use a route of administration other than mouse skin. It might be possible to examine all the data and develop a "joint" toxicity equivalence factor which is more representative of the larger data set. Relative potency might be estimated from merging of the results from different kinds of studies; further, the set of PAHs under consideration might be expanded. Some participants felt, however, that the development of one set of relative potency factors for all 3 routes of exposure

is complicated and has serious limitations; for example, both local and systemic effects would be merged. It is also questionable whether different animal models can be justifiably considered to be comparable and whether all animal models are similarly relevant to humans.

Information Needs

It was suggested that testing needs be prioritized. Issues to address included (1) whether BaP is still the most suitable compound to test and to use as a reference standard or whether there were other PAHs that might be more toxic/more prevalent in PAH mixtures, and thus more appropriate for testing and use as a reference; (2) what chemicals should be presented to NTP for testing; (3) whether recommendations for testing should be for individual PAHs or for complex mixtures (e.g., diesel fuel, coke oven emissions, and others) be prioritized. Dr. Mauderly noted that the list of relevant PAHs should be revisited — better data and a longer list of compounds are needed. It was recommended that a group of scientists/regulators review the literature and develop a priority list of compounds to be tested at a later date, including recommendations of route of exposure. Dr. Muller suggested that epidemiology data are also needed. Dr. Muller also recommended additional information needs, specifically the development of transformation markers – indicative of how much transformation of the mixture occurs between stack emission and human exposure, and the development of source markers or fingerprints to identify the mixture sources. It was also suggested that the use of urinary metabolic markers to indicate exposure to PAHs should be explored.

It was generally agreed that data on PAHs in different media, from different sources, and from different exposure routes are all important information needs. Media play a role in terms of PAH bioavailability. Information on the source of the mixture influences the selection of the approach used for PAH assessment. Additional data on different exposure routes, particularly dermal and dermal absorption, are needed. Dr. DiGiovanni noted that National Institute for Environmental Health Sciences (NIEHS) is examining the bioavailability of a range of compounds via different routes; for skin, isolated human skin cultures are being used. Dr. DiGiovanni also noted that with regard to individual PAHs, there are some data showing that BaP and dibenz(*a,h*)anthracene are absorbed through the skin; the degree of absorption in general depends on the molecular weight of the compound.

5.0 SUMMARY OF OBSERVER COMMENTS

Larry Rosengrant, a chemist in OSWER who is involved in the development of analytical test methods, asked the experts whether any test methods are used that analyze for total PAHs, such as immunoassay tests. This is an approach that OSWER is considering as a possible screening tool. Dr. Nesnow replied that he is familiar with an ELISA assay that measures PAH adducts but that this assay is not commonly used.

David Carlson, FDA, noted that tumor promotion is not usually dealt within standard EPA risk assessments; complete carcinogenicity studies are typically utilized. He asked whether the use of tumor promotion in PAH risk assessment was an issue. Dr. DiGiovanni replied that tumor promotion data might be utilized if there are no other data. The best data would be from a low-dose chronic exposure bioassay; however, chronic exposure data for PAHs are very limited. Dr. Thorslund noted that BaP does not seem to show tumor promotion.

Dennis Devlin, Exxon-Mobil, noted that the oil industry has evaluated the systemic carcinogenicity of a number of compounds tested in the mouse skin-painting assay and that lung tumors have been observed in some of these studies. These results have been published either in the open literature or in trade association publications, and might be useful to EPA.

6.0 ACTION ITEMS: FUTURE INFORMATION AND RESEARCH NEEDS

Throughout the discussion many recommendations were provided on information that is needed to improve the risk assessment approaches for PAHs. Some of these comments addressed evaluating existing data sets while others called for new research or assessments.

Recommendations for future information and research needs included: (1) EPA should convene a panel to re-evaluate the validity and usefulness of the relative potency factor approach, using all available data sets; (2) the oral cancer slope factor of BaP should be updated, using the data from the recent chronic feeding study (Culp et al., 1998); (3) EPA should develop an inhalation unit risk estimate for BaP, using available data; (4) EPA should commission a new inhalation study, preferably with two species and two sexes per species, conducted by NTP; (5) the validity of using BaP as the indicator compound should be re-evaluated; (6) 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); and (7) existing dermal carcinogenicity studies should be evaluated to obtain information on the absorption and distribution of PAHs and PAH-containing mixtures, and data on the systemic tumorigenicity of exposure via this route.

Information needs are numerous and need to be prioritized. Recommendations for additional specific testing were considered to be beyond the scope of the charge for this peer consultation. Participants recommended that EPA convene another peer review to review the literature and to develop a priority list of PAH compounds and PAH-containing mixtures to be tested, as well as exposure routes for testing (particularly for oral and inhalation routes). Additional epidemiologic data are also needed. Existing data sets should be re-evaluated to determine the degree of similarity/difference among complex mixtures. Other suggestions included research on: (1) the development of markers for characterizing the degree of transformation that occurs between source emissions and the point of exposure; (2) the development of markers for identifying sources of mixtures of unknown origins; and (3) the use of urinary metabolites of PAH compounds, such as 1-hydroxypyrene (a metabolite of pyrene), as biological markers of exposure.

Particularly for the relative potency factor approach, the following testing should be prioritized: (1) whether BaP is still the most suitable compound to test and to use as a reference standard or whether there were other PAHs that might be more toxic/more prevalent in PAH mixtures, and thus more appropriate for testing and use as a reference; (2) what chemicals should be presented to NTP for testing; (3) whether recommendations for testing should be for individual PAHs or for complex mixtures (e.g., diesel fuel, coke oven emissions, and others). In addition, the list of relevant PAHs should be revisited — better data and a longer list of compounds are needed. It was recommended that a group of scientists/regulators review the literature and develop a priority list of compounds to be tested at a later date, including recommendations of route of exposure.

It was generally agreed that data on PAHs in different media, from different sources, and from different exposure routes are all important information needs. Media play a role in terms of PAH bioavailability. Information on the source of the mixture influences the selection of the approach

used for PAH assessment. Additional data on different exposure routes, particularly dermal and dermal absorption, are needed. The National Institute for Environmental Health Sciences (NIEHS) is examining the bioavailability of a range of compounds via different routes; for skin, isolated human skin cultures are being used. With regard to individual PAHs, there are some data showing that BaP and dibenz(*a,h*)anthracene are absorbed through the skin; the degree of absorption in general depends on the molecular weight of the compound.

APPENDIX A

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**WORKSHOP ON APPROACHES TO THE
HEALTH ASSESSMENT OF PAH MIXTURES
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APPENDIX C

Agenda



Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment

Key Bridge Marriott
Arlington, VA
October 24-25, 2001

Agenda

W e d n e s d a y , O c t o b e r 2 4 , 2 0 0 1

- 8:30 am **Registration**
- 9:00 am **Chair's Opening Remarks, Introductions & Charge to Panel**
Joe Mauderly, Chair, Lovelace Respiratory Research Institute
- 9:25 am **Introduction and Background**
- Background** -- Susan Rieth, USEPA, ORD, National Center for Environmental Assessment
PAH Assessment in OAQPS -- Roy Smith, USEPA, OAR, Office of Air Quality Planning & Standards
PAH Assessment in OSWER -- Lee Hofmann, USEPA, Office of Solid Waste & Emergency Response
- 10:00 am BREAK
- 10:15 am **Surrogate Approach -- Discussion**
Overview -- Gary Foureman, USEPA, ORD, National Center for Environmental Assessment
- 12:00 pm LUNCH
- 1:00 pm **Comparative Potency Approach -- Discussion**
Overview -- Stephen Nesnow, USEPA, ORD, National Health & Environmental Effects Research Laboratory
- 2:15 pm BREAK
- 2:30 pm **Relative Potency Factor Approach -- Discussion**
Overview -- Lynn Flowers, USEPA, ORD, National Center for Environmental Assessment
- 4:00 pm **Observer comments**
- 4:30 pm **Discussion Session I -- General Discussion**
- 4:50 pm **Closing Comments**
Joe Mauderly, Chair
- 5:00 pm ADJOURN FOR THE DAY

T h u r s d a y , O c t o b e r 2 5 , 2 0 0 1

8:30 am **Opening Remarks**
 Joe Mauderly, Chair

8:35 am **Discussion Session II -- General Discussion and Recommendations**

10:30 am **BREAK**

10:45 am **Discussion Session II (continued)**

11:30 pm **Observer comments**

12:00 pm **LUNCH**

1:00 pm **Discussion Session III -- Recommendations**

2:45 pm **BREAK**

3:00 pm **Wrap-up -- Summary of Individual Expert Comments and Recommendations**

3:30 pm **ADJOURN**

APPENDIX D

Presenter Overheads

Susan Rieth

Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment

Susan H. Rieth

Integrated Risk Information System

NCEA, ORD



US EPA Office of Research and Development

D-2



PAH Workshop Steering Committee

Susan Rieth, Chair, ORD
Vincent J. Cogliano, ORD
Lynn Flowers, ORD
Gary Foureman, ORD
Richard Hertzberg, ORD
Elizabeth L. Hofmann, OSWER
Deirdre Murphy, OAQPS
Stephen Nesnow, ORD
Rita Schoeny, Office of Water
Daniel Stralka, EPA Region 9



Integrated Risk Information System (IRIS)

- The IRIS Program develops EPA consensus scientific positions on potential human health effects that may result from chronic exposure to chemical substances found in the environment.
- Assessments for ~540 chemicals.
- IRIS assessment of PAHs initiated at the request of several EPA Program Offices.

IRIS Assessments for PAHs

What's Currently on IRIS

- Entries developed in the early 1990's for 15 non-methylated PAHs with 3 or more rings ("Priority Pollutant" list PAHs)
 - Acenaphthene, acenaphthylene, anthracene, benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[ghi]perylene, chrysene, dibenz[ah]anthracene, fluoranthene, fluorene, indeno[1,2,3-cd]pyrene, phenanthrene & pyrene
- Entries for 3 PAH-containing mixtures
 - Coke oven emissions, diesel engine emissions & creosote

IRIS Assessments for PAHs (con't)

Not Addressed

- Assessments for other PAHs with carcinogenic potential (e.g., “supercarcinogens,” methylated PAHs with 3+ rings)
- Procedure for addressing the environmental occurrence of PAHs as complex mixtures
- Consideration of the literature published in the past decade

History of PAH Assessment

Surrogate Approach

- Early 1970s -- B[a]P proposed as an indicator (surrogate) of all urban air pollution
- Subsequent years, B[a]P was used as an indicator of PAH contamination only

Comparative Potency Approach

- Early 1980s -- proposed as part of an approach for assessing the carcinogenic risk of PAHs in diesel emissions

History of PAH Assessment (con't)

Relative Potency Factor Approach

- 1983 -- EPA's Ambient Water Quality Criteria Document presented relative cancer potencies for 5 PAHs; B[a]P as reference compound
- Late 1980's and early 1990's -- a number of applications of the methodology
- 1993 -- EPA's *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons*

2000 Mixtures Guidance

- EPA Risk Assessment Forum's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*
- EPA's risk assessment paradigm for mixtures

Workshop Objectives

- EPA is seeking individual scientific opinions on:
 - The extent to which alternative approaches are supported by the current scientific literature.
 - The applicability of the various approaches for different exposure situations of interest to EPA.
- Recommendations for revising existing approaches consistent with the available toxicological literature.
- Suggestions for further analyses that might be undertaken.

Roy Smith

PAH Risk Characterization in the EPA Office of Air and Radiation

Roy L. Smith
OAQPS
RTP, NC

Introduction

- Description of OAR's current handling of PAHs in risk assessments
 - ◆ National-scale
 - ◆ Urban- or local-scale (e.g., residual risk)
- Emphasis
 - ◆ Process summaries
 - ◆ Our problems
 - ◆ Our Q&D solutions
 - ◆ Our hopes for better solutions

PAHs Under the Clean Air Act

- Act defines 188 hazardous air pollutants (HAPs)
 - ◆ 19 of the 188 are categories, e.g., “glycol ethers”
 - ◆ One such category is polycyclic organic matter (POM)
 - ★ “Two or more benzene rings, boiling point > 100C
 - ◆ All PAH compounds are POM, and therefore HAPs

Risk Assessment Activities Under the Clean Air Act

- National-scale assessment
 - ◆ Guides the air toxics program in prioritizing HAPs and sources
 - ◆ Provides baseline for assessing progress
 - ◆ Assists in scoping more refined assessments
 - ◆ Inhalation only
- Residual risk assessments (local scale)
 - ◆ Risk remaining after control technologies are implemented
 - ◆ CAA provides for additional controls if cancer risk > 1e-6
 - ◆ Oral & inhalation

Residual Risk Assessments: Process

- Exposure
 - ◆ Begin with best available (e.g., state/industry) PAH emissions data for sources of interest
 - ★ Speciated, wherever possible
 - ◆ Model dispersion, ambient air & multimedia concentrations
 - ◆ Model inhalation and ingestion exposure
- Dose-response
 - ◆ Utilize available UREs (inhalation and oral) for 7 carcinogenic PAHs and RfCs for miscellaneous PAHs
 - ◆ Aggregate cancer risk and noncancer hazard index for PAHs

National-Scale Assessment: Process

- Exposure
 - ◆ Begin with national emissions inventory for POM
 - ◆ Model dispersion, ambient air concentrations
 - ◆ Model exposure
- Dose-response...

National-Scale Assessment: Problems

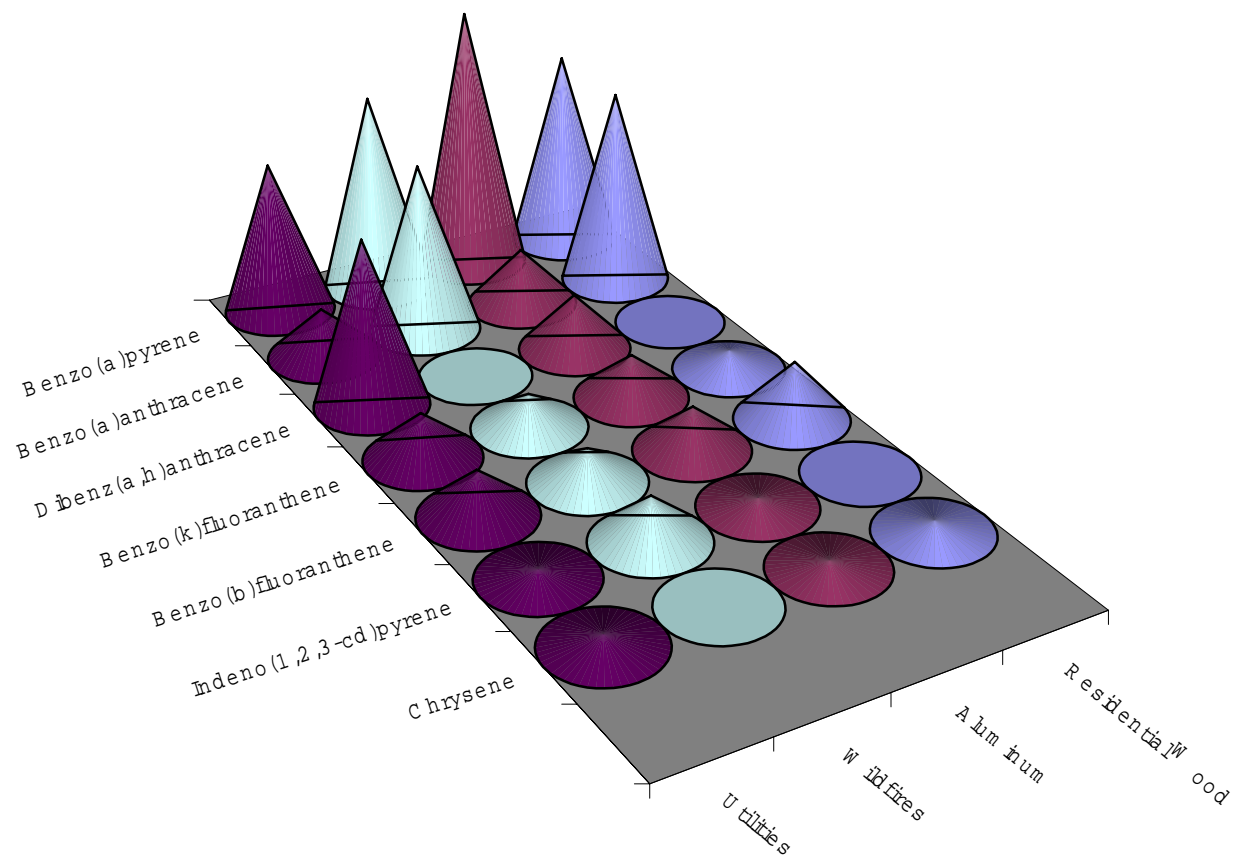
- POM Emissions data largely unspiciated
 - ◆ Speciation applied *ex post facto*
- Lack of EPA consensus inhalation inhalation dose-response assessment
 - ◆ CalEPA UREs used
- Lack of convincing inter-media transport models for use on national scale, so only inhalation considered

National-Scale Assessment: Approach to Dose-Response

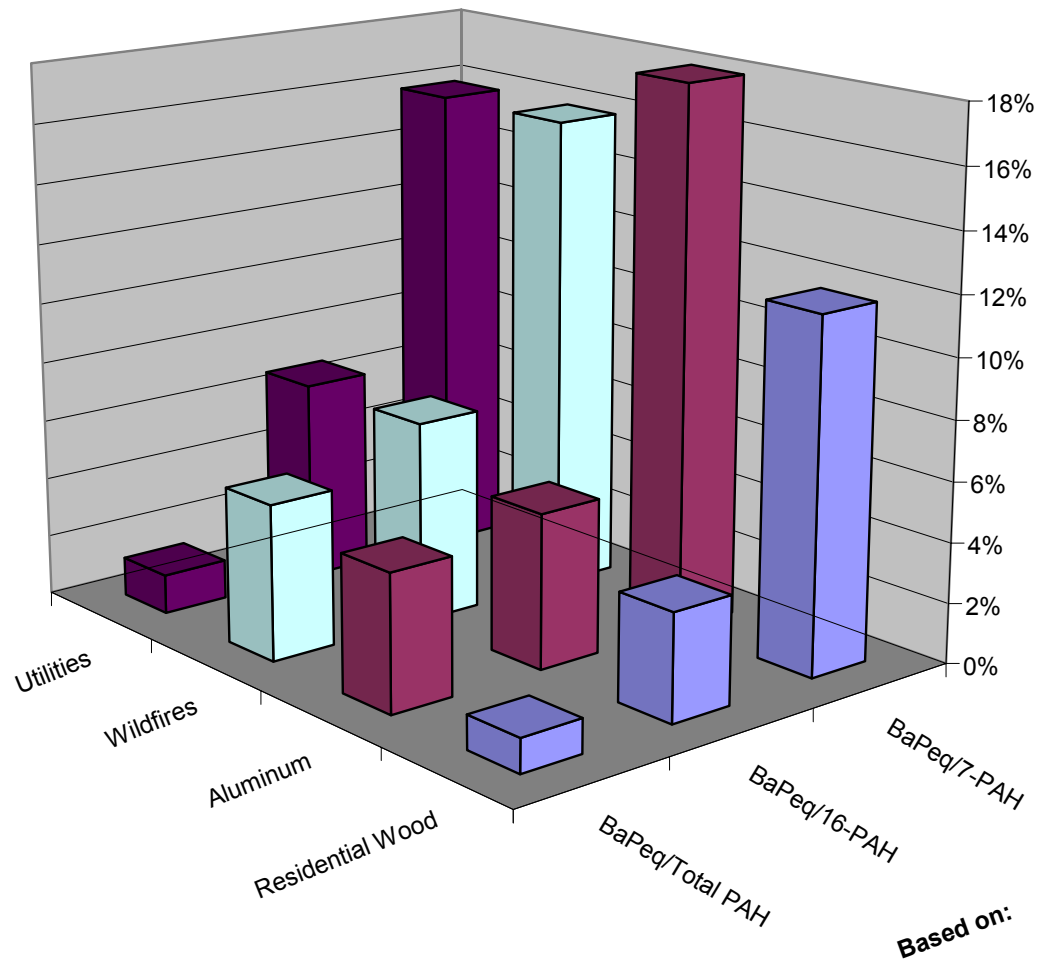
Table 2. Residential wood combustion (EPA, 1997, Table 4.1-1, pg. 4-11). Emission factors are expressed as lb of pollutant emitted per ton of wood combusted.

CHEMICAL NAME	CAS NO	BaP TEF	Emission Factor (lb/t)	Adjusted EF (lb/t BaP eq.)	Percentage of Total
Acenaphthene	83329	0.00%	0.01	0	0.00%
Anthracene	120127	0.00%	0.014	0	0.00%
Benzo(a)anthracene	56553	10.00%	0.02	0.002	40.65%
Benzo(b)fluoranthene	205992	10.00%	0.006	0.0006	12.20%
Benzo(k)fluoranthene	207089	10.00%	0.002	0.0002	4.07%
Benzo(g,h,i)perylene	191242	0.00%	0.004	0	0.00%
Benzo(a)pyrene	50328	100.00%	0.002	0.002	40.65%
Carbazole	86748	0.52%		0	0.00%
beta-Chloronaphthalene	91587	0.00%		0	0.00%
Chrysene	218019	1.00%	0.012	0.00012	2.44%

Figure 1. Distribution of BaP equivalence among 7 carcinogenic PAHs emitted from 4 large POM sources



**Figure 2. Benzo[a]pyrene equivalence
for four large POM sources**



Air Toxics Assessments: Hopes

- *(1) OAR is working with states and others to get speciated POM data into 1999 National Toxics Inventory*
 - ◆ Expectation that POM will be significant part of total emissions (and risk), therefore...
- *(2) ...An EPA-consensus approach to PAH dose-response will be crucial*
- *(3) We also hope that approach can be extended to non-PAH POM compounds*

Lee Hofmann

PAH Assessment in OSWER

PAH Peer Consultation Workshop

October 24, 2001

Lee Hofmann, Ph.D.

Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons

- Developed by ORD for Superfund - 1993
– EPA/600/R-93/089
- 7 PAHs: benz[a]anthracene, benzo[b]-fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-cd]pyrene
- Relative potency approach

Chemicals Contributing to Carcinogenic Risk at SF Sites

- #7 - Benzo[a]pyrene
- #10 - Benzo[b]fluoranthene
- #11 - Benz[a]anthracene
- #14 - Chrysene
- #17 - Benzo[k]fluoranthene
- #22 - Ideno[1,2,3-cd]pyrene
- #39 - Dibenz[a,h]anthracene

Gary Foureman

Overview & Example of “Surrogate Approach” in Evaluating Exposures to PAH Mixtures

Gary L. Foureman

US EPA

Hazardous Pollutant Assessment Group

RTP, NC



IDEAL ASSESSMENT OF A MIXTURE

Human Exposure Information
to
the “Mixture of Interest”
with
D-R of Effects in Humans

REALISTIC ASSESSMENT OF A MIXTURE

Human/Animal/no Exposure Information

to

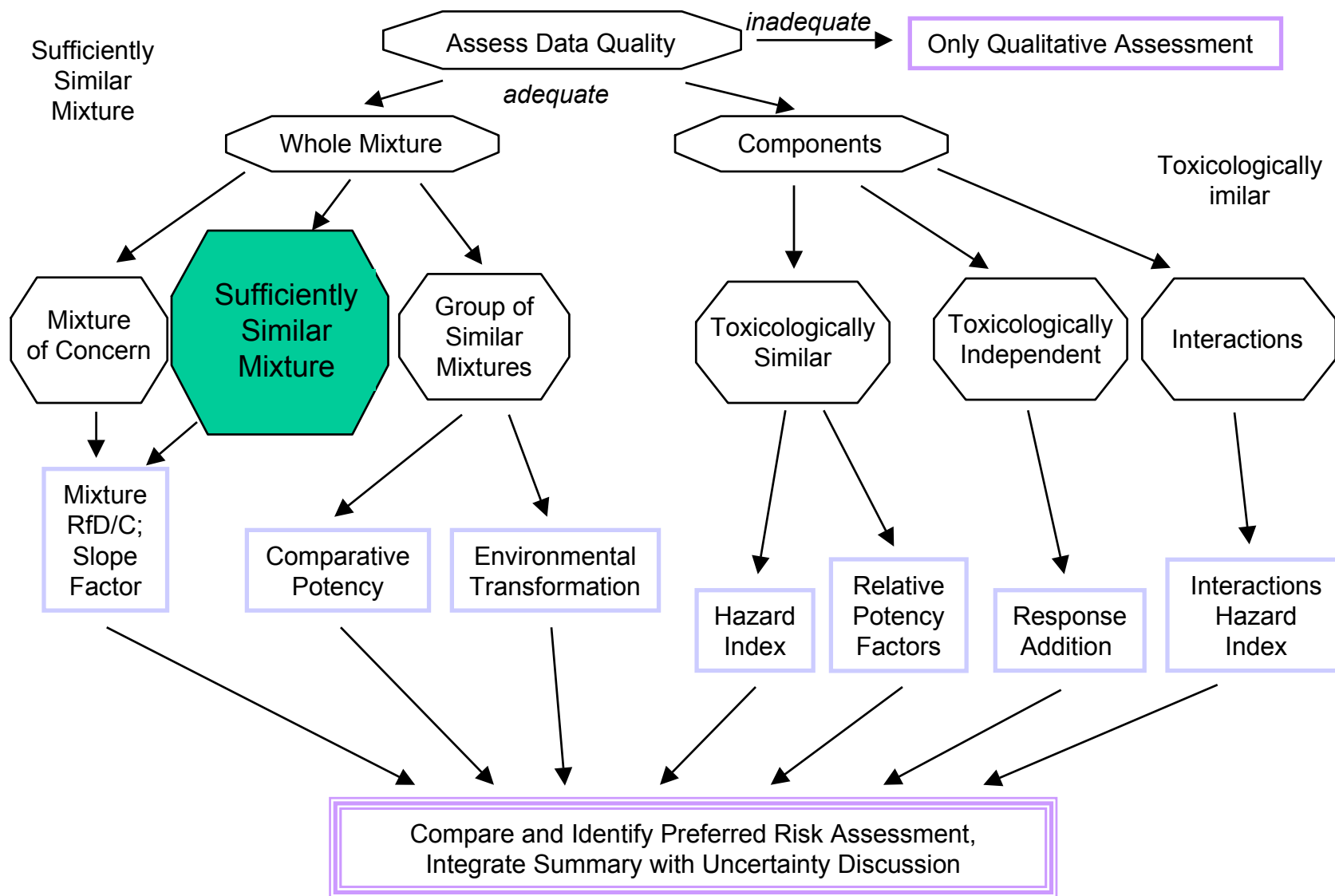
Substitute/“*Sufficiently Similar*”/

Surrogate Mixture

with

Little/Incomplete D-R of Effects in

Humans or Animals



2001 Guidance

The different types of mixtures assessments based on the availability and quality of the data.

All possible assessment paths should be performed.



Key Concepts: Assumption of Similarity

- **Sufficiently Similar Mixture (e.g., diesel emissions)**
 - A mixture close in composition to the “mixture of concern”
 - Small differences in their components and their proportions
- **Similar Components (e.g., liver toxicants at a Superfund site)**
 - Individual chemicals within a mixture
 - Act by same mode-of-action; similarly shaped dose-response curves
- **Group of Similar Mixtures (e.g., dioxins, PCBs)**
 - Chemically related classes of mixtures, closely related chemical structures
 - Act by similar mode-of-action
 - Occur together routinely in environmental samples

“Surrogate” Approach for PAH Mixture
Assessment

=

Use of **Surrogate** or
Sufficiently Similar Mixture of PAH

Relevancy of PAH Surrogate

- **Individual PAH**
 - **Potent Component (BaP)**
 - **Several Selected PAHs**
 - **Mixture 1 of PAHs**
 - **Mixture 2 of PAHs**
 - **nth Mixture of PAHs**
 - **“Mixture of Interest”**
- ↓ ↓

Relevancy of PAH Surrogate

- **Some Bases for Surrogate Mixture “Similarity”**
 - **similar by Mode-of-action**
 - **similar by source**
 - **similar by specific potent component (e.g., BaP)**
 - **similar by presence of certain PAH**
 - **similar by proportion of certain PAH**
 - **similar by presence/absence of other contributory components (nitro- or alky-PAH)**

Relevancy of PAH Surrogate

- **Some considerations for choice of PAH surrogate mixture?**
 - **Are components monitored? (few are)**
 - **Are components found in the environment**
 - **Toxicologic vs analytic data base?**
 - **Components may be super- to noncarcinogenic**
 - **Interactions ???**
 - **Other contributory components**

Example and Use of Surrogate Approach

Surrogate Mixture Example

(Foureman & Smith, 1999)

“Mixture of
Concern”



Human Risk from
“Mixture of Concern”

Surrogate Mixture Example

(Foureman & Smith, 1999)

where

“Mixture of
Concern”

\approx

Surrogate
Mixture

and therefore

risk

“Mixture of
Concern”

\propto

risk

Surrogate
Mixture

Surrogate Mixture Example

(Foureman & Smith, 1999)

Surrogate
Mixture

=

Coal Tar Pitch (CTP)

- PAH & PAH ratios in SRM 1597
- air values of PAH given by Heinrich (1994)

Surrogate Mixture Example

(Foureman & Smith, 1999)

where

risk

Surrogate
Mixture

=

Inhalation Unit Risk (IUR)
of CTP (Heinrich, 1994) -

$1 \times 10^{-4} / (1 \mu\text{g CTP}/\text{m}^3)$

CTP as a PAH Mixture Surrogate

General

- Are components monitored? (few are)
- Are components found in the environment
 - Toxicologic vs analytic data base?
- Components may be super- to noncarcinogenic
 - Interactions
- Other components

CTP

- “PAHs of Concern” are routinely monitored
- “PAHs of Concern” are in the environment
 - Some chronic animal studies with CTP
 - SRM 1597 complete analysis
- tested as a the mixture
 - SRM 1597 analysis

Surrogate Mixture Example

(Foureman & Smith, 1999)

- **Individual PAH**
 - **Potent Component (BaP)**
 - **Several Selected PAHs**
 - **Mixture 1 of PAHs**
 - **Mixture 2 of PAHs**
 - **nth Mixture of PAHs**
- ↓ ↓
- **“Mixture of Interest” = CTP**

Surrogate Mixture Example

(Foureman & Smith, 1999)

- **Some Bases for Surrogate Mixture being “Sufficiently Similar”**
 - similar by etc.
 - all PAH mixtures = CTP (or dilutions thereof)

Surrogate Mixture Example

(Foureman & Smith, 1999)

“Mixture of
Concern”

=

BaP @1.2 ng/m³
CHR @5 ng/m³

Human Risk from
“Mixture of Concern”

?

Surrogate Mixture Example

(Foureman & Smith, 1999)

where

BaP @1.2 ng/m³
CHR @5 ng/m³

≈

[BaP] & [CHR]
of CTP

and 17.7 ng BaP/m³ in 1 μg CTP/m³ (Heinrich, 1994)

BaP @1.2 ng/m³
CHR @5 ng/m³

=

0.07 μg CTP/ m³



Table 6. Information for determining cancer risk estimation^a of air values for PAHs of concern. (From Foureman and Smith, 1999).



PAHs of Concern	SRM1597 Ratio	ng PAH/m³ / 1 μg CTP/m³	TEFs	Example 5
benzo(a)pyrene	1	17.7	1	1.2
benz(a)anthracene	1	22.3	0.1	
benzo(b)fluoranthene	0.7	8.8	0.1	
benzo(k)fluoranthene	0.4	7 ^b	0.1	
indeno(1,2,3-c,d)pyrene	0.6	11.2	0.1	
chrysene	0.8	22.7	0.01	5.0
dibenz(a,h)anthracene	-	-	5	
Total		89.7 ng/m³		

^a Inhalation Unit Cancer Risk = 1×10^{-4} per ($\mu\text{g CTP}/\text{m}^3$). ^b Estimated from SRM 1597 ratio to BaP.

Surrogate Mixture Example

(Foureman & Smith, 1999)

therefore

$$\frac{\text{Risk}}{0.07 \mu\text{g CTP}/\text{m}^3}$$

\propto

$$\frac{1 \times 10^{-4} \text{ per}}{1 \mu\text{g CTP}/\text{m}^3}$$

Risk

“Mixture of
Concern”

$=$

$$7 \times 10^{-6}$$

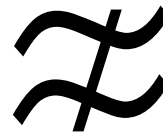
Surrogate Mixture Example

(Foureman & Smith, 1999)

“Mixture of Concern”

Surrogate Mixture

not similar by presence of certain PAH
not similar by proportion of certain PAH



risk ~~“Mixture of Concern”~~

risk

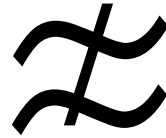


~~Surrogate Mixture~~

Surrogate Potent Component Example

(Muller et al., 1997)

“Mixture of Concern”



Surrogate Mixture
with
Potent Component (BaPS)

not similar



Individual PAH Model

Summary - the Charge Questions

- What are important considerations in judging whether a PAH mixture is “sufficiently similar” to a given surrogate for which D-R data are available?
- Of the available data sets, which is (are) most appropriate for estimating the potency of a PAH mixture? Which would not be appropriate?

Summary - the Charge Questions

- What are some of the limitations?
- Are there clear examples of when this approach is or is not applicable?

Summary - the Charge Questions (con't)

- Is there a surrogate (a single PAH, a group of key PAHs, or a certain mixture) that can be viewed as appropriate for all carcinogenic PAHs?
- For what kinds of exposures/situations is this approach applicable? Could it be considered the preferred (or only viable) approach?

Stephen Nesnow

**MOUSE SKIN TUMORS AND HUMAN LUNG CANCER FOR
INDIVIDUAL PAH AND COMPLEX PAH CONTAINING MIXTURES**

SKIN CARCINOGENESIS BY ORGANIC EXTRACTS OF PARTICULATES: Historical Summary

Particulate Source	Mouse Strain	Tumor Type*	Reference
Ambient	Swiss ICR C57 Black	Car; Pap Car; Pap	Wynder & Hoffmann, 1965 Kotin et al, 1954
Coal Chimney Soot	"White"	Car; Pap	Passey, 1922 Campbell, 1939
Diesel Engine	C57 Black A	— Car; Pap	Kotin et al, 1955 Kotin et al, 1955
Gasoline Engine	C57 Black Swiss	Car; Pap Car; Pap	Kotin et al, 1954 Wynder & Hoffmann, 1962
Industrial Carbon Black	Swiss	Car; Pap	Von Haam & Mallette, 1952
Oil Shale Soot	"White"	Car; Pap	Võsamäe, 1979
Road Dust	—	Car; Pap	Campbell, 1939

*Car = Carcinoma
Pap = Papilloma

THE CONSTANT RELATIVE POTENCY ASSUMPTION

$$\frac{\text{POTENCY [LUNG CANCER IN MAN] OF X}}{\text{POTENCY [LUNG CANCER IN MAN] OF Y}} = K \left[\frac{\text{POTENCY [MOUSE SKIN] OF X}}{\text{POTENCY [MOUSE SKIN] OF Y}} \right]$$

THE CONSTANT RELATIVE POTENCY ASSUMPTION

$$K = \frac{\text{POTENCY [LUNG CANCER IN MAN] OF X}}{\text{POTENCY [LUNG CANCER IN MAN] OF Y}} = \frac{\text{POTENCY [MOUSE SKIN] OF X}}{\text{POTENCY [MOUSE SKIN] OF Y}}$$

HUMAN RESPIRATORY CARCINOGENS

COKE OVEN EMISSIONS

[MAZUMDAR ET AL., 1975]

ROOFING TAR EMISSIONS

[HAMMOND ET AL., 1976]

CIGARETTE SMOKE EMISSIONS

[DOLL AND PETO, 1978]

DIESEL ENGINE EMISSIONS

[GARSHICK ET AL, 1987, 1988]

DIESEL AND GASOLINE SAMPLES

Sample	Description	Fuel	Driving Cycle
Diesel			
Cat	Caterpillar 3304	Diesel No. 2	Mode II
Nissan	Nissan Datsun 220C	Diesel No. 2	HWFET
Olds	Oldsmobile 350	Diesel No. 2	HWFET
VW Rabbit	VW Rabbit	Diesel No. 2	HWFET
Mercedes	Mercedes 300D	Diesel No. 2	HWFET
Furnace	Residential Furnace	Diesel No. 2	10 min on/ 20 min off
Gasoline			
Mustang	1978 Mustang, II-302 , V-8 catalyst and EGR	Unleaded gasoline	HWFET
Ford Van	1970 Ford Van, 6 cylinder	Leaded gasoline	HWFET

COMPARATIVE SOURCES

CIGARETTE: CIGARETTE SMOKE CONDENSATE
2R1 KENTUCKY REFERENCE CIGARETTE

COKE: COKE OVEN AMBIENT SAMPLE
REPUBLIC STEEL, GADSDEN
AMBIENT SAMPLING ON TOP THE BATTERY

ROOF TAR: ROOFING TAR EMISSION SAMPLE
TAR POT PARTICULATE EMISSIONS
PITCH-BASED TAR

MOBILE SOURCE, COKE OVEN & ROOFING TAR EMISSIONS

**SOXHLET
EXTRACTION
DICHLOROMETHANE (DCM)**

DCM, SOLVENT REMOVAL

EVAPORATION

BIOASSAY SOLVENT ADDITION

DMSO

ACETONE

OTHER BIOASSAYS

**SKIN CARCINOGENESIS
SYRIAN HAMSTER EMBRYO ASSAYS**

RESPONSE OF CARCINOGENS IN HUMANS, ANIMALS, AND MOUSE SKIN

	Occupational respiratory carcinogen	Animal respiratory carcinogen	Mouse skin tumorigen
Arsenic	+		
Asbestos	+	+	
Beryllium	+	+	
Carbamates		+	+
Chloromethylethers	+	+	+
Chromium	+		
Coke oven	+		+
Isopropyl oil	+		
MOCA	+	+	
Mustard gas	+	+	
Nickel	+	+	
Nitrosamines		+	+
Polycyclic aromatics		+	+
Quinolines		+	+
Radiation	+	+	+
Vinyl chloride	+	+	

COMPARISON OF THE TUMOR INITIATING ACTIVITY OF BENZO(a)PYRENE IN THREE MOUSE STRAINS

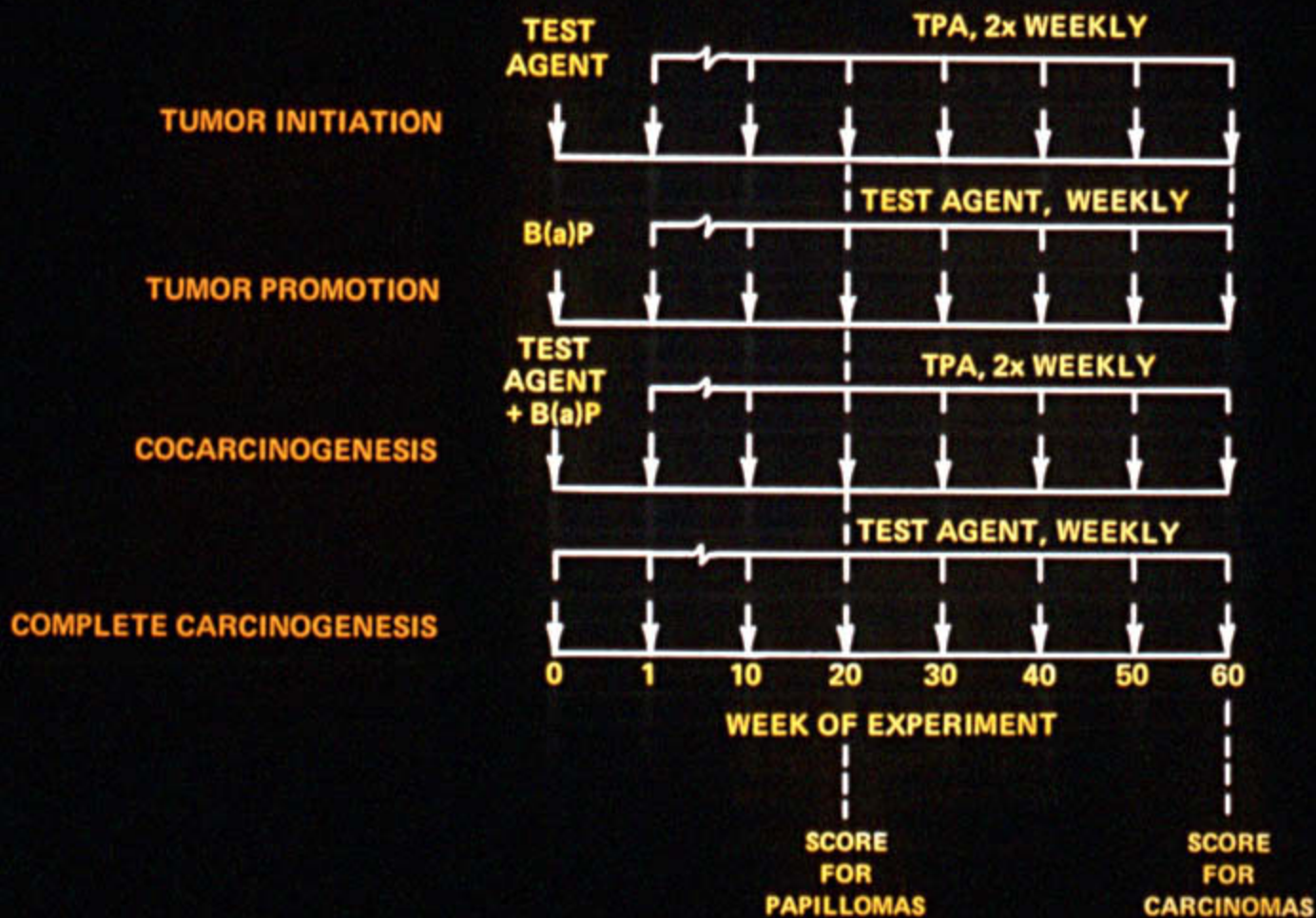
Strain	B(a)P Dose, μ g	Papillomas/Mouse ^a	Mice with Papillomas, percent ^a
Sencar	50.4	8.2	100
	25.2	3.8	80
	12.5	1.6	60
	2.5	0.9	42
CD 1	50.4	3.8	72
	25.2	1.8	58
	12.6	0.7	40
	2.5	0.1	10
C57 Black	404	0	0
	202	0	0
	101	0	0
	50.4	0	0
	25.2	0	0
	12.6	0	0

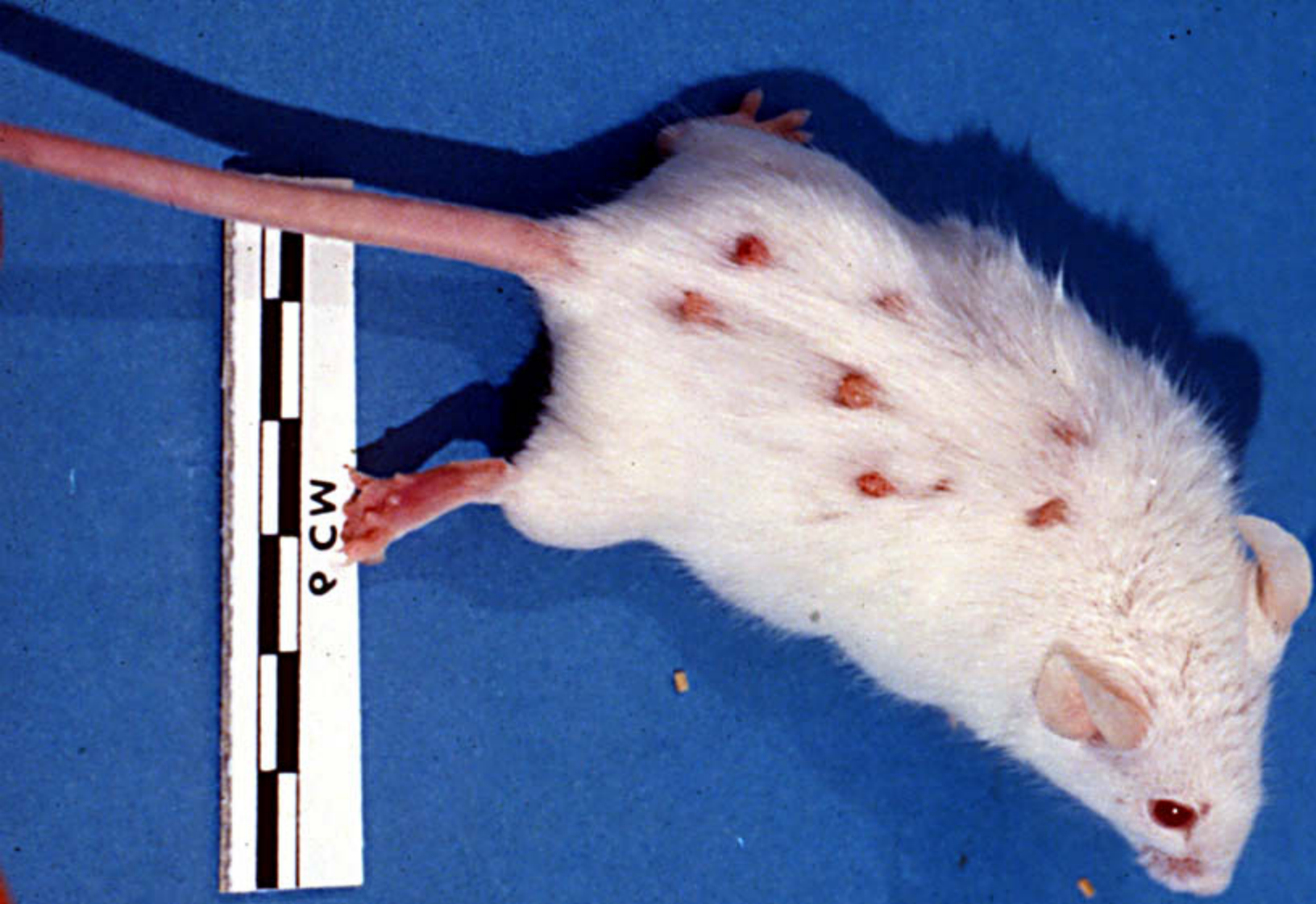
From: DiGiovanni et al, 1980; Slaga and Nesnow, unpublished observations

^aScored at 6 months

MOUSE SKIN TUMORIGENESIS BIOASSAYS

PROTOCOLS





Environmental Sample Description

Sample	Type	Sampling Apparatus
Coke Oven	Tar	Separator in Coke Oven Battery
Roofing Tar	Particulate Emission	Baghouse
Cigarette Smoke	Condensate	Acetone—Cold Trap
Diesel	Particulate Emission	Pallflex-Teflon Coated Fiberglass Filter

TEST AGENT CODE: 0051 PROTOCOL: TI STRAIN: S SEX: F WEEK: 26
 TEST AGENT NAME: NISSAN DCM 1979 START DATE: 072879

DOSE	#NICE	%PAPS	MEAN	S.D.
.000	118	5.085	.059	.271
100.000	39	2.564	.026	.160
500.000	39	23.077	.385	.847
1000.000	38	39.474	.526	.762
2000.000	40	57.500	1.600	1.892
10000.000	38	97.368	5.658	3.656

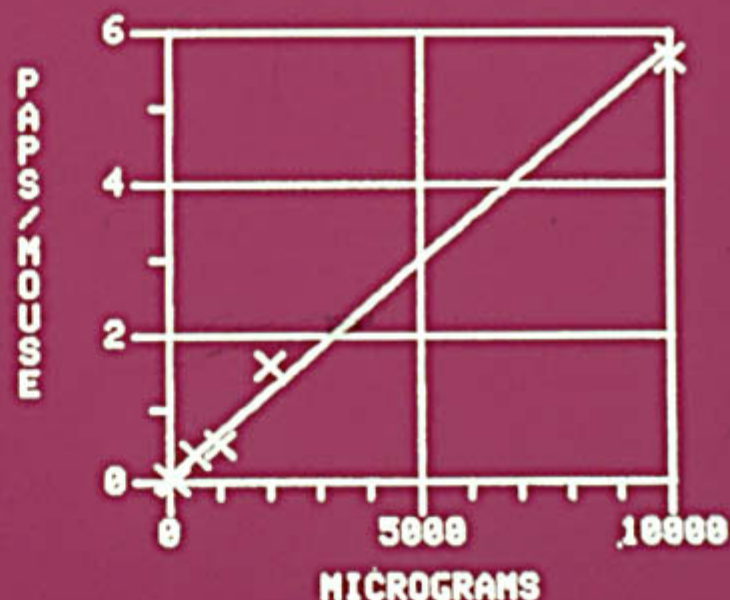
NONLIN POISSON MODEL WITH BACKGROUND ESTIMATES

BETA	INITIAL	FINAL	ASYM	VAR
0	.0593	.0479		.0003
1	-1.7472	-7.1132		.1688
2	.3138	.9624		.0022

TEST	CHI-SQ	DF	P
POISS	326.69	306	.1990
ADQCY	9.01	3	.0291
DOSE	674.83	2	.0000

PAPS/M @ 1 MG	LOWER	95%	UPPER
SPEC	.676	.573	.798
EXCS	.628	.521	.757

OBS & EXP VS DOSE



Induction of Papillomas in SENCAR Mouse Skin under a Tumor Initiation Protocol

Carcinogen	Papillomas/mouse at 1 mg organics	Relative Rank
Coke Oven	2.1	1.0
Roofing Tar	0.40	0.20
Diesel	0.31	0.15
Cigarette Smoke	0.0024	0.0011

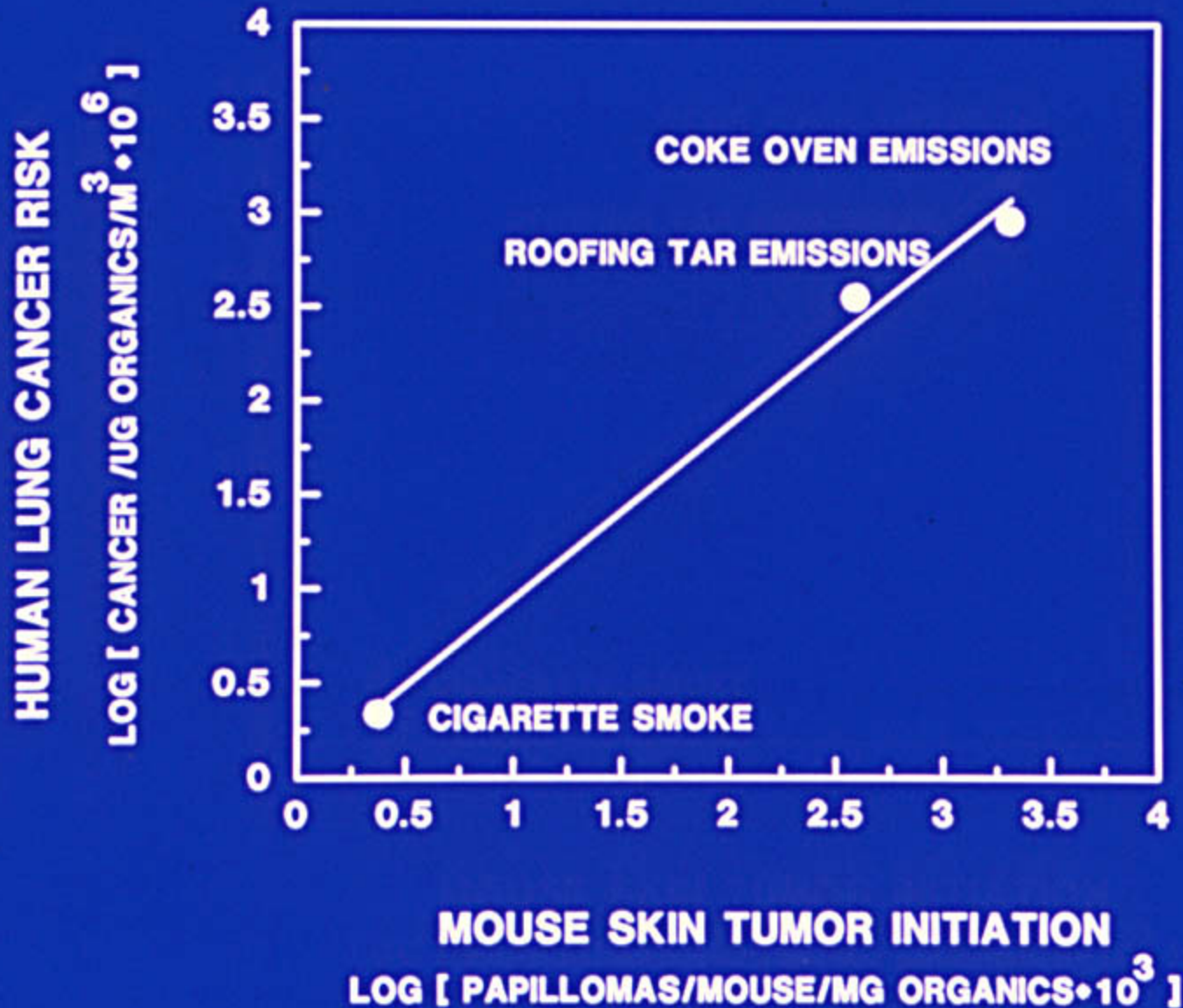
Induction of Papillomas in SENCAR Mouse Skin under a Tumor Initiation Protocol

Carcinogen	TD25, Dose in mg yielding 25% mice with papillomas	Relative Rank
Coke Oven	0.16	1.0
Roofing Tar	0.71	0.22
Diesel	1.0	0.16
Cigarette Smoke	92	0.0017

Human Lung Cancer Unit Risks for Three Complex Mixtures

Emission Source	Human Lung Cancer Unit Risk	Relative Rank
Coke Oven	9.3×10^{-4}	1.0
Roofing Tar	3.6×10^{-4}	0.39
Cigarette Smoke	2.2×10^{-6}	0.0024

RELATIONSHIP BETWEEN MOUSE SKIN TUMORS AND HUMAN LUNG CANCER



EXTRAPOLATION OF RAT DIESEL INHALATION STUDY

MAUDERLY RAT DIESEL INHALATION DATA APPLIED TO
THE LINEARIZED MULTISTAGE EXTRAPOLATION MODEL

ALL TUMORS INCLUDED EXCEPT SQUAMOUS CYSTS

POTENCY EXPRESSED AS THE UNIT RISK

[INDIVIDUAL LIFETIME EXCESS LUNG CANCER RISK FROM CONTINUOUS
EXPOSURE TO TO 1 MICROGRAM CARCINOGEN /CUBIC METER OF INHALED AIR]

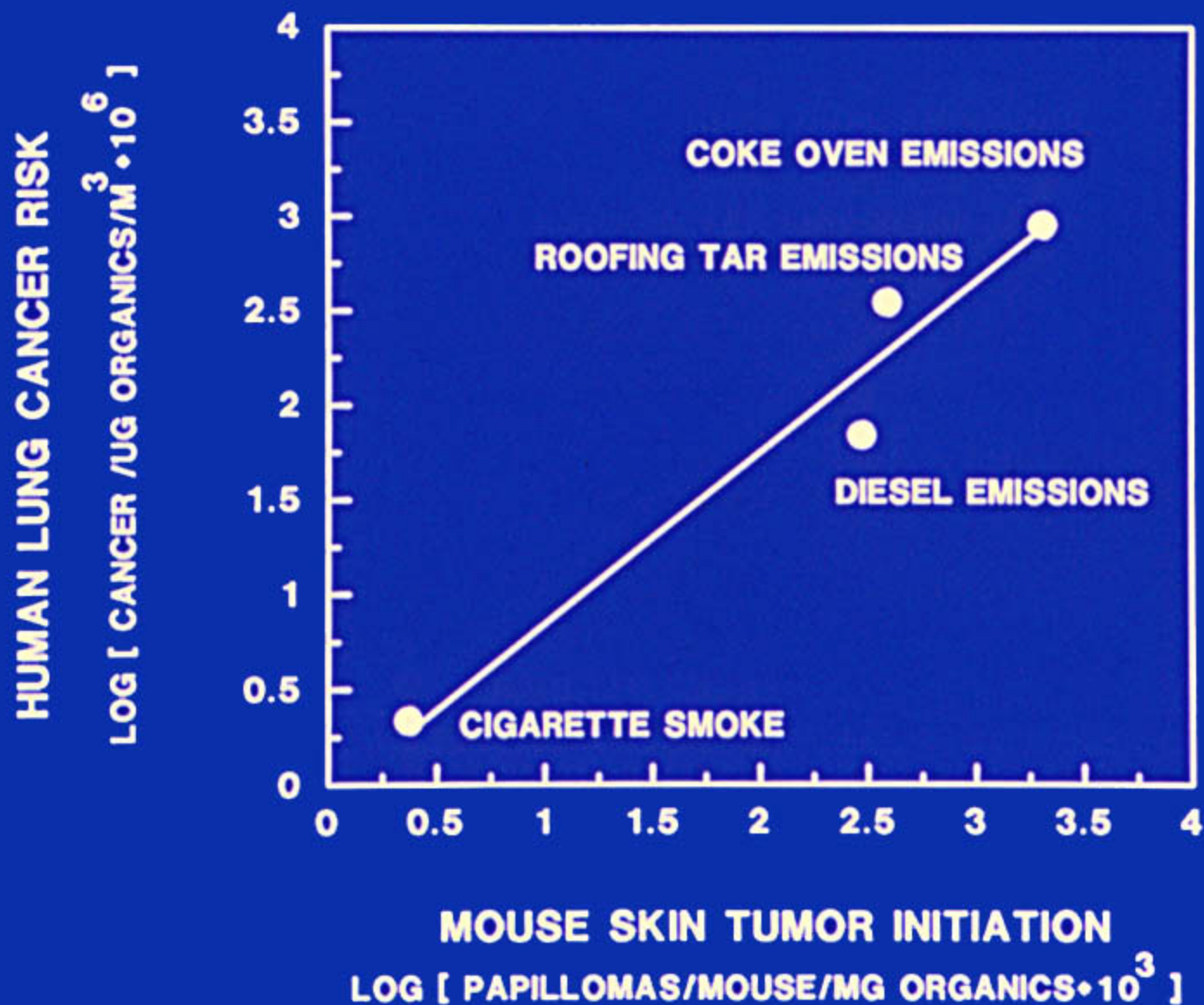
UNIT RISK: 1.2×10^{-5} LIFETIME RISK / μg PARTICULATES / M^3

UNIT RISK: 0.7×10^{-4} LIFETIME RISK / μg ORGANICS / M^3

Human Lung Cancer Unit Risks for Four Complex Mixtures

Emission Source	Human Lung Cancer Unit Risk	Relative Rank
Coke Oven	9.3×10^{-4}	1.0
Roofing Tar	3.6×10^{-4}	0.39
Diesel	0.7×10^{-4}	0.075
Cigarette Smoke	2.2×10^{-6}	0.0024

RELATIONSHIP BETWEEN MOUSE SKIN TUMORS AND HUMAN LUNG CANCER

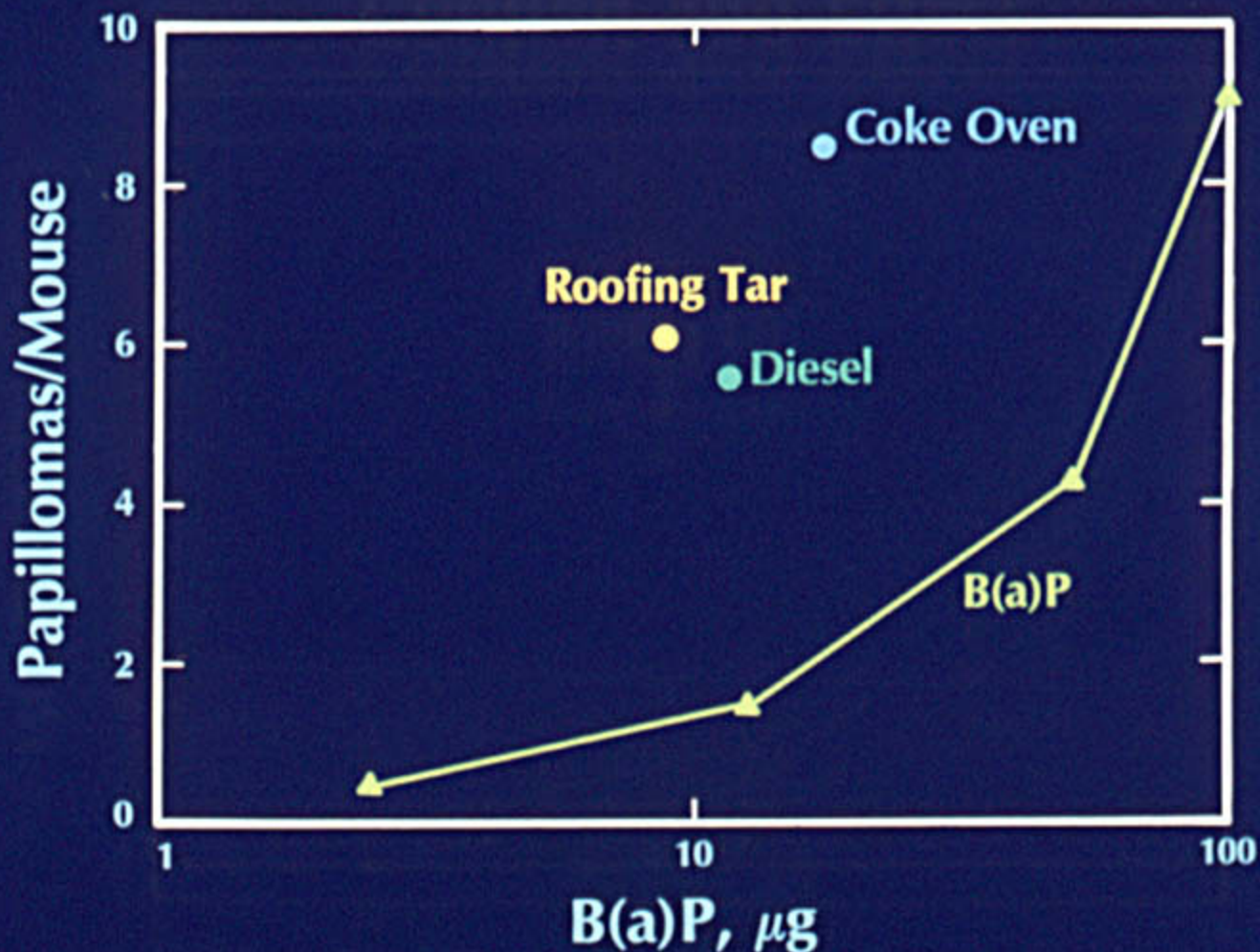


K Constants for Pairs of Human Respiratory Carcinogens

	Roofing Tar	Diesel	Cigarette Smoke
Coke Oven	2.0	0.51	2.1
Roofing Tar	--	0.25	1.0
Diesel	--	--	4.0

Calculated from each unique pair of human respiratory carcinogens using the mouse skin tumor multiplicity and human cancer unit risk data. By convention, the more active agent was placed in the numerator.

Mouse Skin Tumor Initiation— Relationship Between B(a)P Content and Effect



Lynn Flowers

RELATIVE POTENCY FACTOR APPROACH FOR THE HEALTH ASSESSMENT OF PAH MIXTURES

Lynn Flowers

National Center for Environmental Assessment

Office of Research and Development

Washington, DC



US EPA Office of Research and Development

D-79



BASICS OF THE RELATIVE POTENCY FACTOR APPROACH

- Based on the toxicity of select individual components of mixtures
- Eliminates the issue of complex differences between PAH mixtures; presents a compromise in that toxicity of other key components and interactive effects may not be considered
- Estimate risk by assigning relative values to select individual PAH which are known to play a role in toxicity and for which toxicity data are available

Selected Applications

- EPA/ORD (1993) *Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons*
- Nisbet and LaGoy (1992)
- California EPA (1999)
- Ontario Ministry of the Environment (1997)

EPA 1993 Provisional Guidance

- B[a]P used as the standard PAH with the highest ranking
- “Estimated order of potential potency” of 6 PAH determined relative to B[a]P
- Order of magnitude rankings (B[a]P = 1.0)
- All 7 PAH classified as B2 carcinogens by IRIS Program

EPA 1993 Provisional Guidance

- Based on data from complete carcinogenesis assays in mouse skin
- Assumption of additivity of PAH response
- Application relegated to cancer risk and oral exposure only

Example Application

- Cancer risk posed by individual PAH from a mixture is expressed relative to B[a]P
- Individual PAH cancer risks are summed to estimate PAH mixture cancer risk

Example Application: Adult Recreational Exposure Soil Ingestion

PAH	RPF	Slope Factor (mg/kg-day) ⁻¹	Soil Conc. (mg/kg)	Cancer Risk
Benzo[a]pyrene	1.0	7.3	15	6.4 x 10 ⁻⁵
Dibenz[a,h]anthracene	1.0	7.3	10	4.3 x 10 ⁻⁵
Benz[a]anthracene	0.1	0.73	2	8.6 x 10 ⁻⁷
Benzo[b]fluoranthene	0.1	0.73	5	2.1 x 10 ⁻⁶
Indeno[1,2,3-c,d]pyrene	0.1	0.73	2	8.6 x 10 ⁻⁷
Benzo[k]fluoranthene	0.01	0.073	8	3.4 x 10 ⁻⁷
Chrysene	0.001	0.0073	10	4.3 x 10 ⁻⁸
			Total	1 x 10 ⁻⁴

Charge Questions

- What are the important issues to consider in developing an application of the RPF approach?
- What are important factors to consider in determining which PAH to include in a RPF scheme? (e.g., weight-of-evidence of carcinogenicity; chemical structure (QSAR); mode/mechanism of action; availability of certain types of studies, such as *in vivo* cancer bioassays, etc.)
- Should a RPF scheme take into account evidence that PAH appear to induce different types of DNA damage via more than one mode of action? If so, how can this be accomplished?

Charge Questions

(con't)

- B[a]P has traditionally been used as the standard PAH to which the tumorigenic potency of other PAH has been related. Does the current science support the continued use of B[a]P as the standard for all exposure routes, especially in the context of the more newly discovered highly potent species of PAH? If so, what data should be used to establish a cancer slope factor for B[a]P by the oral route? By the inhalation route? By the dermal route?
- Which assay systems (including whole animal, *in vitro*) are most relevant for developing RPFs? Should a “joint analysis,” where data sets are combined, be attempted?

Charge Questions

(con't)

- What are the limitations associated with developing one set of RPFs for all three routes of exposure (i.e., inhalation, oral & dermal)? What are important considerations in developing RPFs for each route?
- EPA's 1993 Provisional Guidance adopted the assumption that the carcinogenicity of individual PAH is additive. Is the default assumption of dose additivity supported by the current science?
- For what kinds of exposure situations is this the preferred (or only viable) approach?

APPENDIX E

Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment - Discussion Document

NCEA-3-1105
September 2001
Discussion Document

**Workshop on Approaches to
Polycyclic Aromatic Hydrocarbon (PAH)
Health Assessment**

Discussion Document

National Center for Environmental Assessment – Integrated Risk Information System
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC 20460

DISCLAIMER

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I. INTRODUCTION

A. Background

At the request of several U.S. Environmental Protection Agency (EPA) program offices, the EPA Integrated Risk Information System (IRIS) Program is undertaking a health assessment for polycyclic aromatic hydrocarbons (PAHs). The IRIS Program develops EPA consensus scientific positions on potential human health effects that may result from chronic exposure to chemical substances found in the environment; assessments for approximately 540 chemical substances can be found in the IRIS database.

Currently, the IRIS database contains entries developed in the early 1990s for 15 non-methylated PAHs with three or more rings. These entries provide assessments of the carcinogenic and noncarcinogenic effects of individual PAHs; however, the IRIS database does not provide assessments for other PAHs with carcinogenic potential (e.g., “supercarcinogens,” methylated PAHs, etc.), and does not consider issues associated with the environmental occurrence of PAHs as complex mixtures.

The objective of the IRIS Program in conducting a health assessment for PAHs is to provide assessments of the carcinogenic and noncarcinogenic properties of PAHs occurring as mixtures.

The initiation of the IRIS PAH assessment follows closely on the release of the EPA Risk Assessment Forum’s *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA, 2000a), which sets forth EPA’s risk assessment paradigm for mixtures. The framework for chemical mixture assessment provided in the supplemental guidance will be applied in the current IRIS effort.

B. Charge to Workshop Participants

Because of the complexity of the scientific literature related to PAH mixtures, the IRIS Program is sponsoring a two-day peer consultation workshop with experts in PAH toxicology and the assessment of chemical mixtures to examine alternative approaches to the health assessment of PAH mixtures. Because information needed to support development of a mixtures approach for assessing the noncancer effects of PAHs is limited or lacking, it is expected that the workshop will largely focus on the extensive carcinogenicity literature for PAHs.

EPA is asking workshop experts to consider the alternative approaches to PAH health assessment presented in this document and to offer their scientific opinions on the extent to which each approach is supported by the current scientific literature. Expert opinion will also be sought on how well the approaches address the range of exposure situations and monitoring data encompassed by EPA program offices. The expert opinions and recommendations generated in this workshop will be taken into consideration by EPA in developing an appropriate and

scientifically defensible health assessment procedure(s) that can be used in combination with exposure assessment information to evaluate the potential health risk of PAH mixtures.

The remainder of this document presents background information on PAHs and on current EPA regulatory approaches to PAH health assessment, and provides specific charge questions that the workshop participants may wish to consider during the two-day workshop.

II. BACKGROUND INFORMATION ON PAHs

A. Overview of PAHs

The term “polycyclic aromatic hydrocarbon” (PAH) refers to a large class of organic compounds formed during the incomplete combustion of coal, oil, gas, wood, and other organic substances. PAH has been variously defined to include organic compounds containing either two or more, or three or more, fused rings made up of carbon and hydrogen atoms (i.e., unsubstituted parent PAH and their alkyl-substituted derivatives) (IPCS, 1998; Schoeny et al., 1998). The more general term “polycyclic aromatic compound” also includes functional derivatives (e.g., nitro- and hydroxy-PAHs) and the heterocyclic analogs that contain one or more hetero atoms (i.e., atoms other than carbon and hydrogen) in the aromatic structure (IPCS, 1998). More than 100 different PAHs have been identified in atmospheric particulate matter and in emissions from coal-fired residential furnaces, and about 200 have been found in tobacco smoke (IPCS, 1998). Because PAHs generally occur in the environment as complex mixtures and because many have similar toxicological, structural, and environmental fate properties, they are often evaluated as a single class. For purposes of the current undertaking, EPA is limiting the universe of PAHs to include those PAHs consisting of three or more fused rings, methylated or non-methylated, and to exclude all compounds with anything other than carbon and hydrogen in their compositions.

B. Health Effects Data

Reliable health effects information exists for relatively few of the individual PAHs, and this information is limited to data from various experimental models.¹ Thus, the potential health effects of the less-well studied PAHs must be inferred from the group as a whole. Supplementing these data on individual PAHs is human and animal health effects literature for various PAH-containing mixtures (e.g., coke oven emissions, emissions from smoky coal burning, and coal tar residues); however, because chemicals other than PAHs occur in these complex mixtures, the observed toxicity cannot necessarily be ascribed to PAHs.

C. Environmental Monitoring

Environmental occurrence of PAHs, as a measure of exposure potential and thus one determinant of potential risk, is relevant to the identification of those PAHs that will be the focus

¹The International Programme on Chemical Safety (IPCS, 1998) selected for evaluation 33 individual compounds based on the availability of relevant toxicological and exposure data; the Agency for Toxic Substances and Disease Registry (ATSDR, 1995) considered data to be reliable for only 17 PAHs.

of EPA's review. Unfortunately, the large body of environmental monitoring data for PAHs suffers from some significant limitations. Although PAH-containing mixtures can contain hundreds of constituents, most monitoring programs routinely report analytical results for only 17 PAHs.² Historically, 16 of the 17 PAHs were included on the Priority Pollutant List generated in the 1970s under provisions of the Clean Water Act. These PAHs were subsequently included on the Contract Laboratory Program (CLP) Target Compound List (TCL), a list of chemicals for which monitoring is routinely performed at Superfund and other waste sites. (Organic chemicals on this list are referred to as target compounds.) There are many PAHs, some now recognized as more toxic than those on the TCL, for which routine analysis is not performed. The remainder of this section is not intended to provide a complete or necessarily representative characterization of current PAH monitoring data, but rather to highlight some issues to be considered when comparing those PAHs for which routine monitoring is performed and those PAHs with a relatively high carcinogenic potential.

As noted above, PAHs identified in various combustion products include those for which routine analysis is performed and others for which analysis is not routinely performed. For example, analysis of indoor air samples (particle-phase organics) from a mobile home with a kerosene heater identified 10 target compound PAHs, two non-target compound (non-methylated) PAHs, and four nitro-PAHs (Mumford et al., 1991). Cyclopenta[*cd*]pyrene, one of the two non-target compound PAHs and a demonstrated carcinogen in experimental animal models, comprised approximately 5 percent of the mass of particle-phase PAHs analyzed. PAH analysis of the organic extract of indoor air particles from smoky coal combustion³ in four homes in Xuan Wei, China during cooking revealed 10 target compound PAHs, six non-target compound (non-methylated) PAHs, three methylated PAHs, and two heterocyclic PAHs (Mumford et al., 1995). Cyclopenta[*cd*]pyrene was also present in smoky coal emissions, comprising approximately 3 percent of the total mass of particulate-phase PAHs analyzed. Also present in indoor air in association with the use of smoky coal were the non-target compound

²Acenaphthene, acenaphthylene, anthracene, benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*ghi*]perylene, chrysene, dibenz[*ah*]anthracene, fluoranthene, fluorene, indeno[1,2,3-*cd*]pyrene, 2-methylnaphthalene, naphthalene, phenanthrene, and pyrene.

Naphthalene and 2-methylnaphthalene, both two-ring PAHs, are among the 17 PAHs for which routine monitoring is performed, but are not included in the scope of the current assessment.

³Smoky coal is comparable to low sulfur (0.2%), medium volatile bituminous coal (Mumford et al., 1999). Indoor air particles from smoky coal combustion contain mostly (51%) submicron particles with approximately 80% organic content, including high concentrations (43% of the organic mass) of PAHs (Mumford et al., 1993).

PAHs 5-methylchrysene, coronene, dibenzo[*ae*]pyrene, dibenzo[*al*]pyrene, and dibenz[*ac*]anthracene (Mumford et al., 1995). Review of monitoring data summarized by IPCS (1998) indicates that anthanthrene (dibenzo[*def,mno*]chrysene), benzo[*e*]pyrene, and coronene, none of which are target compounds, are detected relatively frequently in air samples impacted by various combustion sources (e.g., industrial emissions, vehicle emissions, indoor residential heating, roofing operations).

EPA risk assessments of PAHs have focused on the target compound PAHs, which (with one exception) are unsubstituted homocyclic PAHs. Alkylated PAHs (e.g., methylated PAHs), however, may be important contributors to PAH risk. Chuang et al. (1992) reported that the most bioreactive fraction from the PAH mixture from smoky coal combustion emissions (which have been linked to human lung cancer) contained mainly alkylated PAHs and that these alkylated PAHs were more bioactive in mutagenicity assays than the parent non-alkylated PAHs. Animal studies have shown that methylated PAHs, e.g., dimethylbenz[*a*]anthracene and 5-methylchrysene, are more potent carcinogens than their parent compounds. Many nitrogen-containing heterocyclic PAH compounds also coexist with PAHs in combustion emissions, including coal combustion emissions and coke oven emissions. These compounds are known to be carcinogenic in animals.

Further, various investigators have more recently identified highly bioactive PAHs for which quantitative analytical determinations have not been historically performed. For example, dibenzo[*al*]pyrene (DB[*al*]P) has been identified as one of the most potent PAH carcinogens tested. Cavalieri et al. (1991) stated that “This compound has not been considered a very important environmental carcinogen for two reasons. First, tumorigenicity tests before 1968 used the weakly active dibenzo[*ae*]fluoranthrene instead of DB[*al*]P. Second, analytical data quantitating its presence in cigarette smoke and other environmental hazards have not been pursued until now.” DB[*al*]P has been detected in the combustion emissions of Tennessee coal (Mumford et al., 1987) and in the ambient air near industrial emissions (IPCS, 1998). Review of the extensive summary of PAH monitoring data in IPCS (1998), however, reveals relatively few detections of DB[*al*]P. Whether this apparent low detection frequency reflects a true low frequency of occurrence of DB[*al*]P in environmental emissions, or a failure to analyze for this PAH, is unclear.

Waste site sampling shows the number of PAHs present in environmental media to be substantially greater than the 17 PAHs on the TCL. ATSDR (1995) stated that 54 PAHs have been identified at one or more National Priority List (NPL, or Superfund) hazardous waste sites. The 54 PAHs include those PAHs on the TCL as well as other unsubstituted PAHs, 16 methylated PAHs, and nine heterocyclic PAHs containing atoms other than carbon and hydrogen in their structure (e.g., sulfur, oxygen and nitrogen). Superfund’s Contract Laboratory Program (CLP) conducted an analysis of tentatively identified compounds (TICs) reported 10 or more

times in soil matrix samples collected from 2/1/1995 through 12/31/2000 from predominantly Superfund sites located across the country. Of 39,741 field samples evaluated, 16 homocyclic PAHs not present on the TCL were identified. The number of occurrences for the 16 individual PAHs ranged from 11 to 1,037. These PAHs identified only as TICs would not be routinely included in site risk assessments.

Appendix A provides summary lists of PAHs for which routine monitoring is conducted (i.e., PAHs on the TCL), PAHs reported as TICs at Superfund sites, and PAHs addressed in health assessments undertaken by IRIS, California EPA, and other authoritative bodies (IPCS and ATSDR).

III. CURRENT EPA PRACTICES FOR ASSESSING PAH HEALTH RISK

A. Guidance Developed by EPA's Office of Research and Development (ORD)

1. Toxicity Assessments for Individual PAHs in IRIS

In the early 1990s, EPA's IRIS Program developed assessments for 15 PAHs.⁴ Of these 15, a quantitative cancer dose-response assessment was prepared for one carcinogenic PAH, benzo[*a*]pyrene (B[*a*]P). Qualitative cancer weight-of-evidence (WOE) designations were established for 14 of the 15 PAHs, and noncancer assessments for five PAHs. The cancer assessments for the PAHs in IRIS are described further below.

Cancer WOE Evaluations

A WOE designation reflects a qualitative evaluation of the carcinogenicity data for a chemical, and characterizes the likelihood, based on the available scientific data, that the agent in question is a human carcinogen. Between 1990 and 1992, EPA assigned cancer WOE designations of "D," not classifiable as to human carcinogenicity, to acenaphthylene, anthracene, benzo[*ghi*]perylene, fluoranthene, fluorene, phenanthrene, and pyrene. B[*a*]P, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*ah*]anthracene, and indeno[1,2,3-*cd*]pyrene were classified as "B2," or probable human carcinogens, based on sufficient evidence of carcinogenicity in animals, and inadequate or no evidence in humans.

For all of the B2 carcinogens except B[*a*]P, the scientific data were considered insufficient to develop quantitative estimates of carcinogenic potency.

B[*a*]P

In 1992, EPA derived an oral cancer slope factor for B[*a*]P of 7.3 (mg/kg/day)⁻¹. This estimate of carcinogenic potency was calculated as a geometric mean of four slope factors derived from two bioassays, one in mice (Neal and Rigdon, 1967) and one in rats (Brune et al., 1981). No estimate of cancer potency for B[*a*]P by inhalation was recommended by EPA at that time. An inhalation cancer unit risk (UR) of $8.8 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ had been previously derived based on a bioassay in hamsters exposed to B[*a*]P condensed onto aerosols of NaCl (Thyssen et al., 1981); however, consensus verification of this UR by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) Workgroup (representative

⁴The IRIS database also includes an assessment for the two-ring PAH naphthalene. The naphthalene assessment was updated in September 1998. Naphthalene is not included within the scope of the current IRIS assessment for PAH mixtures.

of Agency consensus until 1995) was not obtained. [Note: The California EPA used Thyssen et al. (1981) as the basis for an inhalation UR of $1.1 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$ (Cal EPA, 1999).]

The toxicity of B[a]P is currently being reassessed by the IRIS Program under the lead of EPA's Office of Solid Waste and Emergency Response (OSWER).

A summary of the individual PAH assessments currently contained in the IRIS data base is provided in Table 1 below.

TABLE 1 Summary of PAH Assessments Currently in IRIS			
PAH (CAS No.)	Cancer WOE Classification	Quantitative Cancer Assessment (Oral Slope Factor) ^a	Noncancer Assessment (Oral Reference Dose) ^b
Acenaphthene (83-32-9)			RfD = 0.06 mg/kg/day
Acenaphthylene (208-96-8)	D		
Anthracene (120-12-7)	D		RfD = 0.3 mg/kg/day
Benz[a]anthracene (56-55-3)	B2		
Benzo[a]pyrene (50-32-8)	B2	SF = 7.3 (mg/kg/day) ⁻¹	
Benzo[b]fluoranthene (205-99-2)	B2		
Benzo[k]fluoranthene (207-08-9)	B2		
Benzo[ghi]perylene (191-24-2)	D		
Chrysene (218-01-9)	B2		
Dibenz[ah]anthracene (53-70-3)	B2		
Fluoranthene (206-44-0)	D		RfD = 0.04 mg/kg/day
Fluorene (86-73-7)	D		RfD = 0.04 mg/kg/day
Indeno[1,2,3-cd]pyrene (193-39-5)	B2		
Phenanthrene (85-01-8)	D		

TABLE 1 Summary of PAH Assessments Currently in IRIS			
PAH (CAS No.)	Cancer WOE Classification	Quantitative Cancer Assessment (Oral Slope Factor) ^a	Noncancer Assessment (Oral Reference Dose) ^b
Pyrene (129-00-0)	D		RfD = 0.03 mg/kg/day
<p>^a A slope factor (SF) is a plausible upper-bound estimate of the probability of a response (cancer) per unit intake of a chemical over a lifetime and is expressed as risk per mg/kg/day.</p> <p>^b A reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) 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. It is based on the assumption that thresholds exist for certain toxic effects.</p>			

2. Assessments for PAH Mixtures

a. IRIS Toxicity Assessments for PAH-containing Mixtures

IRIS currently includes assessments for three PAH-containing mixtures: coke oven emissions, creosote, and diesel emissions. A quantitative carcinogenicity assessment has been performed only for coke oven emissions.

EPA's carcinogenicity assessment of coke oven emissions was conducted in 1984; Agency-wide consensus of the assessment was obtained in 1989. EPA classified coke oven emissions as an "A" (human) carcinogen, having concluded that there was sufficient evidence of carcinogenicity in humans (based on studies in coke oven workers showing increased risk of mortality from cancer of the lung, trachea and bronchus, cancer of the kidney, cancer of the prostate, and cancer at all sites combined) and in laboratory animals (based on studies of coke oven emission extracts and condensates showing a carcinogenic response in inhalation studies and skin-painting bioassays). EPA also derived an inhalation unit risk estimate for coke oven emissions of $6.2 \times 10^{-4} (\mu\text{g}/\text{day})^{-1}$ (expressed as benzene-soluble organics extracted from the particulate phase of coal tar pitch volatiles from coke oven emissions). This unit risk was based on respiratory cancer in male coke oven workers.

b. Provisional Guidance for Oral Exposure to PAH Mixtures

In the early 1990s, EPA gave consideration to practices for estimating cancer risk for exposure to PAH mixtures. The Office of Health and Environmental Assessment (subsequently the National Center for Environmental Assessment) developed an "estimated order of potential potency" (EOPP) for six PAHs classified as B2 carcinogens (probable human carcinogens) [*Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons* (EPA, 1993)]. EOPPs are

summarized in Table 2.

Specifically, EOPPs were developed for benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*ah*]anthracene, and indeno[1,2,3-*cd*]pyrene relative to the potency of B[*a*]P. The values represent ratios that were calculated by application of a form of the two-stage model of carcinogenesis (generally defaulting to a one-stage model) to complete carcinogenesis assays in mouse skin, comparing the point estimates to those for B[*a*]P tested at the same time, and rounding to orders of magnitude. It was observed that the data for PAHs did not meet all the criteria for development of a toxicity equivalence factor (TEF) approach as described by the Risk Assessment Forum (e.g., demonstration of additivity, consistency of relative toxicity across endpoints). Thus, EPA recommended that EOPPs be confined to use only for cancer, a subset of PAHs (unsubstituted PAHs classified as B2 carcinogens), and estimation of risk from oral exposure.

EOPPs provided in the 1993 Provisional Guidance are summarized below.

TABLE 2 Estimated Order of Potential Potencies (from EPA, 1993)	
PAH (CAS No.)	EOPP
Benzo[<i>a</i>]pyrene (50-32-8)	1
Benz[<i>a</i>]anthracene (56-55-3)	0.1
Benzo[<i>b</i>]fluoranthene (205-99-2)	0.1
Benzo[<i>k</i>]fluoranthene (207-08-9)	0.01
Chrysene (218-01-9)	0.001
Dibenz[<i>ah</i>]anthracene (53-70-3)	1.0
Indeno[1,2,3- <i>cd</i>]pyrene (193-39-5)	0.1

c. Guidance for Inhalation Exposure to PAH Mixtures

In 1993, the CRAVE Workgroup undertook the evaluation of inhalation cancer risks for certain PAH-containing mixtures (diesel engine emissions, gasoline engine emissions, aluminum smelter emissions, wood burning emissions, and polycyclic organic matter (POM)). A comparative potency approach was considered for deriving

quantitative estimates of inhalation cancer risk for POMs in various source categories. (A description of the comparative potency approach is included in Section IV). Agreement was not reached on either inhalation unit risks for the specific PAH-containing mixtures or the use of the comparative potency approach for application to various source categories. Other than the assessment for diesel emissions (EPA, 2000b), no attempts have been made by the Agency to estimate cancer potency via inhalation for PAH-containing mixtures.

B. Current Practices within EPA Program Offices

Program offices within EPA have regulatory responsibility for PAHs present in different environmental media and from various sources. The Office of Air and Radiation (OAR) deals largely with PAHs present in emissions to the air from various industrial processes (e.g., the production of coal tar and coke, petroleum catalytic cracking), incomplete combustion (e.g., incinerators), or diffuse sources such as motor vehicles. According to ATSDR (1995), stationary sources account for approximately 80% of total annual PAH emissions, and mobile sources account for the remainder. The PAH composition of these emissions is largely a function of the combustion source and, in some instances, the emissions at the source may differ from the PAH profile found at the site of exposure.

PAHs present in soil and sediment may be associated with a variety of sources, including atmospheric deposition after either local or long-range transport, disposal of sludge from public sewage treatment plants, automobile exhaust, leachate from bituminous coal storage sites, releases from creosote production, wood-preserving, and coking plants, and residues from former manufactured gas plants (ATSDR, 1995). Because of partitioning and weathering (i.e., changes in composition due to microbial degradation, photolysis, hydrolysis, and oxidation) and difficulties in associating current contamination with historical sources of contamination, PAHs in soil and sediments are less readily characterized in terms of emissions source category.

How an EPA program office addresses PAH health risk for media or sources for which it has regulatory authority is in large part a function of the type of monitoring data collected for that regulated medium or source. A brief description of regulatory practices in OAR and OSWER—two offices that have requested an IRIS assessment for PAH mixtures—follows.

1. Office of Air and Radiation

PAHs fall within the Clean Air Act listed hazardous air pollutant group, polycyclic organic matter (POM).⁵ Accordingly, OAR hazardous air pollutant risk assessment activities routinely include PAHs. Two current OAR activities that assess PAH risk include:

⁵POM includes organic compounds with more than one benzene ring, and which have a boiling point greater than or equal to 100°C.

(1) the assessment of risk remaining (i.e., residual risk per CAA 112(f)) from air emissions of the hazardous air pollutant source categories following the implementation of control technologies (e.g., maximum achievable control technology, “MACT”) (USEPA, 1999), and (2) the cumulative risk assessment performed as part of the National-Scale Assessment for the 1996 base year (USEPA, 2001). The former activity encompasses oral and inhalation exposure pathways, while limitations in national scale modeling tools have limited the latter to inhalation only. Exposure estimates are primarily based on modeling estimates due to scarce air monitoring data for PAHs.

In the source category specific risk assessments performed for the residual risk program, inhalation and ingestion exposures to emitted PAHs have been assessed using currently available cancer dose-response information (e.g., cancer weight of evidence and unit risk estimates and relative potency factors from IRIS and California EPA) in a cumulative manner. For the National-Scale Assessment, consideration of PAHs was limited by a near total lack of speciated emissions data. OAR was obliged to use generic PAH profiles for a few large emissions sources and apply them to all areas of the country. These generic profiles were assigned unit risk estimates based on dose-response assessments developed by California EPA for seven carcinogenic PAHs.

Current OAR assessments for POM are driven by the PAH component, and with regard to cancer risk assessment, by the seven PAHs identified by EPA as probable human carcinogens.

2. Office of Solid Waste and Emergency Response (OSWER)

EPA’s Superfund Program, within OSWER, is charged with cleaning up the nation’s uncontrolled hazardous waste sites. Under this program, EPA evaluates potential health risks associated with site-related contaminants present in contaminated media, via various pathways of potential exposure. For PAHs, this may involve consideration of exposures to contaminated media via ingestion, inhalation and dermal contact. Risks are based on analytical data or modeled concentrations for target compounds in soil, sediment, surface water, ground water, and air. Among these target compounds are the 17 individual PAHs on Superfund’s Target Compound List.

Most EPA regional offices limit their evaluation of PAHs to risks associated with ingestion of the seven carcinogenic PAHs included in EPA’s 1993 provisional guidance for PAHs. Some regions additionally include evaluation of potential carcinogenic risk associated with inhalation exposure using the inhalation unit risk that was initially proposed by the CRAVE workgroup in 1994 but was not finalized. A few regions have also attempted to quantify risks associated with dermal contact with PAH-containing soil/sediment. Guidance on dermal assessment for PAHs is limited to the following language from EPA’s *Risk Assessment Guidance for Superfund* (EPA, 1989):

It is inappropriate to use the oral slope factor to evaluate the risks associated with dermal exposure to carcinogens such as benz(a)pyrene, which cause skin cancer through a direct action at the point of application... Generally only a qualitative assessment of risks from dermal exposure to these chemicals is possible.

As indicated above, the profile of PAHs in soil and sediment is typically not representative of the original PAH source. Unlike OAR, characterization of the health risk for a sample containing PAHs based on source category is less likely to be a useful approach for the situations addressed under the Superfund Program.

IV. APPROACHES TO HEALTH ASSESSMENT FOR PAH MIXTURES

A. Introduction

The Risk Assessment Forum recently published *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (“Mixtures Guidance”) (EPA, 2000a), as a supplement to the Agency’s 1986 *Guidelines for the Health Risk Assessment of Chemical Mixtures* (EPA, 1986). This guidance will be used as a framework for organizing and presenting the methods that have applicability to PAH mixtures.

The Mixtures Guidance describes assessment procedures using data on the mixture of interest, data on toxicologically similar mixtures, and data on the mixture component chemicals. The guidance is intended to assist the risk assessor in selecting an appropriate mixtures method, beginning with an assessment of data quality, followed by evaluation of the type of data available. As noted in the Mixtures Guidance, “The major concerns for the user are whether the available data are on components or whole mixtures, whether the data are composed of either similar components or similar mixtures that can be thought of as acting by similar toxicologic processes, and whether the data may be grouped by emissions source, chemical structure, or biologic activity.”

The preferred approach to the health risk evaluation of chemical mixtures is an assessment using health effects and exposure data on the whole mixture. Whole mixtures data can be divided into the following subsets: data directly on the mixture of interest, data on a sufficiently similar mixture, and data on a group of similar mixtures. If data are not available for a reasonably similar mixture, an assessment may be based on the toxic or carcinogenic properties of the components in the mixture. A relative potency factor approach is one type of components approach that can be applied when the components are toxicologically similar.

EPA has prepared dose-response assessments for several whole PAH-containing mixtures, including coke oven emissions (cancer assessment) and diesel emissions (noncancer assessment). Because the number of PAH-containing mixtures with adequate dose-response data is limited, a whole mixtures approach that uses only data directly on the mixture of interest can not begin to address the large number of diverse PAH-containing mixtures to which exposure may occur. Therefore, various approaches to the evaluation of the health risk of PAH mixtures that can be applied to a diversity of PAH-containing mixtures have been proposed. Because information on the noncancer effects of PAHs is limited, existing approaches are based on the assessment of potential carcinogenic risk posed by PAH mixtures. Those approaches that appear to have some practical application to the situations addressed by EPA program offices are the following: (1) surrogate approach (based on data for similar mixtures), (2) comparative potency approach (based on data for a group of similar mixtures), and (3) relative potency factor approach (based on component PAHs). Basic features of each are briefly summarized below and

in Table 3. More complete discussions of each approach, including principles and assumptions, validation, existing applications, and advantages and disadvantages, appear in IPCS (1998) and Schoeny et al. (1998).

TABLE 3 Summary of Major Features of Existing PAH Assessment Approaches			
Feature	Surrogate Approach	Comparative Potency Approach	Relative Potency Factor Approach
Whole mixture vs. component approach?	whole mixture approach	whole mixture approach	component approach
Estimates the potency of the whole mixture or the PAH component of the mixture?	PAH component of the whole mixture	whole mixture	Selected PAHs only (specifically those analyzed and for which RPFs are available)
Type of study from which dose-response assessment is obtained	Dose-response data for a whole mixture, preferably for a mixture whose carcinogenic potency is largely attributable to its PAH component	Human epidemiologic data and bioassay data (e.g., mouse skin tumor initiation assay) for a set of similar mixtures from which a scaling factor is derived	Bioassay data for the index PAH (e.g., B[a]P)
How are interactions handled?	Interactions are addressed implicitly; knowledge of specific interactions (synergism, antagonism, additivity) among PAHs is unnecessary		Assumes dose additivity
Data required to apply approach to mixture of interest	(1) Data demonstrating “sufficient similarity” to mixture with dose-response data (2) Concentration of surrogate PAH (e.g., B[a]P)	(1) Data demonstrating “sufficient similarity” to set of mixtures used to derive scaling factor (2) Bioassay data for the mixture of interest (e.g., mouse skin tumor initiation data)	Data on concentrations of component PAHs

B. Surrogate Approach (Using Data for Sufficiently Similar Mixtures)

The Mixtures Guidance (Section 3.1.2) states that:

If adequate data are not available on the mixture of concern, but health effects data are available on a similar mixture, a decision should be made whether the mixture on which health effects data are available is or is not “sufficiently similar” to the mixture of concern to permit a risk assessment.

Dr. Gary Foureman of EPA's National Center for Environmental Assessment and Dr. Roy Smith of EPA's Office of Air Quality Planning and Standards developed a similar approach for assessing the health risk of PAH mixtures in air using data for a sufficiently similar PAH mixture that also includes a procedure for evaluating whether or not differences in composition are likely to be toxicologically significant. The approach assumes that all PAH-containing mixtures in air are essentially the same as a mixture of coal tar pitch (CTP), a PAH mixture of known composition and carcinogenic potency, and that the concentrations of B[a]P and other detected airborne PAHs are simply dilutions of CTP. Other information, including an inhalation unit risk derived for CTP, is used in conjunction with actual exposure information in making a judgment on use of this approach. This application of a surrogate approach using data for sufficiently similar mixtures is presented in Foureman and Smith (1999) and is summarized in Appendix B.

C. Comparative Potency Approach (Based on Data for a Group of Similar Mixtures)

In some cases, data are available on a group of similar mixtures. A procedure developed for environmental mixtures that applies data for similar mixtures is the comparative potency approach. In this procedure, a set of mixtures of highly similar composition is used to estimate a scaling factor that relates the toxic potency of a mixture in one assay to the potency in a second assay of the same toxic endpoint. The mixture of interest can then be tested in one of the assays (preferably a relatively simple, low-cost assay), and the resulting potency can be adjusted by the scaling factor to estimate the potency in the second assay (preferably an "assay" which constitutes human data). The comparative potency approach is used to estimate the potency of a PAH-containing mixture without having to identify or quantify individual PAH compounds.

This approach rests on the assumption that the similar mixtures in a set act in a similar manner toxicologically, and that for all members of the group of similar mixtures there exists a constant linear relationship between the potencies derived from the two assays. Where the data sets for a group of similar mixtures consist of data from an experimental assay and from human epidemiological studies, the relationship can be shown as follows:

$$\frac{\textit{Human cancer potency}_{mixture1}}{\textit{Bioassay potency}_{mixture1}} = \frac{\textit{Human cancer potency}_{mixture2}}{\textit{Bioassay potency}_{mixture2}} = k$$

For a mixture of interest ("mixture A") that is considered to be a member of the group of similar mixtures and for which appropriate bioassay data exist, human cancer potency can be estimated by rearranging the above equation as follows:

$$\text{Human cancer potency}_{\text{mixture } A} = \text{Bioassay potency}_{\text{mixture } A} \times k$$

This approach was originally developed as the basis for estimating the human lung cancer unit risk for the polycyclic organic matter (POM) associated with diesel emissions (Albert et al., 1983). Measures of comparative potency were derived from data for the complex POM emissions from coke ovens, roofing tar, and cigarette smoke (Albert et al., 1983; Lewtas, 1985, 1991; Nesnow, 1990).⁶ These three combustion-related mixtures were ones that had human data sufficient to derive a human cancer unit risk estimate and that had been tested in the Sencar mouse skin tumor initiation assay. Based on the relationship between human lung cancer risk and potency in the mouse skin tumor initiation assay, a scaling factor (“k”) could be derived.

This approach can be used to estimate cancer potency for other PAH-containing mixtures – after making a weight of evidence (WOE) determination that the mixture is a potential human carcinogen and a demonstration of sufficient similarity to the set of mixtures used to develop the scaling factor.

Further description of this approach is provided in Nesnow (1990) and in Section 3.3.2.3 of the Mixtures Guidance.

D. Relative Potency Factor Approach (Component Approach)

Unlike the first two approaches presented in this section that rely on dose-response data for whole mixtures, the relative potency factor (RPF) approach is based on an evaluation of individual components of the mixture. The premise of this approach is that the health effects of a mixture of related chemical compounds can be estimated as the sum of the effects of the individual components of the mixture. The approach relies on both the existence of toxicological dose-response data for at least one component of the mixture (referred to as the index compound) and scientific judgment about the toxicity of the other individual compounds in the mixture relative to the index compound. The RPF methodology is described in the Mixtures Guidance (Section 4.4.1) as follows:

The toxicity of the related compounds is predicted from the index compound by scaling the exposure level of each compound by its toxicity relative to the index compound. This scaling factor or proportionality constant is based on an evaluation of the results of a (usually) small set of toxicologic assays or analyses of the chemical structures. This constant is called the RPF and

⁶The coke oven unit risk estimate was reviewed and verified by EPA’s CRAVE work group in 1989. The inhalation potency estimates based on human data for roofing tar and cigarette smoke have not undergone an EPA review similar to that for coke oven emissions, and do not represent Agency consensus values.

represents the relative toxicity with respect to the index compound. For example, if compound A is judged to be one-tenth as toxic as the index compound, i.e., it requires ten times the exposure to cause the same toxicity, then the RPF for compound A is 0.1. If all components of the mixture are assumed to be as toxic as the index compound, then all of the RPFs would be 1.0; conversely, if all of the related compounds have negligible toxicity, all of their RPFs could be assigned a value of 0.

In the RPF approach, an exposure equivalent to the index compound is the product of the measured concentration of the mixture component and the RPF. These dose equivalents are summed to express the mixture exposure in terms of an equivalent exposure to the index compound; risk can be quantified by comparing the mixture's equivalent dose in terms of the index compound to the dose-response assessment of the index compound.

Mathematically, the procedure can be expressed as follows, where C_m is the mixture concentration expressed as index compound; C_k is the concentration of the k^{th} mixture component; and RPF_k is the proportionality constant for toxicity of the k^{th} mixture component relative to the toxicity of the index compound:

$$C_m = \sum_{k=1}^n C_k \times RPF_k$$

Various strategies for evaluating PAH health risk using a relative potency factor approach have been developed. Seven such schemes, all of which use B[a]P as the index chemical, are described in IPCS (1998) and Schoeny et al. (1998). The relative potency factor paradigm adopted in EPA's 1993 Provisional Guidance, which is applied in most assessments of PAH health risk by EPA, was described in a previous section.

V. CHARGE QUESTIONS

EPA's IRIS Program intends to develop an approach (or approaches) to assessing the cancer risk posed by environmental mixtures of PAHs. The ideal situation, but one infrequently supported by the available data, is to base the health risk evaluation of a PAH mixture on dose-response and exposure data for that whole mixture. EPA is interested in developing guidance for those situations when health effects data for the specific PAH-mixture of interest are not available. EPA has reviewed existing approaches to the assessment of cancer risk from exposure to PAH mixtures. The principal approaches are the surrogate approach (based on similar mixtures), comparative potency approach (based on sets of similar mixtures), and relative potency factor approach (based on analysis of component PAHs). Summaries of the approaches are provided in Section IV. EPA recognizes that each approach has certain limitations and that each may have varying applicability to the program offices that regulate PAHs from different sources and environmental media, and use different types of monitoring data. For example, a whole-mixtures approach based on dose-response data for a specific PAH-containing mixture may not be useful in evaluating the health risk associated with soil samples containing PAHs from unknown (or possibly multiple) sources.

Thus, in evaluating the alternative approaches to the cancer assessment of PAH mixtures, workshop participants might wish to consider the following:

- the scientific merits of each approach, and recommendations for revising the approaches consistent with the available toxicological literature; and
- the applicability of each approach for different exposure situations of interest to EPA (e.g., PAHs present in stack emissions from various industrial processes or incomplete combustion sources, PAHs present in emissions to air from diffuse sources such as motor vehicles, or PAHs present in soils or sediments associated with releases from various industrial processes (e.g., wood-preserving operations, coking plants) or atmospheric deposition).

A. Surrogate Approach (Using Data for Sufficiently Similar Mixtures)

The surrogate approach assumes that the cancer risk associated with the PAH component of complex mixtures is proportional to the level of a surrogate PAH (typically B[a]P) in the mixture, and that this assumption holds for mixtures with a similar relative composition of component PAHs. Given this proportionality, the potency of a PAH mixture of interest can be predicted from information on the level of the surrogate (e.g., B[a]P) in that mixture and an estimate of the cancer potency for a similar mixture (expressed as risk per unit amount of surrogate PAH). Two applications of the surrogate approach – OMOE (1997) and Foureman and

Smith (1999) – were presented in Section IV.

Workshop participants may wish to consider the following questions in their deliberations concerning this approach.

1. What are the important issues to consider in developing an application of this approach? In particular, what are important considerations in judging whether a PAH mixture is “sufficiently similar” to a mixture for which dose-response data are available? (e.g., analysis of component PAHs; source categories; stratification by different combinations of fuel type and combustion technology; response in assays of carcinogenic potency; environmental fate resulting in “weathering”).
2. The surrogate approach is intended to characterize risk associated with the PAH component of a complex “sufficiently similar” mixture – not the whole mixture (since no one surrogate PAH can be an indicator for non-PAH components of a complex mixture). Of the available epidemiologic and experimental animal data sets, which toxicity data set (or sets) is (are) most appropriate for estimating the cancer potency of a PAH mixture? Which would not be appropriate?
3. What are some of the limitations that must be recognized in applying this approach? Are there clear examples of when this approach is or is not applicable?
4. Is there a surrogate that can be viewed as appropriate for all carcinogenic PAHs? For a subset of PAHs (e.g., 4- to 7-ring unsubstituted PAHs) only? Rather than a single PAH, is there a group of key PAHs responsible for the majority of toxicity (e.g., PAHs with four or more rings, methylated PAHs) that might be scientifically preferable for use as a surrogate?
5. For what kinds of exposures is this approach applicable? For which situations, taking both exposure and data availability into account, could it be considered the preferred (or only viable) approach?

B. Comparative Potency Approach (Based on Data for a Group of Similar Mixtures)

The comparative potency approach assumes that the relative potency of two carcinogens (or mixtures) in one bioassay system is directly proportional to the relative potency in a second bioassay system (where ideally, one “bioassay” constitutes human data). This assumption was specifically examined for three complex organic emission products from coke ovens, roofing tar and cigarettes, all three of which are PAH-containing mixtures and known human lung carcinogens. For these three emission products, the relative potencies in the mouse skin tumor initiation assay were (within a factor of two) directly proportional to the relative potencies

estimated for these emissions from human lung cancer epidemiological data. From this empirical relationship, a scaling factor can be developed that relates potency in the animal bioassay to human cancer risk. A PAH-containing mixture without epidemiological data can be tested in bioassay systems (e.g., mouse skin tumor initiation assay, mouse lymphoma assay, Ames bioassay, etc.), and the resulting potency can be adjusted by the scaling factor to estimate the potency in humans.

Workshop participants may wish to consider the following points in their deliberations concerning this approach.

1. What are the important issues to consider in developing an application of this approach?
2. How widely applicable is this approach?
3. Are there potential alternatives to the mouse skin tumor initiation assay to use in developing scaling factors?
4. Is it appropriate to relate the response of a PAH-containing mixture in the mouse skin tumor initiation assay to human cancer risk via inhalation and oral exposure? Can we use mouse skin data and PBPK models to extrapolate to inhalation and oral routes of exposure?
5. Are there other examples of complex mixtures that could be used to expand the original data set (cigarette smoke, roofing tar emissions, and coke oven emissions)?
6. For what kinds of exposures is this approach applicable? For which situations, taking both exposure and data availability into account, could it be considered the preferred (or only viable) approach?

C. Relative Potency Factor Approach (Component Approach)

Unlike the two approaches considered above that are based on data for whole mixtures, the relative potency factor (RPF) approach is based on data for individual components of the mixture. Carcinogenic potency is calculated for the index PAH, typically B[a]P, and the toxicity of related PAHs in the mixture is predicted from the index PAH by scaling the exposure level of each PAH by its toxicity relative to the index PAH. Dose equivalents are summed to express the mixture exposure in terms of an equivalent exposure to the index PAH.

EPA's 1993 Provisional Guidance, which is the principal method used by EPA program and regional offices to characterize potential PAH cancer risk for PAHs in various media or for PAHs from mixed sources, is an example of the RPF (component) approach.

Workshop participants may wish to consider the following points in their deliberations

concerning this approach.

1. What are the important issues to consider in developing an application of this approach?
2. What are important factors to consider in determining which PAHs to include in a RPF scheme? (e.g., weight-of-evidence (WOE) of carcinogenicity; chemical structure (QSAR); mode/mechanism of action; availability of certain types of studies, such as *in vivo* cancer bioassays, etc.)⁷
3. Should a RPF scheme take into account evidence that PAHs appear to induce different types of DNA damage via more than one mode of action? If so, how can this be accomplished?
4. B[a]P has traditionally been used as the “index” PAH to which the tumorigenic potency of other PAHs has been related. Does the current science support the continued use of B[a]P as the index for all exposure routes, especially in the context of the more newly discovered highly potent species of PAHs? If so, what data should be used to establish a cancer slope factor (SF) for B[a]P by the oral route? By the inhalation route? By the dermal route?
5. A RPF approach requires that data from a certain assay or assays be used to establish the potency of one PAH relative to another. For example, in developing relative potency estimates, Thorslund & Farrah (1990) relied on data from lung implants in rodents, and to a much lesser extent, complete carcinogenesis in mouse skin. EPA interim relative potency factors are based on skin painting results (EPA, 1993). What about the AJ mouse cancer model of Nesnow and Ross? Goldstein et al. (1998) recommended that lung tumor incidence be used as the most appropriate basis for quantitative risk assessment of coal tars. Which assay systems (including whole animal, *in vitro*) are most relevant for developing RPFs? Should a “joint analysis,” where data sets are combined, be attempted?
6. What are the limitations associated with developing one set of RPFs for all three routes of exposure (i.e., inhalation, oral, and dermal)? What are important considerations in developing RPFs for each route?

⁷Note: EPA’s 1993 Provisional Guidance developed RPFs for seven PAHs only. These RPFs were limited to unsubstituted PAHs with three or more fused aromatic rings that were classified by EPA as probable human carcinogens (B2 carcinogens) based on sufficient data from animal bioassays; substituted PAHs and PAHs with elements other than carbon and hydrogen in their composition were excluded. OMOE, in contrast, developed RPFs for over 200 PAHs.

7. EPA's Provisional Guidance (EPA, 1993) adopted the assumption that the carcinogenicity of individual PAHs is additive. Is the default assumption of dose additivity supported by the current science?

8. For what kinds of exposures is this approach applicable? For which situations, taking both exposure and data availability into account, could it be considered the preferred (or only viable) approach?

D. General Questions

1. EPA's objective is to develop a scientifically supportable approach (or approaches) for assessing the health risk of PAH mixtures that will be useful to EPA program offices. Are there approaches other than the three presented above that should be considered?

2. What is the most appropriate approach for:

- a. PAHs in various media (i.e., soils, sediments, ground water, surface water or air) associated with a known source (e.g., residues from former manufactured gas plants, creosote production, or sludge from public sewage treatment plants)?
- b. PAHs in various media from mixed or unknown sources?
- c. PAHs in various media that were subject to partitioning and weathering?
- d. PAHs in air as a result of emissions from various industrial processes (e.g., the production of coal tar and coke, petroleum catalytic cracking) or incomplete combustion sources (e.g., incinerators)?
- e. PAHs in air as a result of emissions from a diffuse source such as motor vehicles?

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APPENDICES

APPENDIX A
PAHs Included on Selected Monitoring and Assessment Lists

PAH	CAS No.	IRIS (a)	Cal EPA (b)	WHO EHC (1998) (c)	ATSDR Tox. Profile (1995) (d)	TCL (Priority Pollutant) List (e)	Superfund Site TIC (f)
Acenaphthene	83-32-9	✓		✓	✓	✓	
Acenaphthylene	208-96-8	✓		✓	✓	✓	
Anthanthrene (dibenzo[def,mno] chrysene)	191-26-4			✓			✓
Anthracene	120-12-7	✓		✓	✓	✓	
Benzo[a]fluorene	238-84-6			✓			✓
Benzo[a]pyrene	50-32-8	✓	✓	✓	✓	✓	
Benzo[b]fluoranthene	205-99-2	✓	✓	✓	✓	✓	
Benzo[b]fluorene	243-17-4			✓			✓
Benzo[c]phenanthrene	195-19-7			✓			
Benzo[e]pyrene	192-97-2			✓	✓		✓
Benzo[ghi]fluoranthene	203-12-3			✓			
Benzo[ghi]perylene	191-24-2	✓		✓	✓	✓	
Benzo[j]fluoranthene	205-82-3		✓	✓	✓		✓
Benzo[k]fluoranthene	207-08-9	✓	✓	✓	✓	✓	
Benz[a]anthracene	56-55-3	✓	✓	✓	✓	✓	
Benz[a]anthracene, 7,12-dimethyl-	57-97-6		✓				✓
Chrysene	218-01-9	✓	✓	✓	✓	✓	
Chrysene, 5-methyl	3697-24-3		✓	✓			
Coronene	191-07-1			✓			
Cyclopenta[cd]pyrene	27208-37-3			✓			
Cyclopenta[def] phenanthrene, C2-4H-							✓
Cyclopenta[def] phenanthrene, C3-4H-							✓
Cyclopenta[def] phenanthrene, C4-4H-							✓

PAH	CAS No.	IRIS (a)	Cal EPA (b)	WHO EHC (1998) (c)	ATSDR Tox. Profile (1995) (d)	TCL (Priority Pollutant) List (e)	Superfund Site TIC (f)
Cyclopenta[def] phenanthrene, C5-4H-							✓
Dibenzo[ae]pyrene	192-65-4		✓	✓			✓
Dibenzo[ah]pyrene	189-64-0		✓	✓			
Dibenzo[ai]pyrene	189-55-9		✓	✓			
Dibenzo[al]pyrene	191-30-0		✓	✓			
Dibenz[ah]anthracene	53-70-3	✓	✓	✓	✓	✓	
Dibenz[ah]acridine	226-36-8		✓				
7H-Dibenzo[cg]carbazole	194-59-2		✓	✓			
Dibenz[aj]acridine	224-42-0		✓				
Dinitropyrenes, 1,6-	42397-64-8		✓				
Dinitropyrene, 1,8-	42397-65-9		✓				
Fluoranthene	206-44-0	✓		✓	✓	✓	
Fluorene	86-73-7	✓		✓	✓	✓	
Indeno[1,2,3-cd]pyrene	193-39-5	✓	✓	✓	✓	✓	
Methylcholanthrene, 3-	56-49-5		✓				
Naphthalene	91-20-3	✓		✓		✓	
Naphthylene, 1-methyl	90-12-0						✓
Naphthalene, 2-methyl						✓ [on TCL, but not PP]	✓
Nitroacenaphthene, 5-	602-87-9		✓				
Nitrochrysene, 6-	7496-02-8		✓				
Nitrofluorene, 2-	607-57-8		✓				
Nitropyrene, 1-			✓				
Nitropyrene, 4-	57835-92-4		✓				
Perylene	198-55-0			✓			
Phenanthrene	85-01-8	✓		✓	✓	✓	
Phenanthrene, 1-methyl	832-69-9			✓			
Pyrene	129-00-0	✓		✓	✓	✓	

PAH	CAS No.	IRIS (a)	Cal EPA (b)	WHO EHC (1998) (c)	ATSDR Tox. Profile (1995) (d)	TCL (Priority Pollutant) List (e)	Superfund Site TIC (f)
Triphenylene	217-59-4			✓			
<p>(a) Included in EPA's Integrated Risk Information System (IRIS) database.</p> <p>(b) Included among the PAHs for which California EPA has derived potency equivalency factors (Cal EPA, 1999).</p> <p>(c) Included in the International Programme on Chemical Safety (IPCS)/WHO 1998 Environmental Health Criteria document for selected non-heterocyclic PAHs on the basis of the availability of relevant data on toxicological end-points and/or exposure.</p> <p>(d) Included in the Agency for Toxic Substances and Disease Registry toxicological profile for PAHs (ATSDR, 1995) on the basis of the availability of reliable health-based and environmental information.</p> <p>(e) Included on the Target Compound List (TCL) – the list of organic compounds for which monitoring is routinely performed at Superfund and other waste sites. All but one of the TCL compounds are also priority pollutants.</p> <p>(f) Reported as a tentatively identified compound (TIC) at least 10 times in soil samples collected between 2/1/1995 and 12/31/2000 at predominately Superfund sites.</p>							

APPENDIX B

Surrogate Approach Developed by Foureman and Smith (1999)

Dr. Gary Foureman of EPA's National Center for Environmental Assessment and Dr. Roy Smith of EPA's Office of Air Quality Planning and Standards developed an approach for assessing the health risk of PAH mixtures in air using data for a sufficiently similar PAH mixture that is similar to the standard surrogate approach but also includes a procedure for evaluating whether or not differences in composition are likely to be toxicologically significant. The approach assumes that all PAH-containing mixtures in air are essentially the same as a mixture of coal tar pitch (CTP) – a PAH mixture of known composition and carcinogenic potency, and that the concentrations of B[a]P and other detected airborne PAHs are simply dilutions of CTP. This application of a surrogate approach using data for sufficiently similar mixtures is presented in Foureman and Smith (1999).

In applying this approach, an inhalation unit risk (UR) of $1 \times 10^{-4} (\mu\text{g CTP}/\text{m}^3)^{-1}$ was obtained for CTP based on lung tumor formation in female Wistar rats exposed to a CTP aerosol (Heinrich et al., 1994). The actual concentration of individual PAHs in CTP was obtained from the Heinrich et al. (1994) study (see Table B-1).

TABLE B-1				
Information Applied in the Surrogate Approach of Foureman and Smith (1999)				
PAH of Concern	PAHs in CTP Used in the Heinrich et al. Bioassay (ng PAH/m³ in 1 μg CTP/m³)	PAH Conc. in ARM 1597		RPF
		Absolute Conc. (ng/μg)	Conc. Relative to B[a]P	
Benzo[a]pyrene	17.7	95.8	1	1
Benz[a]anthracene	22.3	98.6	1	0.1
Benzo[b]fluoranthene	8.8	66	0.7	0.1
Benzo[k]fluoranthene	7	43	0.4	0.1
Indeno[1,2,3-cd]pyrene	11.2	60.2	0.6	0.1
Chrysene	22.7	71.7	0.8	0.01
Dibenz[ah]anthracene	--	--	–	5

Assuming B[a]P (or some other PAH) is present in the PAH mixture of interest in the same proportion as it is in CTP (i.e., that the airborne PAHs in the mixture of interest occur as dilutions of CTP), the carcinogenic risk of the environmental mixture can be calculated by ratio. For example, given a B[a]P concentration in an environmental mixture of 3 ng B[a]P/m³, the incremental cancer risk associated with the mixture would be estimated as follows:

$$\frac{17.7 \text{ ng BaP} / \text{m}^3}{1 \text{ } \mu\text{g CTP} / \text{m}^3} = \frac{3 \text{ ng BaP} / \text{m}^3}{x}$$

$$x = 0.17 \text{ } \mu\text{g CTP} / \text{m}^3$$

$$\text{Risk} = 0.17 \text{ } \mu\text{g CTP} / \text{m}^3 \times [1 \times 10^{-4} (\text{ } \mu\text{g CTP} / \text{m}^3)^{-1}]$$

The above procedure holds only if the environmental mixture of interest is “sufficiently similar” to CTP, the reference mixture. This determination is made by comparison of the mixture of interest to the composition of PAHs in a standard coal tar material. The National Institute of Standards and Technology has developed and analyzed a Standard Reference Material (SRM) 1597, Complex Mixture of Polycyclic Aromatic Hydrocarbons from Coal Tar. This mixture is described as a natural combustion-related mixture of PAHs isolated from a coal tar. [The distribution of PAHs in the CTP used in the Heinrich et al. (1994) bioassay closely resembles the distribution in SRM 1597.] The composition of SRM 1597 for six PAHs of concern is shown in Table B-1. Concentrations are presented both as the absolute concentration in SRM 1597 and as the concentration relative to B[a]P. The concentration of individual PAHs in the mixture of interest, also expressed relative to B[a]P, can be compared to the relative PAH concentrations in SRM 1597 to reach a judgment about the similarity of the mixtures.

To determine whether differences in composition are likely to be of toxicological significance, qualitative evaluations based on the relative potency factors (RPFs) from Nisbet and LaGoy (1992) are performed.⁸ For example, compositional differences in chrysene, with a small RPF, would not be expected to significantly alter the potency of the mixture relative to the reference mixture. In contrast, compositional differences in benz[a]anthracene, with a RPF of 1, might alter the mixture potency.

⁸ Note that Nisbet and LaGoy (1992) used the term TEF (toxicity equivalence factor), but because of their limited scope of application these factors are more properly termed RPFs according to current EPA guidance.

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