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DEVELOPMENT OF A RELATIVE POTENCY FACTOR (RPF) APPROACH FOR POLYCYCLIC AROMATIC HYDROCARBON (PAH) MIXTURES

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency's (U.S. EPA's) Integrated Risk Information System (IRIS) Program is releasing for scientific review a relative potency factor (RPF) approach for polycyclic aromatic hydrocarbon (PAH) mixtures as one approach for assessing cancer risk from exposure to PAH mixtures. The RPF analysis under review is not a reassessment of individual PAH carcinogenicity, but rather provides a cancer risk estimate for PAH mixtures by summing doses of component PAHs after scaling the doses (with RPFs) relative to the potency of an index PAH (i.e., benzo[a]pyrene). The cancer risk is then estimated using the dose-response curve for the index PAH. RPFs for seven individual PAHs were developed in the U.S. EPA (1993) *Provisional Guidance for Quantitative Risk Assessment of PAHs* (*Provisional Guidance*) and are utilized extensively within U.S. EPA program offices and other regulatory agencies. The RPF analysis provided in the current report includes more recent data and an analysis of both tumorigenicity and genotoxicity data for PAHs.

The Supplemental Guidance for Conducting Health Risk Assessment of Chemical Mixtures (U.S. EPA, 2000) indicates that approaches based on whole mixtures are preferred to component approaches, such as the RPF approach. Risk assessment approaches based on toxicity evaluations of whole mixtures inherently address specific interactions among PAHs and account for the toxicity of unidentified components of PAH mixtures. They also do not require assumptions regarding the toxicity of individual components (e.g., dose additivity or response additivity). While whole mixture assessment is preferred, there are challenges associated with using these approaches. There are very few toxicity data available for whole PAH mixtures and, in most cases, chemical analyses of the composition of mixtures are limited. In addition, PAH-containing mixtures tend to be very complex; the composition of these mixtures appears to vary across sources releasing these mixtures to the environment and in various environmental media in which they occur. For these reasons, a whole mixtures approach may not always be practicable for risk assessment purposes. This report provides recommendations for development of the RPF approach for PAH mixtures health risk assessment and includes:

(1) A rationale for recommending an RPF approach (Chapter 2);

(2) A summary of previous approaches for developing the RPF approach for PAHs (Chapter 3);

(3) An evaluation of the carcinogenicity of individual PAHs (Chapter 4);

(4) Methods for dose-response assessment and individual study RPF calculation (Chapter 5);

(5) Selection of PAHs for inclusion in the RPF approach (Chapter 6);

(6) Derivation of RPFs for selected PAHs (Chapter 7); and

(7) Characterization of strengths, weaknesses, and uncertainties associated with the RPF approach to PAH cancer risk assessment (Chapter 8).

The RPF approach involves two key assumptions related to the application of a dose-additivity model: (1) a imilar toxicological action of PAH components in the mixture; and (2) interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment. Mechanistic studies indicate that the mutagenic and tumor-initiating activity of carcinogenic PAHs requires metabolic activation to reactive intermediates (e.g., dihydrodiol epoxides, quinones, radical cations), which covalently modify deoxyribonucleic acid (DNA) targets resulting in mutation, and that tumor promotion and progression phases may involve parent compound binding to the Ah receptor (AhR) and subsequent alterations of gene expression or a cell proliferation response to metabolite cytotoxicity (see Section 2.4, Similarities in Mode of Carcinogenic Action for PAHs, and Figure 2-3, Overview of the proposed key events in the mode of action for PAH carcinogenicity). As such, there is evidence that an assumption of a similar toxicological action is reasonable; however, the carcinogenic process for individual PAHs is likely related to some unique combination of multiple molecular events resulting from the formation of several reactive species. The second assumption of no interactions at low levels of exposure is also reasonable, but cannot be conclusively demonstrated in experimental systems (see Section 2.8, Dose Additivity of PAHs in Combined Exposures). Use of the RPF approach assumes that doses of component chemicals that act in a similar manner can be added together, after scaling the potencies relative to the index chemical. The assumptions of toxicological similarity and no interaction effects at low environmental exposure levels that are inherent in the dose-additivity model are generally supported by the experimental data for PAHs (see Sections 2.4 and 2.7).

Several approaches have been used previously for the determination of RPFs for PAHs (see Chapter 3). In the published literature, RPF values were proposed in at least one analysis for a total of 27 PAHs (see Table 3-1). Because these approaches generally relied on similar bioassay data and modeling methods, the resulting RPF values are considered comparable for most PAHs across analyses.

There is a large PAH database on carcinogenicity in animal bioassays, genotoxicity in various test systems, and bioactivation to tumorigenic and/or genotoxic metabolic intermediates. The RPF analysis presented here includes only unsubstituted PAHs with three or more fused aromatic rings containing only carbon and hydrogen atoms, because these are the most widely studied members of the PAH chemical class. The study types that were considered most useful for RPF derivation were rodent carcinogenicity bioassays (all routes) in which one or more PAH was tested at the same time as benzo[a]pyrene. In addition, in vivo and in vitro data for cancer-related endpoints in which one or more PAH and benzo[a]pyrene was tested simultaneously were

obtained, including studies on the formation of DNA adducts, mutagenicity, chromosomal aberrations, sister chromatid exchange frequency, aneuploidy, DNA damage/repair/ recombination, unscheduled DNA synthesis, and cell transformation. Although it would be possible to calculate RPFs from studies where a PAH and benzo[a]pyrene were tested by the same laboratory using the same test system but at different times, this approach was not considered because it could introduce differences in the dose-response information that are unrelated to the chemical (e.g., variability associated with laboratory environment conditions, animal handling, food supply, etc.). Thus, studies in which benzo[a]pyrene was not tested simultaneously with another PAH were not considered in the RPF calculations.

Studies of AhR binding/activation were not considered for use in deriving RPFs because there does not appear to be a clear relationship between affinity for the AhR and carcinogenic potency. For example, highly mutagenic fjord-region PAHs are potent carcinogens despite exhibiting lower AhR affinity (reviewed by Bostrom et al., 2002). Likewise, some PAHs that strongly activate the AhR, such as benzo[k]fluoranthene (Machala et al., 2001), are only weakly carcinogenic. In addition, some studies have demonstrated the formation of DNA adducts in the liver of AhR knock-out mice following intraperitoneal or oral exposure to benzo[a]pyrene (Sagredo et al., 2006; Uno et al., 2006; Kondraganti et al., 2003), indicating that Ah responsiveness is not strictly required for metabolic activation and genotoxicity. These findings suggest that there may be alternative (i.e., non-AhR-mediated) mechanisms of benzo[a]pyrene activation in the mouse liver, and that AhR affinity would not be a good predictor of carcinogenic potency. Also, several studies indicate that AhR-mediated CYP1A1 induction potency does not correlate well with carcinogenic potency. These studies compared CYP1A1 induction potency for several PAHs using assays to measure ethoxyresorufin O-deethylase (EROD) activity, CYP1A1 protein, and messenger ribonucleic acid (mRNA) levels, or chemical-activated luciferase reporter gene expression (Bosveld et al., 2002; Machala et al., 2001; Bols et al., 1999; Till et al., 1999; Willett et al., 1997).

Several study types were excluded from the database because they did not provide carcinogenicity or cancer-related endpoint information for individual PAHs. These include biomarker studies measuring DNA adducts in humans, studies of PAH metabolism, and studies of PAH mixtures. Although these studies contain important information on human exposure to PAH mixtures and the mode of action for PAH toxicity, they generally do not contain dose-response information that would be useful for calculation of RPF estimates.

A database of primary literature relevant to the RPF approach for PAHs was developed by performing a comprehensive review of the scientific literature dating from the 1950s through 2009 on the carcinogenicity and genotoxicity of PAHs. The search identified over 900 individual publications for a target list of 74 PAHs (see Table 2-1) that have been identified in environmental media or for which toxicological data are available. Review of these publications

resulted in the identification of more than 600 papers that included carcinogenicity or cancer-related endpoint data on at least one PAH and benzo[a]pyrene tested at the same time.

References in the PAH database were sorted into the following major categories: cancer bioassays, in vivo studies of cancer-related endpoints, and in vitro studies of cancer-related endpoints. These categories were further sorted by route (for bioassays) or by endpoint (for cancer-related endpoints). Each study was reviewed, and critical study details were extracted into tables for each individual endpoint (see Chapter 4). The tables also include an initial determination of whether the data from each study meet selection criteria for use in the RPF analysis. Studies with data on selected PAHs and benzo[a]pyrene were considered for RPF determination, even if a particular PAH has not been classified by U.S. EPA or International Agency for Research on Cancer (IARC) as a carcinogen. Studies were included in the analysis if the following selection criteria were met:

- Benzo[a]pyrene was tested simultaneously with another PAH;
- A statistically increased incidence of tumors was observed with benzo[a]pyrene administration, compared with control incidence;
- Benzo[a]pyrene produced a statistically significant change in a cancer-related endpoint finding;
- Quantitative results were presented;
- The carcinogenic response observed in either the benzo[a]pyrene- or other PAH-treated animals at the lowest dose level was not saturated (i.e., tumor incidence at the lowest dose was <90%), with the exception of tumor multiplicity findings; and
- There were no study quality concerns or potential confounding factors that precluded use (e.g., no concurrent control, different vehicles, strains, etc. were used for the tested PAH and benzo[a]pyrene; use of cocarcinogenic vehicle; PAHs of questionable purity; unexplained mortality in treated or control animals).

If the above criteria were met, studies were selected for use in the analysis regardless of whether positive or nonpositive results were reported. Studies with positive findings were used for calculation of RPFs. Studies with nonpositive findings were used in a weight of evidence evaluation to select PAHs for inclusion in the RPF approach (see Section 6.1).

Dose-response data were extracted from studies with positive findings that met selection criteria. For studies that reported results graphically, individual data points were extracted using digitizing software. In all, over 300 data sets were extracted, reflecting dose-response data from at least one study for 51 of the 74 PAHs included in the analysis. All of the extracted data are presented in Appendix C of this report.

While tumor multiplicity data from tumor bioassays are not generally used to estimate *cancer potency*, these data were included in the dose-response assessment in order to determine whether they could serve as a reliable measure of *relative cancer potency*. Several bioassays reported data on both tumor incidence and tumor number, providing information that was later used to compare relative potencies estimated from these two endpoints. Statistical analyses were performed on tumor bioassay data to determine whether the tumor incidence or multiplicity observed at a particular dose represented a statistically significant increase over controls. If statistical analyses were not described in the original report, incidence data were analyzed using Fisher's exact test and the Cochran-Armitage trend test. Positive findings were indicated by a significant ($p < 0.05$) difference for at least one dose group by comparison to control (in Fisher's exact or an equivalent test) or a significant dose-response trend (Cochran-Armitage or equivalent) for multidose studies. For tumor bioassay data reported as tumor count, a t-test was conducted (when variance data were available) to determine whether the count was significantly different from control ($p < 0.05$). The results of the statistical analyses are shown with the dose-response data in Appendix C. Statistical analyses of the cancer-related endpoint data were not conducted; the study author's conclusions as to response (positive or nonpositive) was used.

Chapter 5 describes the methods used for both the dose-response assessment and the RPF calculation in detail. The general equation for estimating an RPF was the ratio of the slope of the dose-response curve for the subject PAH to the slope of the dose-response curve for benzo[a]pyrene. For bioassay data, tumor incidences were modeled using the multistage model within the U.S. EPA Benchmark Dose (BMD) Software (Version 1.3.2). For cancer-related endpoint data in quantal form, this model was also used; for continuous data (either tumor multiplicity or cancer-related endpoint data), the simplest continuous model (linear) within the software was applied. Whenever the data allowed, benchmark response (BMR) values of 10% for quantal data and 1 standard deviation (SD) from the control value for continuous data were used to calculate the slope by linear extrapolation to the origin for consistency across data sets. Alternative BMR values were used in select instances, as described in Section 5.3. For data sets that included only a single dose, or those for which no model fit was achieved with the selected models, a point estimate RPF[1] was calculated. As Table G-2 indicates, final RPFs for five compounds (benz[a]anthracene, benz[b,c]aceanthrylene, benz[j]aceanthrylene, dibenzo[a,h]pyrene, and naphtho[2,3-e]pyrene) are based exclusively on point estimates; the remaining 19 PAHs had at least one dataset that could be modeled (see Appendix G).

The RPFs calculated from individual studies for each PAH were used in a weight of evidence evaluation to select PAHs for inclusion in the RPF approach (see Chapter 6) and in the derivation of a final RPF for each compound (Chapter 7). The selection of PAHs to be included

[1]For the purpose of this report, the term "point estimate RPF" is used to describe an RPF calculated from a single point on the dose-response curve for both the PAH of interest and benzo[a]pyrene. This term distinguishes the RPF from one calculated using a BMD modeling result from multidose data.

in the RPF approach began with an evaluation of whether the available data were adequate to assess the carcinogenicity of each compound. At least one RPF value was calculated for each of 51 PAHs. For 16 of these compounds, only a single RPF value derived from an in vitro cancer-related endpoint (primarily mutagenicity assays) was available (see Table 6-1). Due to the limited data available for these 16 compounds, no further evaluation of these PAHs was conducted, and they were not selected for inclusion in the RPF approach.

For the remaining 35 PAHs, a weight of evidence evaluation (see Figure 6-1) was conducted to assess the evidence that each PAH could induce a carcinogenic response. For the purposes of this analysis, PAHs were assumed to be carcinogenic due to toxicological similarity to the indicator compound, benzo[a]pyrene. The weight of evidence approach was developed to determine whether the available information for each PAH was adequate for inclusion in the RPF approach. If the data were not considered adequate, then the PAH was excluded. In vivo tumor bioassays that included benzo[a]pyrene were given the greatest weight in assessing the carcinogenicity of a given PAH; data from other bioassays and cancer-related endpoint studies were used to supplement the weight of evidence when the bioassay data that included benzo[a]pyrene were conflicting or nonpositive. Structural alerts for PAH carcinogenicity or mutagenicity (as defined in Section 2.5 as the presence of a classic bay or fjord region in a PAH containing at least four benzene rings) were noted in the evaluation for each PAH, but were not used explicitly in the weight of evidence evaluation.

The weight of evidence evaluation (Chapter 6) indicated that the available data were adequate to determine that 24 of the 35 PAHs were carcinogenic, that 3 PAHs (anthracene, phenanthrene, and pyrene) were not carcinogenic, and that data were inadequate to evaluate the carcinogenicity for 8 PAHs. The eight PAHs with inadequate data were excluded from the RPF approach. For the three PAHs for which there were sufficient data to conclude that they were not carcinogenic (i.e., robust nonpositive tumor bioassay data and cancer-related endpoint data), a final RPF of zero was recommended. While there is little quantitative difference between selecting a final RPF of zero for a given PAH and excluding that PAH from the RPF approach, this is an important distinction for uncertainty analysis. There is substantial uncertainty in the risk associated with PAHs that are excluded from the RPF approach due to inadequate data; these compounds could be of low or high potency. However, for PAHs with an RPF of zero, there is evidence to suggest that these compounds are not carcinogenic, and the uncertainty associated with the cancer risk for these compounds is markedly reduced.

For each of the remaining 24 compounds, a final nonzero RPF was derived. A number of options were considered for deriving an RPF from among the numerous values calculated for each individual PAH. These options included: prioritizing bioassay RPFs from different exposure routes based on environmentally relevant routes; prioritizing bioassay RPFs based on target organs considered relevant to human susceptibility to PAH carcinogenesis; prioritizing RPFs based on quality of the underlying study; prioritizing cancer-related endpoints by their

correlation with bioassay potency (i.e., ability to predict bioassay potency); and aggregating RPFs across all bioassays, across all cancer-related endpoints, or across all endpoints. In the end, it was concluded that the available data did not provide a clear scientific basis for prioritizing RPFs except for a preference for bioassay data over cancer-related endpoints. As a consequence, final RPFs were derived from bioassay data for any PAH that had at least one RPF based on a bioassay.

For each carcinogenic PAH with bioassay data, the average RPF was calculated from bioassays with positive results. For those PAHs that did not have an estimated RPF based on a bioassay, but for which the weight of evidence evaluation indicated a carcinogenic response (e.g., dibenz[a,c]anthracene), the final RPF was calculated from all cancer-related endpoint studies with positive results. In both cases, nonpositive results were not included in the calculation. The final RPF for each PAH was reported to one significant figure. The range of RPF values was also reported. Presenting the RPFs in this manner provides an average and maximum estimate for each PAH that has data from multiple studies.

Several options were considered for the determination of final RPFs (e.g., arithmetic mean, geometric mean, weighted average, maximum, or order of magnitude estimates). The arithmetic mean and range were chosen as a simple approach to describing the calculated RPF values available for each PAH. Other estimates were not considered appropriate due to the limited number of RPF values calculated for most PAHs and the variability in the RPF estimates. Most PAHs (18/24, 73%) had ≤3 calculated RPF values and the range of RPF values was greater than an order of magnitude for several compounds (7/24 PAHs). The variability in RPF estimates is likely due to differences in study design parameters (e.g., route, species/strain, exposure duration, exposure during sensitive time periods, initiation versus promotion and complete carcinogenesis protocols, tumor incidence versus multiplicity reporting) and dose-response methods (modeled versus point estimates). Calculation of a weighted average was not possible because there is no clear scientific rationale for choosing among study types or tumor data outcomes. Providing order of magnitude estimates, as has been previously done for estimating RPFs for PAHs, was not considered to be superior to calculating simple means. Including the range in the estimated RPFs was considered to be informative to the user for characterizing uncertainty.

Once a final RPF was derived for a given PAH, the resulting value was assigned a relative confidence rating of *high, medium,* or *low confidence*. The relative confidence rating characterized the nature of the database upon which the final RPF was based. Confidence rankings were based on the robustness of the database. For final RPFs based on tumor bioassay data, confidence ratings considered both the available tumor bioassays and the availability of supporting data for cancer-related endpoints. The most important factors that were considered included the availability of in vivo data and whether multiple exposure routes were represented. Other database characteristics that were considered included the availability of more than one in

vivo study, and whether effects were evident in more than one sex or species. *Very low relative confidence* was reserved for final RPFs based on cancer-related endpoint data only (e.g., dibenz[a,c]anthracene). An RPF of zero was only applied if the data implied *high* or *medium relative confidence*.

Table 1 shows the average RPFs based on tumor bioassay data with their associated range and relative confidence ratings, and an overview of the tumor bioassay database (total number of studies, exposure routes tested, species tested, and sexes tested) for each PAH. Table 2 shows the average RPF for dibenz[a,c]anthracene, the only RPF based on cancer-related endpoint data, with its associated range, relative confidence rating, and an overview of the database for this compound.

Table 1. PAHs with final RPFs based on tumor bioassay data

PAH	Average RPF	Range of RPFs	Relative confidence	Number of datasets	Exposure routes tested	Species tested	Sexes tested
Anthanthrene	0.4	0.2–0.5	Medium	2	Dermal, lung implantation	Mouse, rat	Female
Anthracene	0	0	Medium[a]	1 (nonpositive)	Dermal	Mouse	Female
Benz[a]anthracene	0.2	0.02–0.4	Medium	3	Dermal, intraperitoneal	Mouse	Female, male
Benz[b,c]aceanthrylene, 11H-	0.05	0.05	Low	1	Dermal	Mouse	Female
Benzo[b]fluoranthene	0.8	0.1–2	High	5	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Benzo[c]fluorene	20	1–50	Medium	2	Oral, intraperitoneal	Mouse	Female
Benz[e]aceanthrylene	0.8	0.6–0.9	Low	2	Dermal	Mouse	Female, male
Benzo[g,h,i]perylene	0.009	0.009	Low	1	Lung implantation	Rat	Female
Benz[j]aceanthrylene	60	60	Low	1	Intraperitoneal	Mouse	Male
Benzo[j]fluoranthene	0.3	0.01–1	High	5	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Benzo[k]fluoranthene	0.03	0.03–0.03	Medium	2	Dermal, lung implantation	Mouse, rat	Female
Benz[l]aceanthrylene	5	4–7	Low	2	Dermal	Mouse	Female, male
Chrysene	0.1	0.04–0.2	High	7	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Cyclopenta[c,d]pyrene	0.4	0.07–1	Medium	5	Dermal, intraperitoneal	Mouse	Female, male
Cyclopenta[d,e,f]chrysene, 4H-	0.3	0.2–0.5	Low	2	Dermal	Mouse	Female
Dibenzo[a,e]fluoranthene	0.9	0.7–1	Low	2	Dermal	Mouse	Female
Dibenzo[a,e]pyrene	0.4	0.3–0.4	Low	2	Dermal	Mouse	Female
Dibenz[a,h]anthracene	10	1–40	High	3	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Dibenzo[a,h]pyrene	0.9	0.9	Low	1	Dermal	Mouse	Female
Dibenzo[a,i]pyrene	0.6	0.5–0.7	Low	2	Dermal	Mouse	Female
Dibenzo[a,l]pyrene	30	10–40	Medium	3	Dermal, intraperitoneal	Mouse	Female, male
Fluoranthene	0.08	0.009–0.2	Low	5	Intraperitoneal	Mouse	Female, male
Indeno[1,2,3-c,d]pyrene	0.07	0.07	Low	1	Lung implantation	Rat	Female
Naphtho[2,3-e]pyrene	0.3	0.3	Low	1	Dermal	Mouse	Female
Phenanthrene	0	0	High	3 (nonpositive)	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Pyrene	0	0	Medium	7 (nonpositive)	Dermal, intraperitoneal	Mouse	Female, male

[a]Reflects availability of data from anthracene exposure via another exposure route in a study that did not include benzo[a]pyrene.

Table 2. PAHs with final RPFs based on cancer-related endpoint data (no tumor bioassay data available)

PAH	Average RPF	Range of RPFs	Relative confidence	Types of studies	Multiple dose studies
Dibenz[a,c]anthracene	4	0.04–50	Very low	Total = 14 studies One in vivo DNA adduct Six in vitro bacterial mutagenicity One in vitro mammalian mutagenicity One in vitro morphological/ malignant transformation Three in vitro DNA damage Two in vitro DNA adducts	Total = 6 studies Four in vitro bacterial mutagenicity One in vitro DNA damage One in vitro DNA adduct

The cancer risk for a PAH mixture of concern is determined by multiplying the benzo[a]pyrene equivalent dose or concentration by the benzo[a]pyrene cancer toxicity value (e.g., oral slope factor). Benzo[a]pyrene equivalents are calculated by multiplying the concentration (or dose) of a particular PAH component in the mixture by its RPF. The proposed RPF approach considers each of the bioassay types used for RPF derivation to be equivalent for the purpose of determining relative potency to benzo[a]pyrene.

According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), benzo[a]pyrene is carcinogenic by a mutagenic mode of action. A common mutagenic mode of action for other carcinogenic PAHs is hypothesized based on information available for the indicator chemical, benzo[a]pyrene (U.S. EPA, 2005b). When assessing PAH cancer risks for lifestages under 16 years of age, or for lifetime exposures that include early-life exposures, the RPF values should be applied with specific exposure information to the benzo[a]pyrene cancer risk estimates including adjustment for early-life susceptibility, through the application of age-dependent adjustment factors (ADAFs).

A description of uncertainties and limitations is crucial to interpretation of the RPF approach for PAH mixtures risk assessment (see Chapter 8). Many of the general uncertainties related to chemical-specific risk assessment are also applicable to the proposed RPF approach for PAHs (e.g., appropriateness of animal models, low-dose and interspecies extrapolation, variability within the human population). Use of a component-based approach for mixtures risk assessment leads to additional uncertainties related to adequate characterization of the mixture and the potential interactions that may occur between individual components within the mixture (i.e., PAHs and other chemicals). The RPF approach is limited by the small number of PAHs for which there are analytical chemistry and toxicology data, and thus may result in underestimation of actual cancer risks from complex PAH mixtures. There are uncertainties and limitations related to the size and nature of the PAH database, the human relevance of animal data,

assumptions regarding mode of action and dose additivity, and cross-route extrapolation. Specific uncertainties that are related to dose-response assessment (i.e., calculation of RPFs) and the selection of single RPF values for each PAH are also discussed in Chapter 8.

In summary, the current analysis represents a significant improvement upon the previous component-based approaches for PAH mixtures risk assessment. One of the most important improvements is the consideration of data from a comprehensive review of the scientific literature dating from the 1950s through 2008 on the carcinogenicity and genotoxicity of PAHs. The search identified over 900 individual publications for a target list of 74 PAHs that have been identified in environmental media and for which toxicological data are available. Review of these publications resulted in the identification of more than 600 papers that included carcinogenicity or cancer-related endpoint data on at least one PAH and benzo[a]pyrene tested at the same time. Dose-response data were extracted, and RPFs from individual studies were calculated from over 300 data sets representing 51 individual PAHs. For 35 compounds, a weight of evidence evaluation was conducted to select PAHs for inclusion in the RPF approach; data were inadequate to conduct such an evaluation for the remaining 16 compounds. A final RPF was derived for each PAH based on tumor bioassay data (if available) or cancer-related endpoint data (if no tumor bioassay RPFs were available). Final RPFs were derived for 27 PAHs, significantly increasing the number of PAHs that can be addressed through this approach. Each RPF was assigned a relative confidence rating reflecting the nature of the tumor bioassay or cancer-related endpoint database that was used to derive the final RPF for that PAH.

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LIST OF ABBREVIATIONS AND ACRONYMS*

ADAF	age-dependent adjustment factor
AEL	acceptable exposure level
Ah	aryl hydrocarbon
AhR	Ah receptor
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BMD	benchmark dose
BMR	benchmark response
CASRN	Chemical Abstract Service Registry Number
CCRIS	Chemical Carcinogenesis Research Information System
CHO	Chinese hamster ovary
CYP	cytochrome P450
dG	deoxyguanosine
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSSTOX	Distributed Structure-Searchable Toxicity
EOPP	estimated order of potential potency
EROD	ethoxyresorufin O-deethylase
HPRT	hypoxanthine-guanine phosphoribosyl transferase gene
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
MGP	manufactured gas plant
MN-PCE	micronuleated polychromatic erythrocyte
mRNA	messenger ribonucleic acid
MVK	Moolgavkar-Venson-Knudsen two-stage model
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment, California EPA
PAC	polycyclic aromatic compound
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCR	polymerase chain reaction
PEF	potency equivalency factor
QSAR	quantitative structure activity relationship
RNA	ribonucleic acid
RPF	relative potency factor
RTD	relative tumor dose
SD	standard deviation
TK	thymidine kinase locus
TIDAL	time-integrated DNA adduct level
TEF	toxicity equivalency factor
TK	thymidine kinase
TPA	12-O-tetra-decanoylphorbol-13-acetate
TSCATS	Toxic Substances Control Act Test Submissions

U.S. EPA	U.S. Environmental Protection Agency
WHO	World Health Organization

*Abbreviations for PAH chemical names are provided in Table 2-1.

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1. BACKGROUND FOR THE DEVELOPMENT OF A RELATIVE POTENCY FACTOR APPROACH FOR PAH MIXTURES HEALTH ASSESSMENT

This analysis focuses on the relative potency factor (RPF) approach that is based on component PAHs in PAH mixtures. U.S. EPA held a peer consultation workshop to outline some of the important issues related to approaches for PAH mixtures risk assessment. These issues are discussed in *Peer Consultation Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment* (U.S. EPA, 2002) and the accompanying discussion document. Health assessments for 15 unsubstituted, nonheterocyclic polycyclic aromatic hydrocarbons (PAHs) with three or more rings are currently entered on EPA's IRIS database. Benzo[a]pyrene is the only PAH for which there are robust animal dose-response data for the oral, dermal, and inhalation routes.

In 1993, U.S. EPA published the *Provisional Guidance for Quantitative Risk Assessment of PAHs* (*Provisional Guidance*). The *Provisional Guidance* recommended estimated orders of potential potency (EOPP) for individual PAHs that could be used in a component-based approach to PAH mixtures risk assessment. The *Provisional Guidance* recommended EOPPs for seven PAHs categorized as Group B2 (probable human carcinogens) under the 1986 U.S. EPA Cancer Guidelines: benzo[a]pyrene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene (U.S. EPA, 1993). The current analysis extends the 1993 *Provisional Guidance* and provides recommendations for further development of this approach to PAH mixtures risk assessment. The assessment includes the following:

(1) A rationale for recommending an order of potency, or RPF, approach;

(2) A summary of previous approaches for developing the RPF approach for PAHs;

(3) Identification of individual carcinogenic PAHs that could be included in the RPF approach;

(4) Identification of potential index chemicals;

(5) Presentation of the available literature for in vivo carcinogenicity and both in vivo and in vitro cancer-related endpoint assays for individual PAHs;

(6) Development of a recommendation for the RPF approach for PAH mixtures; and

(7) Characterization of strengths, weaknesses, and uncertainties associated with the recommended approaches.

2. RATIONALE FOR RECOMMENDING AN RPF APPROACH

PAHs are a concern as human health hazards, because many PAHs are demonstrated tumorigenic agents in animal bioassays and are active in in vivo or in vitro tests for genotoxicity or deoxyribonucleic acid (DNA) damage. PAHs do not occur in the environment as isolated entities; they primarily occur in complex mixtures generated from the combustion or pyrolysis of substances containing carbon and hydrogen. Several complex mixtures of PAHs have been classified as possibly carcinogenic, probably carcinogenic, or carcinogenic to humans (Straif et al., 2005; U.S. EPA, 2002; Bostrom et al., 2002; WHO, 1998; ATSDR, 1995; IARC, 1985, 1984a, b, 1983).

In accordance with U.S. EPA (2000, 1986) guidance for health risk assessment of chemical mixtures, assessment of the cancer risk from long-term human exposure to a particular PAH mixture would best be conducted with quantitative information on the dose-response relationship for cancer from chronic exposure to the mixture of concern. When data for the mixture of concern are not available, U.S. EPA (2000, 1986) guidance recommends using toxicity data on a "sufficiently similar" mixture. However, quantitative cancer dose-response information exists only for a few complex mixtures generated from the combustion or pyrolysis of organic matter; for example, tobacco smoke, coke oven emissions, and emissions from roofing tar pots (see Bostrom et al., 2002; Albert et al., 1983). U.S. EPA's IRIS database currently includes assessments for only three PAH-containing mixtures: coke oven emissions, creosote, and diesel emissions. The availability of oral carcinogenicity bioassays of manufactured gas plant (MGP) residue (Weyand et al., 1995) and coal tar preparations (Culp et al., 1998; Gaylor et al., 1998) has expanded the PAH mixture cancer database.

Component-based approaches, involving an analysis of the toxicity of components of the mixture, are recommended when appropriate toxicity data on a complex mixture of concern, or on a "sufficiently similar" mixture, are unavailable (U.S. EPA, 2000, 1986). Component-based approaches involving dose addition (such as the RPF approach) are recommended when components in the mixture are judged to act in a toxicologically similar manner. In the RPF approach, doses of component chemicals that act in a toxicologically similar manner are added together, after scaling the doses relative to the potency of an index chemical (U.S. EPA, 2000, 1986). Then, using the dose-response curve of the index chemical, the response to the total equivalent dose in the mixture is estimated. The index compound is typically the best-studied member of the class with the largest body of available data describing exposure and health effects. The index chemical should have a quantitative dose-response assessment of acceptable scientific quality and must have (or be expected to have) similar toxic effects to the rest of the members of the class.

For exposure situations in which dose-response data for the PAH mixture or a sufficiently similar mixture are not available (e.g., the source of the PAH contamination may be mixed or unknown), there are at least three practical advantages of an RPF approach that uses benzo[a]pyrene as the index PAH:

(1) Benzo[a]pyrene is routinely assayed and detected in environmental media contaminated with PAH mixtures;

(2) Benzo[a]pyrene is the only PAH for which robust cancer dose-response data involving chronic exposures are available; and

(3) There is a large database of studies in which the potency of benzo[a]pyrene is compared with the potency of other PAHs in various assays.

The database includes animal tumorigenicity[2] assays involving dermal or parenteral administration, and in vivo and in vitro assays of cancer-related endpoints (e.g., various genotoxic endpoints). Thus, RPFs for a number of PAHs can be derived.

The RPF approach involves two key assumptions related to the application of a dose-additivity model: (1) the assumption of similar toxicological action; and (2) the assumption that interactions among PAH mixture components do not occur at low levels of exposure typically encountered in the environment.

Mechanistic studies indicate that the mutagenic and tumor-initiating activity of most carcinogenic PAHs requires metabolic activation to reactive intermediates (e.g., stereospecific dihydrodiol epoxides). For several PAHs (e.g., benzo[a]pyrene, dibenz[a,h]anthracene, dibenzo[a,l]pyrene), there is evidence that DNA damage associated with metabolism can lead to mutations in cancer-related genes. Tumor promotion and progression by PAHs may involve parent compound binding to the aryl hydrocarbon (Ah) receptor and subsequent alterations of gene expression, as well as by cell proliferation in response to cytotoxic effects from metabolites (see Section 2.4, Similarities in Mode of Carcinogenic Action for PAHs). As such, there is evidence that an assumption of similar toxicological action is reasonable; however, the carcinogenic process for individual PAHs is likely to be related to some unique combination of multiple molecular events resulting from the formation of several reactive species. The second assumption of no interactions at low levels of exposure is also reasonable, but has not been conclusively demonstrated in experimental systems (see Section 2.8, Dose Additivity of PAHs in Combined Exposures).

Key limitations to the RPF approach, relative to whole mixture approaches, are: (1) RPFs have been derived for a limited number of PAHs; and (2) cancer risks from non-PAH components, unidentified PAHs, and heterocyclic and substituted PAHs in PAH mixtures are not

[2]Throughout this report, the term "tumorigenicity" is used to describe the production of either benign or malignant tumors.

estimated. The first of these limitations is being addressed, to the degree allowable by available data, by the derivation of RPFs for numerous PAHs as discussed in Chapters 4 through 7 of this report. If non-PAH carcinogenic components are identified and quantified in the complex mixture of concern and appropriate dose-response data are available, the second limitation can be addressed by adding the cancer risk from PAH components estimated by the RPF approach to cancer risks estimated for the non-PAH carcinogenic components of the mixture. Previous efforts to validate the RPF approach using data for PAH mixtures are discussed in Section 3.1. These validation efforts compared the cancer risk of a PAH mixture measured experimentally with the cancer risk that was predicted using the RPF method but were limited by the small number of compounds for which RPFs and analytical data were available (Muller et al., 1997; McClure, 1996; Goldstein et al., 1994; Clement Associates, 1990, 1988; Krewski et al., 1989). Validation of the updated approach presented here would be of value, either using previous data on PAH mixtures (human and animal) or using new data collected with the main purpose of evaluating the validity of the approach.

2.1. PAHs AS A CHEMICAL CLASS

The PAH chemical class 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 PAHs and their alkyl-substituted derivatives) (WHO, 1998). Most PAHs are high-melting, high-boiling point, lipophilic compounds, predominately generated from the incomplete combustion or pyrolysis of organic matter. The PAH chemical class includes alkylated PAHs (e.g., 1,4-dimethylphenanthrene and 5-methylchrysene), but not heterocyclic compounds containing N, S, or O or PAHs substituted with N-, S-, or O-containing groups; these are included in a larger chemical class, often referred to as polycyclic aromatic compounds (PACs) (WHO, 1998). The number of chemicals that comprise the PAHs class is unknown; however, there are thought to be hundreds of individual PAHs present as components of complex mixtures (WHO, 1998). The analysis presented here is limited in focus to include only unsubstituted PAHs with three or more fused aromatic rings containing only carbon and hydrogen atoms, because these are the most widely studied members of the PAH chemical class. Naphthalene is a widely studied two-ring PAH compound; however, a separate toxicological review and carcinogenicity assessment is being developed by the IRIS Program for this compound and it is not included in this RPF approach. The list of PAH compounds that were considered for inclusion in this analysis is presented in Table 2-1 along with the Chemical Abstracts Service Registry Numbers (CASRNs) and the abbreviations that are utilized in tables throughout the report.

Table 2-1. PAHs evaluated in the RPF analysis

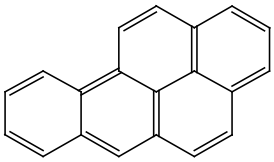
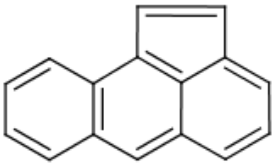
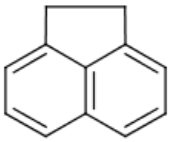
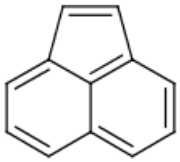
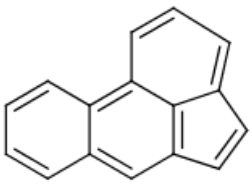
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Benzo[a]pyrene	50-32-8	BaP		252.31
Aceanthrylene	202-03-09	ACEA		202.26
Acenaphthene	83-32-9	AN		154.21
Acenaphthylene	208-96-8	ANL		152.20
Acephenanthrylene	201-06-9	APA		202.26

Table 2-1. PAHs evaluated in the RPF analysis

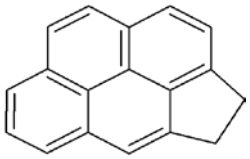
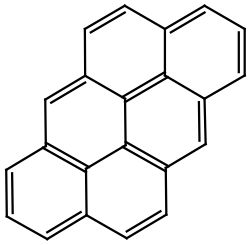
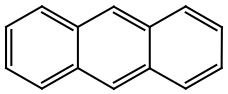
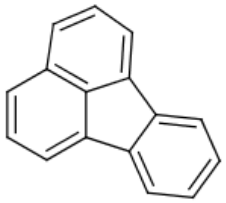
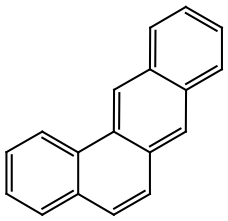
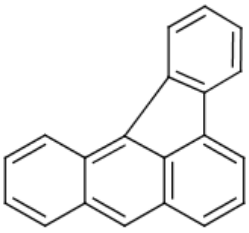
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Acepyrene, 2,3-	25732-74-5	ACEP		228.29
Anthanthrene	191-26-4	AA		276.34
Anthracene	120-12-7	AC		178.23
Benzacenaphthylene	76774-50-0	BAN		202.26
Benz[a]anthracene	56-55-3	BaA		228.29
Benzo[a]fluoranthene	203-33-8	BaF		252.32

Table 2-1. PAHs evaluated in the RPF analysis

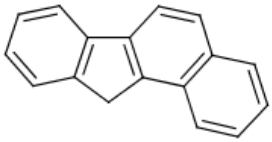
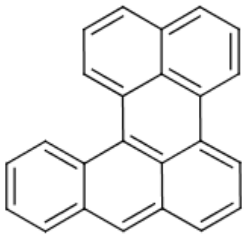
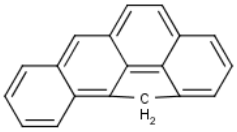
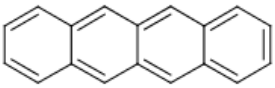
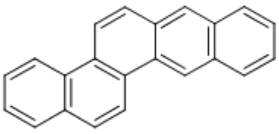
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Benzo[a]fluorene	238-84-6	BaFE		216.28
Benzo[a]perylene	191-85-5	BaPery		302.38
Benz[b,c]aceanthrylene, 11H-	202-94-8	BbcAC		240.30
Benz[b]anthracene (naphthacene)	92-24-0	BbA		228.29
Benzo[b]chrysene	214-17-5	BbC		278.35

Table 2-1. PAHs evaluated in the RPF analysis

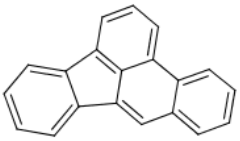
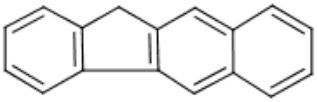
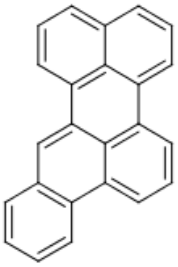
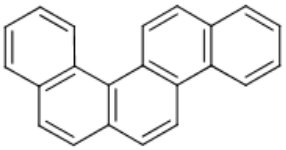
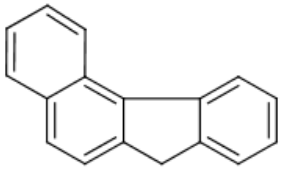
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Benzo[b]fluoranthene	205-99-2	BbF		252.32
Benzo[b]fluorene, 11H	243-17-4	BbFE		216.28
Benzo[b]perylene	197-70-6	BbPery		302.38
Benzo[c]chrysene	194-69-4	BcC		278.35
Benzo[c]fluorene	205-12-9	BcFE		216.28

Table 2-1. PAHs evaluated in the RPF analysis

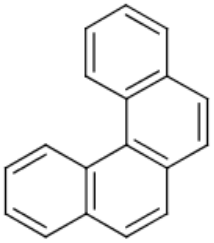
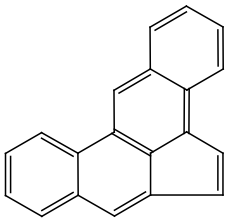
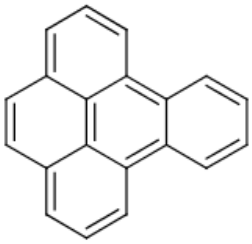
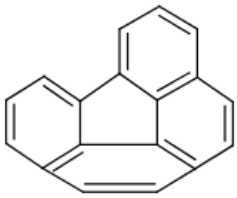
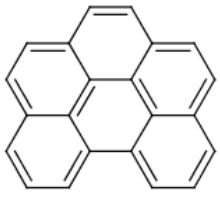
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Benzo[c]phenanthrene	195-19-7	BcPH		228.29
Benz[e]aceanthrylene	199-54-2	BeAC		252.32
Benzo[e]pyrene	192-97-2	BeP		252.32
Benzo[g,h,i]fluoranthene	203-12-3	BghiF		226.28
Benzo[g,h,i]perylene	191-24-2	BghiP		276.34

Table 2-1. PAHs evaluated in the RPF analysis

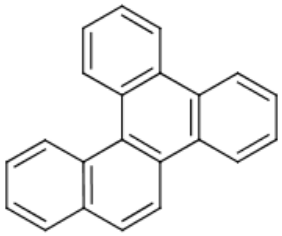
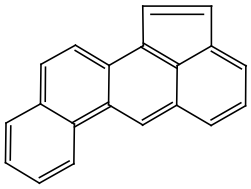
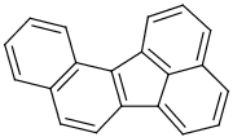
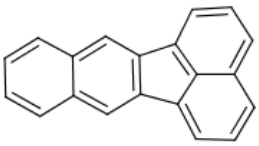
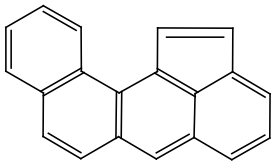
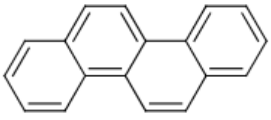
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Benzo[g]chrysene	196-78-1	BgC		278.35
Benz[j]aceanthrylene	202-33-5	BjAC		252.32
Benzo[j]fluoranthene	205-82-3	BjF		252.32
Benzo[k]fluoranthene	207-08-9	BkF		252.32
Benz[l]aceanthrylene	211-91-6	BlAC		252.32
Benzophenanthrene	65777-08-4	BPH		228.29

Table 2-1. PAHs evaluated in the RPF analysis

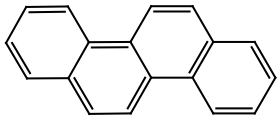
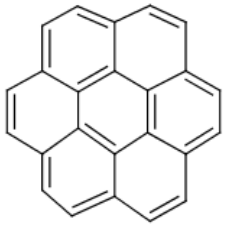
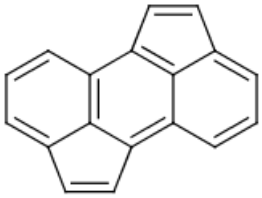
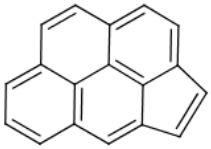
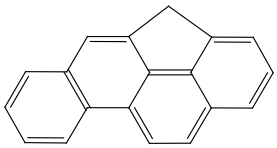
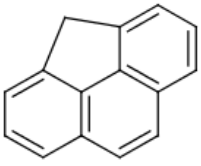
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Chrysene	218-01-9	CH		228.29
Coronene	191-07-1	CO		300.36
Cyclopent[h,i]aceanthrylene	131581-33-4	CPhiACEA		226.28
Cyclopenta[c,d]pyrene	27208-37-3	CPcdP		226.28
Cyclopenta[d,e,f]chrysene, 4H-	202-98-2	CPdefC		240.30
Cyclopenta[d,e,f]phenanthrene	203-64-5	CPdefPH		190.24

Table 2-1. PAHs evaluated in the RPF analysis

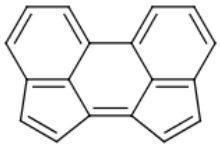
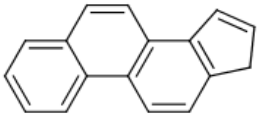
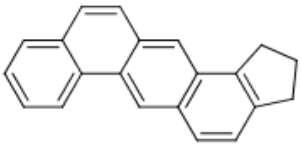
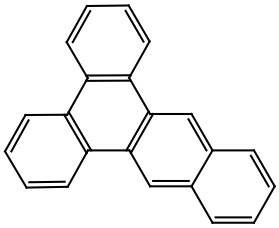
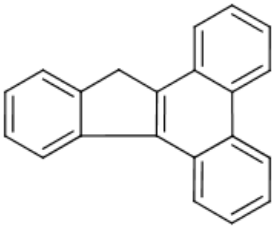
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Cyclopenta[h,i]acephenanthrylene	114959-37-4	CPhiAPA		226.28
Cyclopentaphenanthrene	219-08-9	CPPH		216.28
Cyclopenteno-1,2-benzanthracene, 5,6-	7099-43-6	CPBA		268.36
Dibenz[a,c]anthracene (benzotriphenylene)	215-58-7	DBacA		278.35
Dibenzo[a,c]fluorene, 13H-	201-65-0	DBacFE		266.34

Table 2-1. PAHs evaluated in the RPF analysis

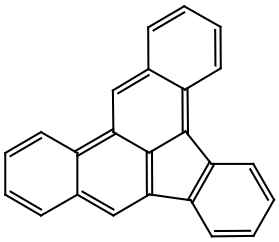
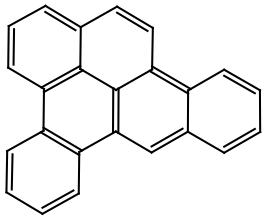
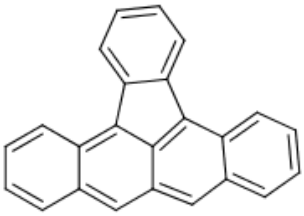
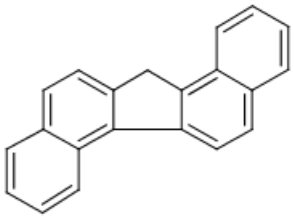
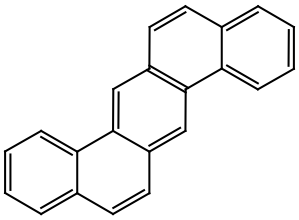
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Dibenzo[a,e]fluoranthene	5385-75-1	DBaeF		302.38
Dibenzo[a,e]pyrene	192-65-4	DBaeP		302.38
Dibenzo[a,f]fluoranthene (indeno[1,2,3-fg]naphthacene)	203-11-2	DBafF		302.38
Dibenzo[a,g]fluorene, 13H-	207-83-0	DBagFE		266.34
Dibenz[a,h]anthracene	53-70-3	DBahA		278.35

Table 2-1. PAHs evaluated in the RPF analysis

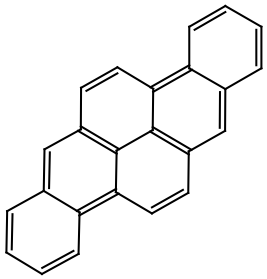
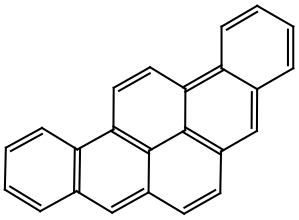
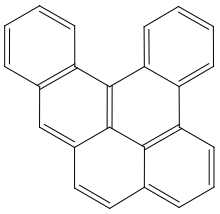
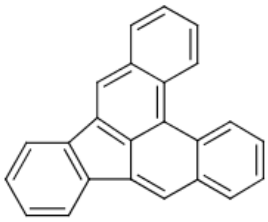
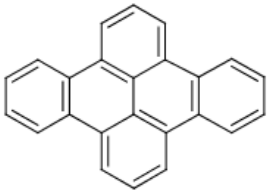
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Dibenzo[a,h]pyrene	189-64-0	DBahP		302.38
Dibenzo[a,i]pyrene	189-55-9	DBaiP		302.38
Dibenzo[a,l]pyrene	191-30-0	DBalP		302.38
Dibenzo[b,e]fluoranthene	2997-45-7	DBbeF		302.38
Dibenzo[e,l]pyrene (dibenzo[fg,op]naphthacene)	192-51-8	DBelP		302.38

Table 2-1. PAHs evaluated in the RPF analysis

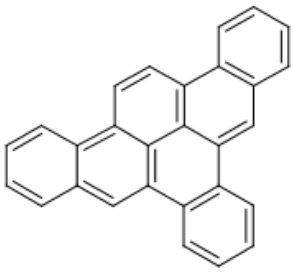
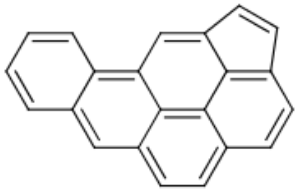
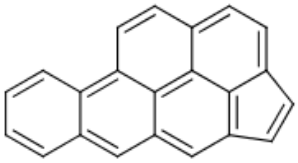
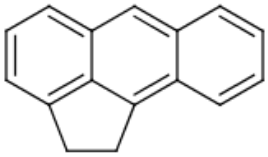
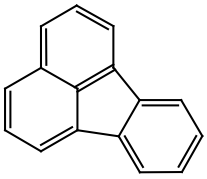
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Dibenzo[h,rst]pentaphene	192-47-2	DBhrstPent		352.43
Dibenz[j,mno]acephenanthrylene	153043-82-4	DBjmnoAPH		276.34
Dibenz[k,mno]acephenanthrylene	153043-81-3	DBkmnoAPH		276.34
Dihydroaceanthrylene, 1,2-	641-48-5	DACEA		204.27
Fluoranthene	206-44-0	FA		202.26

Table 2-1. PAHs evaluated in the RPF analysis

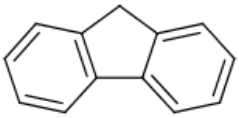
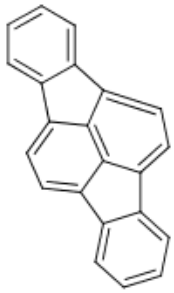
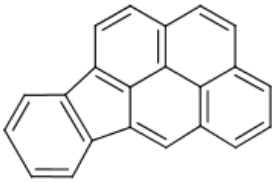
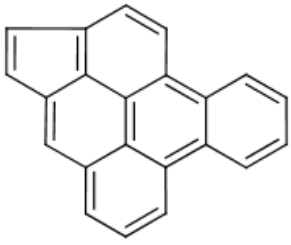
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Fluorene	86-73-7	FE		166.22
Indeno[1,2,3-c,d]fluoranthene	193-43-1	IF		276.34
Indeno[1,2,3-c,d]pyrene	193-39-5	IP		276.34
Naphth[1,2,3-mno]acephenanthrylene	113779-16-1	N123mnoAPH		276.34

Table 2-1. PAHs evaluated in the RPF analysis

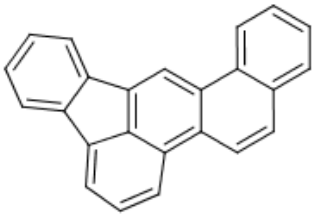
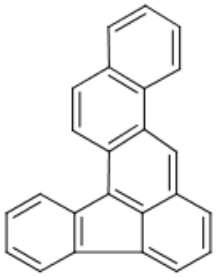
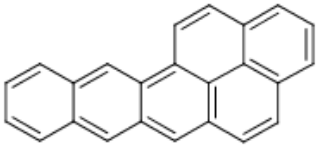
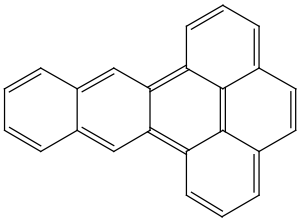
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Naphtho[1,2-b]fluoranthene	111189-32-3	N12bF		302.38
Naphtho[2,1-a]fluoranthene	203-20-3	N21aF		302.38
Naphtho[2,3-a]pyrene (naphtho[2,1,8-qra]naphthacene)	196-42-9	N23aP		302.38
Naphtho[2,3-e]pyrene (dibenzo[de,qr]naphthacene)	193-09-9	N23eP		302.38

Table 2-1. PAHs evaluated in the RPF analysis

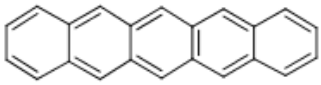
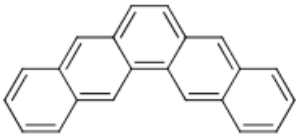
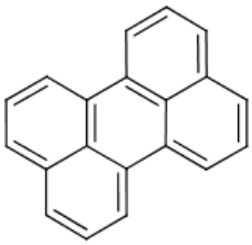
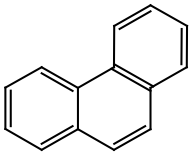
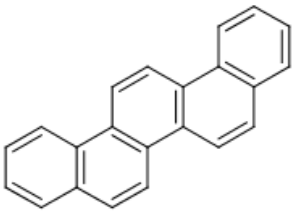
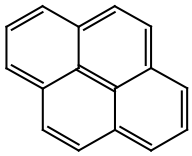
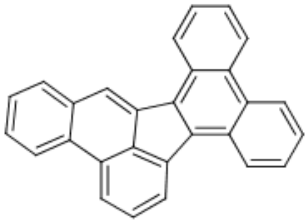
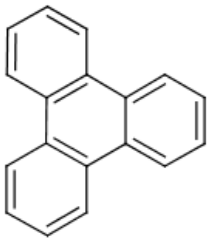
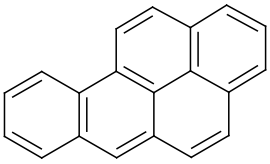
PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Pentacene	135-48-8	PCE		278.35
Pentaphene (dibenzphenanthrene, 2,3:6,7-)	222-93-5	Pent		278.35
Perylene	198-55-0	Pery		252.32
Phenanthrene	85-01-8	PH		178.23
Picene	213-46-7	Pic		278.35

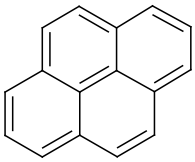
Table 2-1. PAHs evaluated in the RPF analysis

PAH (common synonyms)	CASRN	Abbreviation	Structure	Molecular weight (g/mol)
Pyrene	129-00-0	Pyr		202.26
Tribenzofluoranthene 3,4-10,11-12,13-	13579-05-0	TBF		352.43
Triphenylene	217-59-4	Tphen		228.29

Unsubstituted PAHs have been further classified into alternant and nonalternant compounds. Alternant PAHs are those compounds composed solely of fused benzene rings, while nonalternant PAHs contain both benzene and five carbon rings. Among alternant PAHs, important structural features related to enhanced mutagenicity and carcinogenicity include the presence of at least four rings (Bostrom et al., 2002). Common structural features of PAH compounds are illustrated in Figure 2-1.

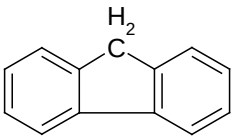


Benzo[a]pyrene

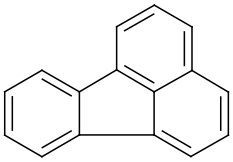


Pyrene

Examples of Alternant PAHs

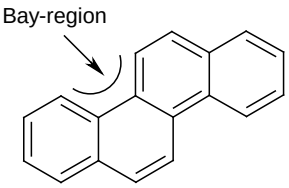


Fluorene

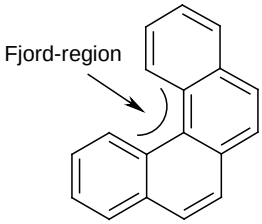


Fluoranthene

Examples of Nonalternant PAHs



Chrysene



Benzo[c]phenanthrene

Bay-region and Fjord-regions of PAHs

Figure 2-1. Structural features of PAHs.

2.2. THE TOXICOLOGICAL DATABASE FOR PAHs

Over the last 30- to 50-years, a large PAH database has been generated including studies of carcinogenicity in animal bioassays, genotoxicity in various test systems, and metabolism (bioactivation) to tumorigenic and/or genotoxic intermediates. Carcinogenicity and genotoxicity data are sufficient to classify a number of individual PAHs as possibly carcinogenic to humans (WHO, 1998; U.S. EPA, 1993; IARC, 1989, 1986, 1985, 1984a, b, 1983). Other PAHs have been tested for tumorigenicity and/or genotoxicity, but either nonpositive or equivocal results were obtained; for many PAHs, positive results were only observed in genotoxicity assays (e.g., pyrene). Many studies have been performed to provide further understanding about the carcinogenic mode of action of PAHs (see Bostrom et al., 2002; WHO, 1998; ATSDR, 1995). Therefore, the PAH database contains studies that evaluate:

- Metabolism to reactive intermediates;
- Characterization of PAH-DNA adducts;
- Mutagenicity of PAHs in bacterial and mammalian cells;
- Mutation spectra in identified oncogene and tumor suppressor genes;
- Clastogenic effects;
- Cell transformation; and
- Initiation and promotion of carcinogenicity (complete carcinogenesis).

A limitation to the database is the lack of data from long-term oral or inhalation cancer studies for most individual PAH compounds. The only PAH for which there are robust animal dose-response data is benzo[a]pyrene (Kroese et al., 2001; Culp et al., 1998, 1996a, b; Thyssen et al., 1981, 1980; Rigdon et al., 1969; Rigdon and Neal, 1969, 1966; Neal and Rigdon, 1967). Furthermore, most of the toxicological data available for PAHs relate to cancer or genotoxicity. Available information on the systemic, noncarcinogenic effects of PAHs is limited, although immunological, neurotoxic, and developmental effects have been noted in animal studies and some human studies (for earlier reviews, see WHO, 1998; ATSDR, 1995). As a result, the relative potency methodology described here is applied only to cancer risk assessment for PAHs.

2.3. BENZO[A]PYRENE AS AN INDEX CHEMICAL

Because long-term animal studies are not available for many individual PAHs, it is necessary to choose an appropriate index chemical for comparison of relative carcinogenic potency. The index compound is typically the best-studied member of the class, with the largest body of available data describing exposure and health effects. The index chemical should have a quantitative dose-response assessment of acceptable scientific quality and must have (or be expected to have) similar toxic effects to the rest of the members of the class.

Although the PAH composition of complex mixtures varies, benzo[a]pyrene is considered to be present in significant amounts in certain occupational environments and urban settings (WHO, 1998; Petry et al., 1996; ATSDR, 1995). Benzo[a]pyrene is one of the most potent of the carcinogenic PAHs and has, therefore, been proposed to contribute significantly to the carcinogenicity of a PAH mixture, even when present in low concentrations (Petry et al., 1996). Benzo[a]pyrene is also the best-studied PAH compound, with carcinogenicity bioassay data available for several routes of exposure and a considerable number of studies on carcinogenic mode of action. Benzo[a]pyrene has been characterized as reasonably anticipated to be a human carcinogen (NTP, 2005) or carcinogenic to humans (Straif, 2005).

The laboratory animal database for benzo[a]pyrene is robust. Benzo[a]pyrene has been shown to induce tumors at the site of administration and at distal sites in numerous studies. Dose-response data for tumors are available for the oral, inhalation, and dermal routes of administration in multiple species. There are methodological limitiations associated with the

inhalation data (Thyssen et al., 1981), although positive findings in intratracheal instillation studies support the observed positive response. Dermal exposure studies with several strains of mice also provide data on dose-related tumor incidences (Albert et al., 1991; Warshawsky and Barkley, 1987; Habs et al., 1984, 1980; Nesnow et al., 1983; Wynder et al., 1957).

The animal carcinogenicity database for benzo[a]pyrene includes several well-conducted oral cancer bioassays. Kroese et al. (2001) conducted a well-designed gavage study of benzo[a]pyrene carcinogenicity and found that benzo[a]pyrene induced tumors at multiple sites in rats of both sexes, specifically in the liver, forestomach, auditory canal, and oral cavity. In another well-conducted study, using Ah-responsive B6C3F_1 female mice exposed to benzo[a]pyrene in the diet (Beland and Culp, 1998; Culp et al., 1998), only portal-of-entry tumors were found, including papillomas and/or carcinomas of the forestomach, esophagus, tongue, and larynx. Earlier, a number of related studies were conducted to evaluate the carcinogenicity of benzo[a]pyrene in feed in Ah-responsive white Swiss mice (Rigdon and Neal, 1969, 1966; Neal and Rigdon, 1967). These studies were not conducted using standard, modern toxicological methods and have several limitations, including inconsistent dosing protocols; varying ages of the animals; use of benzene as a solvent; small numbers of animals; and evaluation of only a limited number of tissues. These studies do, however, provide useful dose-response information on benzo[a]pyrene carcinogenicity. Following oral administration via feeding of benzo[a]pyrene, site-of-contact tumors (both papillomas and carcinomas) were induced in the forestomach, esophagus, and larynx of mice (Culp et al., 1998; Neal and Rigdon, 1967) and rats (Brune et al., 1981). The results following inhalation, dermal, or oral exposure are further supported by numerous mechanistic studies or assays using infant mice, susceptible transgenic strains, or Ah-receptor knockout mice.

Benzo[a]pyrene is a complete carcinogen and likely acts by initiating tumors through direct DNA damage as well as by promoting tumor growth. Benzo[a]pyrene has been shown to be mutagenic in multiple assay systems. Several modes of carcinogenic action are possible. These include:

(1) Alteration of pathways regulating cell proliferation and survival (Tannheimer et al., 1998);

(2) Inhibition of intracellular communication (Sharovskaia et al., 2003; Blaha et al., 2002; Rummel et al., 1999);

(3) Altered intracellular Ca^{2+} signaling (Tannheimer et al., 1998);

(4) Modulation of cell survival, cell proliferation, and altered growth via generation of oxidative stress and activation of oxidant stress signaling (Burdick et al., 2003; Miller and Ramos, 2001);

(5) Altered apoptosis processes (Chen et al., 2003);

(6) Dysregulation of normal circulating hormone levels or activity affecting tumorigenesis in reproductive tissues (Safe and Wormke, 2003; Archibong et al., 2002) or the central nervous system (Dasgupta and Lahiri, 1992);

(7) Disruption of cell cycle kinetics in breast cancer cells (Jeffy et al., 2002, 2000); and

(8) Disruption of DNA repair through alteration of ribonucleic acid (RNA) polymerase activity (Shah and Bhattacharya, 1989).

Oral (dietary) carcinogenicity bioassays are available that compare MGP residue (Weyand et al., 1995) or coal tar preparations (Culp et al., 1998; Gaylor et al., 1998) with benzo[a]pyrene. In both cases, there were significant differences in the target organ distribution of tumors between benzo[a]pyrene and complex mixtures of PAHs. Following dietary administration, benzo[a]pyrene-induced tumors were observed primarily at the point of contact (i.e., the forestomach), while MGP residue and coal tar produced tumors in the lung, liver, forestomach, skin, and other organs. Tissue-specific differences in metabolic activation and DNA binding of PAHs may contribute to the observed differences in target organ sensitivity (Weyand and Wu, 1995; Culp and Beland, 1994). However, a dietary study in A/J mice (Weyand et al., 2004) showed that benzo[a]pyrene could induce significant increases in the incidences of lung adenomas and forestomach carcinomas. Further, a gavage study in rats (Kroese et al., 2001) demonstrated that oral exposure to benzo[a]pyrene could induce tumors in the liver and auditory canal; no lung tumors were observed. The latter two studies indicate that, contrary to the conclusions of earlier studies, benzo[a]pyrene can induce tumors at distal sites.

In summary, benzo[a]pyrene is the most appropriate compound to use as an index chemical for carcinogenic PAHs. It is well-studied, with a robust database of both bioassay data and mode of action information. Benzo[a]pyrene is a complete carcinogen with both initiating and promoting properties, is among the most potent PAH carcinogens, and is prevalent in many complex environmental mixtures. No alternative index chemical was identified from the list of target PAHs.

2.4. SIMILARITIES IN MODE OF CARCINOGENIC ACTION FOR PAHs

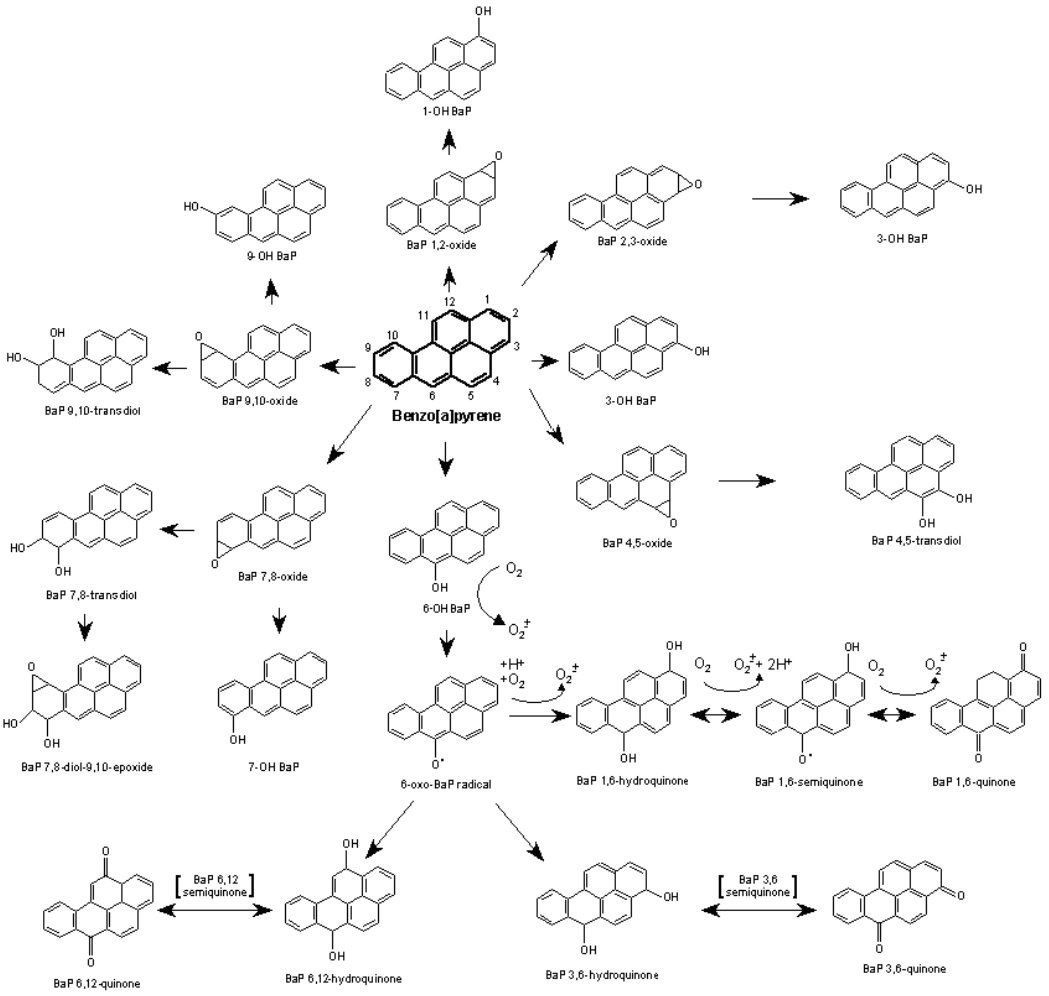
Toxicological similarity of chemicals is the basis for the assumption of dose additivity that underlies the RPF approach (U.S. EPA, 1990). The carcinogenic mode of action for PAHs has been extensively reviewed (Ramesh, 2004; CCME, 2003; Bostrom et al., 2002; Larsen and Larsen, 1998; WHO, 1998; Muller et al., 1997; Sjogren et al., 1996; ATSDR, 1995; Malcolm and Dobson, 1994; U.S. EPA, 1990). Key events that have been associated with PAH carcinogenicity include:

- Oxidative metabolism to reactive intermediates that covalently bind to DNA, RNA, and proteins (benzo[a]pyrene metabolism is illustrated in Figure 2-2);

- Formation of DNA adducts;

- Tumor initiation due to mutations in cancer-related genes (e.g., tumor suppressor genes or oncogenes); and

- Tumor promotion related to cytotoxicity and formation of reactive oxygen species, and/or Ah receptor (AhR) affinity and upregulation of genes related to biotransformation, growth, and differentiation.



Reprinted from Impact of cellular metabolism on the biological effects of benzo[a]pyrene and related hydrocarbons, 2001 by Miller, KP; Ramos, KS; with permission of Taylor & Francis.

Source: Miller and Ramos (2001).

Figure 2-2. Metabolic pathways for benzo[a]pyrene.

Formation of reactive intermediates and DNA adducts. Each of the key events identified above is affected by the chemical structure of the individual PAH. At least three distinct molecular mechanisms have been proposed to explain the tumor initiation process of PAHs (Xu et al., 2009; Jiang et al., 2007, 2005; Xue and Warshawsky, 2005; Bolton et al., 2000; Penning et al., 1999; Harvey, 1996; Cavalieri and Rogan, 1995). These modes of action include the formation of diol epoxides, radical cations, and o-quinones (Figure 2-3). Diol epoxide formation leads to stable and unstable DNA adducts, mainly at guanine and adenine, which can lead to mutations in proto-oncogenes and tumor-suppressor genes. Radical cation formation may lead to the generation of unstable adducts at guanine and adenine, leading to apurinic sites and mutation in *HRAS*. o-Quinone formation could lead to stable and unstable DNA adducts and generation of reactive oxygen species, inducing mutations in RP53. The evidence supporting the role of these reactive metabolites in tumor initiation includes a characterization of the specific DNA adducts arising from PAH metabolism and observations of mutagenesis resulting from direct exposure. Figure 2-3 illustrates the proposed key steps in the mode of action for PAH carcinogenesis. These include the interaction of reactive metabolites with DNA to form adducts, induction of depurination, transversion mutations (e.g., GC→TA or AT→TA), and oxidative damage to DNA, and tumor promotion mediated by AhR-mediated effects on gene regulation.

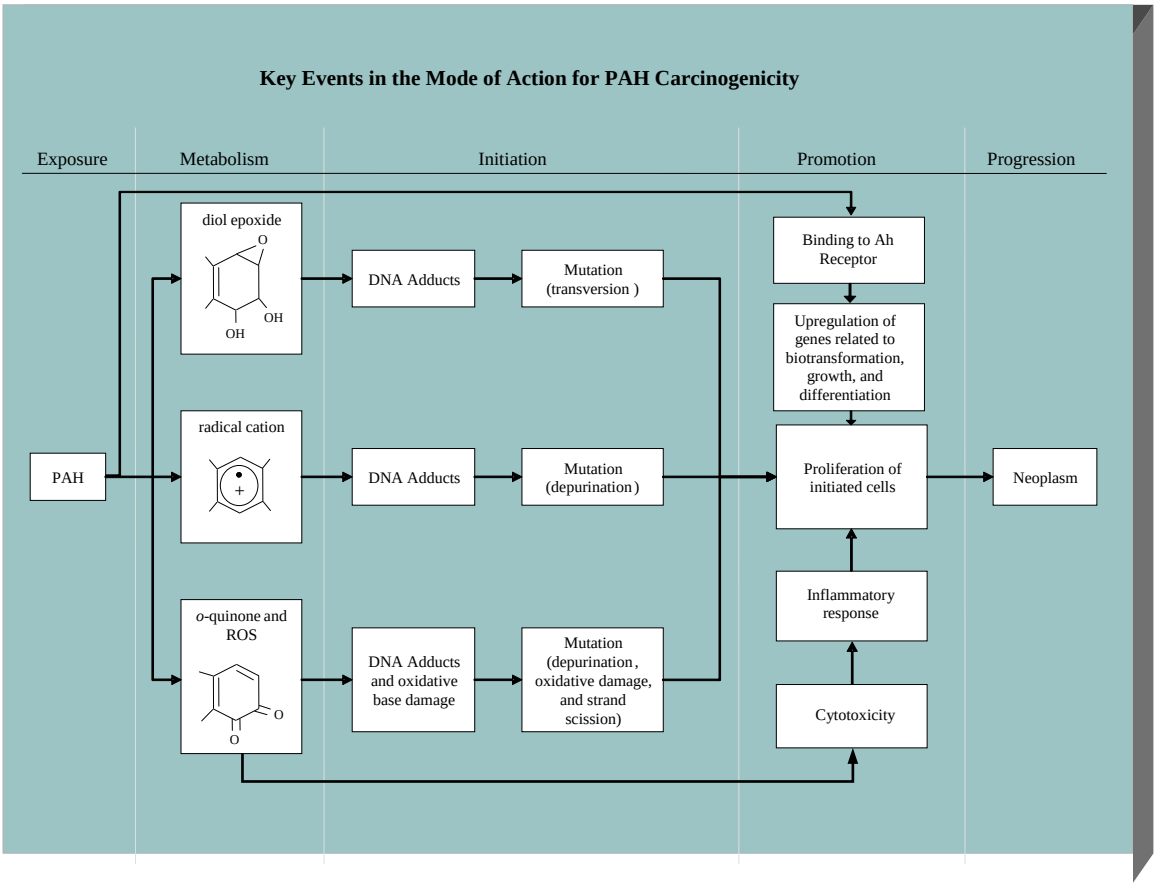
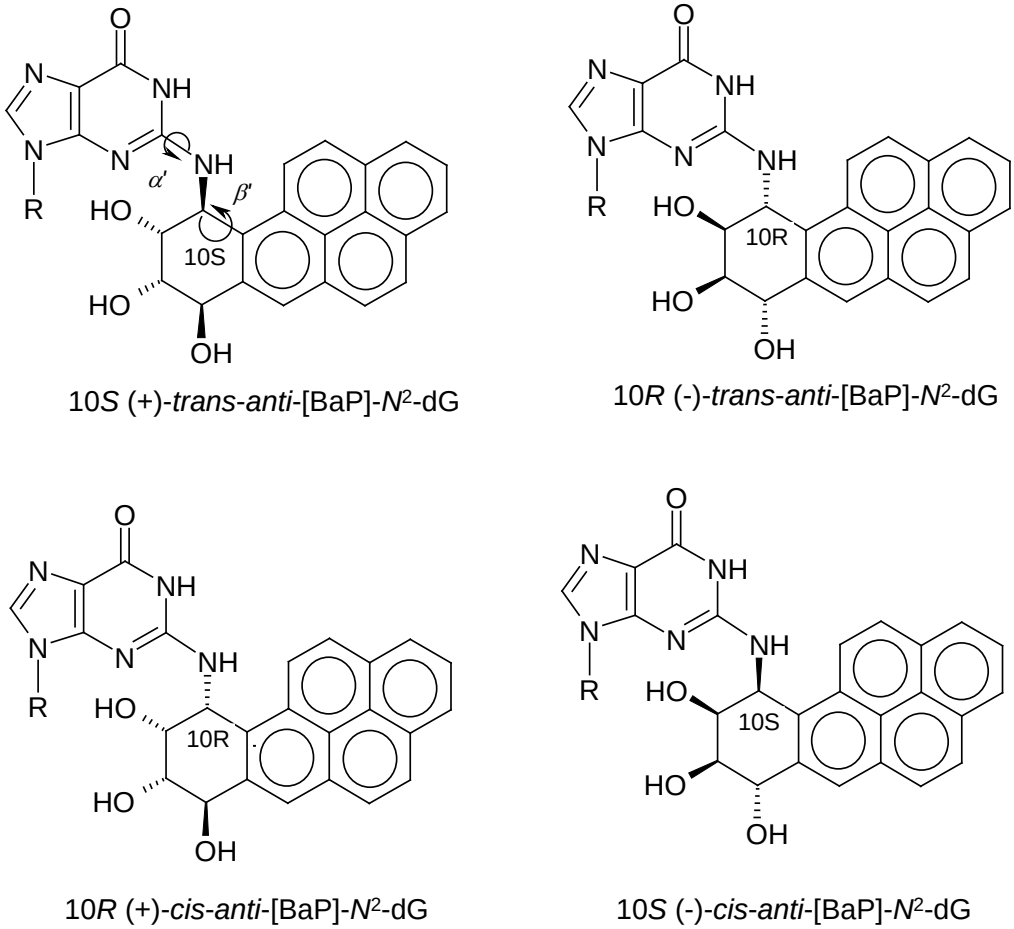


Figure 2-3. Overview of the proposed key events in the mode of action for PAH carcinogenicity.

The formation of diol epoxides is a proposed key step in the most established mode of action for PAH-induced carcinogenicity. Extensive studies of the metabolism of carcinogenic PAHs suggest that bay- and fjord-region diol epoxides are some of the ultimate reactive metabolites of PAHs (Jerina et al., 1978; Jerina and Lehr, 1977). These metabolites are generally formed through cytochrome P450 (CYP) oxidation to form epoxides and epoxide hydrolase cleavage resulting in diol formation. CYP1A1 appears to be the primary isozyme involved in diol epoxide formation; however, other isozymes may also contribute to PAH metabolism (i.e., CYPIA2, CYP1B1, CYP3A4) (Bostrom et al., 2002; ATSDR, 1995). Non-alternant PAHs, composed of fused benzenoid and five-membered rings, may be metabolized through other pathways resulting in the formation of reactive intermediates that bind to DNA. Classic bay- and fjord-region diol epoxides may be formed from these compounds; however, epoxide formation at cyclopenta-ring structures has also been demonstrated to result in DNA adduct formation (Bostrom et al., 2002).

Many studies have been performed to evaluate the formation of DNA adducts following in vivo or in vitro exposure to PAHs. Diol epoxide metabolites interact preferentially with the exocyclic amino groups of deoxyguanine and deoxyadenine (Geacintov et al., 1997; Jerina et al.,

1991). Adducts may give rise to mutations, unless these adducts are removed by DNA repair processes prior to replication. The stereochemical nature of the diol epoxide metabolite (i.e., anti- versus syn-diol epoxides) affects the number and type of adducts and mutation that occurs. Figure 2-4 presents the structures of four stereoisomeric adducts arising from the interaction of benzo[a]pyrene diol epoxide metabolites with the deoxyguanosine (dG) residues in DNA (Geacintov et al., 1997). Transversion mutations (e.g., GC→TA or AT→TA) are the most common type of mutation found in mammalian cells following diol epoxide exposure (Bostrom et al., 2002).

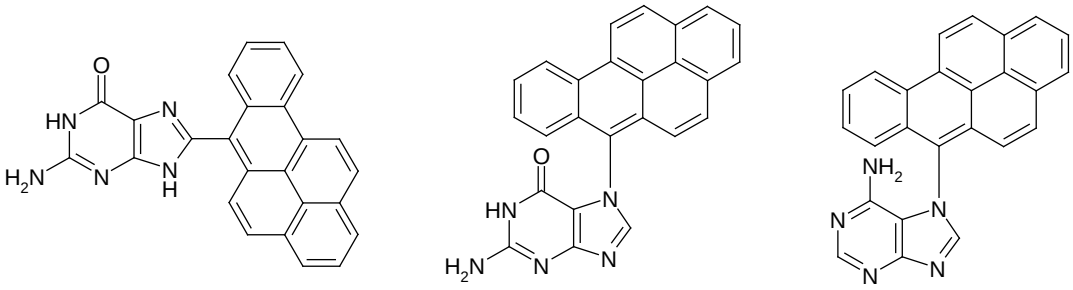


Source: Geacintov et al. (1997).

Figure 2-4. Structures of the four stereoisomeric adduct moieties, *anti*-[BaP]-N^2-dG, derived from the *trans*- or *cis*- covalent binding of (+)-*anti*-BaP diol epoxide or (-)-*anti*-BaP diol epoxide to dG residues in DNA.

Radical cation formation involves a one-electron oxidation that produces electrophilic radical cation intermediates (Cavalieri and Rogan, 1995, 1992). Oxidation of this type can occur by CYP or peroxidase enzymes (i.e., horseradish peroxidase, prostaglandin H synthetase). Radical cations can be further metabolized to phenols and quinones (Cavalieri et al., 1988a), or

they can form unstable adducts with DNA that ultimately result in depurination (Cavalieri et al., 2005, 1993; Rogan et al., 1993). Radical cations have been shown to play a major role in formation of DNA adducts for several carcinogenic PAHs (e.g., 7,12-dimethylbenzanthracene, benzo[a]pyrene, dibenzo[a,l]pyrene). The predominant depurinating adducts occur at the N-3 and N-7 positions of adenine and the C-8 and N-7 positions of guanine (Cavalieri and Rogan, 1995; Li et al., 1995). Figure 2-5 illustrates three depurinating adducts of benzo[a]pyrene formed by one-electron oxidation. Abasic sites resulting from base depurination undergo error-prone excision repair to induce mutations. In the case of dibenzo[a,l]pyrene-treated mouse skin, repair error from abasic sites resulted in H-ras oncogene mutations that underwent rapid clonal expansion and regression (Chakravarti et al., 2000). H-ras mutations in mouse skin papillomas also corresponded to adenine and guanine depurinating adducts resulting from exposure to dibenzo[a,l]pyrene, 7,12-dimethyl-benz[a]anthracene, benzo[a]pyrene, and benzo[a]pyrene-7,8-dihydrodiol (Chakravarti et al., 2008).



BaP-6-C8-guanine BaP-6-N7-guanine BaP-6-N7-adenine

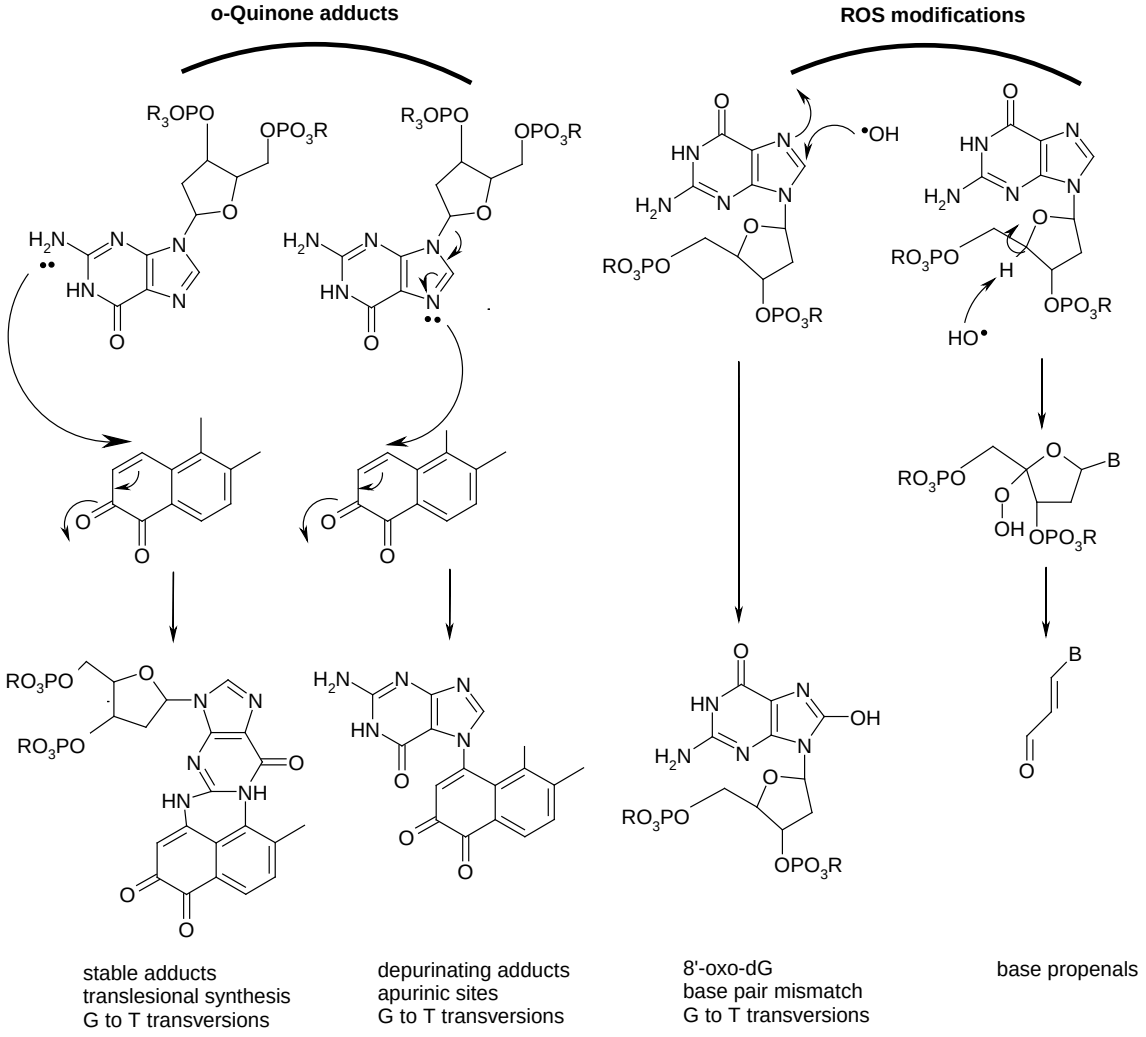
Reprinted from Central role of radical cations in metabolic activation of polycyclic aromatic hydrocarbons, 1995 by Cavalieri, EL; Rogan, EG; with permission of Taylor & Francis.

Source: Cavalieri and Rogan (1995).

Figure 2-5. Depurinating adducts of benzo[a]pyrene formed by one-electron oxidation.

o-Quinone metabolites of PAHs are formed by enzymatic dehydrogenation of dihydrodiols (Bolton et al., 2000; Penning et al., 1999; Harvey, 1996; ATSDR, 1995). Dihydrodiol dehydrogenase enzymes are members of the α-keto reductase gene superfamily. o-Quinone metabolites are potent cytotoxins, are weakly mutagenic, and are capable of producing a broad spectrum of DNA damage. These metabolites can interact directly with DNA and can also result in production of reactive oxygen species (i.e., hydroxyl and superoxide radicals) that may produce further cytotoxicity and DNA damage. The DNA damage caused by

o-quinones may include the formation of stable adducts (Balu et al., 2006), N-7 depurinating adducts (McCoull et al., 1999), oxidative base damage (i.e., 8-oxo-2'-dG or 8-oxo-dG) (Park et al., 2006, 2005), and strand scission (Flowers-Geary et al., 1997). The reactive oxygen species generated by the o-quinone of benzo[a]pyrene and other PAH o-quinones have been shown to induce mutation in the p53 tumor suppressor gene (Park et al., 2008; Shen et al., 2006; Yu et al., 2002). Figure 2-6 illustrates the spectrum of DNA adducts associated with PAH o-quinones.



Source: Bolton et al. (2000).

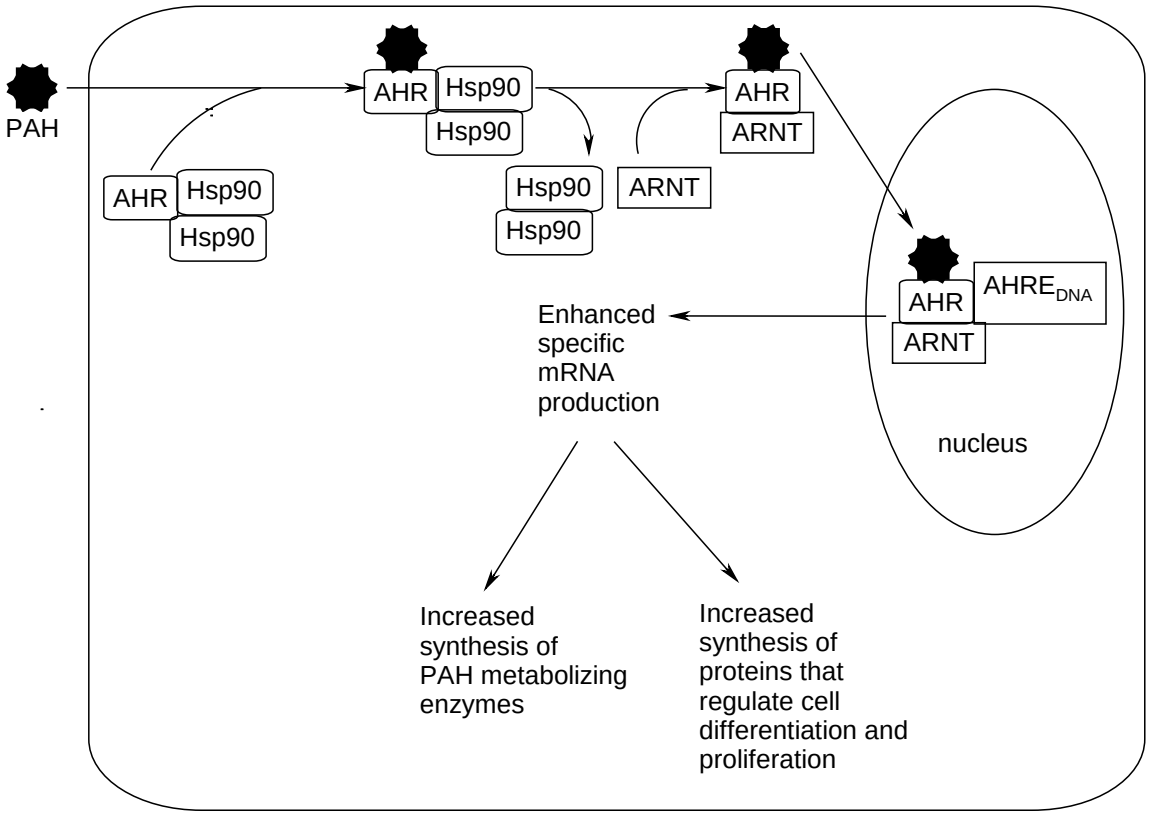
Figure 2-6. Spectrum of DNA adducts anticipated with PAH o-quinones.

The cytotoxicity of o-quinone metabolites may also contribute to tumor promotion via inflammatory responses leading to cell proliferation (Burdick et al., 2003).

Genotoxicity and mutagenicity. The genotoxicity and mutagenicity of PAHs have been demonstrated in various bacterial and mammalian assays (see Section 4.3.2 below) (reviewed in WHO, 1998; ATSDR, 1995). Mutagenesis of PAHs in the Ames assay (*Salmonella*

typhimurium) as well as other bacterial assays requires the presence of a mammalian metabolic enzyme system. In most cases, this is supplied by postmitochondrial supernatant (S9) from the liver of rodents treated with an enzyme inducer. Mammalian cell mutagenesis in Chinese hamster V79 cells and mouse lymphoma L5178Y cells also requires metabolic activation in the form of a rodent S9 mix or co-cultivation with metabolically active rodent cells (i.e., cell-mediated assay). Several studies have noted a correlation between mutagenic potency and tumor initiation potency in the two-stage dermal carcinogenicity assay for multiple PAH compounds (LaVoie et al., 1985, 1979; Raveh et al., 1982).

Tumor promotion and the AhR. The ability of certain PAHs to act as tumor promoters as well as initiators may increase their carcinogenic potency (Andrews et al., 1978). The promotional effects of PAHs appear to be related to AhR affinity and the upregulation of genes related to growth and differentiation (Bostrom et al., 2002). Figure 2-7 illustrates the function of the AhR and depicts the genes regulated by this receptor as belonging to two major functional groups (i.e., induction of metabolism or regulation cell differentiation and proliferation). PAHs bind to the cytosolic AhR in complex with heat shock protein 90. The ligand-bound receptor is then transported to nucleus in complex with the AhR nuclear translocator protein. The AhR complex interacts with AhR elements of DNA to increase the transcription of proteins associated with induction of metabolism and regulation of cell differentiation and proliferation.



Reprinted from Molecular biology of the aromatic hydrocarbon (dioxin) receptor, 1994 by Okey, AB; et al. with permission of Elsevier.

Source: Okey et al. (1994).

Figure 2-7. Interaction of PAHs with the AhR – regulation of genes related to induction of metabolism and cell differentiation and proliferation.

Tumor promotion and cytotoxicity. PAHs are metabolized to o-quinones, which are cytotoxic and can generate reactive oxygen species (Bolton et al., 2000; Penning, 1999). PAH o-quinones reduce the viability and survival of rat and human hepatoma cells (Flowers-Geary et al., 1996, 1993). Inflammatory responses to cytotoxicity may contribute to the tumor promotion process. For example, benzo[a]pyrene quinones (1,6-, 3,6-, and 6,12-benzo[a]pyrene-quinone) generated reactive oxygen species and increased cell proliferation by enhancing the epidermal growth factor receptor pathway in cultured breast epithelial cells (Burdick et al., 2003). Dermal exposure of mice to dibenzo[a,l]pyrene and dimethyl-benz[a]anthracene resulted in an inflammatory response that was correlated with epidermal hyperplasia and skin tumor promotion (Casale et al., 2000, 1997). The extent of epidermal hyperplasia was correlated with the cytokine mRNA response in lymph nodes and skin of treated mice (Casale et al., 2000).

Genetic targets and tumor formation. DNA adducts and oncogenes/tumor suppressor gene mutations have been demonstrated in tumor tissue from humans and laboratory animals.

DeMarini et al. (2001) demonstrated mutations in the p53 tumor suppressor gene and the K-ras oncogene in the lung tumors of nonsmokers, whose tumors were associated with exposure to smoky coal. Lung tumors were obtained from 24 nonsmoking women from China (age 30–63 years, mean age 48.5 ± 8.8 years) who used smoky coal in their homes without chimneys. Bronchioloalveolar adenocarcinoma and acinar adenocarcinoma were observed in 54 and 46% of the women studied, respectively. The observed mutations in lung tumors were primarily G→T transversions at either K-ras or p53. The mutation hotspots in the lung tumors that were examined corresponded with hot spots for PAH adducts (codon 154), cigarette smoke associated mutations (codon 249), and both of these events together (codon 273). The mutation spectrum was described as unique and consistent with exposure to PAHs in the absence of cigarette smoke.

Mutations in the K-ras, H-ras, and p53 genes were assessed in forestomach tumors (n = 31) of mice fed benzo[a]pyrene in the diet (0, 5, 25, or 100 ppm) for 2 years (Culp et al., 2000). Sixty-eight percent of 31 forestomach tumors analyzed had K-ras mutations, which were G→T or C transversions in codon 12 or 13. H-ras (codon 13) and p53 mutations characterized as G→T or C transversions were also each found in 10% of forestomach tumors. [^{32}P]-postlabeling of forestomach DNA of benzo[a]pyrene-treated mice revealed one major adduct characterized as dG N^2 BPDE. In mice exposed to benzo[a]pyrene at several concentrations in the diet for 4 weeks (5, 25, and 100 ppm), there was an approximate linear relationship between the daily dose of benzo[a]pyrene (in units of µg/day) and the concentration of dG-N^2-BPDE-DNA adducts in the forestomach (Culp et al., 2000, 1996a). In contrast, the tumor dose-response data in mice exposed for 2 years showed a sharp increase in incidence between the 5-ppm group (6% of mice had forestomach tumors) and the 25-ppm group (78% had forestomach tumors) (Culp et al., 1996a). The appearance of increased levels of BPDE-DNA adducts in the target tissue at 28 days is temporally consistent with the contribution of these adducts to the initiation of forestomach tumors at 25 and 100 ppm benzo[a]pyrene in the diet. However, the absence of a sharp increase in the BPDE-DNA relationship between 5 and 25 ppm benzo[a]pyrene is consistent with the possible contributions of mutagenic modes of action other than the diol epoxide pathway (i.e., formation of depurinated DNA adducts from the radical cation or aldo-keto-reductase pathways and reactive oxygen species DNA damage from the aldo-keto-reductase pathway).

A series of experiments designed to evaluate the mechanistic relationship between PAH DNA adducts, oncogene mutations, and lung tumorigenesis were performed in the A/J mouse lung model (Nesnow et al., 1998a, 1996, 1995; Mass et al., 1993). Tumorigenic potency in the lung of A/J mice varied over 2 orders of magnitude following a single intraperitoneal injection of seven PAHs of varying structure (benzo[a]pyrene, benzo[b]fluoranthene, benz[j]aceanthrylene, dibenz[a,h]anthracene, dibenzo[a,l]pyrene, cyclopenta[c,d]pyrene, and 5-methylchrysene). When considering the non-alkylated PAHs, the number of lung adenomas per mouse was highest

for benz[j]aceanthrylene and cyclopenta[c,d]pyrene, each of which contain a pentacyclic ring feature. The major DNA adducts identified in the mouse lung included:

(1) Bay region diol epoxide adducts for benzo[a]pyrene, dibenz[a,h]anthracene, and 5-methylcholanthrene;

(2) Phenolic diol epoxide adducts for benzo[b]fluoranthene;

(3) Cyclopenta-ring adducts for cyclopenta[c,d]pyrene and benz[j]aceanthrylene;

(4) Bisdihydrodiol epoxide adducts for dibenz[a,h]anthracene; and

(5) Fjord-region diol epoxide adducts for dibenzo[a,l]pyrene (Nesnow et al., 1998a, 1996, 1995; Mass et al., 1993).

Guanine adducts were most common for all PAHs; however, adenine adducts were also demonstrated for dibenzo[a,l]pyrene and benz[j]aceanthrylene. Quantitative analysis of DNA adducts by [^{32}P]-postlabeling illustrates the importance of measuring DNA adduct levels over time. A time-integrated DNA adduct level (TIDAL) was linearly related to the dose of a particular PAH. The relationship of TIDAL level to tumor formation was similar for PAHs that produce different types of adducts and different mutations in the Ki-ras oncogene. This suggests that the probability of tumor formation for these PAHs may be related to the extent of overall DNA damage and repair rather than the formation of a specific adduct at specific sites.

The DNA sequence analysis of Ki-ras mutations in lung adenomas at codons 12 and 61 was generally consistent with the DNA adduct data in that PAHs that produced guanine adducts also produced Ki-ras guanine mutations (Nesnow et al., 1998a, 1996, 1995; Mass et al., 1993). Cyclopenta[c,d]pyrene, benz[j]aceanthrylene, and 5-methylchrysene produced large numbers of adenomas per mouse (>90) and also produced a large proportion of tumors with CGT mutations at Ki-ras codon 12. Cyclopenta-ring adduct formation by cyclopenta[c,d]pyrene and benz[j]aceanthrylene was correlated with the formation of GGT→CGT mutations at Ki-ras codon 12. The primary mutation type for benzo[a]pyrene, benzo[b]fluoranthene, and dibenzo[a,l]pyrene was the GGT→TGT mutation, which is associated with the formation of diol epoxide guanine adducts. Dibenz[a,h]anthracene did not induce mutations in Ki-ras codons 12 or 61; however, diol epoxide guanine adducts and lung adenomas in A/J mice were observed. This suggests that a different genetic target may be involved in carcinogenicity of this compound.

H-ras mutations were studied in skin papillomas of SENCAR mice resulting from dermal initiation by benzo[a]pyrene or benzo[a]pyrene-7,8-dihydrodiol (400 nmol) followed by 12-O-tetra-decanoylphorbol-13-acetate (TPA) promotion (Chakravarti et al., 2008). Polymerase chain reaction (PCR) amplification of the H-*ras* gene and sequencing revealed that codon 13

(GGC to GTC) and codon 61 (CAA to CTA) mutations in papillomas corresponded to the relative levels of depurinating adducts of guanine and adenine, despite the formation of significant amounts of stable DNA adducts.

Other studies also suggest that multiple genetic targets may be involved in PAH mutagenicity and carcinogenicity (Conney et al., 2001; Smith et al., 2000). Smith et al. (2000) indicated that diol epoxide adducts and mutations were observed in the p53 tumor suppressor gene following in vitro exposure of cultured human bronchial epithelial cells to metabolites of benzo[a]pyrene, chrysene, benzo[c]phenanthrene, and benzo[g]chrysene. PAH adducts and corresponding mutations preferentially formed at lung mutational hot spots (codons 154, 157, 158, 245, 248, and 273), suggesting that PAHs may contribute to the mutation spectrum observed in human lung cancer. Conney et al. (2001) provided evidence that dose-dependent differences may exist for the mutation spectra seen in PAH-induced tumors. Skin papillomas induced by benzo[a]pyrene in female mice were examined for mutations in the c-Ha-ras proto-oncogene. The major difference between high- and low-dose groups was mutations at exon 2 of the c-Ha-ras gene, with the proportion of AT base pair mutations higher in the low-dose group. Dose-dependent changes in the mutation profile were also evident in Chinese hamster V79 cells exposed to the diol epoxides of benzo[a]pyrene and benzo[c]phenanthrene (i.e., the proportion of AT mutations decreased with increasing concentration).

In conclusion, there is evidence that an assumption of a similar toxicological action is reasonable for PAHs; however, the carcinogenic process for individual PAHs is likely to be related to some unique combination of multiple molecular events resulting from formation of several reactive species. For these reasons, the use of an RPF approach to estimate cancer risk associated with PAH exposure is considered appropriate. A common mutagenic mode of action for carcinogenic PAHs is hypothesized based on information available for the indicator chemical, benzo[a]pyrene (U.S. EPA, 2005b). The uncertainties and limitations related to the mode of action assumption for PAH-induced cancer are further discussed in Section 8.5.

2.5. STRUCTURAL ALERTS FOR PAH CARCINOGENESIS

The carcinogenic activity of PAH compounds is influenced by specific structural features. For example, alternant PAHs having four or more benzene rings exhibit greater carcinogenic potency than PAHs with two or three benzene rings (Bostrom et al., 2002). The carcinogenic activity of PAHs is also related to the specific arrangement of the benzene rings. As described in Section 2.4, PAHs that form bay- and fjord-region diol or dihydrodiol epoxides are more potent carcinogens compared with linear PAHs that lack this structural feature (Bostrum et al., 2002). These metabolites are resistant to detoxification due to stereochemical effects and, consequently, are more likely to be mutagenic and cause cancer (Buterin et al., 2000; Chang et al., 1981; Buening et al., 1979; MacLeod et al., 1979; Flesher et al., 1976). Dihydrodiol epoxides formed at other positions on the PAH molecule (i.e., not the bay- or fjord-

regions) are more accessible to glutathione transferase detoxification and are less potent mutagens and carcinogens (MacLeod et al., 1979; Flesher et al., 1976). Nonalternant PAHs containing fused benzenoid and five-membered rings, can also be metabolized to bay- and fjord-region diol epoxides (Bostrum et al., 2002); however, epoxide formation at the cyclopenta- ring structure may also contribute to carcinogenicity (Bostrum et al., 2002; Nyholm et al., 1996).

PAHs with at least four rings and a classic bay- or fjord-region (formed entirely by benzene rings; see Figure 2-1) may be characterized as containing structural alerts for carcinogenesis. However, this structural characterization is likely to be overly simplistic and other features may be important to carcinogenesis. Recent studies have applied quantitative structure activity relationship (QSAR) methods to evaluate the relationship between specific PAH structural features and mechanistic events related to carcinogenesis (Bruce et al., 2008; Vijayalakshmi et al., 2008).

2.6. SIMILARITIES IN RELATIVE POTENCY ACROSS ENDPOINTS

Studies that have evaluated the association between cancer-related endpoints and tumorigencity of PAHs are briefly summarized below.

Several studies have been performed that compare the bacterial or mammalian cell mutagenicity of various PAHs with tumor initiating activity or complete carcinogenesis (Blackburn et al., 1996; LaVoie et al., 1985, 1981, 1979; Raveh et al., 1982; Andrews et al., 1978). In general, mutagenicity appears to correlate best with tumor initiation. Complete carcinogenicity is not well-predicted by positive findings in short-term mutagenicity assays. Andrews et al. (1978) tested 24 PAHs for bacterial mutagenicity in the Ames test and compared these findings to evidence of carcinogenicity (parent and metabolites) from previously published studies. Positive findings of both mutagenicity and carcinogenicity were only reported for 14 of the 24 PAHs evaluated. Eight of the 10 remaining PAHs were found to be mutagenic in the Ames assay, but were not carcinogenic in animal studies. LaVoie et al. (1979) compared the mutagenicity, tumor-initiating activity, and complete carcinogenicity of several series of structurally related PAHs. Tumor-initiating activity was found to correspond with complete carcinogenicity. Quantitation of mutagenicity in the Ames assay for structurally related PAHs failed to provide a reliable indication of tumor-initiating activity or complete carcinogenicity. In addition, mutagenicity results could not be used to predict which PAHs would be noncarcinogenic. Many PAHs were active mutagens, but were not shown to be carcinogenic. Studies using methylated derivatives of anthracene demonstrated a correlation between mutagenicity of specific metabolites and tumor initiating activity in mouse skin (LaVoie et al., 1985). Raveh et al. (1982) reported that the mutagenic response to PAHs in Chinese hamster V79 cells was similar to the skin tumor initiating activity observed in SENCAR mice. Benzo[a]pyrene was demonstrated to be a more potent mutagen and skin tumor initiator than cyclopenta[c,d]pyrene.

Blackburn et al. (1996) compared the predictive power of a mutagenicity test (the Modified Ames Test, which uses enhanced extraction techniques and greater levels of S9 to improve performance when oils are tested) and DNA adduct formation (measured by P32-postlabelling) to predict the dermal carcinogenicity of 120 PAH-containing oils. The Modified Ames Test provided greater accuracy in predicting carcinogenicity (96%). In addition, the mutagenicity index estimated from this test correlated strongly ($r^2 \geq 0.83$) with PAH content of the oils. The DNA adduct assay predicted carcinogenicity correctly with about 73% accuracy; however, the study authors indicated that the lower predictability may have resulted from the use of adduct data that were collected while the assay was still undergoing development.

Sjogren et al. (1996) performed a multivariate analysis of data for 29 PAHs to evaluate the relevance of different biological assays to the carcinogenic properties of PAHs. This analysis considered carcinogenicity (International Agency for Research on Cancer [IARC] weight of evidence and QSAR predictions), bacterial mutagenicity, inhibition or enhancement of bacterial mutagenicity, AhR affinity, and enzyme induction. Bacterial mutagenicity data were poorly correlated with observed and predicted cancer data, while AhR affinity variables were statistically relevant to describe these data.

Other studies suggest that the relationship between affinity for the AhR and carcinogenic potency is unclear. For example, highly mutagenic fjord-region PAHs are potent carcinogens despite exhibiting lower AhR affinity (reviewed by Bostrom et al., 2002). Likewise, some PAHs that strongly activate the AhR, such as benzo[k]fluoranthene (Machala et al., 2001), are only weakly carcinogenic. In addition, some studies have demonstrated the formation of DNA adducts in the liver of AhR knock-out mice following intraperitoneal or oral exposure to benzo[a]pyrene (Sagredo et al., 2006; Uno et al., 2006; Kondraganti et al., 2003), indicating that Ah responsiveness is not strictly required for metabolic activation and genotoxicity. These findings suggest that there may be alternative (i.e., non-AhR mediated) mechanisms of benzo[a]pyrene activation in the mouse liver, and that AhR affinity would not be a good predictor of carcinogenic potency.

AhR-mediated CYP1A1 induction by PAHs is considered to contribute to tumorigenesis by increasing the production of DNA-reactive metabolites (Ayrton et al., 1990). However, CYP1A1 induction potency alone does not appear to correlate well with carcinogenic potency of PAHs. Ethoxyresorufin O-deethylase (EROD) activity was evaluated as a measure of CYP1A1 induction in rat hepatocytes (Bosveld et al., 2002; Till et al., 1999; Willett et al., 1997) and trout liver cells (Bols et al., 1999). Till et al. (1999) additionally measured levels of CYP1A1 protein and mRNA. Machala et al. (2001) measured PAH activation of the AhR using a chemical-activated luciferase reporter gene assay. Comparable results were observed across studies, and benzo[k]fluoranthene was consistently demonstrated to be the most potent inducer of CYP1A1. Chrysene, benzo[b]fluoranthene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene were also demonstrated to be more potent inducers of CYP1A1 than benzo[a]pyrene. However, most of

these PAH compounds (except dibenz[a,h]anthracene) are considerably less potent as carcinogens in animal bioassays.

Ross et al. (1995) evaluated the relationship between TIDAL values for DNA adduct formation and lung adenoma formation in A/J mice. The TIDAL value versus tumor relationship was similar for five different PAHs, suggesting a correlation between adduct levels and tumor formation (regression analysis was not performed). As described above, the relationship of TIDAL level to tumor formation was similar for PAHs that produce different types of adducts and different mutations in the Ki-ras oncogene, suggesting that the probability of tumor formation may be related to the extent of overall DNA damage and repair (Nesnow et al., 1998a, 1996, 1995; Mass et al., 1993).

To summarize, various cancer-related endpoints have been associated with PAH carcinogenicity. Tumor initiation ability was shown to correspond well with complete carcinogenicity, while some studies suggested that bacterial mutagenesis assays of individual PAHs were not highly correlated with tumor formation (Sjogren et al., 1996; Lavoie et al., 1979). DNA adduct formation corresponded with lung adenoma formation in A/J mice for several PAHs (Sjogren et al., 1996; Ross et al., 1995; LaVoie et al., 1979). The development of RPFs in this analysis considered both tumorigenicity and cancer-related endpoints (e.g., mutagenicity, clastogenicity, morphological transformation). Studies of AhR binding/activation were not considered for use in deriving RPFs because there does not appear to be a clear relationship between affinity for the AhR and carcinogenic potency of PAHs.

2.7. SIMILARITIES IN RELATIVE POTENCY ESTIMATES ACROSS SPECIES AND EXPOSURE ROUTES

Available studies suggest that the potency of individual PAHs is generally consistent across species and study protocols. The consistency of potency estimates based on in vivo tumorigenicity studies conducted using different study protocols and exposure routes in varying species/strains of test animals is summarized below.

Nisbet and LaGoy (1992) and Clement Associates (1988) reported that RPFs for PAHs are reasonably consistent across different study protocols using varying species/strains of laboratory animals. RPF estimates were calculated in multiple test systems including mouse skin complete carcinogenesis studies, mouse skin tumor initiation studies, studies in rat lung (implantation), other rat studies (intrapulmonary injection, subcutaneous injection), and newborn mouse studies (intraperitoneal injection). The RPF estimates for specific PAHs calculated from different assay systems varied by less than an order of magnitude. The relative potency of individual PAHs to benzo[a]pyrene was also shown to be very similar when based on data in different strains of mice using different mouse tumor initiation models (Slaga and Fisher, 1983). Muller et al. (1997) compared the relative potency of benzo[a]pyrene and 3-methylcholanthrene from data generated in three species (rat, mouse, and hamster). Similar RPF values (i.e., within a

factor of 2) were derived for oral exposures in mice, rats, and hamsters. In their comparison across different exposure routes (oral, respiratory, and dermal), Muller et al. (1997) reported similar relative potencies for benzo[a]pyrene and 3-methylcholanthrene (within a factor of 2) for data from rats exposed via oral and respiratory routes, and for mice exposed via oral and dermal routes. The relative potency for respiratory exposure in mice was an order of magnitude lower than relative potencies for the other two exposure routes.

Schneider et al. (2002) performed a more recent evaluation of the impact of exposure route on the determination of RPFs. Potency ratios were calculated for several carcinogenicity bioassays by dividing the carcinogenic potency of a PAH mixture by the carcinogenic potency of benzo[a]pyrene as a single substance. The potency ratios were observed to vary by exposure route and target organ. For example, potency ratios associated with forestomach tumors from oral exposure ranged from 0.7 to 1.2 (i.e., the potencies of the PAH mixtures and benzo[a]pyrene to induce forestomach tumors were approximately equal). This suggested that these tumors may be attributable to the benzo[a]pyrene content of the mixture. Potency ratios for skin tumor production from dermal exposure ranged from 2 to 11, whereas RPFs calculated for lung tumors from oral exposure, pulmonary implantation, or inhalation were greater than 20. These results suggested that the benzo[a]pyrene content of PAH mixtures may be only slightly responsible for lung and dermal carcinogenicity. Schneider et al. (2002) suggested that RPF estimates should be derived separately for oral, dermal, and inhalation exposure using studies with the relevant exposure pathway.

To summarize, there is some consistency within the in vivo carcinogenicity database for relative potency estimates derived from different species and strains exposed by various routes, although this is an area for which further research is needed. However, Schneider et al. (2002) have cautioned that potency ratios appear to cluster by exposure route and target organ and have suggested that route-specific RPFs be developed. There is also some concern regarding the use of benzo[a]pyrene as an index chemical to estimate lung cancer from PAH mixtures, considering that the lung is relatively insensitive to benzo[a]pyrene-induced tumorigenicity following oral exposure (Gaylor et al., 1998). Section 8.6 provides a comparison of RPF values calculated in this report, using bioassay data from different exposure routes and study designs. RPF values were comparable across most exposure routes, with the exception of the newborn mouse intraperitoneal injection studies.

2.8. DOSE ADDITIVITY OF PAHs IN COMBINED EXPOSURES

Use of the RPF approach assumes that doses of component chemicals that act in a similar manner can be added together, after scaling the potencies relative to the index chemical, and that interaction effects do not occur at low environmental exposure levels (U.S. EPA, 2000, 1986). The level of confidence in the RPF approach is increased if dose additivity can be demonstrated experimentally, even with simple mixtures. For PAHs, the assumption of dose additivity at low

exposures cannot be confirmed or refuted based on the available experimental data. It appears that interactions may occur at higher doses of complex PAH mixtures (see below).

The complexity of potential interactions for tumorigenesis of binary mixtures of PAHs is illustrated in Table 2-2. The nature of the interaction varies with the PAHs evaluated and the study conditions (e.g., vehicle used, dose selection, study method). Many studies were designed to evaluate the combined administration of a known carcinogen with either a weak carcinogen or a noncarcinogenic PAH. The true nature of the interaction (i.e., additive, synergistic, or antagonistic) can be difficult to determine in studies wherein the tumorigenic response is not measured for both PAHs given alone and in combination. These studies can distinguish between an enhanced or cocarcinogenic response and an inhibitory response, but a further classification cannot be made. The interactions described as cocarcinogenic in Table 2-2 may be either additive or synergistic in nature.

Table 2-2. Studies of binary mixtures of PAHs and tumorigenicity

Reference	Endpoint	Findings	Net effect
Cavalieri et al., 1983	Mouse skin carcinogenicity	BaP and CPcdP given together resulted in a synergistic effect at low and intermediate doses; three- to sevenfold increase in relative risk at intermediate dose of both BaP and CPcdP as compared to the sum of the relative risk for the same dose of each PAH given alone.	S
DiGiovanni et al., 1982	Skin tumor initiation in mice	BeP increased BaP tumor initiation (30%↑), inhibited tumor initiation by DMBA (84%↓) and DBahA (48%↓) and produced no change in combination with 3-MC; DBacA inhibited tumor initiation by DMBA (92%↓), DBahA (39%↓), and 3-MC (61%↓) and produced no change in combination with BaP.	Co, I
Falk et al., 1964	Sarcoma induction in mice by subcutaneous injection	PH inhibited tumor response of DBahA in ethyl laurate vehicle (approximately 30%↓, estimated from graph); tumor response was enhanced in triethylene glycol vehicle (approximately 50%↑ to 100% tumor-bearing animals, estimated from graph).	Co, I
Lavik et al., 1942	Mouse skin tumors	3-MC and BaP, DBahA, or BaA essentially additive.	A
Pfeiffer, 1973	Sarcoma induction in mice by subcutaneous injection	BaP and DBahA less than additive; tumor response for combined treatment was within 10% of DBahA response.	I
Slaga et al., 1979	Skin tumor initiation in mice	BeP, Pyr, or FA increased skin tumor initiation by BaP (30, 35, and 23%↑, respectively); BeP, Pyr, or FA decreased skin tumor initiation by DMBA (84, 50, and 34%↓, respectively).	Co, I
Steiner, 1955; Steiner and Falk, 1951	Sarcoma induction in mice by subcutaneous injection	DBahA and 3-MC in combination roughly additive; BaA and CH in combination resulted in a synergistic effect (9%↑ above additive response); BaA and DBahA in combination resulted in inhibition (48%↓ below additive response).	A, S, and I
Van Duuren and Goldschmidt, 1976; Goldschmidt et al., 1973	Mouse skin carcinogenicity	BeP, BghiP, Pyr, or FA and BaP increased tumors over BaP alone (>50% increase in incidence, also ↑ multiplicity); no tumors were observed for PAHs without BaP.	S
Van Duuren et al., 1973	Mouse skin carcinogenicity	BaP and BghiP had cocarcinogenic effect (23%↑ over BaP response alone).	Co
Warshawsky et al., 1993	Mouse skin carcinogenicity	Nontumorigenic dose of BaP increased tumor incidence produced by CH (16%↑), AC (8%↑), and FA (8%↑).	S

3-MC = 3-methylchloanthrene; A = additive; Co = cocarcinogenic (enhanced tumorigenicity, study design does not allow for determination of A or S); DMBA = 7,12-dimethyl-benz[a]anthracene; I = inhibitory; S = synergistic

Slooff et al. (1989) reviewed the available data addressing the carcinogenicity of individual PAHs and in combination. It was concluded that a generally additive effect was observed following administration of more than two different PAHs in weight ratios similar to those occurring in ambient air or in various emissions. Combinations of only two PAHs

produced either additive, synergistic, or inhibitory effects. The complexity of the interaction among single PAH compounds is thought to be related to effects on metabolic enzyme systems including induction processes and competitive inhibition. The generally additive response noted for a more complex mixture may reflect the balance between inhibitory and synergistic processes.

Additivity has been observed in carcinogenicity studies of complex mixtures of PAHs. Schmähl et al. (1977) evaluated the production of skin tumors following combined dermal treatment with 11 PAHs found as constituents of automobile exhaust. Tumor findings were presented separately for two groups of PAHs. High potency carcinogens (Group 1) included benzo[a]pyrene, dibenz[a,h]anthracene, benz[a]anthracene, and benzo[b]fluoranthene. Lower potency PAHs (Group 2) included anthracene, benzo[e]pyrene, benzo[g,h,i]perylene, chrysene, fluoranthene, phenanthrene, and pyrene. Chronic dermal exposure to PAHs in both groups resulted in an additive response when compared to the tumor response for each group alone.

Nesnow et al. (1998b) evaluated lung tumor formation in A/J mice following combined administration of five carcinogenic PAH compounds (benzo[a]pyrene, benzo[b]fluoranthene, dibenz[a,h]anthracene, 5-methylchrysene, and cyclopenta[c,d]pyrene). High and low doses were selected for each PAH in this study based on toxicity, survival, range of response, and predicted tumor yield. The ratio of PAH doses was designed to simulate PAH ratios found in environmental air and emissions samples. PAHs were administered to mice in a 2^5 factorial study design yielding 32 dose groups (combination of five PAHs at high and low doses). The formation of lung adenomas was evaluated 8 months following intraperitoneal injection of PAH mixtures. A response surface model was used to evaluate specific interactions among PAHs. The results of the study indicated that greater-than-additive effects were seen at low doses, while less-than-additive effects were observed at high doses. However, the magnitude of the interactions was relatively small (twofold), suggesting that potential interactions are limited in extent.

Dermal application of binary mixtures of PAHs has also been shown to produce additive, synergistic, and inhibitory effects on DNA binding in mouse skin (Hughes and Phillips, 1993, 1990). Hermann (1981) demonstrated that many PAHs could both enhance and inhibit the bacterial mutagenicity of benzo[a]pyrene depending on the relative concentrations in the binary mixture. Binary mixtures of benzo[a]pyrene and benzo[e]pyrene produced a synergistic response in the TA98 strain of *S. typhimurium* (which detects frameshift mutations) and antagonistic and additive effects in strain TA100 (which detects a broad spectrum of mutations) depending on the concentration (Hass et al., 1981). Binary mixtures of PAHs have also been shown to produce antagonistic or less-than-additive effects in the Ames assay of bacterial mutagenicity (Barrai et al., 1992; Salamone et al., 1979a). Vaca et al. (1992) demonstrated an additive effect for sister chromatid exchange induction by combined administration of

benzo[a]pyrene and fluoranthene in human peripheral lymphocytes cocultured with polychlorinated biphenyl-induced rodent liver cells.

The effects of binary PAH mixtures on gene expression, DNA adduct formation, apoptosis, and cell cycle are additive compared to the effects of the individual compounds in human hepatoma cells (HepG2) (Staal et al., 2007). Equimolar and equitoxic mixtures of benzo[a]pyrene with either dibenzo[a,l]pyrene, dibenz[a,h]anthracene, benzo[b]fluoranthene, fluoranthene, or 1-methylphenanthrene were studied. PAH mixtures showed an additive effect on apoptosis and on cell cycle blockage. The effects of binary mixtures of PAHs on gene expression were generally additive or slightly antagonistic.

Additivity has also been observed for the mutagenicity of PAHs administered as a complex mixture (Bostrom et al., 1998; Kaden et al., 1979). Kaden et al. (1979) evaluated the bacterial mutagenicity of the PAH fraction of kerosene soot using resistance to 8-azaguanine as a genetic marker for forward mutation in *S. typhimurium*. Approximately half of the PAHs tested (34 of 70) produced a significant increase in the mutant fraction in this assay system. The mutagenicity of the complex soot mixture was demonstrated to be approximately equal to the additive mutagenicity of the individual components. Bostrom et al. (1998) reported additivity in the Ames test of bacterial mutagenesis (i.e., reversion to histidine independence) for a mixture of four PAHs (benzo[a]pyrene, benz[a]anthracene, fluorene, and pyrene) using four different strains of *S. typhimurium.*

Mechanistic studies have suggested that the outcome of the interaction between two PAHs in a binary mixture is dependent on changes in metabolism. PAHs can act as both inducers and competitive inhibitors of the CYP enzymes that are responsible for generation of reactive metabolites. Benzo[e]pyrene has been shown to alter the oxidative metabolism of benzo[a]pyrene, which may be related to the cocarcinogenic effect seen in skin tumor initiation studies (Baird et al., 1984). Alterations in the types and amounts of benzo[a]pyrene metabolites suggest that benzo[e]pyrene-induced changes may be isozyme specific (Smolarek and Baird, 1984). An increase in the formation of benzo[a]pyrene DNA adducts has also been demonstrated for coadministration of benzo[e]pyrene in SENCAR mouse skin (Smolarek et al., 1987). Fluoranthene and pyrene have been shown to increase the formation of benzo[a]pyrene-DNA adducts in mouse skin following a combined treatment (Rice et al., 1988, 1984). Enhancement of the metabolism of benzo[a]pyrene to diol epoxide metabolites and subsequent DNA binding may explain the increased carcinogenic effect in this case. Phenanthrene did not increase the formation of benzo[a]pyrene-DNA adducts and was not shown to be cocarcinogenic following combined administration with benzo[a]pyrene in this study. Cherng et al. (2001) demonstrated that benzo[g,h,i]perylene increased the formation of benzo[a]pyrene adducts in hepatoma cells (HepG2) by enhancing benzo[a]pyrene induction of CYP1A1. Benzo[g,h,i]-perylene increased the nuclear accumulation of the AhR and/or the activation of the AhR to a DNA-binding form (Cherng et al., 2001). Benzo[k]fluoranthene altered the metabolic profile of

benz[a]anthracene by increasing the activity of CYP1A1 (Schmoldt et al., 1981). The bacterial mutagenicity of benz[a]anthracene was enhanced by use of a rodent liver S9 that was obtained from animals previously exposed to other PAHs (Norpoth et al., 1984). Coadministration of benzo[a]pyrene and benz[a]anthracene to hamster embryo cell cultures resulted in decreases in the metabolism of benzo[a]pyrene, the level of DNA binding, and the mutation frequency in hamster V79 cells (Smolarek et al., 1986).

In summary, combined administration of binary mixtures of PAHs can result in several types of joint action (i.e., additive, synergistic, or antagonistic). The nature of the joint action appears to be dependent on the characteristics of the individual PAHs, related changes in metabolism and possibly the test species/strain. PAHs can act as both inducers and competitive inhibitors of the CYP enzymes that are responsible for generation of reactive metabolites. Additivity has been observed for some complex mixtures of PAHs, suggesting a balance in the relative metabolism of individual PAHs. For the purposes of this analysis, an assumption is made that the combination of individual PAHs results in additive effects. Additional research is needed to characterize the validity of this assumption.

3. DISCUSSION OF PREVIOUSLY PUBLISHED RPF APPROACHES

There are multiple analyses available for the derivation of relative potency estimates for individual PAHs. All of these analyses utilize benzo[a]pyrene as the index chemical. Table 3-1 compares relative cancer potency values for PAHs presented by several authors. A review of the derivation of these relative potency values follows.

1

Table 3-1. Comparison among various relative potency estimates for PAHs from the published literature and regulatory agencies (1984–2004)

PAH	Abbr	U.S. EPA (1993)	Chu and Chen (1984)	Clement (1988)	Clement (1990)	Rugen et al. (1989)	Slooff et al. (1989)	Kroese et al. (2001)	Nisbet and LaGoy (1992)	Malcolm and Dobson (1994)	Meek et al. (1994)	Muller et al. (1997)	Larsen and Larsen (1998)	Collins et al. (1998)	Cali-fornia EPA (2004)
Acenaphthene	AN								0.001	0.001					
Acenaphthylene	ANL								0.001	0.001					
Anthanthrene	AA			0.32	0.316							0.28	0.3		
Anthracene	AC						0	0	0.01	0.01			0.0005		
Benzo[a]pyrene	BaP	1	1	1	1	1	1	1	1	1	1	1	1	1	
Benz[a]anthracene	BaA	0.1	0.013	0.145		0.004–0.006	0–0.04	<0.1	0.1	0.1		0.014	0.005	0.1	
Benzo[b]fluoranthene	BbF	0.1	0.08	0.14	0.1228	0.0235			0.1	0.1	0.06	0.11	0.1	0.1	0.62
Benzo[c]phenanthrene	BcPH											0.023	0.023		
Benzo[e]pyrene	BeP			0.004	0.007					0.01		0	0.002		
Benzo[g,h,i]perylene	BghiP			0.022	0.0212		0.01–0.03	0.03	0.01	0.01		0.012	0.02		
Benzo[j]fluoranthene	BjF			0.061	0.0523	0.0763				0.1	0.05	0.045	0.05	0.1	0.52
Benzo[k]fluoranthene	BkF	0.01	0.004	0.066	0.0523		0.03–0.09	<0.1	0.1	0.1	0.04	0.037	0.05	0.1	
Chrysene	CH	0.001	0.001	0.0044			0.05–0.89	0.1–0.03	0.01	0.01		0.026	0.03	0.01	0.17
Coronene	CO									0.001					
Cyclopenta[c,d] pyrene	CPcdP			0.023						0.1		0.012	0.02		
Dibenz[a,h] anthracene	DBahA	1	0.69	1.11		0.599			5	1		0.89	1.1		
Dibenz[a,c]anthracene	DBacA									0.1					
Dibenzo[a,e]pyrene	DBaeP												0.2	1	
Dibenzo[a,h]pyrene	DBahP											1.2	1	10	11
Dibenzo[a,i]pyrene	DBaiP											1.1	0.1	10	12
Dibenzo[a,l]pyrene	DBalP												1	10	
Fluoranthene	FA						0–0.06	0.01	0.001	0.001			0.05		
Fluorene	FE								0.001	0.001					
Indeno[1,2,3-c,d]pyrene	IP	0.1	0.017	0.232	0.278	0.00599	0–0.08	0.1	0.1	0.1	0.12	0.067	0.1	0.1	
Perylene	Pery									0.001					

Table 3-1. Comparison among various relative potency estimates for PAHs from the published literature and regulatory agencies (1984–2004)

PAH	Abbr	U.S. EPA (1993)	Chu and Chen (1984)	Clement (1988)	Clement (1990)	Rugen et al. (1989)	Slooff et al. (1989)	Kroese et al. (2001)	Nisbet and LaGoy (1992)	Malcolm and Dobson (1994)	Meek et al. (1994)	Muller et al. (1997)	Larsen and Larsen (1998)	Collins et al. (1998)	Cali-fornia EPA (2004)
Phenanthrene	PH						0.01	<0.01	0.001	0.001		0.00064	0.0005		
Pyrene	Pyr			0.081					0.001	0.001		0	0.001		

Abbr = abbreviation

U.S. EPA (1993) presented RPFs (termed EOPPs) for seven PAHs (benzo[a]pyrene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene) as *Provisional Guidance* for the risk evaluation of PAHs. On the IRIS database, the current entries for all seven of these compounds contain a cancer weight of evidence classification of Group B2 (probable human carcinogen, based on sufficient evidence of carcinogenicity in animals) (www.epa.gov/iris). U.S. EPA (1993) indicated that the data for PAHs did not meet the criteria for the development of toxicity equivalency factors (TEFs). In particular, the existing database was limited primarily to studies of metabolism, genotoxicity, and cancer, and the assumptions of the dose-additivity model (i.e., toxicological similarity and no interactions at low concentrations) were not proven or refuted. The EOPP terminology was used because this approach was limited to skin painting data and was based on benzo[a]pyrene exposure from a single (oral) pathway (for the derivation of the slope factor). This analysis considered only a small subset of PAHs routinely measured in PAH mixtures at hazardous waste sites. The EOPP values were based on previous evaluations conducted by Chu and Chen (1984) and Clement Associates (1988) and were calculated for various test systems (i.e., mouse skin carcinogenesis, subcutaneous injection in mice, intrapulmonary administration to rats, tumor initiation on mouse skin, and intraperitoneal injection in newborn mice) (Clement Associates, 1988). Various statistical methods for combining data sets were considered; however, final EOPP values were based on a single test system (skin painting) and were rounded to the closest order of magnitude. The EOPPs were recommended for the oral exposure route only, because the quantitative dose-response assessment for benzo[a]pyrene was from an oral carcinogenicity bioassay (i.e., an oral cancer slope factor). This recommendation was, however, complicated by the fact that the EOPPs were derived from comparisons based on dermal exposure.

Chu and Chen (1984) presented RPF values for the seven PAH compounds described in the *Provisional Guidance* described above (U.S. EPA, 1993) (see Table 3-1). These values were calculated using mouse skin painting data only. Tumor incidence data were modeled using the linearized multistage model and the resulting ED_{10} and q1* (upper confidence limit of the linear slope) were presented for target PAHs and benzo[a]pyrene. The RPFs listed in Table 3-1 represent the ratio of the q1* value for a PAH compound to the q1* value for benzo[a]pyrene (i.e., $q1^*_{PAH} \div q1^*_{BaP}$).

Clement Associates (1988) identified 11 published studies that concurrently compared the carcinogenicity of benzo[a]pyrene with one or more other PAHs, and used the data to derive relative cancer potencies for 13 PAHs, including benzo[a]pyrene. Test protocols used in this analysis included mouse skin complete carcinogenesis, initiation-promotion on mouse skin, subcutaneous injection into mice, lung implantation in rats, and intraperitoneal injection into newborn mice. Tumor incidence data were fit to a simplified version of the Moolgavkar-Venson-Knudsen (MVK) two-stage model and to the linearized multistage model to obtain low-

dose cancer potency values (transition rates and low-dose slope factors, respectively). Most of the estimates were derived using data for multiple exposure levels and controls, but some were based on a single exposure level and a control. RPFs were calculated as the ratio of the estimated transition rate or slope factor for a particular PAH to the corresponding values for benzo[a]pyrene from the same study. Clement Associates (1988) selected representative RPFs for each of the studied PAHs based on evaluations of the quality of the studies from which the estimates were obtained.

Clement Associates (1990) also derived relative cancer potencies for eight PAHs based on tumor incidence data from rat lung implantation data only (Deutsch-Wenzel, 1983). The data were restricted to a single group of studies using a defined experimental protocol in order to address issues of questionable data quality associated with other studies. Data quality concerns cited for other studies include variation in survival, saturation of the carcinogenic effect, outmoded pathological classification, and inadequate controls. The RPF values based on rat lung implantation data were comparable to those originally derived by Clement Associates (1988) (see Table 3-1).

Rugen et al. (1989) proposed a relative potency approach to establish acceptable exposure levels (AELs) for six carcinogenic PAHs in drinking water (listed in Table 3-1). These authors reviewed mouse skin painting studies in which the cancer potency of benzo[a]pyrene was compared with those of other PAHs (Bingham and Falk, 1969; Wynder and Hoffmann, 1961, 1959a, b). The following relationship was used to calculate conversion factors to derive AELs for these PAHs from the AEL for benzo[a]pyrene: relative tumor dose (RTD) = $(d_1/n_1)/(d_2/n_2)$; where d_1 and n_1 represented a dosage level and associated tumor incidence after a given exposure duration to a certain PAH, PAH_1, and d_2 and n_2 represented similar quantities for exposure to the index PAH, benzo[a]pyrene, for the same exposure duration. The AEL for a particular PAH was then derived with the following relationship: $AEL_{(PAHi)} = AEL_{(benzo[a]pyrene)} \times RTD_{(PAHi)}$. In this approach, RTDs for PAHs more potent than benzo[a]pyrene were less than 1 and RTDs for PAHs less potent than benzo[a]pyrene were greater than 1. The reciprocal of the RTDs derived by Rugen et al. (1989) were comparable to the RPFs presented by other authors and are presented as such in Table 3-1.

The Netherlands (RIVM) proposed RPF values for 10 PAHs (naphthalene, anthracene, phenanthrene, fluoranthene, chrysene, benz[a]anthracene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[g,h,i]perylene, and indeno[1,2,3-c,d]pyrene) (Slooff et al., 1989). RPFs were calculated as a ratio of ED_{50} values that were calculated using a simple linear model. For dermal studies in which the latency period was determined, the tumor incidence was divided by latency and concentration, and the values were averaged for the different concentrations. Kroese et al. (2001) provided an update of the RPF values calculated by Slooff et al. (1989) by incorporating more recent evaluations conducted by other authors (Larsen and Larsen, 1998; Nesnow et al.,

1998b; Muller, 1997; Nisbet and LaGoy, 1992). The RPF values for chrysene and fluoranthene were decreased, while other values remained similar to those originally proposed (see Table 3-1).

Nisbet and LaGoy (1992) proposed toxicity equivalence factors for 17 PAHs commonly found at hazardous waste sites. These authors reviewed published studies in which the tumorigenic potencies of one or more PAHs were compared with benzo[a]pyrene (essentially the same as those reviewed by Clement Associates, 1988) and rounded, to an order of magnitude, the estimates presented by Clement Associates (1988) for seven carcinogenic PAHs (dibenz[a,h]-anthracene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-c,d]-pyrene, benzo[g,h,i]perylene, and chrysene) (see Table 3-1). Nisbet and LaGoy (1992) argued that the rounded estimates more accurately reflected the uncertainty in the estimates than the values presented by Clement Associates (1988). Nisbet and LaGoy (1992) stated that Clement Associates (1988) proposed a TEF of 0.32 for anthracene (CASRN 120-12-7), but examination of the original report shows that Clement Associates (1988) proposed this value for anthanthrene (CASRN 191-26-4) and did not propose a value for anthracene. Nisbet and LaGoy (1992) assigned a value of 0.01 to anthracene. In addition, Nisbet and LaGoy (1992) arbitrarily assigned TEFs of 0.001 to eight other PAHs for which adequate evidence of carcinogenicity in animals was not available (acenaphthene, acenaphthylene, fluoranthene, fluorene, 2-methyl-naphthalene, naphthalene, phenanthrene, and pyrene). In defense of this assignment, the argument was made that some of these PAHs have been shown to have some, albeit limited, evidence for carcinogenic or genotoxic activity in some studies (e.g., phenanthrene and naphthalene[3]). The RPF value proposed for dibenz[a,h]anthracene was substantially higher than that proposed by Clement Associates (1988). Nisbet and LaGoy (1992) indicate that their analysis of the dose-response data suggests that an RPF value of 5 is more appropriate for environmental exposures where the chemically-related tumor incidence rate would be approximately <25%.

Malcolm and Dobson (1994) used RPFs for 23 PAHs to calculate environmental assessment levels for atmospheric PAHs (sponsored by the Great Britain Department of the Environment). The RPFs were derived from previously reported review papers (Nisbet and LaGoy, 1992; Rugen et al., 1989; Clement Associates, 1988; Chu and Chen, 1984), as well as the primary literature describing pulmonary implant, skin painting, subcutaneous injection, and mouse skin DNA binding studies. No information was provided regarding the methodology used to derive RPFs from specific experimental studies. The proposed RPF values for individual PAHs were the highest values reported in the literature. Many of the RPF values are similar to those reported by Nisbet and LaGoy (1992). RPFs were additionally reported for benzo[e]pyrene, coronene, cyclopenta[c,d]pyrene, dibenz[a,c]anthracene, and perylene. The benzo[e]pyrene and cyclopenta[c,d]pyrene RPFs were apparently calculated directly from mouse

[3]It should be noted that a recent bioassay for naphthalene has shown increased incidence of nasal tumors in exposed rats (NTP, 2000).

skin painting studies (Habs et al., 1980; Hoffmann and Wynder, 1966; Wynder and Hoffmann, 1959a, b). Coronene and perylene were arbitrarily assigned RPF values of 0.001 given the IARC and U.S. EPA designation as "not classifiable as to human carcinogenicity" (similar approach to Nisbet and LaGoy, 1992). Dibenz[a,c]anthracene was assigned an RPF value of 0.1 based on the IARC designation of "possibly carcinogenic to humans."

Health Canada (Meek et al., 1994) proposed RPFs for five PAHs (benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, and indeno[1,2,3-cd]pyrene) based on the results of multistage modeling of incidence data in Osborne-Mendel rats treated by lung implantation (Deutsch-Wenzel et al., 1983). Values were based on a comparison of the doses that caused a 5% increase in tumor incidence (ED_{05}). RPFs were calculated as the ratio of the ED_{05} for benzo[a]pyrene to the ED_{05} for a specific PAH compound.

The Ontario Ministry of Environment and Energy (Muller et al., 1997) proposed RPF values for 209 PAHs using data from dermal studies in mouse skin or rat lung bioassays. Most of these PAHs were alkylated PAHs, PAH metabolites, or heterocyclic PAH compounds. The 17 unsubstituted PAHs that were evaluated in this analysis are listed in Table 3-1. Muller et al. (1997) derived a standard time of observation in order to account for varying study duration across experiments. Several dose-response models were considered for the evaluation of tumor incidence and multiplicity, and linear regression was selected as the preferable method. Tumorigenic potency (i.e., the slope of incidence/mg) was determined separately for each data set based on the following order of preference regarding study type: tumor initiation in CD-1 mice, tumor initiation in SENCAR mice, rat lung implantation, and complete carcinogenicity in C57BL mice. RPFs were determined as the ratio of PAH potency to the potency of benzo[a]pyrene. RPF values derived by Muller et al. (1997) were comparable to values estimated by other authors.

Larsen and Larsen (1998) estimated RPFs for 23 PAHs based on a compilation of available carcinogenicity data in animals using oral, pulmonary, and skin application of PAHs. The authors indicated that these values represent an entirely subjective estimate of relative potency; however, further detail regarding the derivation of RPF estimates was not provided.

Collins et al. (1998) developed RPFs (termed potency equivalency factors [PEFs]) for 21 PAHs; 10 of these were either methyl- or nitro-substituted or heterocyclic PAHs. A hierarchy of data types was utilized to provide an order of preference for data utilization in calculating RPFs. Because the analysis focused on PAHs as air contaminants, tumor data from inhalation studies were preferred (although none were found), followed by intratracheal or intrapulmonary instillation, oral administration, skin-painting, and subcutaneous or intraperitoneal injection. Genotoxicity and structure activity data were considered the least-preferred data type for calculation of RPFs. Collins et al. (1998) noted that a wide range of PEFs were observed for individual chemicals using different types of data (e.g., mutagenicity versus tumor data). The basis for the derivation of individual RPF values was presented in a California EPA (2002)

technical support document. RPF values for benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-c,d]pyrene, and chrysene were similar to those described by Clement Associates (1988). Additional RPFs for dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and dibenzo[a,l]pyrene were calculated using mouse skin and rat mammary gland data (Cavalieri et al., 1991, 1989). A cancer slope factor was directly calculated for dibenz[a,h]anthracene using the tumor incidence data from a drinking water study (Snell and Stewart, 1962). The relative potency of dibenz[a,h]anthracene was estimated to be 0.1, when compared to the oral potency for benzo[a]pyrene.

Revised California EPA RPFs were recently developed for benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, dibenzo[a,h]pyrene, and dibenzo[a,i]pyrene (California EPA, 2004). Cancer potency estimates were derived from lung adenoma data in newborn mice treated by intraperitoneal injection. Potency estimates represented the upper 95% confidence limit on the linear term of the multistage model fit for the newborn mouse dose-response data. Because benzo[a]pyrene was demonstrated to be 75 times more toxic in newborn mouse intraperitoneal assays than in adult oral studies, oral equivalent potencies for individual PAHs were derived by adjusting the cancer potency downward by a factor of 75. The RPFs listed in Table 3-1 were calculated as the ratio of the oral equivalent potency for a PAH to the oral potency estimate for benzo[a]pyrene. This methodology resulted in a significant increase in RPF values for benzo[b]fluoranthene, benzo[j]fluoranthene, and chrysene when compared with other approaches.

In summary, several approaches are available for the determination of RPFs for PAHs. RPF values are proposed in at least one study for a total of 27 PAHs (see Table 3-1). Because these approaches generally rely on similar bioassay data and modeling methods, the resulting RPF values are fairly comparable for most PAHs across studies. Reports by Larsen and Larsen (1998) and Malcolm and Dobbs (1994) did not provide sufficient information on the methodology used to calculate RPF estimates and are therefore more uncertain. Variable RPF estimates were reported for benz[a]anthracene, chrysene, and indeno[1,2,3-c,d]pyrene. RPF values were also highly variable for dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and dibenzo[a,l]pyrene; however, these were only presented in a few recent studies. As indicated above, the recent California EPA (2004) approach to estimating RPFs provides considerably higher RPF values for benzo[b]fluoranthene, benzo[j]fluoranthene, and chrysene, compared with other approaches.

U.S. EPA is reevaluating the RPF approach for PAHs in this analysis due to the evolution of the state of the science and increased understanding of PAH toxicology. A great deal of scientific research on PAHs has been conducted since the 1993 *Provisional Guidance* was developed. Toxicological data are available for a larger number of PAHs and cancer-related endpoints. However, the database for PAHs still does not meet the criteria for the derivation of TEFs. U.S. EPA (2000) defines TEFs as special types of RPFs that are derived when there are

abundant data supporting a specific mode of action that is pertinent to all health endpoints. RPFs may be derived when the mode of action is less certain or is known for only a subset of all health endpoints. The major differences in the use of TEFs and RPFs is that TEFs are applied to all health endpoints, exposure routes, and exposure durations (U.S. EPA, 2000), while RPFs may be limited to specific endpoints, routes, or durations. In the case of PAHs, there are inadequate data to identify a specific mode of action that is applicable across all health endpoints. Most of the available toxicological data are limited to cancer endpoints and there are few data on the potential mode(s) of action for other effects. As a result, the more generalized RPF approach is considered appropriate for PAHs.

3.1. PREVIOUS EFFORTS TO VALIDATE THE RPF APPROACH

Several studies have attempted to validate the RPF approach by comparing the cancer risk of a PAH mixture measured experimentally with the cancer risk that was predicted using the RPF method (Muller et al., 1997; McClure, 1996; Goldstein et al., 1994; Clement Associates, 1990, 1988; Krewski et al., 1989). These studies provide semi-quantitative information on the overall uncertainty in using a component-based approach. Consistent findings were not reported across these studies. Some studies suggested that the RPF approach would closely predict the cancer risks associated with PAH mixtures, while others indicated that cancer risks might be over- or underestimated.

Clement Associates (1988) evaluated the usefulness of selected RPFs to predict the tumor incidence observed in a mouse skin painting assay. Schmähl et al. (1977) exposed groups of mice to multiple doses of benzo[a]pyrene alone or to one of two defined mixtures of PAHs. The first of these mixtures was comprised of benzo[a]pyrene, dibenz[a,h]anthracene, benz[a]anthracene, and benzo[b]fluoranthene. The second mixture contained seven PAHs: phenanthrene, anthracene, fluoranthene, pyrene, chrysene, benzo[e]pyrene, and benzo[g,h,i]perylene. The predicted tumor incidences for the animals treated with the mixtures were calculated from benzo[a]pyrene equivalents of the mixture and dose-response modeling of the Schmähl et al. (1977) data for benzo[a]pyrene alone. Predicted tumor incidences for the first mixture were comparable to observed tumor incidences, while predicted values were greater than the observed values for the second mixture.

Clement Associates (1990) examined the utility of a relative potency approach, in which relative cancer potency estimates of eight PAHs were used, to predict the cancer potencies of each of four complex mixtures containing many PAHs and other substances: gasoline engine exhaust condensate, flue-gas condensate from coal-fired residential furnaces, diesel engine exhaust condensate, and sidestream smoke condensate of cigarettes. Relative cancer potencies (compared to benzo[a]pyrene) for each of the four complex mixtures were calculated using a simplified version of the MVK two-stage model and tumor incidence data from a series of published rat lung implantation studies that examined the carcinogenicity of each complex

mixture, various subfractions of the mixtures, and benzo[a]pyrene (Grimmer et al., 1988, 1987a, b, 1984). Lung implantation data (Deutsch-Wenzel, 1983) were used to calculate RPFs for benzo[b]fluoranthene, benzo[e]pyrene, benzo[j]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-c,d]pyrene, anthanthrene, benzo[g,h,i]perylene, and benzo[a]pyrene. The sum of the benzo[a]pyrene exposure equivalents for the eight PAHs (i.e., the sum of the products of the relative cancer potencies of the eight PAHs multiplied by their concentrations in the respective complex mixtures) accounted for only minor fractions of the total carcinogenicity of each of the four complex mixtures. When the assumption was made that each of the eight PAHs was as potent as benzo[a]pyrene, the sum of the benzo[a]pyrene equivalents still accounted for only minor fractions of the carcinogenicity of each mixture. Clement Associates (1990) concluded that the cancer risk associated with a complex PAH mixture could not be estimated reliably from measurements of a few indicator components, and further speculated that the underestimation occurred because complex mixtures that occur in the environment contain many PAHs that have not been studied in cancer tests, but may be carcinogenic. In addition, complex PAH mixtures found in the environment contain other potential carcinogens including substituted and heterocyclic PAHs and non-PAH components.

Krewski et al. (1989) compared the observed tumor response rate for two PAH mixtures in mice with the tumor response predicted using the RPFs for 13 individual PAHs; chemical characterization of the mixture was not provided. With the exception of the highest dose, the predicted tumor response for mixture 1 was similar to the observed response. For mixture 2, the predicted tumor response value was higher than the observed response.

Goldstein et al. (1994) compared the experimental carcinogenicity of a MGP residue to the predicted cancer risk using the Nisbet and LaGoy (1992) RPF scheme. The RPF method underestimated the carcinogenicity of the mixture. The lack of correspondence was suggested to be related to the presence of unidentified carcinogens in the mixture or possible synergistic interactions between PAHs.

McClure et al. (1996) compared the tumor response predicted using U.S. EPA's 1993 provisional values (i.e., EOPPs) to the observed response reported in studies of mice exposed to synthetic and complex mixtures of PAHs. The results of this analysis were mixed. EOPP values closely predicted the mouse tumor response to subcutaneous or dermal application of synthetic mixtures containing relatively potent carcinogens, while overestimating the response to synthetic mixtures containing only relatively weak carcinogens (similar to findings of Clement Associates, 1988). Mouse skin tumor initiation with several coal liquids was closely predicted by the EOPP approach; however, this method underestimated the tumor response from lung implantation of coal furnace emission condensate and its PAH-containing neutral fraction.

The validation analyses that were performed by Muller et al. (1997) consisted of component versus whole mixture risk comparisons using data for smoky coal and coke oven emissions. The human lung cancer risks that were estimated using the RPF approach were

compared to the whole mixture cancer risk derived from epidemiology studies. The relative content of PAHs (compared to benzo[a]pyrene) in the mixture was determined analytically (for smoky coal and coke oven emissions) or was estimated as a standard mixture assumed to represent an average PAH profile. The RPF method produced PAH cancer risk estimates that were significantly lower than the risk estimates derived from epidemiology studies.

4. EVALUATION OF THE CARCINOGENICITY OF INDIVIDUAL PAHs

4.1. DATABASE OF STUDIES ON PAH CARCINOGENICITY AND CANCER-RELATED ENDPOINTS

A database of primary literature relevant to the RPF approach for PAHs was developed. This was accomplished through the following means:

- Definition of the study types that were considered relevant to relative potency development;
- Review of reference lists from review articles and other secondary sources;
- Identification of selected PAHs to be included in search of open literature;
- Performance of targeted searches of open literature on selected PAHs; and
- Population of the database with references and meaningful keywords.

The study types that were considered most useful for RPF derivation were rodent carcinogenicity bioassays (all routes) in which one or more PAH was tested at the same time as benzo[a]pyrene. In addition, in vivo and in vitro data for cancer-related endpoints (in which one or more PAH and benzo[a]pyrene was tested simultaneously) were obtained, including studies on the formation of DNA adducts, mutagenicity, chromosomal aberrations, aneuploidy, DNA damage/repair/recombination, unscheduled DNA synthesis, and cell transformation. Although it would be possible to calculate RPFs from studies where a PAH and benzo[a]pyrene were tested by the same laboratory using the same test system but at different times, this approach was not considered because it could introduce differences in the dose-response information that are unrelated to the chemical (e.g., variability associated with laboratory environment conditions, animal handling, food supply). Thus, studies in which benzo[a]pyrene was not tested simultaneously with another PAH were not considered for use in calculating RPFs. Studies that did not include benzo[a]pyrene were, however, considered useful for evaluating the weight of evidence for selecting PAHs to be included in the RPF approach.

Several study types were initially excluded from the database because they did not provide carcinogenicity or cancer-related endpoint information for individual PAHs. These include biomarker studies measuring DNA adducts in humans, studies of PAH metabolism, and studies of PAH mixtures. Although these studies contain important information on human exposure to PAH mixtures and the mode of action for PAH toxicity, they generally do not contain dose-response information that would be useful for calculation of RPF estimates. In addition to the primary bioassay and cancer-related endpoint studies described above, the RPF

database also includes information on PAH mode of carcinogenic action, interactions among PAHs in mixtures, and the influence of exposure route on carcinogenic action of PAHs.

Primary studies were identified through the review of available secondary sources and review articles, supplemented by a targeted literature search. A complete list of the secondary sources that were reviewed is contained in Appendix A. A literature search strategy was developed by first constructing a list of the individual PAHs to be included. The list of PAHs was restricted to unsubstituted PAHs with three or more fused aromatic rings containing only carbon and hydrogen atoms, because these are the most widely studied members of the PAH chemical class. Heterocyclic PACs or PAHs with substituted groups (e.g., alkyl, hydroxyl, sulfhydryl, amino, or nitro groups) were not included. An initial search yielded a list of PAHs for which toxicological data are available. Individual PAHs were then chosen for the literature search because they were known to have toxicological information relevant to cancer, and in most cases, their presence in environmental sources of PAH exposure was known. Using these criteria and excluding benzo[a]pyrene, 74 PAHs were identified from primary and secondary sources (see Table 2-1 in Chapter 2).

A search of the open literature was conducted in the MEDLINE (PubMed) database for the 74 PAHs that were identified. This database encompasses many of the studies that would also be found in TOXLINE and CANCERLIT (the latter is no longer available as a separate database). MEDLINE was searched by CASRN in conjunction with cancer and cancer-related endpoint keywords. The search was not limited by publication date to ensure that all relevant studies were identified. A few compounds did not show any result when searched by CASRN. For these PAHs, an additional search by name was conducted. Search results, including MEDLINE keywords, were downloaded directly into the working RPF database.

In addition to MEDLINE, computer searches of the following databases and websites were conducted: IARC, World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR), Health Canada, the National Toxicology Program (NTP), California EPA's Office of Environmental Health Hazard Assessment (OEHHA), the Substance Registry System, the Chemical Carcinogenesis Research Information System (CCRIS), the Toxic Substance Control Act Test Submission (TSCATS) database, and the Distributed Structure-Searchable Toxicity (DSSTOX) database.

Primary and secondary studies were entered in the RPF database and relevant keywords (identifying study type, whether benzo[a]pyrene was included, route of administration, target organ, etc.) were identified for each study. The list of keywords was developed in order to facilitate database searching for references on a specific topic. Quality assurance procedures were employed to ensure that database references were properly keyword-coded for retrieval.

4.2. STUDIES IN HUMANS

Numerous studies have evaluated cancer outcomes in PAH-exposed individuals (reviewed in Bostrom et al., 2002; WHO, 1998; ATSDR, 1995; IARC, 1987, 1983, 1973). However, since these exposures were to complex mixtures containing multiple PAH carcinogens, they did not provide adequate data to evaluate the human carcinogenicity of individual PAH compounds. Epidemiology studies have focused on occupational exposure to PAH mixtures. Emissions from coke production, coal gasification, aluminum production, iron and steel founding, coal tars, coal tar pitches, and soot have produced lung cancer in humans (Bostrom et al., 2002). Skin and scrotal cancers have resulted from exposure to coal tar, coal tar pitches, nonrefined mineral oils, shale oils, and soot (Larsen and Larsen, 1998; WHO, 1998; ATSDR, 1995). Occupational studies clearly demonstrate exposure-response relationships for PAH mixtures; however, quantitative estimates of risk are limited primarily to lung cancer in coke oven workers (Bostrom et al., 2002; Larsen and Larsen, 1998; ATSDR, 1995).

Biomonitoring of exposure to PAHs includes measurement of DNA and protein adducts and measurement of urinary metabolites of PAHs, studies on genetic polymorphisms of CYP450 and other enzymes, and changes in PAH metabolism (Bostrom et al., 2002; Larsen and Larsen, 1998; ATSDR, 1995). While these studies demonstrate the degree of exposure to PAHs from various settings, quantitative dose-response data for humans exposed to individual PAHs are not available. Cancer-related endpoint studies that were performed using human cell lines are presented with similar assays in other mammalian species in Section 4.3.

4.3. STUDIES IN ANIMALS

The database of studies investigating cancer or cancer-related endpoints in animals exposed to PAHs is extensive. For the purpose of developing relative potency estimates, only those studies that included at least one selected PAH and benzo[a]pyrene as a reference compound were reviewed. Studies were excluded if PAH potency comparisons were not conducted in the same laboratory in concurrent experiments. Studies without benzo[a]pyrene are listed in two separate bibliographies in Appendix B. Table B-1 shows PAHs that were assayed with or without benzo[a]pyrene. Table B-1 shows that 32 of the 74 PAHs were assayed with benzo[a]pyrene; an additional 14 PAHs were not tested in the same study as benzo[a]pyrene. The remaining 28 PAHs either have only cancer-related endpoint data, or have neither bioassays nor cancer-related endpoint data. Bioassays without benzo[a]pyrene were considered in the weight of evidence evaluation for individual PAHs (Section 6.1). Studies that provided only information on PAH mixtures or PAH metabolites were not reviewed or summarized for this analysis.

References in the database were sorted by keyword into the following major categories: cancer bioassays, in vivo studies of cancer-related endpoints, and in vitro studies of cancer-related endpoints. These categories were further divided by route (for bioassays) or by endpoint

(for cancer-related endpoints). Each study was reviewed, and critical study details were extracted into tables (Tables 4-1 through 4-14) for each individual endpoint. Studies with data on selected PAHs and benzo[a]pyrene were used, even if a particular PAH has not been evaluated by U.S. EPA or IARC for carcinogenicity. Studies were included in the analysis if the following selection criteria were met:

- Benzo[a]pyrene was tested simultaneously with another PAH;
- A statistically increased incidence of tumors was observed with benzo[a]pyrene administration;
- Benzo[a]pyrene produced a statistically significant change in a cancer-related endpoint finding;
- Quantitative results were presented;
- The carcinogenic response observed in either the benzo[a]pyrene- or other PAH-treated animals at the lowest dose level was not saturated (i.e., tumor incidence at the lowest dose was <90%); and
- There were no study quality concerns or potential confounding factors that precluded use (e.g., no concurrent control, different vehicles, strains, etc. were used for the tested PAH and benzo[a]pyrene; use of cocarcinogenic vehicle; PAHs of questionable purity; unexplained mortality in treated or control animals).

Table 4-1. Study summaries: dermal bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Mouse[a] strain	Exposure	Follow up	Vehicle	Promoter	Tumor type	Positive result	Nonpositive result	Meets selection criteria?	Comments
Complete carcinogenicity studies											
480	Bingham and Falk, 1969	CH3/He	3 times/wk	50 wk	Toluene or n-do-decane	None	Malignant and benign	BaA		No	BaP administered in different vehicle. n-Dodecane cocarcinogenic with BaA. No concurrent untreated, toluene, or n-dodecane control.
600	Habs et al., 1980	NMRI	2 times/wk (4 times for CO) for life	Until moribund or dead	Acetone (DMSO for CO)	None	Papilloma, carcinoma, sarcoma	BbF	BkF, BjF, CPcdP, CO, IP	Yes	
22390	Wynder and Hoffmann, 1959a	Swiss	3 times/wk	6–14 mo	Cyclo-hexane	None	Papilloma, carcinoma	BbF, BjF	BghiF, BkF	No	Deaths prior to first tumor appearance. No concurrent control.
19320	LaVoie et al., 1979	HA/ICR Swiss albino	3 times/wk	Unspecified	Acetone	None	Unspecified	CH, BbF, BjF, DBaeP, DBahP, DBaiP	AC, Pyr, BghiF, BkF, AA, BeP, DBelP, IP, BghiP, N23eP	No	Reiterates data published elsewhere.
22400	Wynder and Hoffmann, 1959b	Swiss	3 times/wk	10–22 mo	Acetone	None	Papilloma, carcinoma	CH, DBahA, DBaiP	AC, BeP, Pyr, FA	No	Deaths prior to first tumor appearance. Not clear if BaP administered simultaneously. No concurrent control.
13640	Cavalieri et al., 1983	Swiss	2 times/wk for 48 wk	Until 2 cm tumor or 61 wk	Acetone	None	Papilloma, adenoma, carcinoma	CPcdP		Yes	Reports both incidence and multiplicity.
13650	Cavalieri et al., 1981b	Swiss	2 times/wk for 30 wk	Until 2 cm tumor, moribund, or 57 wk	Acetone	None	Primarily squamous cell carcinoma	CPcdP	ACEP	Yes	Tumor incidence not useable because BaP tumor incidence was 100%. Tumor multiplicity data available for dose-response assessment.
620	Hoffmann and Wynder, 1966	Ha/ICR/ Mil Swiss	3 times/wk for 12 mo	Up to 15 mo	Dioxane	None	Papillomas	DBaeP, DBahP, DBaiP, DBaeF		Yes	Paper in German. Paper reports compound as DBalP; LaCassagne et al. (1968) state that it is actually DBaeF. DBahP incidence ≥90% at lowest dose.
17660	Cavalieri et al., 1977	Swiss	2 times/wk for 30 wk	Until moribund, dead, or after 70 wk	Acetone	None	Papilloma, kerato-acanthoma, carcinoma	DBahP, AA	BaA	Yes	DBahP incidence ≥90% at lowest dose.
610	Higginbotham et al., 1993	Swiss	2 times/wk	40 wk	Acetone	None	Papilloma, carcinoma	DBalP		No	No tumors with BaP.
19760	Masuda and Kagawa, 1972	Ha/ICR/ Mil Swiss	3 times/wk for 60 applica-tions	7 mo	Dioxane	None	Unspecified	DBalP		No	No concurrent untreated or vehicle control; lowest dose DBalP gave 100% incidence.
18570	Hecht et al., 1974	Ha/ICR/ Mil Swiss	3 times/wk for 17 mo	72 wk	Acetone	None	Unspecified	CH		No	BaP dose not reported.

Table 4-1. Study summaries: dermal bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Mouse[a] strain	Exposure	Follow up	Vehicle	Promoter	Tumor type	Positive result	Nonpositive result	Meets selection criteria?	Comments
21310	Shubik et al., 1960	Syrian golden hamster	2 times/wk for 10 wk	75 wk	Mineral oil	None	None		DBahA, BaA	No	Small number of animals (5/sex/dose).
23310	Pfeiffer and Allen, 1948	Rhesus monkey	various	Various	Sesame oil	None	Various	Multiple		No	Sequential exposure to multiple compounds; no concurrent untreated control.
23840	Barry et al., 1935	Un-specified	2 times/wk	1–2+ yr	Benzene	None	Epithelioma, papilloma	Multiple		No	Test compounds from various sources gave differing results; purity may be suspect; use of benzene vehicle confounds tumorigenicity results; no benzene or untreated control.
Initiation studies											
24800	Nesnow et al., 1984	SENCAR	Single	31 wk	Acetone	TPA 2 µg 2 times/wk for 30 wk	Papilloma	BeAC, BlAC		Yes	Reports both incidence and multiplicity.
21410	Slaga et al., 1978	CD-1	Single	27 wk	Acetone	TPA 10 µg 2 times/wk for 26 wk	Papilloma	BaA		Yes	Tumor incidence data not useable because BaP gave 93% tumor incidence. Tumor multiplicity data available for dose-response assessment.
630	LaVoie et al., 1982	Crl:CD-1[ICR] BR	10 subdoses every other d	Unspecified	Acetone	TPA 2.5 µg 3 times/wk for 20 wk	Primarily squamous cell papilloma	BbF, BjF, BkF		Yes	Reports both incidence and multiplicity.
16310	Weyand et al., 1992	Crl:CD-1	5 or 10 applica-tions given every other d	Until promotion complete	Acetone	TPA 2.5 µg 3 times/wk for 20 wk	Unspecified	BjF		Yes	Tumor incidence data not useable because BaP gave 100% tumor incidence. Tumor multiplicity data available for dose-response assessment. DNA adducts, mutagenicity also evaluated.
10200	El-Bayoumy et al., 1982	Crl:CD-1[ICR] BR	10 subdoses every other d	Unspecified	Acetone	TPA 2.5 µg 3 times/wk for 25 wk	Primarily squamous cell papilloma	CH	Pery, Pyr	Yes	Tumor incidence data not useable because single dose CH gave 100% tumor incidence; BaP gave 90% tumor incidence. Tumor multiplicity data available for dose-response assessment.
18570	Hecht et al., 1974	Ha/ICR/ Mil Swiss	10 subdoses every other d	Until promotion complete	Acetone	TPA 2.5 µg 3 times/wk for 20 wk	Unspecified	CH		Yes	Reports both incidence and multiplicity.
22500	Van Duuren et al., 1966	ICR/HA	Single	63 wk	Acetone	Croton resin, 25 µg 3 times/wk	Papilloma, carcinoma	CH, BbF	BghiF	No	BaP gave 100% tumor incidence. Corollary data with acetone only as promotion agent not included.

Table 4-1. Study summaries: dermal bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Mouse[a] strain	Exposure	Follow up	Vehicle	Promoter	Tumor type	Positive result	Nonpositive result	Meets selection criteria?	Comments
24300	Rice et al., 1985	CD-1	10 subdoses every other d	Until promotion complete	Acetone	TPA 0.0025% 3 times/wk for 20 wk	Unspecified	CH, CPdefC		Yes	Tumor incidence data not useable because all compounds gave >90% tumor incidence. Tumor multiplicity data available for dose-response assessment.
19320	LaVoie et al., 1979	HA/ICR Swiss albino	10 subdoses every other d	Until promotion complete	Acetone or dioxane	TPA 2.5 µg 3 times/wk for 20 wk or croton oil 2.5% 3 times/wk	Unspecified	CH, DBaeP, DBahP, DBaiP, N23eP	FA, AA, DBelP, BghiP, IP	No	Reiterates data published elsewhere.
21420	Slaga, et al., 1980	SENCAR	Single	15 wk	Acetone	TPA 2 µg 2 times/wk	Papilloma	CH, DBahA,	BeP, DBacA	Yes	Not clear if BaP done simultaneously but protocol, vehicle, and follow-up are the same. Reports both incidence and multiplicity.
15640	Raveh et al., 1982	SENCAR	Single	25 wk	Un-specified	TPA 2 µg 2 times/wk for 25 wk	Papilloma	CPcdP		Yes	Reports both incidence and multiplicity.
620	Hoffmann and Wynder, 1966	Ha/ICR/ Mil Swiss	Single	6 mo	Dioxane	Croton oil	Papillomas	DBaeF, DBaeP, DBahP, DBaiP, N23eP	IP, AA, BghiP, DBelP	Yes	Paper reports compound as DBalP; LaCassagne et al. (1968) state that it is actually DBaeF.
610	Higginbotham et al., 1993	SENCAR	Single	27 wk	Acetone	TPA 2.6 nmol, 2 times/wk	Papillomas, few carcinomas	DBalP		No	No tumors with BaP.
13660	Cavalieri et al., 1991	SENCAR	Single	16 wk and 27 wk (two experiments)	Acetone	TPA 3.24 nmol 2 times/wk for 11 wk	Primarily papilloma	DBalP		Yes	Tumor incidence data not useable because lowest dose DBalP gave >90% tumor incidence. Tumor multiplicity data from both experiments available for dose-response assessment.
19360	LaVoie et al., 1985	Crl:CD/1 (ICR)BR	10 subdoses every other d	Unspecified	Acetone	TPA 2.5 µg 3 times/wk for 20 wk	Unspecified		AC	Yes	
13650	Cavalieri et al., 1981b	CD-1	10 subdoses every other d	57 wk	Acetone	TPA 0.017 µmol 2 times/wk for 40 wk	Papilloma	CPcdP	ACEP	Yes	Reports both incidence and multiplicity.
20830	Roe, 1962	Albino	Single	Until promotion complete	Acetone	Croton oil once/wk for 20 wk	Papilloma		PH	No	BaP not simultaneous.

Table 4-1. Study summaries: dermal bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Mouse[a] strain	Exposure	Follow up	Vehicle	Promoter	Tumor type	Positive result	Nonpositive result	Meets selection criteria?	Comments
16440	Wood et al., 1980	CD-1	Single	27 wk	Acetone	TPA 16 nmol 2 times/wk for 26 weeks	Unspecified		Pyr, CPcdP	Yes	
17450	Brune et al., 1978	NMRI	Unspecified	Unspecified	Un-specified	TPA	Unspecified		AC	No	Study design not reported. Results reported qualitatively.
18680	Hoffmann et al., 1972	Ha/ICR/ Mil Swiss	10 subdoses every other d	Until promotion complete	Acetone	Croton oil 2.5% for 20 wk	Unspecified		FA	Yes	
19420	LaVoie et al., 1981	HA/ICR Swiss albino	10 subdoses every other d	Unspecified	Acetone	TPA 2.5 µg 3 times/wk for 20 wk	Unspecified		PH	Yes	
13660	Cavalieri et al., 1991	SENCAR	Single	27 wk	Acetone	None	Primarily papilloma	DBalP		Yes	Initiating dose only; no promoter. Tumor incidence data not useable because lowest dose DBalP gave >90% tumor incidence. Tumor multiplicity data available for dose-response assessment.
15700	Rice et al., 1988	CD-1	10 subdoses every other d	24 wk	Acetone	TPA 2.5 µg 3 times/wk for 20 wk	Unspecified	CH, BbcAC, CPdefC		Yes	Not clear if BaP done simultaneously for all PAHs.
Cocarcinogenicity studies											
18700	Horton and Christian, 1974	C3H	2 times/wk for 80 wk	82 wk	n-Do-decane/ decalin mixture	None	Carcinoma, papilloma	DBacA, Pyr	CH, FA, Tphen, Pery,	No	Not clear if BaP done simultaneously. Experiments with decalin (noncarcinogen) and 50/50 decalin/ dodecane mix (cocarcinogenic). No data for BaP in 50/50 mix. No vehicle control in decalin.
21430	Slaga et al., 1979	CD-1	Single	30 wk	Acetone	TPA 10 µg 2 times/wk for 30 wk	Papilloma	BeP		No	No concurrent control. Study aimed at exploring interactions; not clear if BaP done simultaneously.
21840	Van Duuren and Goldschmidt, 1976	ICR/Ha Swiss	3 times/wk	368 or 440 d	Acetone	None	Papilloma		Pyr, BghiP, BeP, FA	Yes	
21850	Van Duuren et al., 1973	ICR/HA	3 times/wk for 52 wk	52 wk	Acetone	None	None		Pyr, BghiP, BeP	No	Qualitative results reported.
21920	Warshawsky et al., 1993	C3H/HEJ	2 times/wk	Until lesion developed or 104 wk	Toluene or n-do-decane	None	Unspecified		AC, CH, Pyr, FA, PH	No	No tumors with BaP.

[a]Except where noted, all studies were conducted in mice.

DMSO = dimethyl sulfoxide

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Table 4-2. Study summaries: intraperitoneal bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Mouse strain[a]	Exposure	Follow up	Vehicle	Target organ(s)	Tumor type(s)	Positive result	Non-positive result	Meets selection criteria?	Comments
Newborn mouse studies											
13610	Busby et al., 1984	Swiss-Webster BLU:Ha (ICR)	1st, 8th, 15th d	26 wk	DMSO	Lung	Adenoma, adenocarcinoma	FA		Yes	Tumor incidence data not useable because lowest dose BaP gave >90% tumor incidence. Tumor multiplicity data available for dose-response assessment.
17560	Busby et al., 1989	Swiss-Webster BLU:Ha (ICR)	1st, 8th, 15th d	26 wk	DMSO	Lung	Adenoma, adenocarcinoma	FA	Pyr, CH	Yes	Reports both incidence and multiplicity.
640	LaVoie et al., 1987	CD-1	1st, 8th, 15th d	52 wk	DMSO	Lung, liver	Adenoma, hepatoma	BbF, BjF	BkF, IP	Yes	
7510	LaVoie et al., 1994	CD-1	1st, 8th, 15th d	12 mo	DMSO	Lung, liver	Foci, adenoma, carcinoma	FA		Yes	Reports both incidence and multiplicity.
22040	Weyand and LaVoie, 1988	CD-1	1st, 8th, 15th d	Not reported	DMSO	Lung, liver	Unspecified	Not reported		No	Abstract only; dose-response information not included.
22510	Wislocki et al., 1986	CD-1	1st, 8th, 15th d	12 mo	DMSO	Lung, liver, lymphatic system	Adenoma, carcinoma, lymphoma	CH, BaA	Pyr	Yes	Reports both incidence and multiplicity.
Studies in A/J mice											
11190	Mass et al., 1993	A/J	Single	8 mo	Tri-caprylin	Lung	Adenoma, carcinoma	BjAC		No	Reiterates data reported elsewhere (Record 24590).
23960 and 23450	Nesnow et al., 1998a, 1995	A/J	Single	8 mo	Tri-caprylin	Lung	Adenoma	BbF, DBahA, CPcdP		No	Reiterates data reported elsewhere (Record 24590).
22670	Nesnow et al., 1996	A/J	Single	8 mo	Tri-caprylin	Lung	Adenoma	BbF, DBahA, CPcdP		No	(Reiterates data reported elsewhere (Record 24590).)
24590	Nesnow et al., 1998b	A/J	Single	8 mo	Tri-caprylin	Lung	Adenoma	CPcdP, BbF, DBahA, BjAC, DBalP		Yes	Raw data (both incidence and multiplicity) obtained courtesy of S. Nesnow.

Table 4-2. Study summaries: intraperitoneal bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Mouse strain[a]	Exposure	Follow up	Vehicle	Target organ(s)	Tumor type(s)	Positive result	Non-positive result	Meets selection criteria?	Comments
20920	Ross et al., 1995	A/J	Single	240 d	Tri-caprylin	Lung	Adenoma	BbF, DBahA, CPcdP	Pyr	No	Reiterates data reported elsewhere (Record 24590).
24801	Weyand et al., 2004	A/J	Single	260 d	Tri-caprylin	Lung	Adenoma	BcFE		Yes	

[a]All studies were conducted in mice.

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Table 4-3. Study summaries: subcutaneous bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Species	Strain	Exposure site	Exposure	Follow up	Vehicle	Target organ(s)	Tumor type(s)	Positive result	Nonpositive result	Meets selection criteria?	Comments
23840	Barry et al., 1935	Mouse	Unspeci-fied	Unspecified	Single	1–2+ yr	Lard	Injection site	Sarcoma	Multiple		No	Test compounds from various sources gave differing results; purity may be suspect; no untreated control.
220	Bryan and Shimkin, 1943	Mouse	C3H	Right axilla	Single	until 20 mm tumor	Tricaprylin	Injection site	Unspecified	DBahA		No	No concurrent untreated control.
18350	Grant and Roe, 1963	Mouse	Albino	Neck	1st d after birth	52–62 wk	Aqueous gelatin	Lung	Adenoma		PH	Yes	
23200	Homburger et al., 1972	Hamster	Various	Groin	Single	52 wk	Tricaprylin	Injection site; lung	Various	BaA		No	Study aimed at evaluating strain specificity of tumorigenicity. BaA results equivocal. Not clear if BaP treatment simultaneous. "Aged" mice used as controls; aged mice allowed to live 16 weeks longer.
660	Pfeiffer, 1977	Mouse	NMRI	Neck	Single	114 wk	Tricaprylin	Injection site	Sarcoma	DBahA		No	Less than 10% of 100 control mice alive at 114 wk; control data not provided.
23310	Pfeiffer and Allen, 1948	Monkey	Rhesus	Various	Various	variable	Sesame oil	Various	Various	Multiple		No	Sequential exposure to multiple compounds; no concurrent untreated control.
24290	Rask-Nielson, 1950	Mouse	Street	Thymus, lung, mammary area	Single	30 mo	Paraffin	Various	Various	DBahA		No	Number of control and exposed varies by tumor type reported; BaP nontumorigenic; DBahA results equivocal; results unclear.
24310	Roe and Waters, 1967	Mouse	Swiss albino	Not specified	1st d after birth	50–60 wk	Aqueous gelatin	Liver	Hepatoma	PH		No	Study methodology and results not detailed; PH results equivocal.
21560	Steiner, 1955	Mouse	C57BL	Interscapular	Single	22–28 mo	Tricaprylin	Injection site	Sarcoma	DBahA, BaA, CH	AC, PH	No	No concurrent untreated control; study aimed at evaluating interactions.

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Table 4-4. Study summaries: oral bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Species	Strain	Exposure route	Exposure	Follow up	Target organ(s)	Tumor type(s)	Positive result	Non-positive result	Meets selection criteria?	Comments
17280	Biancifiori and Caschera, 1962	Mouse	BALB/c	Gavage	2 times/wk, 15 wk	Variable; 50–60 wk	Mammary gland	Carcinomas and sarcomas	DBahA		No	Tumors observed after DBahA only in pseudopregnant mice, not virgin mice.
23880	Huggins and Yang, 1962	Rat	Sprague-Dawley	Gavage	Single	Not reported	Mammary gland	Unspecified		BaA, PH	No	Untreated control information not included.
24801	Weyand et al., 2004	Mouse	A/J	Diet	Daily, 260 d	260 d	Lung	Adenoma	BcFE		Yes	

Table 4-5. Study summaries: other route bioassays of benzo[a]pyrene and at least one other PAH

Record number	Reference	Species	Strain	Exposure route	Exposure	Follow up	Vehicle	Target organ(s)	Tumor type(s)	Positive result	Non-positive result	Meets selection criteria?	Comments
21750	Topping et al., 1981	Rat	F344	Implantation in transplanted tracheas	Release from pellet	28 mo	Beeswax pellet	Tracheal epithelium	Carcinoma, sarcoma		BeP	No	Interaction information included.
17620	Cavalieri et al., 1988b	Rat	Sprague-Dawley	Intramammillary	Single	20 wk	None	Mammary	Adeno-carcinoma, adenofibroma, fibrosarcoma		DBahA, BaA	No	Control data from untreated mammary glands of same rats.
13660	Cavalieri et al., 1991	Rat	Sprague-Dawley	Intramammillary	Single	Until 2 cm tumor or 24 wk	Trioctanoin	Mammary, other	Adeno-carcinoma, adenofibroma, fibrosarcoma, squamous cell carcinoma	DBalP		No	DBalP produced tumors in all animals at the lowest dose.
21620	Sugiyama, 1973	Rat	Long-Evans	Intramuscular	Single	9 mo	Sesame oil	Injection site	Sarcoma		BaA	No	BaP gave 100% tumor incidence.
20280	Pataki and Huggins, 1969	Rat	Sprague-Dawley	Intravenous	3 doses 3 d apart	98 d	Lipid emulsion	Mammary	Unspecified		BaA	No	No control group.
17940	Deutsch-Wenzel et al., 1983	Rat	Osborne-Mendel	Lung implantation	Release from pellet	Until moribund or dead	Beeswax/ trioctanoin	Lung	Carcinoma, sarcoma	BbF, BjF, BkF, IP, AA, BghiP	BeP	Yes	
22000	Wenzel-Hartung et al., 1990	Rat	Osborne-Mendel	Lung implantation	Release from pellet	Until moribund or dead	Beeswax/ trioctanoin	Lung	Carcinoma	CH, DBahA	PH	Yes	
21500	Solt et al., 1987	Hamster	Syrian golden	Painting buccal pouch	2 times/wk for 20 wk	Up to 44 wk	Paraffin oil	Buccal pouch	Carcinoma		BaA	No	Fewer than 20 animals per group; negative result.
23910	Nikonova, 1977	Mouse	A	Subcutaneous (F0) and transplacental (F1)	GD 18 or 19	1 yr	Sunflower oil	Lung, mammary, liver, injection site	Adenoma		Pyr	No	Transplacental exposure not quantified.

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Table 4-6. Study summaries: in vivo DNA adducts with benzo[a]pyrene and at least one other PAH

Record number	Reference	Route of administration	Exposure frequency	Hours between dosing and sacrifice	Tissue analyzed	Method of analysis	PAHs evaluated[a]	Meets selection criteria?	Comments
6210	Arif et al., 1997	Intramammillary	Single dose	48	Mammary epithelium, lung	[^{32}P] postlabeling	DBalP	Yes	
17420	Brookes and Lawley, 1964	Dermal	Single dose	various to ~12 d	Skin	[^{3}H] prelabeling	DBacA, DBahA	No	Data on individual compounds not reported.
17630	Cavalieri et al., 1981a	Dermal	Single dose	4, 24	Skin	[^{3}H] or [^{14}C] prelabeling	CPcdP, ACEP	Yes	
18810	Hughes and Phillips, 1990	Dermal	Single dose	0.5, 1, 2, 4, 7, 21, 84 d	Skin, lung	[^{32}P] postlabeling	DBalP, DBaeP, DBahP, DBaiP	Yes	24-hr experiment with DBaeP and DBalP; 84-d experiment with all.
18790	Hughes and Phillips, 1991	Dermal	Single dose	24	Skin	[^{32}P] postlabeling	DBaeP	No	No quantitative information; abstract only.
10900	Koganti et al., 2000	Oral-diet	14 d	not stated	Lung	[^{32}P] postlabeling	BcFE, BaFE, BbFE	No	Not quantified.
13200	Li et al., 2002	Gavage or oral-diet	1 time/d for 1–4 d; diet 14 d		Mammary gland and liver; lung	[^{32}P] postlabeling	BcFE	No	Not quantified; BaP administered by gavage, BcFE admin in diet.
11190	Mass et al., 1993	Intraperitoneal	Single dose	24, 48, 72	Lung	[^{32}P] postlabeling	BjAC	Yes	
8010	Nesnow et al., 1993b	Intraperitoneal	Single dose	1, 3, 7, 14, 28, 56 d	Lung, liver, peripheral blood lymphocytes	[^{32}P] postlabeling	BbF	Yes	Peaks differ temporally; study also correlates number of adducts in organs.
22670	Nesnow et al., 1996	Intraperitoneal	Single dose	7 d	Lung	[^{32}P] postlabeling	BbF, DBahA, CPcdP	No	Not quantified.
23960	Nesnow et al., 1995	Intraperitoneal	Single dose	7 d	Lung	[^{32}P] postlabeling	BbF, DBahA, CPcdP	No	Not quantified.
24590	Nesnow et al., 1998a	Intraperitoneal	Single dose	various to 21 d	Lung	[^{32}P] postlabeling	BbF, CPcdP, DBahA, DBalP	Yes	Used data from Ross et al., 1995 (ref 20920) to calculate slope.
22810	Phillips et al., 1979	Dermal	Single dose	19, 24, 48, 72, 96, 120, 144	Skin	[^{3}H]-Prelabeling	BaA, DBacA, DBahA	Yes	
20650	Reddy et al., 1984	Dermal	4 doses (0, 6, 30, 54 hr)	24	Skin	[^{32}P] postlabeling	AC, BaA, BghiP, BeP, CH, DBacA, DBahA, Pery, Pyr	No	Semiquantitative data only.
20920	Ross et al., 1995	Intraperitoneal	Single dose	0, 1, 3, 5, 7, 14, 21 d	Lung	[^{32}P] postlabeling	BbF, CPcdP, DBahA	No	Reiterates data published elsewhere (Record 24590).
16310	Weyand et al., 1992	Dermal	Single dose	24	Skin	[^{32}P] postlabeling	BjF	No	Not quantified.
22040	Weyand and LaVoie, 1988	Intraperitoneal	Postnatal d 1, 8, 15	24	Lung, liver	[^{32}P] postlabeling	BbF, BjF, BkF	No	No quantitative data; abstract only.

Table 4-6. Study summaries: in vivo DNA adducts with benzo[a]pyrene and at least one other PAH

Record number	Reference	Route of administration	Exposure frequency	Hours between dosing and sacrifice	Tissue analyzed	Method of analysis	PAHs evaluated[a]	Meets selection criteria?	Comments
24801	Weyand et al., 2004	Oral-diet or intraperitoneal	14 d diet; single dose intraperitoneal	24	Lung, forestomach	[^{32}P] postlabeling	BcFE	Yes	
24790	Kligerman et al., 2002	Intraperitoneal and oral	Single dose	7 d	Peripheral blood lymphocytes	[^{32}P] postlabeling	BaA, BbF, CH	Yes	Data in both rats and mice.

[a]Positive findings were reported for all PAHs evaluated.

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Table 4-7. Study summaries: in vivo clastogenicity or sister chromatid exchange with benzo[a]pyrene and at least one other PAH

Record number	Reference	Species	Strain	Route of administration	Vehicle	Exposure	Hours between dosing and sacrifice	Tissue analyzed	Clasto-genic endpoint	Positive results	Non-positive results	Meets selection criteria?	Comments
24740	Allen et al., 1999	Mice	A/J or p53 +/+, +/-, and -/-	Intraperitoneal	Tricaprylin	Single	48 or 72 hr	Bone marrow or peripheral blood	Micro-nuclei	DBalP		Yes	
14270	He and Baker, 1991	Mice	HRA/Skh hairless	Dermal	Acetone	Single	24 hr	Keratino-cytes	Micro-nuclei	CH	Pyr	Yes	
17190	Bayer, 1978	Hamsters	Chinese	Intraperitoneal	Tricaprylin	Single	24 hr for aberrations; 30 hr for micronuclei	Bone marrow	Gaps, breaks, micro-nuclei, sister chromatid exchanges	PH (high dose only)		Yes	
19030	Katz et al., 1981	Mice	B6C3F$_1$/ BR	Intraperitoneal	DMSO	At 0 and 24 hr	various; 24, 30, 48, 72 hr after last dose	Bone marrow	micro-nuclei		DBaiP, AC, BghiP, Pyr	No	No quantitative data.
24720	Kligerman et al., 1986	Mice	C57BL6	Gavage	Corn oil	Single	23.5–25 hr	Peripheral blood	Sister chromatid exchanges	BlAC		Yes	
24790	Kligerman et al., 2002	Mice and rats	CD-1 Swiss mice; CD rats	Oral and intraperitoneal	Sunflower seed oil	Single	7 d	Whole blood or mono-nuclear leukocytes	Sister chromatid exchange, micro-nuclei	BaA, BbF, CH		Yes	All positive for sister chromatid exchange via intraperitoneal administration; mixed results for oral administration.
20200	Oshiro et al., 1992	Mice	CD-1	Peroral	Polyethylene glycol	1 time/d, 4 d	24 hr after 2nd and 4th treatment	Peripheral blood	Micro-nuclei		Pyr, AC	No	No quantitative data; published as abstract.
20230	Paika et al., 1981	Mice	CBA/J	Intraperitoneal	DMSO	single	16–20 hr	Bone marrow	Sister chromatid exchanges		Pyr	No	No quantitative data.
20950	Roszinsky-Kocher et al., 1979	Hamsters	Chinese	Intraperitoneal	Tricapryline	2 doses 24 hr apart	24 hr after 2nd treatment	Bone marrow	Sister chromatid exchanges, aberrations	PH, CH, DBahA, BaA, BbF, BeP	AC	Yes	Positive results for sister chromatid exchanges, not aberrations.
21050	Salamone et al., 1981	Mice	B6C3F$_1$	Intraperitoneal	Not specified	2 doses 24 hr apart	24, 48, 72 hr after 2nd treatment	Bone marrow	Micro-nuclei		AC, Pyr	Yes	
21770	Tsuchimoto and Matter, 1981	Mice	CD-1	Intraperitoneal	DMSO	2 doses 24 hr apart	6 hr after 2nd treatment	Bone marrow	Micro-nuclei		Pyr	Yes	

Table 4-7. Study summaries: in vivo clastogenicity or sister chromatid exchange with benzo[a]pyrene and at least one other PAH

Record number	Reference	Species	Strain	Route of administration	Vehicle	Exposure	Hours between dosing and sacrifice	Tissue analyzed	Clasto-genic endpoint	Positive results	Non-positive results	Meets selection criteria?	Comments
21390	Sirianni and Huang, 1978	Mice	C3H/St	V79 cells in dif-fusion chamber implanted in peritoneal cavity of mice				Chinese hamster V79 cells	Sister chromatid exchanges		AC, Pyr, Pery	Yes	
21620	Sugiyama, 1973	Rats	Long-Evans	Intravenous	Lipid emulsion	Single	12, 24 hr	Bone marrow	Gaps, breaks		BaA	Yes	

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Table 4-8. Study summaries: in vivo mutagenicity with benzo[a]pyrene and at least one other PAH

Record number	Reference	Species/strain	Route of administration	Exposure frequency/follow up	Mutagenic endpoint	Positive result	Non-positive result	Meets selection criteria?	Comments
18130	Fahmy and Fahmy, 1980	*Drosophila melanogaster*	Suspension in media	48–72 hr	Somatic mutation; eye color mosaicism		BaA	Yes	
13980	Frolich and Wurgler, 1990	*D. melanogaster*	Suspension in media	48–72 hr	Somatic mutation and recombination test; wing spots		BaA	No	Inconsistent results for BaA; significant effects only seen with cross-breeding of strains selected for enhanced metabolic activity (not standard strains).
11190	Mass et al., 1993	A/J mice	Intraperitoneal	3 d/8 mo	Mutations in codon 12 of the Ki-ras oncogene; PCR and DNA sequencing of lung tumor DNA	BjAC		No	Quantitative dose-response data were not available. Different mutation sequences observed; GGT→TGT for BaP and GGT→CGT for BjAC; mutation sequence for BjAC may correlate with cyclopenta-adduct formation.
23960	Nesnow et al., 1995	A/J mice	Intraperitoneal	Single injection/ 8 mo	Mutations in codon 12 of the Ki-ras oncogene; PCR and DNA sequencing of lung tumor DNA	BbF, DBahA, CPcdP		No	Quantitative dose-response data were not available. GGT→TGT mutations for BaP and BbF; GGT→CGT for CPcdP; no mutations seen for DBahA.
22670	Nesnow et al., 1996	A/J mice	Intraperitoneal	Single injection/ 8 mo	Mutations in codon 12 of the Ki-ras oncogene; PCR and DNA sequencing of lung tumor DNA	BbF, DBahA, CPcdP		No	Quantitative dose-response data were not available. GGT→TGT mutations for BaP and BbF; GGT→CGT for CPcdP; no mutations seen for DBahA.
24590	Nesnow et al., 1998b	A/J mice	Intraperitoneal	Single injection/ 8 mo	Mutations in codons 12 and 61 of the Ki-ras oncogene; PCR and DNA sequencing of lung tumor DNA	BbF, DBahA, CPcdP, BjAC, DBalP		No	Quantitative dose-response data were not available. Mutations in codon 12, GGT→TGT for BaP, BbF, and DBalP; GGT→CGT for CPcdP and BjAC; no mutations seen for DBahA; GTT mutations seen for all other PAHs. Only DBalP caused mutations in codon 61.
21370	Simmon et al., 1979	Swiss Webster mice	PAHs intramuscular or peroral; microorganisms intraperitoneal	Single injection/4 hr	Intraperitoneal host mediated assay; mutagenicity in *S. typhimurium* and *Saccharomyes cerevisiae* of recovered microorganisms		AC, BaA, BeP, CH, PH	No	Assay was not considered sensitive enough for detecting carcinogens.
21830	Valencia and Houtchens, 1981	*D. melanogaster*	Filter feeding	48–72 hr	Sex-linked recessive lethal test		Pyr	No	Results were negative for BaP.
22450	Zijlstra and Vogel, 1984	*D. melanogaster*	Abdominal injection	Not applicable	Sex-linked recessive lethal test; 2–3 translocation and ring-X loss		BaA	No	Results were negative for BaP.

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Table 4-9. Study summaries: in vitro bacterial mutagenicity with benzo[a]pyrene and at least one other PAH

Record number	Reference	Salmonella strain(s)	Activation system	Positive result	Nonpositive result	Meets selection criteria?	Comments
17030	Andrews et al., 1978	TA100, TA1527, TA1538	Ar S9 and others	AA, DBahA, DBajA, DBacA, BghiP, BeP		Yes	TA100 results include BaP.
23830	Baker et al., 1980	TA100	Guinea pig MC S9 and others	DBaiP, BaA, DBacA, DBahA		Yes	
23660	Bartsch et al., 1980	TA100, TA1535, TA98	Rat MC S9	BaA		Yes	
17380	Bos et al., 1988	TA98, TA100	Rat Ar S9	PH, Pyr		Yes	Qualitative data for other PAHs (no BaP); quantitative data with BaP comparison for PH and Pyr in TA100.
9560	Carver et al., 1985	TA98, TA100	S9	Pery		No	The response varied at different concentrations of S9; BaP was more potent at low S9 while Pery was more potent at high S9.
17590	Carver et al., 1986	TA100	Ar rat and Ar hamster S9	BaA, BghiF, Pery		Yes	Qualitative data also presented for other PAHs. S9 concentration varied; 400 µL/plate optimal.
17630	Cavalieri et al., 1981a	TM677	Ar S9	CPcdP, ACEP, Pyr		Yes	BaP data from previous publication used. Dose-response data not provided for Pyr.
9620	Chang et al., 2002	TA100	Rat Ar S9	BghiF, BcPH		Yes	
24030	De Flora et al., 1984	TA1535, TA1537, TA1538, TA98, TA100	Rat AR S9	BaA, Pery, BeP	AC	Yes	
13860	Devanesan et al., 1990	TA100, TA98	Rat Ar S9	DBaeP, DBalP		No	No concurrent control.
18030	Dunkel et al., 1984	TA1535, TA1537, TA1538, TA98, TA100	Rat, mouse, hamster Ar S9	BaA, BeP, PH, Pyr	AC	No	Dose-response data not provided.
18050	Eisenstadt and Gold, 1978	TA1537, TA100	Rat Ar S9	CPcdP		Yes	
18180	Florin et al., 1980	TA98, TA100	Rat Ar and MC S9	BaA, CH, Pery, CO		Yes	
24080	Gibson et al., 1978	TA1535, TA1537, TA1538, TA98	Nonenzymatic (gamma radiation)	BaA, BghiP, CH, FE, Pyr	DBahA, AC, Pic, Tphen	Yes	AN, PH also tested; toxicity interfered with mutagenicity testing.
14080	Gold and Eisenstadt, 1980	TA100	Rat MC S9	CPcdP		Yes	BaP and CPcdP maximal responses occurred at different S9 levels.
14170	Guthrie et al., 1982	TA98, TA100	Rat Ar S9 compare to PGS from ram seminal vesicles	BaA, CH		No	BaP tested in TA98, BaA and CH tested in TA100.
14260	Hass et al., 1981	TA98, TA100	Rat Ar S9		BeP	Yes	

Table 4-9. Study summaries: in vitro bacterial mutagenicity with benzo[a]pyrene and at least one other PAH

Record number	Reference	Salmonella strain(s)	Activation system	Positive result	Nonpositive result	Meets selection criteria?	Comments
18650	Hermann, 1981	TA98	Rat Ar S9	BbA, BaA, CH, FA, Tphen, BeP, DBacA, DBahA, BbF, Pery, DBalP, DBaiP, AA, CO	AC, PH, FE, Pyr, BbFE	Yes	
10670	Johnsen et al., 1997	TA98	Rat control or PB S9	BjAC, BlAC		Yes	
19000	Kaden et al., 1979	TM677	Rat Ar or PB S9	AN, ANL, Pyr, BbFE, CPcdP, BaA, CH, Tphen, FA, BeP, Pery, BghiP, AA, DBacA, DBahA, DBbeF	FE, AC, PH, Pic, CO	Yes	Mutagenic activity relative to BaP reported.
24680	Lafleur et al., 1993	TM677	Ar PMS	CPcdP, APA, ACEA, CPhiAPA, CPhiACEA		Yes	
19320	LaVoie et al., 1979	TA98, TA100	Rat Ar S9	BeP, Pery		Yes	Several other PAHs were evaluated, but not concurrent with BaP.
19360	LaVoie et al., 1985	TA98, TA100	Rat Ar S9		AC	Yes	
23650	McCann et al., 1975	TA1535, TA1537, TA98, TA100	Rat Ar S9	DBaiP, BeP, DBacA, DBahA, CH, BaA	Pyr, AC, PH, FE	Yes	
15170	Norpoth et al., 1984	TA100	Rat and mouse S9; induction by Clophen A50 and 18 PAHs	BaA		No	S9 composition was different for BaA and BaP; result cannot be compared.
20220	Pahlman and Pelkonen, 1987	TA100	S9 from control, MC, or TCDD treated rats and mice	BaA, CH, Tphen, DBacA, DBahA	AN, AC, PH, FE, Pyr, BeP, Pery, PCE	Yes	
20530	Penman et al., 1980	TM677	Rat Ar or PB S9	Pery, CPcdP, DBacA		No	No concurrent control values were reported.
20450	Phillipson and Ioannides, 1989	TA100	S9 isolated from mouse, hamster, rat, pig, and human	BaA, DBaiP, DBahA		Yes	
20490	Poncelet et al., 1978	TA1530, TA1535, TA1537, TA1538, TA98, TA100	S9 (origin unknown)	CO, Tphen, FA, BghiP	BbF	No	Qualitative data reported in published abstract.
20560	Probst et al., 1981	TA1530, TA1535, TA1537, TA1538, TA98, TA100	Rat Ar S9	BbA, DBacA	AC, DBahA, PH, Pyr, DBaiP	No	Data reported as minimum mutagenic concentration (nmol/mL).
20880	Rosenkranz and Poirier, 1979	TA1530, TA1535	Uninduced rat S9		AC, BaA, BeP, CH, PH	Yes	
21000	Sakai et al., 1985	TA97, TA98, TA100	Rat Ar S9	FE (equiv.), AC, PH, FA, CH, Pyr, BeP, Pery, BghiP, CO		Yes	
21040	Salamone et al., 1979a	TA1535, TA1537, TA1538, TA98, TA100	Rat Ar S9	BaA, BeP (equiv.), BghiP, DBaiP, BPH, CH, CO, DBacA, PCE	AC, BaFE, BbFE, FA, Pery, Pyr	No	Increase in spontaneous mutation rate was indicated, but dose data were not provided.

Table 4-9. Study summaries: in vitro bacterial mutagenicity with benzo[a]pyrene and at least one other PAH

Record number	Reference	Salmonella strain(s)	Activation system	Positive result	Nonpositive result	Meets selection criteria?	Comments
13260	Salamone et al., 1979b	TA98, TA100	Rat Ar S9	DBaiP		No	Dose-response data were not completely reported; maximal response information (dose and number of revertants) was presented in text; BaP max response at different S9 than DBaiP.
11860	Sangaiah et al., 1983	TA1535, TA1537, TA1538, TA98, TA100	Rat Ar S9	BjAC		Yes	Dose-response data for BaP was presented for TA98 only.
21360	Simmon, 1979a	TA1535, TA1536, TA1537, TA1538, TA98, TA100	Rat Ar S9	BaA, BeP	AC, CH, PH	Yes	
21640	Teranishi et al., 1975	TA1535, TA1536, TA1537, TA1538	S9 from rats treated with PB and MC or DBahA	DBaiP, DBaeP	DBahA, BaA, BeP	Yes	
16180	Utesch et al., 1987	TA100	Intact or homogenized hepatocytes from Ar treated rats	BaA		Yes	
16440	Wood et al., 1980	TA98, TA100	Rat Ar S9 and purified MFO enzymes system	CPcdP		Yes	

Ar = Arochlor 1254-treated; MC = 3-methylcholanthrene-treated; PB = phenobarbital-treated; PMS = postmitochondrial supernatant

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Table 4-10. Study summaries: in vitro mammalian mutagenicity assays with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Mutagenesis assay	Positive result	Non-positive result	Meets selection criteria?	Comments
16900	Allen-Hoffmann and Rheinwald, 1984	Human epidermal keratinocyte	None	6-Thioguanine resistance (HPRT)		BaA	Yes	
16920	Amacher and Paillet, 1982	Mouse lymphoma cells (L5178Y)	Syrian golden hamster S9 mix or cocultivated hamster hepatocytes	Trifluorothymidine resistance (thymidine kinase locus [TK])	BaA		Yes	
16930	Amacher and Paillet, 1983	Mouse lymphoma cells (L5178Y)	Cocultivated rat hepatocytes	Trifluorothymidine resistance (TK)		BaA	Yes	
16940	Amacher and Turner, 1980	Mouse lymphoma cells (L5178Y)	S9 from eight rodent species or strain; one rat strain induced by Ar	Trifluorothymidine resistance (TK)	AC, BaA		Yes	AC data not useable; BaP not simultaneous.
16910	Amacher et al., 1980	Mouse lymphoma cells (L5178Y)	Rat Ar and noninduced S9	Trifluorothymidine resistance (TK)	BaA	AC, Pyr	Yes	
13440	Baird et al., 1984	V79 Chinese hamster cells	Hamster embryo cells	6-Thioguanine resistance (HPRT)		BeP	Yes	
17140	Barfknecht et al., 1982	TK6 human lymphoblast cells	Rat Ar S9	Trifluorothymidine resistance (TK)	FA, BaA, CH, Tphen, CPcdP	PH, AC, ACEP	Yes	
24670	Durant et al., 1999	H1A1v2 human lymphoblastoid cells	Transfected with cyp1a1 cDNA	Trifluorothymidine resistance (TK)	BaPery, BbPery, DBaeF, DBafF, DBahP, DBaiP, DBelP, N23aP, N23eP	DBjlF, N12bF	Yes	
18260	Gehly et al., 1982	C3H/10T1/2 clone 8 mouse fibroblast cells	None	Ouabain resistance (HPRT)		BeP	Yes	
14250	Hass et al., 1982	V79 Chinese hamster cells	Hamster embryo cells	Ouabain and 6-thioguanine resistance (HPRT)	DBaiP, DBahP		Yes	
18750	Huberman, 1975	V79 Chinese hamster cells	Hamster cells	8-Azaguanine resistance (HPRT)		BaA, Pyr	Yes	
18740	Huberman and Sachs, 1976	V79 Chinese hamster cells	Hamster embryo cells	Ouabain and 8-azaguanine resistance (HPRT)	DBacA, DBahA (both weak)	Pyr, PH, CH, BaA	Yes	
24120	Huberman and Sachs, 1974	V79 Chinese hamster cells	Hamster embryo cells	8-Azaguanine resistance (HPRT)		BaA	Yes	
18990	Jotz and Mitchell, 1981	Mouse lymphoma cells (L5178Y)	Rat Ar S9	Trifluorothymidine resistance (TK)	Pyr		Yes	
24720	Kligerman et al., 1986	Mouse lymphoma cells (L5178Y)	Rat Ar S9	Trifluorothymidine resistance (TK)	BlAC		Yes	

Table 4-10. Study summaries: in vitro mammalian mutagenicity assays with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Mutagenesis assay	Positive result	Non-positive result	Meets selection criteria?	Comments
19180	Krahn and Heidelberger, 1977	V79 Chinese hamster cells	Rat MC S9	6-Thioguanine resistance (HPRT)	BaA, DBacA, DBahA		Yes	DBacA and DBahA data not useable; treatment different than BaP.
24680	Lafleur et al., 1993	MCL-3 human lymphoblastoid cells	Transfected with cyp1a2 and cyp2a6 cDNA	Trifluorothymidine resistance (TK)	CPcdP, ACEA, CPhiACEA	APA, CPhiAPA, BghiF	Yes	
24170	Langenbach et al., 1983	V79 Chinese hamster cells	Cocultivation with primary rodent cells from liver, lung, kidney, and bladder	Ouabain resistance (HPRT)		AC	Yes	
7550	Li and Lin, 1996	HS1 HeLa cells (human epithelial cells)	None	6-Thioguanine resistance (HPRT)	BaA		Yes	
19870	Mishra et al., 1978	Fischer rat embryo cells infected with Rauscher leukemia virus	Rat Ar S9	Ouabain resistance (HPRT)		AC, PH, Pyr, BeP	Yes	
20040	Myhr and Caspary, 1988	Mouse lymphoma cells (L5178Y)	Rat Ar and noninduced S9	Trifluorothymidine resistance (TK)	AC, BaA, BeP		No	Results reported as ranges.
11450	Nesnow et al., 1984	V79 Chinese hamster cells	Rat Ar S9	6-Thioguanine resistance (HPRT)	BlAC, BeAC, BjAC		Yes	
15630	Raveh and Huberman, 1983	V79 Chinese hamster cells	Hamster embryo fibroblasts	6-Thioguanine resistance (HPRT); phorbol myristate acetate used to enhance recovery	CPcdP	BaA	Yes	
15640	Raveh et al., 1982	V79 Chinese hamster cells	Hamster embryo fibroblasts	Ouabain and 6-thioguanine resistance (HPRT)	CPcdP		Yes	Mutagenicity correlated with skin tumor initiation.
21410	Slaga et al., 1978	V79 Chinese hamster cells	Hamster embryo cells	Ouabain resistance (HPRT)	BaA (weak)		Yes	
21720	Tong et al., 1983	Rat liver epithelial cells (ARL-18)		6-Thioguanine resistance (HPRT)		BaA, BeP, Pyr	No	Repeats data from Record 21730 Tong et al., 1981b
21730	Tong et al., 1981b	Rat liver epithelial cells (ARL-18)	None	6-Thioguanine resistance (HPRT)		BeP, Pyr, BaA	Yes	

Table 4-10. Study summaries: in vitro mammalian mutagenicity assays with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Mutagenesis assay	Positive result	Non-positive result	Meets selection criteria?	Comments
16190	Vaca et al., 1992	UV-sensitive Chinese hamster ovary (CHO) cells	Rat Ar S9	6-Thioguanine resistance (HPRT)	FA		Yes	
21900	Wangenheim and Bolcsfoldi, 1988	Mouse lymphoma cells (L5178Y)	Rat Ar S9	Trifluorothymidine resistance (TK)	Pyr, FE		Yes	

HPRT = hypoxanthine-guanine phosphoribosyl transferase mutagenicity assay (resistance to 6-thioguanine, 8-azaguanine, or ouabain); TK = thymidine kinase mutagenicity assay (resistance to trifluorothymidine)

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Table 4-11. Study summaries: in vitro morphological/malignant cell transformation with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation system	Positive result	Nonpositive result	Meets selection criteria?	Comments
13390	Atchison et al., 1985	BALB/3T3 mouse embryo fibroblasts	None		FA, Pyr	Yes	
17610	Casto, 1979	Syrian golden hamster embryo cells	None	DBahA	Pyr	Yes	
17730	Chen and Heidelberger, 1969	Adult C3H mouse ventral prostate cells	Cocultivated irradiated C3H mouse embryonic fibroblasts	DBahA	DBacA, Pyr	No	Control data not provided.
24750	Davis, 1999	C3H10T1/2 cells	None	DBalP, DBaeP, BcC, BgC, BcPH		No	Control data not provided.
17970	DiPaolo et al., 1969	Syrian golden hamster embryo cells	Cocultivated irradiated Sprague-Dawley rat fetal cells	DBahA, BaA, BeP, DBacA	Pyr, PH	Yes	
17990	DiPaolo et al., 1972	BALB/3T3	None		AC, Pyr	Yes	
23630	DiPaolo et al., 1973	Syrian golden hamster embryo cells	In vivo (transplacental) exposure		AC, PH, Pyr	No	No quantitative information.
18020	Dunkel et al., 1981	Balb/3T3, Syrian golden hamster embryo, and Rauscher murine leukemia virus-infected F344 rat embryo cells	None	BaA	BeP, PH, AC	Yes	Qualitative data only for R-MuLV-RE cells. BaA positive in SHEM, equivocal in Balb/3T3.
18080	Emura et al., 1980	Syrian golden hamster fetal lung cells	None	BbF, BaA, IP	BkF, BeP	Yes	
23640	Evans and DiPaolo, 1975	Strain 2 guinea pig fetal cells	None		AC, Pyr, PH	No	No quantitative information.
18260	Gehly et al., 1982	C3H10T1/2CL8 mouse embryo fibroblasts	None		BeP	Yes	
14130	Greb et al., 1980	BHK 21/CL 13	Rat Ar S9	CH, BaA, BbF, DBahA, BeP	PH, AC	Yes	
23890	Kakunaga, 1973	BALB/3T3 subclone A31-714	None		PH, Pyr	No	Not clear if BaP administered simultaneously.
14640	Krolewski et al., 1986	C3H10T1/2CL8 mouse embryo fibroblasts	None	CPcdP		Yes	
14700	Laaksonen et al., 1983	Newborn NMRI nu/nu nude mouse skin fibroblasts	None	BaA	AC	Yes	
14850	Lubet et al., 1983	C3H10T1/2CL8 mouse embryo fibroblasts	None	BeP	AC, DBahA, PH	Yes	
19870	Mishra et al., 1978	Rauscher leukemia virus-infected Fischer rat embryo	None		AC, PH, Pyr, BeP	No	No quantitative information.
24710	Mohapatra et al., 1987	C3H10T1/2CL8 mouse embryo fibroblasts	None	BeAC, BjAC, BlAC	BkAC	Yes	
24700	Nesnow et al., 1990	Human neonatal foreskin fibroblasts	None	BlAC		Yes	
7980	Nesnow et al., 1997	C3H10T1/2CL8 mouse embryo fibroblasts	None	DBalP		Yes	
7990	Nesnow et al., 1994	C3H10T1/2CL8 mouse embryo fibroblasts	None	DBahA		Yes	
8000	Nesnow et al., 1993a	C3H10T1/2CL8 mouse embryo fibroblasts	None	DBkmnoAPH	DBjmnoAPH, N123mnoAPH	Yes	
20120	Nesnow et al., 1991	C3H10T1/2CL8 mouse embryo fibroblasts	None		ACEA	Yes	

Table 4-11. Study summaries: in vitro morphological/malignant cell transformation with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation system	Positive result	Nonpositive result	Meets selection criteria?	Comments
23720	Pienta et al., 1977	Syrian golden hamster embryo	Cocultivated X-irradiated cells of same type	BaA, DBahA	CH, BeP, Pyr, AC, DBacA, PH	Yes	
8490	Sheu et al., 1994	BALB/3T3 A31-1-1	None		Pyr, BaA, CH	Yes	

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Table 4-12. Study summaries: in vitro DNA adducts with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type or DNA source	Incubation time	Activation system	Method of analysis	PAHs evaluated[a]	Meets selection criteria?	Comments
16890	Allen and Coombs, 1980	Mouse embryo cells from TO mice	24 hr	None	[^{3}H] prelabeling	BaA	Yes	
6300	Binkova et al., 2000	Human diploid lung fibroblast cells	Various up to 24 hr	None	[^{32}P] postlabeling	DBalP	Yes	
9510	Bryla and Weyand, 1992	Calf thymus DNA	1 hr	None	[^{32}P] postlabeling	BaA, DBacA, PH	Yes	PH did not form measurable DNA adducts. Adduct formation enhanced when reacted under white light.
6570	Cherng et al., 2001	Human hepatoma HepG2 cells	24 hr	None	[^{32}P] postlabeling	BghiP	Yes	BghiP did not form measurable DNA adducts.
13780	Cooper et al., 1982	Fibroblasts and epithelial cells from Wistar rat mammary tissue	24 hr	None	[^{3}H] prelabeling	BaA	Yes	BaA formed little or no measurable DNA adducts.
22800	Grover and Sims, 1968	Salmon testes DNA	Not specified	Rat liver microsomes	[^{3}H] prelabeling	DBahA, DBacA, BaA, Pyr, PH	Yes	
10660	Johnsen et al., 1998	Human lymphocytes and human promyelocytic HL-60 cells	24 hr	None	[^{32}P] postlabeling	BjAC, BlAC	Yes	
10670	Johnsen et al., 1997	Rat lung Clara cells, Type 2 cells, and macrophages	2 hr	PCB pretreatment of whole animals	[^{32}P] postlabeling	BjAC, BlAC	Yes	
13200	Li et al., 2002	MCF-7 cells or rat lung DNA	7–24 hr	Human mammary microsomes with rat lung DNA	[^{32}P] postlabeling	DBalP, BcPH, DBahA	No	No quantitative results.
7870	Melendez-Colon et al., 2000	Human mammary carcinoma MCF-7 cells and leukemia HL-60 cells	4 or 24 hr	None	[^{32}P] postlabeling	DBalP	Yes	No adducts formed in HL-60 cells that lack significant P450 activity.
7990	Nesnow et al., 1994	C3H10T1/2CL8 fibroblasts	24 hr	None	[^{32}P] postlabeling	DBahA	No	No quantitative results.
20120	Nesnow et al., 1991	C3H10T1/2 cells	24 hr	None	[^{32}P] postlabeling	ACEA	No	Measures repair of adducts only, not synthesis.
21200	Segerback and Vodicka, 1993	Calf thymus DNA	3 hr	Rat Ar S9	[^{32}P] postlabeling, ^{3}H-binding	CH, BaA, BbF, DBahA, FA, BghiP, Pyr	Yes	
24810	Baird et al., 2002	MCF-7 cells	24 hr	Morpholinos inhibition (antisense oligomer that blocks protein synthesis of CYPIA1)	[^{32}P] postlabeling	DBalP	No	Confounded by CYP1A1 inhibition by morpholinos.

[a]Except where noted, positive findings were reported for all PAHs evaluated.

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Table 4-13. Study summaries: in vitro DNA damage, repair, or synthesis with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Endpoint	Assay	Positive result	Nonpositive result	Meets selection criteria?	Comments
16840	Agrelo and Amos, 1981	Human fibroblasts	Rat Ar S9	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	Pyr		Yes	
17610	Casto, 1979	Syrian golden hamster embryo	Intrinsic	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake		DBahA, Pyr, PH	Yes	
24030	De Flora et al., 1984	*Escherichia coli* WP2, WP67, and CM871	Rat Ar S9	DNA damage	Differential killing repair-deficient strains	AC, BaA	Pery, BeP	No	Semiquantitative data.
18030	Dunkel et al., 1984	*E. coli* WP-2 *uvr*A	Rat, mouse, hamster Ar S9	DNA damage	Differential killing repair-deficient strains	BaA, BeP, PH, Pyr	AC	No	Dose-response data not provided.
23790	Ichinotsubo et al., 1977	*E. coli* Rec BC	S9 (origin unknown)	DNA damage		DBaiP, DBahA		Yes	
10670	Johnsen et al., 1997	Rat lung Clara cells, Type 2 cells, and macrophages	PCB pretreatment of whole animals	DNA damage	Alkaline elution		BjAC, BlAC	No	No untreated control.
10660	Johnsen et al., 1998	Human lymphocytes and human promyelocytic HL-60 cells	Rat or human liver microsomes	DNA damage	Alkaline elution	BjAC, BlAC		Yes	
19270	Lake et al., 1978	Human foreskin epithelial cells	None	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	DBahA	AC, BeP, PH, Pyr	No	Doses reported as ranges.
19680	Mamber et al., 1983	*E. coli* WP2 and WP100	Rat Ar S9	DNA damage	Growth inhibition of repair deficient strains		AC, FE, Pyr	Yes	
19690	Mane et al., 1990	Human and rat mammary epithelial cells	None	Inhibition of DNA synthesis	[^{3}H] Thymidine uptake	BaA (in human MEC only)	BeP	No	Positive response for BaA not observed consistently.
19730	Martin and McDermid, 1981	HeLa S3 cells	PB-induced rat liver postmitochondrial supernatant	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	Pyr (authors: "dubious" result)	AC	No	No quantitative information.
19740	Martin et al., 1978	HeLa S3 cells	3-MC induced rat liver postmitochondrial supernatant	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	BeP, BaA, DBacA, DBahA	Pyr, AC	Yes	
23800	McCarroll et al., 1981	*E. coli* WP2, WP2 uvrA, WP67, CM611, WP100, W3110polA+, and p3478pola-	Rat Ar S9	DNA damage	Differential killing repair-deficient strains		AC, PH	Yes	

Table 4-13. Study summaries: in vitro DNA damage, repair, or synthesis with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Endpoint	Assay	Positive result	Nonpositive result	Meets selection criteria?	Comments
19830	Mersch-Sundermann et al., 1992	*E. coli* PQ37	Rat Ar S9	Induction of SOS system	SOS chromotest	AA, BaA, BbF, BghiF, BjF, BbFE, BghiP, BeP, CH, DBacA, DBahA, DBalP, DBahP, DBaiP, FA, IP, PH, Tphen	AC, BaFE, CO, FE, Pery, Pyr	Yes	
19850	Milo et al., 1978	Human skin fibroblast NF and Detroit 550 cells	None	DNA damage	Alkaline elution		AC, Pyr, PH, BeP	Yes	
20050	Nagabhushan et al., 1990	Hamster buccal pouch epithelial cells and tissue fragments	Not specified	Inhibition of DNA synthesis	[^{3}H] Thymidine uptake		BaA	No	Abstract only. BaA inhibited synthesis 4%.
20560	Probst et al., 1981	Rat hepatocyte primary culture	None	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	BbA, DBacA	AC, DBahA, PH, Pyr, DBaiP, FE, BeP	No	Artifact of counting method resulted in control responses reported as negative values.
20810	Robinson and Mitchell, 1981	Human fibroblasts WI-38 cells	Rat Ar S9	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	Pyr (with activation)		Yes	
23900	Rosenkranz and Leifer, 1980	*E. coli* pol A1-	Rat liver S9	DNA damage	Differential killing repair-deficient strains		AC, BaA, BeP, CH, PH	Yes	
20880	Rosenkranz and Poirier, 1979	*E. coli* pol A1-	Uninduced rat S9	DNA damage	Differential killing repair-deficient strains		AC, BaA, BeP, CH, PH	Yes	
20940	Rossman et al., 1991	*E. coli* WP2s(λ)	Rat liver S9	DNA damage	Λ prophage induction	AC, DBacA, DBahA, PH	BeP, FA, Pyr	Yes	
21380	Simmon, 1979b	*S. cerevisiae* D3	Rat Ar S9	induced recombination	Colony pigmentation on adenine medium		AC, BaA, BeP, CH, PH	Yes	
21720	Tong et al., 1983	Rat hepatocyte primary culture	None	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	BaA	BeP, AC, CH, Pyr	No	Repeats data from 21730 Tong et al., 1981b.
21730	Tong et al., 1981b	Rat hepatocyte primary culture	None	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake	BaA	BeP, AC, CH, Pyr	Yes	
21790	Tweats, 1981	*E. coli* WP2, WP67(uvrA polA), CM871 (uvrA lexA recA)	Rat Ar S9	DNA damage	Differential killing repair-deficient strains		Pyr, AC	No	No quantitative information.
16190	Vaca et al., 1992	CHO cells	Rat Ar S9	DNA damage	Alkaline elution	FA		No	No untreated or vehicle control.
22260	Williams et al., 1982	Rat hepatocyte primary culture	None	Unscheduled DNA synthesis	[^{3}H] Thymidine uptake		Pyr, BeP	No	No quantitative information.

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Table 4-14. Study summaries: in vitro clastogenicity or sister chromatid exchange with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Clastogenic endpoint(s)	Positive results	Non-positive results	Meets selection criteria?	Comments
16740	Abe and Sasaki, 1977	Pseudodiploid Chinese hamster D-6	None	Aberrations and sister chromatid exchanges		AC, Pyr	Yes	
17890	Dean, 1981	Near-diploid epithelial-type rat liver RL_1	None	Various aberrations		AC, Pyr	No	Semiquantitative results.
17930	DeSalvia et al., 1988	Male Chinese hamster liver epithelial cells	None	Sister chromatid exchanges		Pyr, FA	Yes	
18120	Evans and Mitchell, 1981	CHO	Rat Ar S9	Sister chromatid exchanges	Pyr (with activation)		No	No untreated or vehicle control.
23640	Evans, and DiPaolo, 1975	Diploid strain 2 guinea pig fetal cells	None	Aneuploidy		AC	No	No quantitative data. Pyr, PH also evaluated using different protocol without BaP reference.
18260	Gehly et al., 1982	CH3/10T1/2 clone 8 mouse fibroblasts	None	Sister chromatid exchanges		BeP	Yes	
14620	Kochhar, 1982	Chinese hamster V79	None	Aberrations including gaps, rings, breaks, fragments, exchanges	BaA		Yes	Dose-dependent increase in the percentage cells with aberrations.
14640	Krolewski et al., 1986	CH3/10T1/2 clone 8 mouse embryo cells	None	Sister chromatid exchanges	CPcdP		Yes	CPcdP appears to increase sister chromatid exchanges in dose-dependent fashion (two doses).
19690	Mane et al., 1990	Chinese hamster V79 cells	With and without rat mammary epithelial cell coculture	Sister chromatid exchanges	BaA	BeP	Yes	
19770	Matsuoka et al., 1979	Male Chinese hamster lung	Rat Ar S9	Aberrations and sister chromatid exchanges		PH	No	Not clear if BaP administered simultaneously. No untreated control.
20020	Murison, 1988	P3 clonal isolate from human epithelial teratocarcinoma	BJ-015 human breast epithelial cell coculture	Sister chromatid exchanges	CPcdP	BeP	No	Not clear if BaP administered simultaneously; no concurrent control.
20340	Perry and Thomson, 1981	CHO cells	Rat Ar S9	Sister chromatid exchanges	Pyr	AC	No	No untreated control.

Table 4-14. Study summaries: in vitro clastogenicity or sister chromatid exchange with benzo[a]pyrene and at least one other PAH

Record number	Reference	Cell type	Metabolic activation	Clastogenic endpoint(s)	Positive results	Non-positive results	Meets selection criteria?	Comments
20500	Popescu et al., 1977	Chinese hamster V79-4 cells	With or without irradiated Syrian golden hamster secondary embryo feeder cells	Aberrations and sister chromatid exchanges	Pery, Pyr	PH	No	BaP increased sister chromatid exchanges but Pyr and Pery increased aberrations. Pery increased aberrations w/o activation. 60% of Pyr treated cells (activated) polyploid. Increased aberrations in polyploid cells.
21710	Tong et al., 1981a	Adult rat liver epithelial (ARL 18) cells	None	Sister chromatid exchanges	BaA	BeP, Pyr, AC	Yes	
21720	Tong et al., 1983	Adult rat liver epithelial (ARL 18) cells	None	Sister chromatid exchanges	BaA	BeP, Pyr, AC	No	Repeats data from Record 21710 Tong et al., 1981a.
8780	Vienneau et al., 1995	UDP-Glucuronosyl-transferases-deficient rat (RHA-J/*J*) skin fibroblasts	None	Micronuclei		BeP	Yes	
8850	Warshawsky et al., 1995	Human lymphocytes	None	Micronuclei and sister chromatid exchanges		BaA	Yes	
21980	Weinstein et al., 1977	Human diploid fibroblasts (WI-38)	With or without rat Ar s9	Chromosomal damage, mitotic index, abnormal metaphases		Pyr	Yes	

If the above criteria were met, studies were selected for use in the analysis regardless of whether positive or nonpositive results were reported. Studies with positive findings were used for calculation of RPFs. Studies with nonpositive findings were used in a weight of evidence evaluation for selecting PAHs for inclusion in the RPF approach (discussed later in Section 6.1). To be considered adequate for use in the analysis, nonpositive bioassays were selected only if two additional conditions were met: (1) at least 20 animals were used per dose group, and (2) animals were observed for at least 6 months. More strict criteria were applied to nonpositive studies due to the difficulty in demonstrating the absence of an effect. For example, if a positive tumor response (i.e., statistically significant increase in incidence) was observed after 3 months of treatment with a given PAH, the positive finding is clear; however, if no response (or a nonsignificant response) was observed after 3 months, the absence of response might reflect a lack of carcinogenic action, but might also have resulted from inadequate follow-up time. The use of these additional criteria for nonpositive studies served to ensure that PAHs would not be treated as noncarcinogenic based on inadequate nonpositive bioassays.

Study design details, findings, limitations, and a determination of whether the study met selection criteria are presented in Tables 4-1 through 4-14 for each study reviewed in each category. Except where noted, positive and nonpositive findings reported in the table are based on the author's determination. When statistical analysis of tumor bioassay data was not included in the pertinent publication, statistical analysis was conducted to determine whether the response differed from control. In the sections that follow, overviews of the data available in each category are presented. The overviews address the nature of the studies available, concise information on general study methods, general findings for the tested compounds, and key strengths and limitations of the available data for relative potency development.

4.3.1. In Vivo Cancer Bioassays in Animals

The PAH database contained a large number of cancer bioassay studies in which one or more PAHs was evaluated along with benzo[a]pyrene. The vast majority of the tumor bioassay studies were mouse skin painting studies (n = 43). In addition, there were 12 intraperitoneal studies, 9 subcutaneous exposure studies, 3 oral studies, and 9 studies using miscellaneous exposure routes.

4.3.1.1. *Dermal Exposure*

A summary of the 43 dermal bioassays is provided in Table 4-1. These studies were all conducted in mice. Fifteen studies tested the complete carcinogenicity of PAHs, while 23 studies tested PAHs as initiators in initiation-promotion protocols. In some cases, both complete and initiation-promotion studies were reported in the same reference. For these references, two entries are included in the table.

Complete carcinogenicity studies were conducted in mice using either dropper or paintbrush application. Swiss mice were typically preferred for these studies. PAHs, usually in acetone, were applied to the shaved interscapular skin 2 or 3 times/week. The duration of exposure varied from 10 weeks up to about 70 weeks; most studies continued exposure for at least 30 weeks. Skin tumor counts were recorded on a weekly basis, and animals were sacrificed when tumors reached a minimum size (e.g., 2 cm) or when the animals were moribund. These studies generally focused exclusively on skin papillomas and carcinomas. Skin tumor data were reported as incidence (i.e., number of animals with tumors) and/or tumor count (mean number of tumors per animal) (indicated in Table 4-1).

Several PAHs consistently (in two or more studies) proved to be complete carcinogens in mouse skin painting assays, including benzo[b]fluoranthene, benzo[j]fluoranthene, cyclopenta[c,d]pyrene, dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, and dibenzo[a,l]pyrene. Chrysene gave positive results in two complete carcinogenicity studies (LaVoie et al., 1979; Wynder and Hoffmann, 1959) and equivocal results in a third (Hecht et al., 1974). Anthanthrene, dibenzo[a,e]fluoranthene, and dibenz[a,h]anthracene each gave positive tumorigenicity results in a single assay (Cavalieri et al., 1977; Hoffmann and Wynder, 1966; and Wynder and Hoffmann, 1959; respectively). Nonpositive or equivocal results were reported for benzo[k]fluoranthene, benzo[g,h,i]fluoranthene, dibenzo[e,l]pyrene, indeno[1,2,3-c,d]pyrene, benzo[g,h,i]perylene, naphtho[2,3-e]pyrene, anthracene, pyrene, fluoranthene, 2,3-acepyrene, benz[a]anthracene, coronene, and benzo[e]pyrene (see Table 4-1).

According to LaCassagne et al. (1968), in studies conducted prior to 1966, the compound reported as dibenzo[a,l]pyrene was actually dibenzo[a,e]fluoranthene. In the text and tables of this report, data from Hoffmann and Wynder (1966) are reported as dibenzo[a,e]fluoranthene in Table 4-1.

The initiation studies in Table 4-1 were performed under a generally consistent protocol, as follows. During the early part of the second telogen phase of the hair cycle (at about 7–8 weeks of age), PAHs in acetone were applied to the shaved interscapular skin of mice. In general, female Swiss, CD-1, or SENCAR mice were used. Some studies used dropper administration, but the majority employed a painting method using a camel's hair brush. About half of the initiation studies used a single initiation dose, while the other half administered the initiating compound in 10 subdoses given every other day. One to 2 weeks after the final initiating dose, promotion was begun with twice or thrice weekly applications of a promoting agent, usually TPA or croton oil. The dose of the promoting agent varied by study. Promotion usually continued for about 20 weeks (with a range across studies from 11 to 26 weeks). The incidence of skin papillomas was recorded on a weekly basis until the promotion period was ended. Papillomas were removed at random for histological verification. Some studies reported the number of tumors per animal; some reported only the incidence.

The initiation studies in Table 4-1 consistently showed positive tumorigenicity across two or more studies for the following compounds: benzo[j]fluoranthene, benzo[b]fluoranthene, chrysene, dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, dibenzo[a,l]pyrene, and cyclopenta[d,e,f]chrysene. In at least one study, benzo[k]fluoranthene, benz[l]aceanthrylene, benz[e]aceanthrylene, naphtho[2,3-e]pyrene, dibenz[a,h]anthracene, dibenz[a,c]anthracene, and benz[b,c]aceanthrylene showed positive initiating activity. Nonpositive results were reported for pyrene, perylene, benzo[g,h,i]fluoranthene, fluoranthene, anthanthrene, dibenzo[e,l]pyrene, benzo[g,h,i]perylene, indeno[1,2,3-c,d]pyrene, benzo[e]pyrene, anthracene, 2,3-acepyrene, and phenanthrene. Cyclopenta[c,d]pyrene gave nonpositive results in one study (Wood et al., 1980) and positive results in two studies (Raveh et al., 1982; Cavalieri et al., 1981b) (see Table 4-1).

The vast majority of the initiation and complete carcinogenicity studies were conducted in female mice; thus, data on gender differences in skin tumor susceptibility are not available.

A few studies using dermal application (Warshawsky et al., 1993; Slaga et al., 1979; Van Duuren and Goldschmidt, 1976; Horton and Christian, 1974; Van Duuren et al., 1973) were designed to evaluate the cocarcinogenicity of two or more PAHs, or of a single PAH with dodecane as a vehicle. These were primarily complete carcinogenicity studies, wherein PAHs were administered together over a chronic time period, although Slaga et al. (1979) used an initiation-promotion design. Study design was similar to other complete carcinogenicity experiments. In these studies, the carcinogenicity of single PAHs was evaluated for comparison with the results obtained when the PAHs were administered with a cocarcinogen. Data on single PAHs (without a cocarcinogen) were generally limited to single dose levels. In the cocarcinogenesis studies, only dibenz[a,c]anthracene, benzo[e]pyrene, and pyrene gave positive results when administered without a cocarcinogen; results for pyrene were judged to be equivocal in the absence of statistical confirmation. The PAHs chosen for cocarcinogenesis studies were often those traditionally understood to be nontumorigenic or weakly tumorigenic when administered alone (e.g., perylene, pyrene, benzo[e]pyrene, benzo[g,h,i]perylene, phenanthrene, fluoranthene).

Several issues relating to the potential use of the dermal bioassay data for relative potency development were identified during study review. Several studies did not include a concurrent untreated or vehicle-treated control group (Masuda and Kagawa, 1972; Bingham and Falk, 1969; Wynder and Hoffmann, 1959a, b). In a number of reports, it appears that bioassays were done in batches and reported in a single publication. In these cases, it appears that benzo[a]pyrene treatment may not have been undertaken concurrently with all of the compounds in the report. For some of these studies (Horton and Christian, 1974; Bingham and Falk, 1969), there are differences in the choice of vehicle or promoter, or other issues that argue against using the benzo[a]pyrene data for direct comparison. In several other studies, however (Rice et al., 1988; Slaga et al., 1980; Van Duuren and Goldschmidt, 1976; Wynder and Hoffmann, 1959), the protocols (including vehicle and promoting agent) appear to have been the same.

Among the dermal tumor bioassay studies in Table 4-1, 24 studies met the selection criteria for use in this analysis.

4.3.1.2. *Intraperitoneal Exposure*

Twelve cancer bioassays in the literature used intraperitoneal injection. Six of these studies were carried out in newborn mice, while the other six used adult A/J mice. The studies were focused on lung and liver tumorigenicity after PAH exposure; one study also examined forestomach lesions. Study summaries for all of these references are reported in Table 4-2. Tumor data were reported as incidence (i.e., number of animals with tumors) and/or tumor count (mean number of tumors per animal) (indicated in Table 4-2).

Newborn mouse studies. Six cancer bioassays in newborn mice were identified (LaVoie et al., 1994, 1987; Busby et al., 1989, 1984; Weyand and LaVoie, 1988; Wislocki et al., 1986). In general, PAHs were administered intraperitoneally to newborn mice (usually of the Swiss or CD-1 strains). The dosing schedule called for 1/7th, 2/7ths, and 4/7ths of the total dose to be administered on the 1st, 8th, and 15th days of life. Typically, the mice were sacrificed at either 6 months or 1 year, and lung and/or liver tumors were identified and classified.

The studies in newborn mice showed a distinct gender difference in liver tumorigenicity. Male mice appear to be substantially more susceptible to liver tumor induction than females. In contrast, both male and female mice developed lung tumors after exposure. Three studies (LaVoie et al., 1994; Busby et al., 1989, 1984) reported that fluoranthene induced lung tumors in both male and female mice, while one study reported that fluoranthene induced liver tumors in male mice only (LaVoie et al., 1994). LaVoie et al. (1987) reported that benzo[b]fluoranthene and benzo[j]fluoranthene induced lung adenomas in both male and female mice, but induced liver tumors only in males. Wislocki et al. (1986) reported that treatment with benz[a]anthracene resulted in a significant increase in liver tumors in male mice. In this study, benz[a]anthracene treatment resulted in an increased incidence of lung tumors in both males and females, although the tumor incidence was significantly increased only for females. The same authors (Wislocki et al., 1986) reported a significant increase in liver tumors in male mice treated with chrysene, but no increase in lung tumorigenicity. The lack of lung tumorigenicity in mice treated with chrysene was also reported by Busby et al. (1989).

Nonpositive tumorigenicity results in newborn mouse assays were reported for pyrene, chrysene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene (Busby et al., 1989; LaVoie et al., 1987).

Most of the data from the newborn mouse assays met the criteria for relative potency development, although Weyand and LaVoie (1988) is an abstract and does not provide dose-response information. LaVoie et al. (1994) noted that liver tumorigenicity in newborn mice exposed to weak tumorigenic agents may not be fully realized for 12 months; thus, the failure to

observe liver tumors in studies of shorter duration (Busby et al., 1989, 1984) may result from the longer latency and should be taken into consideration in using these data.

Lung adenoma A/J mouse studies. Six studies (Nesnow et al., 1998a, b, 1996, 1995; Ross et al., 1995; Mass et al., 1993) were carried out in 6- to 8-week-old A/J mice by the same laboratory using a standard protocol (Table 4-2). Mice were given a single intraperitoneal injection of PAH in tricaprylin and followed for 8 months. Upon sacrifice, the lungs were removed and adenomas were counted. Tumor multiplicity was reported, while tumor incidence was not. Several of these studies include estimates of relative potency based on statistical analysis of the tumor multiplicity data. These studies report positive tumor findings (reported as an increase in the number of tumors per animal) for all of the PAHs tested (benz[j]aceanthrylene, benzo[b]fluoranthene, dibenz[a,h]anthracene, cyclopenta[c,d]pyrene, and dibenzo[a,l]pyrene). One additional study by a different group (Weyand et al., 2004) used the same study design to assess effects of benzo[c]fluorene. In this study, both lung adenomas and forestomach lesions were evaluated after 8 months. Both benzo[c]fluorene and benzo[a]pyrene were associated with increased incidences of lung adenomas but not with increased forestomach lesions.

Among the intraperitoneal tumor bioassay studies in Table 4-2, nine studies met the selection criteria for use in this analysis.

4.3.1.3. *Subcutaneous Injection Exposure*

Nine studies employing a subcutaneous exposure design were identified. All of the subcutaneous exposure studies are more than 25 years old; the most recent is Pfeiffer (1977). Study descriptions are presented in Table 4-3.

Two studies utilized newborn mice (Roe and Waters, 1967; Grant and Roe, 1963). In these studies, phenanthrene was administered subcutaneously to newborn albino mice on the first day of life. Ten mice of each group were sacrificed after 52 weeks, and the remaining animals were sacrificed at 62 weeks. Grant and Roe (1963) evaluated lung tumorigenicity and observed no increase with phenanthrene, while Roe and Waters (1967) reported liver tumors in the same group of mice. Roe and Waters (1967) reported an elevated incidence of liver tumors in male mice exposed subcutaneously to phenanthrene; however, it is not clear whether the difference was significant. Roe and Waters (1967) is a brief communication with limited details of the study design and results.

In most of the remaining studies, single subcutaneous doses of one or more PAH and benzo[a]pyrene were administered to mice, followed 1–2.5 years later by an evaluation of injection site and other tumors. Tumors at the injection site were most commonly reported; however, in some studies, investigators also examined other organs for tumors (Homburger et al., 1972; Roe and Waters, 1967; Grant and Roe, 1963; Rask-Nielsen, 1950; Pfeiffer and Allen, 1948).

Most of the subcutaneous bioassays suffer from critical shortcomings in design or reporting. One study used "aged" mice for controls, allowing these animals to live 16 weeks longer than the treated group (Homburger et al., 1972). Three studies gave apparently positive results for dibenz[a,h]anthracene (i.e., substantial tumor induction) (Pfeiffer, 1977; Steiner, 1955; Bryan and Shimkin, 1943). However, neither Bryan and Shimkin (1943) nor Steiner (1955) included untreated control groups. Pfeiffer (1977) included an untreated control group in which there was 90% mortality prior to sacrifice of the treated animals; data on tumor incidence in controls were not reported. Several other studies (Pfeiffer and Allen, 1948; Barry et al., 1935) also did not include a concurrent untreated or vehicle-treated control group. These studies were not used for dose-response assessment due to the lack of appropriate controls.

Fundamental flaws were observed in two older studies. Pfeiffer and Allen (1948) examined the effects of PAHs in Rhesus monkeys. Individual animals were exposed sequentially to several PAHs via multiple exposure routes; thus, the effect of any individual PAH or benzo[a]pyrene cannot be discerned. Barry et al. (1935) treated mice with PAHs from varying sources and of varying purity. Given the age of the study and the attendant issues with nomenclature, purity, and analysis of the treatment compounds, data from this study are excluded from use in relative potency development.

Among the subcutaneous tumor bioassay studies in Table 4-3, only a single study met selection criteria for use in this analysis.

4.3.1.4. *Oral Exposure*

The literature search identified three oral bioassays that included benzo[a]pyrene and at least one other PAH. Critical aspects of the study design for these studies are reported in Table 4-4.

Biancifiori and Caschera (1962) compared the induction of mammary tumors in virgin and pseudopregnant mice (female mice mated with vasectomized males) after gavage exposure to dibenz[a,h]anthracene or benzo[a]pyrene. Tumor incidence was increased in pseudopregnant mice given 1 mg/week of either compound for 15 weeks, but not in virgin mice given the same dose. The relevance of the positive findings in pseudopregnant mice is uncertain given that an increased incidence of tumors was not observed in virgin mice treated at the same dose. One possible explanation for the disparate findings is that circulating hormones in pseudopregnant mice differed from those in virgin mice and interacted with the PAH to enhance tumor formation. Huggins and Yang (1962) also evaluated mammary tumor incidence after a single oral PAH exposure. Sprague-Dawley rats were given gavage doses of benzo[a]pyrene, benz[a]anthracene, or phenanthrene. This study did not include an untreated or vehicle-treated control group. No tumors were observed in the rats treated with either benz[a]anthracene or phenanthrene, while mammary tumors were observed in eight of the nine benzo[a]pyrene-treated animals.

Weyand et al. (2004) conducted an oral bioassay in which female A/J mice were fed diets containing benzo[c]fluorene or benzo[a]pyrene throughout the study. At sacrifice after 260 days, lung adenomas were counted and forestomach lesions were characterized. Exposure to benzo[c]fluorene and benzo[a]pyrene resulted in significantly increased incidences of lung adenomas, but only benzo[a]pyrene exposure resulted in forestomach neoplasms. This was the only oral study that met the selection criteria for use in this analysis.

4.3.1.5. *Other Routes*

Nine bioassays were available that did not fit into other exposure route categories (i.e., dermal, intraperitoneal, subcutaneous, or oral) (see Table 4-5). Among these were studies using intramammillary, intramuscular, and intravenous injection as well as lung implantation, tracheal implantation, and transplacental exposure after subcutaneous injection. Seven studies were in rats, with one each in mice and hamsters.

Deutsch-Wenzel et al. (1983) and Wenzel-Hartung et al. (1990) implanted PAH-containing pellets (consisting of beeswax and trioctanoin) into the lungs of inbred female Osborne-Mendel rats. Lung tumor incidence was reported for a total of 10 PAHs and benzo[a]pyrene. The authors reported relative potency estimates based on the lung tumor data. Lung tumors were induced by benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[g,h,i]perylene, indeno[1,2,3-c,d]pyrene, anthanthrene, chrysene, and dibenz[a,h]anthracene. Nonpositive findings were reported for benzo[e]pyrene and phenanthrene.

Cavalieri et al. (1991) treated Sprague-Dawley rats with single intramammillary injections of dibenzo[a,l]pyrene into the left mammary glands and followed them for up to 24 weeks. Tumors of the mammary gland, mesenchymal tissue, or skin were recorded. Dibenzo[a,l]pyrene produced tumors in all animals at both doses.

In six studies, tumors were not induced after exposure to any target PAH. Intramammillary injection of dibenz[a,h]anthracene and benz[a]anthracene did not induce mammary tumors in rats (Cavalieri et al., 1988b). Pregnant mice receiving subcutaneous injection of pyrene did not develop tumors, nor did their offspring (Nikonova, 1977). Rats treated either intravenously or intramuscularly with benz[a]anthracene did not develop either mammary or injection site tumors (Pataki and Huggins, 1969). Similarly, benz[a]anthracene was not tumorigenic after intramuscular injection in rats (Sugiyama, 1973) or buccal pouch painting in hamsters (Solt et al., 1987). Finally, benzo[e]pyrene was not tumorigenic when it was implanted into tracheas transplanted subcutaneously into isogenic rats (Topping et al., 1981).

Among the tumor bioassays that used alternative exposure routes in Table 4-5, four studies met the selection criteria for use in this analysis.

4.3.2. In Vivo Studies of Cancer-Related Endpoints

The database of cancer-related endpoints measured after in vivo exposure to PAHs is much smaller than the in vitro database. Endpoints examined after in vivo exposure include mutagenicity, DNA adducts, and clastogenicity or sister chromatid exchange. As with the in vitro database, only studies of selected PAHs that included benzo[a]pyrene as a reference compound were reviewed. Each study that was reviewed for consideration in relative potency development is presented in tabular format in subsequent sections. The tables summarize study-specific information and indicate whether a particular study is considered useful for dose-response assessment. The text provides an overall description of the available studies, including a general description of the methodology used for each study type, the results, and the weaknesses or problems associated with specific studies or study types.

4.3.2.1. *DNA Adducts*

Nineteen studies evaluating DNA adduct formation for PAHs and benzo[a]pyrene were identified in the database (Table 4-6). Nine studies presented quantitative data for DNA adduct formation and are discussed below. Among studies with data potentially useful for RPF derivation, the route of exposure was intramammillary injection in one study (Arif et al., 1997), intraperitoneal injection in seven studies (Weyand et al., 2004; Kligerman et al., 2002; Nesnow et al., 1998a, 1996, 1995; Ross et al., 1995; Mass et al., 1993), dermal in three studies (Hughes and Phillips, 1990; Cavalieri et al., 1981b; Phillips et al., 1979), and oral in two studies (Weyand et al., 2004; Kligerman et al., 2002). Adducts were identified by [^{32}P]-postlabeling in all of the studies except for two by Phillips et al. (1979) and Cavalieri et al. (1981b), which utilized [^{3}H]- or [^{14}C]-radiolabeled PAHs. Three papers described experiments with a single time point(s) at 24 or 48 hours or 14 days (Weyand et al., 2004; Arif et al., 1997; Hughes and Phillips, 1990), whereas the rest had multiple time points. The duration of exposure was as short as 4 hours (Cavalieri et al., 1981b), although 24 hours was usually the first time point(s) in time-course studies. The longest duration for a time-course study was 84 days (Hughes and Phillips, 1990), but most were ≤3 weeks. The tissues evaluated included mammary epithelium (Arif et al., 1997), skin (Hughes and Phillips, 1990; Cavalieri et al., 1981b; Phillips et al., 1979), liver and peripheral blood lymphocytes (Kligerman et al., 2002; Nesnow et al., 1993b), lung (Weyand et al., 2004; Nesnow et al., 1998a, 1993b; Arif et al., 1997; Ross et al., 1995; Mass et al., 1993; Hughes and Phillips, 1990), and forestomach (Weyand et al., 2004).

Dermal exposure studies typically involved application of the chemical in solution to the shaved dorsal skin of mice (Hughes and Phillips, 1990; Cavalieri et al., 1981b; Phillips et al., 1979). After the scheduled sacrifice, the treated skin was excised and frozen; a scalpel was used to scrape away the dermis from the epidermis that was subsequently powdered in liquid nitrogen. In one study, the lung was also excised and frozen in liquid nitrogen (Hughes and Phillips, 1990). DNA was isolated from the frozen epidermis or lung. Liquid scintillation counting was

used to quantify DNA adducts to PAH labeled with [^{3}H] or [^{14}C] (Cavalieri et al., 1981b; Phillips et al., 1979). For [^{32}P]-postlabeling, DNA was treated to selectively dephosphorylated nonadducted nucleotides; after postlabeling, adducts were resolved by sequential anion-exchange thin layer chromatography on polyethyleneimine-cellulose plates in several directions using three solvents (Hughes and Phillips, 1990). Adduct spots on chromatograms were located by autoradiography, after which the spots were excised and radioactivity levels were determined by Cerenkov counting.

Most studies reported the mean number of adducts formed within a tissue per unit of DNA, with time-course data displayed graphically. Peak values were sometimes called out specifically in the text or tables. As the shapes of dose-response curves differ among different PAHs, the peak value is an imprecise measure for comparing the relative adduct-forming potency of the different compounds. The TIDAL has also been used for reporting results for a time-course study (Ross et al., 1995). The TIDAL value is the area under the curve (AUC) for adduct persistence (based on the rate of adduct formation and repair) for the duration of the study. The TIDAL value expresses the total DNA adduct burden experienced by the tissue from the time of treatment to the end of the study. The TIDAL versus administered dose curve provides a convenient way to compare adduct-forming potency for different PAHs in time-course experiments. An important limitation of the TIDAL approach is the inherent assumption that the ratios of specific adducts are relatively constant across dose and time course. Ross et al. (1995) demonstrated that this assumption was valid for several different PAHs; however, it was also noted that two adducts of benzo[a]pyrene in rat liver did not conform to this general pattern.

Ross et al. (1995) presented data for lung adenoma incidence (measured at 8 months) in several ways: as a function of administered dose, as a function of adduct levels per dose measured 24 hours after dosing (results for 3 days postdosing were mentioned but not shown), as a function of TIDAL values measured over 21 days (during which period, adduct levels were specifically quantified), and as a function of TIDAL values extrapolated to 8 months. The relative tumor induction potencies of the studied PAHs were similar for each assay for a single PAH when described as functions of administered dose, the adduct levels per dose at 3 days, the TIDAL values over 21 days, or the TIDAL values extrapolated to 8 months. The relative potencies for tumor incidence as a function of adduct levels at 24 hours were not similar to those associated with the other measures of exposure. Ross et al. (1995) suggested that pharmacokinetic differences in adduct formation among the PAHs were responsible for the discrepancy, but suggested that peak levels could be used to compare the potencies of different PAHs if adduct formation for those PAHs followed similar kinetics.

DNA adduct experiments were carried out in replicate and were usually analyzed statistically. It should be noted that, based on the work of Ross et al. (1995), relative potencies determined from studies that administered a single dose level and measured adducts at a single time point will be less reliable unless the shapes of the adduct formation curves are similar.

However, the single dose and single measurement studies were also used for dose-response assessment.

Among the in vivo DNA adduct studies shown in Table 4-6, nine studies met the selection criteria for use in this analysis.

4.3.2.2. *Clastogenicity or Sister Chromatid Exchange Frequency*

The database included 13 studies in which clastogenic effects or frequency of sister chromatid exchanges of benzo[a]pyrene and at least one other PAH were tested in whole animal systems. Table 4-7 lists the studies along with important study design details. The clastogenic endpoints measured in these studies were micronuclei, chromosome gaps and breaks, and nonspecific aberrations; sister chromatid exchanges were also measured. These studies were all conducted in rodents, including mice, rats, and hamsters.

Eight of the studies evaluated micronuclei, sister chromatid exchanges, or chromosome gaps or breaks in bone marrow from treated mice or hamsters (Allen et al., 1999; Katz et al., 1981; Paika et al., 1981; Salamone et al., 1981; Tsuchimoto and Matter, 1981; Roszinsky-Kocher et al., 1979; Bayer, 1978; Sugiyama, 1973). In these studies, one or two doses of PAH were injected intraperitoneally into the animals, and sacrifice occurred at various time points thereafter (typically 24 hours after). Bone marrow smears were examined microscopically and scored for micronuclei, sister chromatid exchanges, gaps, or breaks.

He and Baker (1991) applied multiple dose levels of chrysene or phenanthrene to the skin of hairless mice and harvested keratinocytes upon sacrifice 24 hours later. The keratinocytes were incubated for 2 days and treated with cytochalasin B to identify binucleated cells. After 4 days in vitro, cells were mounted on slides and examined microscopically for micronuclei. Results were reported as the percent of binucleated cells with one or more micronuclei among the total number of binucleated cells scored. Chrysene treatment resulted in a dose-related increase in micronuclei, while pyrene did not.

Kligerman et al. (2002, 1986) measured sister chromatid exchanges and/or micronuclei in the blood of mice or rats given a single dose of PAH either orally or intraperitoneally. The study by Oshiro et al. (1992) involved two or four oral doses of pyrene or anthracene in mice. Blood obtained from the tail 24 hours after the last treatment was examined microscopically and micronuclei were scored in polychromatic erythrocytes. In an unusual study design, Sirianni and Huang (1978) measured sister chromatid exchanges in V79 cells placed in a diffusion chamber implanted in the peritoneal cavity of mice.

Thirteen individual PAHs were evaluated in these studies. Only chrysene gave positive results for more than one endpoint (for sister chromatid exchange and micronucleus frequency; He and Baker, 1991; Roszinsky-Kocher et al., 1979). Five other PAHs (phenanthrene, dibenz[a,h]anthracene, benz[a]anthracene, benzo[b]fluoranthene, and benzo[e]pyrene) increased the frequency of sister chromatid exchange in hamster bone marrow after intraperitoneal

administration (Roszinsky-Kocher et al., 1979). Bayer (1978) also reported an increase in sister chromatid exchange frequency in hamster bone marrow after phenanthrene administration (high dose only). Anthracene and pyrene consistently gave nonpositive results in several studies (Oshiro et al., 1992; He and Baker, 1991; Katz et al., 1981; Paika et al., 1981; Salamone et al., 1981; Tsuchimoto and Matter, 1981; Roszinsky-Kocher et al., 1979; Sirianni and Huang, 1978). Dibenzo[a,i]pyrene and benzo[g,h,i]perylene each gave nonpositive results in an assay for bone marrow micronuclei (Katz et al., 1981).

Among studies with positive results, only He and Baker (1991), Kligerman et al. (1986), and Bayer (1978) administered PAHs at multiple dose levels. Bayer (1978) observed a positive response only with the highest dose of phenanthrene. Of the single dose studies, only Roszinsky-Kocher et al. (1979) reported responses clearly differing from controls.

Among the in vivo clastogenicity or sister chromatid exchange studies shown in Table 4-7, 10 studies met the selection criteria for use in this analysis.

4.3.2.3. *In Vivo Mutagenicity*

The PAH database contains several studies that evaluate specific mutagenic endpoints following in vivo exposure to PAHs (see Table 4-8). These studies include mutagenicity experiments in *Drosophila melanogaster*, an intraperitoneal host-mediated assay using Salmonella strains or yeast, and DNA sequence analysis of specific codons in the Ki-ras oncogene in mouse lung tumors.

Most Drosophila studies administered PAH compounds to either the suspension media or to the diet for 48–72 hours prior to cross-mating and analysis of mutations (Frolich and Wurgler, 1990; Valencia and Houtchens, 1981; Fahmy and Fahmy, 1980). One study used abdominal injection as an exposure pathway (Zijlstra and Vogel, 1984). The mutagenic endpoints evaluated included somatic mutations (i.e., eye color mosaicism, wing spots) (Frolich and Wurgler, 1990; Fahmy and Fahmy, 1980) or sex-linked recessive lethal mutations (Zijlstra and Vogel, 1984; Valencia and Houtchens, 1981). Only two PAHs were evaluated in the Drosophila studies in addition to benzo[a]pyrene (benz[a]anthracene and pyrene), and the results were either nonpositive or inconsistent in all studies (Frolich and Wurgler, 1990; Zijlstra and Vogel, 1984; Valencia and Houtchens, 1981; Fahmy and Fahmy, 1980). A significant effect was seen for benz[a]anthracene only with cross-breeding of strains selected for enhanced metabolic activity (Frolich and Wurgler, 1990). No effect was observed using the standard strains.

An intraperitoneal host-mediated assay was described by Simmon et al. (1979). Five PAHs (anthracene, benz[a]anthracene, benzo[e]pyrene, chrysene, and phenanthrene) were administered to Swiss Webster mice by gavage or intramuscular injection (single dose only). Microorganisms (*S. typhimurium* and *Saccharomyces cerevisiae*) were injected intraperitoneally into exposed mice and were recovered 4 hours later for mutation analysis. Nonpositive results

were observed and the host-mediated assay system was considered insensitive for detecting carcinogenic PAHs.

A series of studies have investigated the mutation sequence in codons 12 and 61 of the Ki-ras oncogene from PAH-induced lung adenomas in A/J mice (Nesnow et al., 1998a, 1996, 1995; Mass et al., 1993). As discussed in Section 2.4 (Similarities in Mode of Carcinogenic Action for PAHs), the purpose of these studies was to correlate the tumorigenic potency of specific PAHs with the formation of DNA adducts and the mutation of specific codons in the Ki-ras oncogene. Six non-alkylated PAHs were utilized in these studies (benzo[a]pyrene, benz[j]aceanthrylene, benzo[b]fluoranthene, dibenz[a,h]anthracene, cyclopenta[c,d]pyrene, and dibenzo[a,l]pyrene). Mutation analysis of the Ki-ras oncogene at codons 12 and 61 was carried out in PAH-induced lung adenomas using PCR amplification and dideoxy nucleotide sequencing methods. The primary mutation type for benzo[a]pyrene, benzo[b]fluoranthene, and dibenzo[a,l]pyrene was the GGT→TGT mutation. This guanine mutation was correlated with the formation of diol epoxide guanine adducts. The GGT→CGT mutation was the primary mutation type for benz[j]aceanthrylene and cyclopenta[c,d]pyrene. The CGT mutation was associated with the formation of cyclopenta-guanine adducts and increased tumorigenic potency (i.e., >90 adenomas per mouse) in A/J mice. Dibenz[a,h]anthracene was the only PAH evaluated that did not induce mutations in Ki-ras codons 12 or 61. This compound produced diol epoxide guanine adducts and lung adenomas in A/J mice, suggesting a possible interaction at a different genetic target. The Ki-ras mutation analysis data were presented as percent of tumors with a specific mutation at either codon 12 or 61. No dose-response data were provided.

Among the in vivo mutagenicity studies shown in Table 4-8, only one study met the selection criteria for use in this analysis.

4.3.3. In Vitro Studies of Cancer-Related Endpoints

Many in vitro studies of cancer-related endpoints are present in the PAH database. As previously discussed, only those studies that included at least one selected PAH and benzo[a]pyrene as a reference compound were reviewed. Each study that was reviewed for the purpose of RPF development is included in Tables 4-9 through 4-14. The tables summarize study-specific information and indicate whether a particular study is considered useful for dose-response assessment. The text provides an overall description of the available studies, including a general description of the methodology used for each study type, the results, and the weaknesses or problems associated with specific studies or study types.

4.3.3.1. *Bacterial Mutagenicity*

The bacterial mutagenicity of many PAHs has been extensively studied (39 studies with benzo[a]pyrene; see Table 4-9). All of the studies used the Ames assay in *S. typhimurium*. A total of 38 PAHs have been evaluated for their ability to induce mutations in bacterial systems.

The Ames Salmonella assay is a bacterial reverse mutation assay, which measures the frequency at which histidine-independent bacteria arise from histidine-requiring bacterial strains in the presence of a chemical mutagen. The results are generally expressed as either the number of revertant colonies per plate or the number of revertants/nmol of the test compound (calculated from the linear portion of the dose-response curve). Several strains of *S. typhimurium* have been used to evaluate specific PAH mutation types; for example, TA98, TA1537, and TA1538 detect various frameshift mutations, TA1535 responds to base-pair substitution, and TA100 responds to a broad spectrum of mutations. Metabolism to reactive intermediates is required for PAH mutagenicity in Salmonella and many metabolic activation systems have been employed. Rat liver postmitochondrial supernatant (known as S9) from Aroclor-induced rats is most often used, although other rodent species and enzyme inducers are sometimes employed. Isolated rat hepatocytes or purified mixed-function oxidase enzymes were occasionally utilized for metabolic activation of PAHs.

Of the PAHs tested for bacterial mutagenicity, most were considered positive in at least one study under optimal study conditions. Compounds that produced nonpositive results in multiple studies include anthracene, fluorene, phenanthrene, and pyrene. The primary weakness of the bacterial mutagenicity database for PAHs is the limited amount of multiple-dose data for many PAHs. Many studies report findings at a single dose level for several PAHs.

Among the in vitro bacterial mutagenicity studies shown in Table 4-9, 29 studies met the selection criteria for use in this analysis.

4.3.3.2. *Mammalian Mutagenicity*

Studies that evaluate the mutagenicity of target PAHs in mammalian cells are described in Table 4-10 (29 studies). The most common cell types used in these studies were the V79 Chinese hamster cells and the L5178Y mouse lymphoma cells. Other cell types include human epidermal keratinocytes, TK6 human lymphoblasts, human epithelial cells (HS1 HeLa), human foreskin fibroblasts (D-550), mouse fibroblasts, rat embryo cells, rat liver epithelial cells (ARL-18), and Chinese hamster ovary (CHO) cells. A total of 14 PAHs have been evaluated for their ability to induce mutations in mammalian cell systems.

Each of the mammalian cell assays detects forward mutations that confer resistance to a toxic chemical. Mutations in the hypoxanthine-guanine phosphoribosyl transferase gene (HPRT) result in resistance to purine analogs such as 6-thioguanine, 8-azaguanine, and ouabain. HPRT mutations induced by PAHs were most often measured in V79 Chinese hamster cells, but have also been detected in human, rat, and mouse cell lines. Forward mutation at the thymidine kinase (TK) locus is measured as colony growth in the presence of thymidine analogs (e.g., trifluorothymidine or 5-bromo-2'-deoxyuridine). PAH-induced TK mutations were measured in mouse lymphoma cells (L5178Y) and human lymphoblasts. Forward mutation assays are considered to respond to a variety of mutation types (including frameshift, base-pair substitution,

deletions, and rearrangements or complex mutations). Exogenous metabolic activation is required for PAH mutagenicity in most mammalian cell assays. This was accomplished using a rat liver S9 mix or cocultivation with other rodent cells able to metabolize PAHs to reactive intermediates (i.e., hamster embryo cells, fibroblasts, or hepatocytes; rat hepatocytes). The results of forward mutation assays in mammalian cell lines are generally expressed as mutant frequency/10^x survivors.

Of the 26 PAHs tested for mammalian cell mutagenicity, all were considered positive in at least one study under optimal study conditions. Compounds that produced nonpositive results in some studies include anthracene, benzo[e]pyrene, phenanthrene, and pyrene. Benzo[a]-anthracene produced positive findings in seven studies and nonpositive findings in four studies. The mammalian mutagenicity studies generally provide more multidose data than the bacterial mutagenicity studies.

Among the in vitro mammalian mutagenicity studies shown in Table 4-10, 27 studies met the selection criteria for use in this analysis.

4.3.3.3. *Morphological/Malignant Cell Transformation*

Twenty-five studies examined the capacity of benzo[a]pyrene and other PAHs to transform cells in culture (Table 4-11). All of these studies were conducted using mammalian cells, most commonly mouse or hamster embryo cells. A few studies added feeder cells or rat liver homogenate to enhance metabolic activation in the test system; however, the majority relied on the intrinsic metabolic capacity of the cells. The general test protocol involved seeding the cultured cells in Petri dishes followed by exposure to a solution of the test compound, usually for a period of 24 hours. The cells were then cultured for about 6 weeks before being fixed and stained. Transformed colonies (foci) were scored based on characteristics such as cell piling, criss-crossing, basophilic staining, and/or invasion of surrounding (nontransformed) cell monolayer. In studies conducted by some laboratories, foci were classified as Type II or Type III; the latter category included those with invasion of the surrounding monolayer, highly criss-crossed arrays, and deep staining. Data were generally reported as the number of foci (colony of transformed cells) per dish or per surviving cells and/or the percent of dishes with foci.

In a few cases (e.g., Greb et al., 1980), transformation was assessed by growth of treated cells in soft agar. Transformed cell colonies growing in semi-solid agar are capable of anchorage-independent growth.

Three studies (Evans and DiPaolo, 1975; Kakunaga, 1973; DiPaolo et al., 1972) confirmed the identification of malignant cells by injecting the transformed cells into rodents and following tumor induction in the animals. In all three cases, cells identified as transformed gave rise to tumors, while the cells without these characteristics did not.

Cell transformation assays were identified that included 22 individual PAHs other than benzo[a]pyrene. Dibenz[a,h]anthracene consistently gave rise to transformed cells in all but one of the seven studies in which it was tested. Cyclopenta[c,d]pyrene, indeno[1,2,3-c,d]pyrene, benzo[j]aceanthralene, benz[e]aceanthrylene, and dibenz[k,mno]acephenanthrylene were each tested in a single study and gave positive results. Benz[a]anthracene, pyrene, phenanthrene, benzo[e]pyrene, and anthracene each gave nonpositive results in a number of studies, while fluoranthene, benzo[k]fluoranthene, dibenz[j,mno]acephenanthrylene, naphth[1,2,3-mno]ace-phenanthrylene, and aceanthrylene were each tested in a single study and gave nonpositive results. Only a single dose of the target PAH was applied in 8 of the 26 studies of in vitro morphological/malignant cell transformation.

Among the in vitro morphological/malignant transformation studies shown in Table 4-11, 19 studies met the selection criteria for use in this analysis.

4.3.3.4. *DNA Adducts*

Several studies (14) were identified in which DNA adducts were measured after either whole cells or extracted DNA were incubated with benzo[a]pyrene and at least one other PAH. Table 4-12 shows general study details for these studies. Most of the studies involved measurement of DNA adducts in whole mammalian cells, while some measured adducts formed when PAHs were incubated with extracted DNA. Whole cells were usually incubated with PAHs for about 24 hours, while extracted DNA was exposed to PAH solutions for a shorter time period (1–3 hours). Some of the studies added metabolic activation (usually rat liver microsomes) to the incubation solution. Melendez-Colon et al. (2000) evaluated DNA adduct formation after dibenzo[a,l]pyrene exposure in two cell types: one having significant CYP450 activity (MCF-7 cells) and one lacking significant CYP450 activity (HL-60). The authors reported that adducts were formed in the cells having CYP450 activity, but no adducts were formed in the cells lacking such activity.

Identification and quantification of adducts was generally done using a [^{32}P]-postlabeling assay as follows. After exposure, DNA was isolated and digested to mononucleotides. Mononucleotides were radiolabeled with [^{32}P]-ATP, separated with thin layer chromatography, and visualized by autoradiography. Relative adduct labeling was measured using a scintillation counter. A few early studies used [^{3}H]-labeled PAHs to identify and quantify adducts. In some cases, adducts were identified by high-performance liquid chromatography and gas chromatography-mass spectrometry.

The 14 studies reviewed examined 15 PAHs other than benzo[a]pyrene. Apart from phenanthrene, which did not result in measurable DNA adducts when incubated with calf thymus DNA under various conditions (Bryla and Weyand, 1992), each of the PAHs produced measurable DNA adducts in at least one study.

Major limitations associated with some of the in vitro DNA adduct data for relative potency development include the lack of data at multiple PAH exposure levels, the use of extracted DNA rather than whole cell assays, and the inconsistent use of extrinsic metabolic activation sources. Only three studies with positive adduct findings reported adduct measurements at multiple doses (concentrations) of PAH (Binkova et al., 2000; Melendez-Colon, 2000; Bryla and Weyand, 1992). Three studies used extracted DNA rather than whole cells to measure DNA binding (Segerback and Vodicka, 1993; Bryla and Weyand, 1992; Grover and Sims, 1968). Finally, the available studies on DNA adduct formation use cell types with varying degrees of PAH metabolic capacity, with and without added metabolic activation sources. Both the types and the quantities of DNA adducts formed are likely to depend on the level of metabolic activation for most PAHs.

Among the in vitro DNA adduct studies shown in Table 4-12, 10 studies met the selection criteria for use in this analysis.

4.3.3.5. *DNA Damage/Repair*

Twenty-four reports in the database evaluated the effects of one or more PAHs on DNA damage, repair, or synthesis. Table 4-13 summarizes the study design information and results of these studies. Studies included measures of unscheduled DNA synthesis and DNA damage. Unscheduled DNA synthesis was generally measured by increased radiolabeled (^{3}H) thymidine uptake in treated cells versus untreated cells. DNA damage was measured either using the alkaline elution assay for DNA strand breakage in mammalian cells, or using the differential killing of DNA repair-deficient bacterial strains. Metabolic activation of PAHs was most often accomplished using a rat liver S9 mix.

Twenty-eight different PAHs have been tested for effects on DNA in one or more assays. In general, pyrene, anthracene, phenanthrene, perylene, fluorene, and benzo[e]pyrene gave nonpositive results in multiple studies. Chrysene gave nonpositive results in four assays and positive results in one assay (Mersch-Sundermann et al., 1992). More positive than nonpositive results were reported for benz[a]anthracene, dibenz[a,h]anthracene, and dibenz[a,c]anthracene. Other PAHs were tested only once, or gave roughly an equal frequency of positive and nonpositive responses in these assays.

Although a large number of PAHs have been tested for DNA damage/repair, the database includes both bacterial and mammalian cells and several different genotoxic endpoints. In addition, the use of external metabolic activation, or cell types with intrinsic metabolic capacity, was inconsistent across these studies. These limitations make it difficult to compare studies using the same target PAHs.

Among the in vitro DNA damage/repair studies shown in Table 4-13, 15 studies met the selection criteria for use in this analysis.

4.3.3.6. *Clastogenicity or Sister Chromatid Exchange Frequency*

The database contains 18 studies in which clastogenicity or sister chromatid exchange frequency was measured in cultured cells after exposure to benzo[a]pyrene and at least one other PAH (Table 4-14). A wide variety of cell types was used in these assays, including hamster liver, lung, CHO, and V79 cells; rat liver epithelial cells; human teratocarcinoma epithelial cells; rat and human mammary epithelial cells; mouse, rat, and human fibroblasts; human lymphocytes; and guinea pig fetal cells. A number of the studies used a metabolic activation system, typically either rat liver S9 or coculture with a cell type able to metabolize PAHs. While laboratory methods varied widely, the general approach involved treating the cultured cells with a solution of the test compound, either with or without metabolic activation. Usually, bromodeoxyuridine was added to the growth medium to provide a means of staining metaphase chromosomes, and colcemid was used to arrest mitotic cells. Chromosomes were examined microscopically and aberrations or exchanges were scored visually. In most cases, the endpoint examined was frequency of sister chromatid exchanges. Other endpoints included frequency of micronuclei and scoring of chromosomal aberrations such as breaks, gaps, deletions, etc.

Only eight PAHs (anthracene, benz[a]anthracene, benzo[e]pyrene, cyclopenta-[c,d]pyrene, fluoranthene, perylene, phenanthrene, and pyrene) have been tested for clastogenic effects in vitro. In many cases, the available studies were aimed at evaluating the validity of a given test system to predict carcinogenicity. In these studies, a range of compounds of known or believed carcinogenicity were used. Often, benzo[a]pyrene was included as a known carcinogen, and other PAHs were chosen because they were known or believed to be noncarcinogenic or weakly carcinogenic.

Among the tested compounds, four gave positive results in at least one study. With few exceptions, PAHs administered without metabolic activation gave nonpositive responses in these assays. Cyclopenta[c,d]pyrene was reported to increase the frequency of sister chromatid exchanges in two assays, one with and one without metabolic activation (Murison, 1988; Krolewski et al., 1986). Benz[a]anthracene gave positive results in three studies of sister chromatid exchange induction (Mane et al., 1990; Tong et al., 1983, 1981a) and nonpositive results in a fourth (Warshawsky et al., 1995). Kochhar (1982) reported a dose-dependent increase in chromosomal aberrations in V79 cells treated with benz[a]anthracene in the absence of metabolic activation. Perylene increased aberrations in one system (Popescu et al., 1977), but did not increase sister chromatid exchanges in another (Sirianni and Huang, 1978). Likewise, pyrene gave positive results in a number of studies that included metabolic activation (Evans and Mitchell, 1981; Perry and Thomson, 1981; Popescu et al., 1977) and nonpositive results in several that did not include activation (DeSalvia et al., 1988; Tong et al., 1983, 1981a; Dean, 1981; Abe and Sasaki, 1977).

The clastogenicity and sister chromatid exchange data for PAHs are variable with respect to cell type and use of extrinsic metabolic activation. Some cells have intrinsic metabolic

activity, while others require activation from an external source. The degree to which metabolic activation is required for PAHs to exert a clastogenic effect in cell cultures is not well established. Another limitation of these data stems from the fact that a small number of PAHs, many traditionally believed to be noncarcinogenic or weakly carcinogenic, have been tested for clastogenic effects in vitro.

Among the in vitro clastogenicity/sister chromatid exchange studies shown in Table 4-14, 10 studies met the selection criteria for use in this analysis.

4.4. SUMMARY OF INFORMATION AVAILABLE TO DEVELOP RPFs FOR INDIVIDUAL PAHs

The PAH database contains several different types of data that may be used to estimate relative potencies of individual PAHs. The data were summarized in Section 4.3 and include in vivo tumor bioassays using various routes of exposure and data for cancer-related endpoints from both in vivo and in vitro studies. As discussed above, the concurrent testing of benzo[a]pyrene as a reference compound was considered essential to allow for RPF calculation. The introduction to Section 4.3 lists criteria for selecting studies or data sets for use in the analysis. Studies that met these criteria were used in the development of the RPF approach. Chapter 5 discusses methods used for dose-response assessment and RPF calculation from each study or dataset, and Chapter 6 discusses the selection of PAHs to be included in the RPF approach using a weight of evidence evaluation of the available data. Chapter 7 describes the derivation of final RPFs for each PAH included in the analysis.

5. METHODS FOR DOSE-RESPONSE ASSESSMENT AND RPF CALCULATION

A discussion of the available data on PAH carcinogenicity and cancer-related endpoints and criteria for selection of studies was presented in Chapter 4. This section describes the selection of dose-response data and methods for dose-response assessment and RPF calculation from the selected datasets. The dose-response data extracted from each study with positive results and the results of the statistical analyses are shown in Appendix C. Appendix C also contains information regarding the source of the dose-response data (i.e., the figure or table number from the study and the particular data points that were used in the dose-response assessment) and additional comments on the use of the data for dose-response assessment and RPF calculation. The results of the RPF calculations are shown in tables in Appendix E. These tables provide summary information for each study, including the PAHs that were tested, the data used to estimate the slopes (point estimate[4] or BMD model result), the calculated RPF value, and any specific comments related to the data analysis.

5.1. CHOICE OF DOSE-RESPONSE DATA

For each of the endpoints evaluated in Chapter 4 (dermal, intraperitoneal, subcutaneous, oral, and other route bioassays; in vivo DNA adducts; in vivo clastogenicity or sister chromatid exchange frequency; in vitro bacterial and mammalian mutagenicity; in vitro morphological/ malignant transformation; in vitro clastogenicity or sister chromatid exchange frequency; and other in vitro endpoints [DNA adducts, unscheduled DNA synthesis, DNA damage, etc.]), there was at least one study that met selection criteria. For those studies with positive findings, dose-response data were extracted for dose-response assessment and calculation of RPFs.

5.1.1. Dose-Response Data for Tumor Bioassays

Data on both benign and malignant tumors were included in the dose-response assessment. In cases where the combined incidence of benign and malignant tumors was reported, these data were selected; however, in some cases, only benign or only malignant tumor incidence was reported. These data were also considered appropriate for derivation of RPFs. There is evidence for progression from benign to malignant tumors (e.g., dermal papillomas progressing to carcinomas) in studies of benzo[a]pyrene (for example, see Albert et al., 1991), and other PAHs are assumed to be toxicologically similar to benzo[a]pyrene. Thus, even when a study reported only the incidence of benign tumors, these data were used in the dose-response assessment.

[4]For the purpose of this report, the term "point estimate RPF" is used to describe an RPF calculated from a single point on the dose-response curve for both the PAH of interest and benzo[a]pyrene. This term distinguishes the RPF from one calculating using a BMD modeling result from multidose data.

While tumor multiplicity data from tumor bioassays are not generally used to estimate *cancer potency*, these data were included in the dose-response assessment in order to determine whether they could serve as a reliable measure of *relative cancer potency*. Several bioassays reported data on both tumor incidence and tumor number, providing information that could later be used to compare relative potencies estimated from these two endpoints.

As discussed in Section 4.3, statistics were used for tumor bioassay data to determine whether the tumor incidence or multiplicity observed at a particular dose represented a statistically significant increase over controls. If statistical analyses were not described in the original report, incidence data were analyzed using Fisher's exact test and the Cochran-Armitage trend test. Positive findings were indicated by a significant ($p < 0.05$) difference for at least one dose group by comparison to control (in Fisher's exact or an equivalent test) or a significant dose-response trend (Cochran-Armitage or equivalent) for multidose studies. For tumor bioassay data reported as tumor count, a t-test was conducted (when variance data were available) to determine whether the count was significantly different from control ($p < 0.05$). The results of the statistical analyses are shown with the dose-response data in Appendix C.

The tumor bioassays that reported both incidence and tumor count were unique in offering two different datasets for the same study. For each dose of each PAH in the tumor bioassays, the decision to calculate an RPF, and in some instances, the selection of the point of departure, was based on whether the tumor incidence or count was statistically significantly increased over the control; if there was a significant increase, an RPF was calculated. There was a single instance where the tumor count was statistically significantly increased, but the incidence of tumors was not. In female mice exposed at the high dose of fluoranthene in the study by Busby et al. (1984), the lung tumor count was significantly increased (albeit borderline, $p = 0.0343$) while the incidence was not, and neither was statistically significantly increased at the lower dose. As there were no higher doses in this study, it is possible that the two measures might have produced consistent findings at higher doses. For the purpose of this analysis, the multiplicity data from this study were treated as an independent measure of carcinogenic potency, and an RPF was calculated for the statistically increased tumor count irrespective of the analysis of incidence. It should be noted that average tumor count can be skewed by an unusual response in a single animal, and no information was available to determine whether such response represented an anomaly unrelated to exposure or an unusual susceptibility to the exposure. Thus, reliance on statistical analysis of mean tumor count alone as a measure of carcinogenic response may be subject to additional uncertainty.

5.1.2. Dose-Response Data for Cancer-Related Endpoint Studies

For cancer-related endpoint data, each study authors' conclusions regarding a positive or nonpositive response for each PAH were accepted, and RPFs were calculated when positive results were reported. Data that were reported in graphical format in published studies of cancer-

related endpoints were digitized (Grab It!™ Graph Digitizer, Datatrend Software) to identify the dose-response data points. In a few cases, the only cancer-related endpoint data in a given publication were reported as relative potency (relative to benzo[a]pyrene). For these publications, which included only in vitro cancer-related endpoint data (primarily mutagenicity), the relative potency estimates calculated by the authors were used without modification (except for dose adjustment where appropriate; see Section 5.5).

5.2. OVERALL FORM OF RPF ESTIMATE

The overall goal of the dose-response analysis was to calculate ratios representing the relative potency of a given PAH compared with benzo[a]pyrene (i.e., RPFs). For all datasets, the RPF was defined as the ratio (PAH_i:BaP) of the slopes of the dose-response curves in the low-dose region, following Equation 5-1 below:

$$RPF = \text{slope } PAH_i \div \text{slope BaP} \qquad (5\text{-}1)$$

Data available for calculation of RPFs consisted of both quantal and continuous endpoints. Quantal endpoints included tumor incidence or incidence of cancer-related endpoints (including frequency of mutations). Continuous endpoint datasets included tumor counts (number of tumors per animal) or cancer-related endpoints of a continuous-variable nature (e.g., number of sister chromatid exchanges, number of morphologically transformed colonies). Dose-response assessment methods were specific to each type of endpoint (quantal or continuous) and differed depending on whether there were multiple dose groups or a single dose group in the dataset. Methods for multidose and single dose quantal and continuous data are described below.

5.3. RPF CALCULATION FOR MULTIDOSE DATASETS

Dose-response modeling using U.S. EPA's Benchmark Dose Software (Version 2.1.1 or 1.3.2) was conducted on multiple-dose data sets to estimate potency for both the target PAHs and benzo[a]pyrene. Modeled estimates consider information about the shape of the dose-response curve and are thus preferred over using a single dose group as the point of departure.

Dose-response modeling. For multidose quantal data, the multistage model was used and the degree of the polynomial was assumed to equal the number of dose groups minus 2. The multistage model was selected because it is the preferred model for cancer risk assessment of animal bioassay data, and it provided a consistent model form for all of the datasets. For tumor bioassay data, the multistage-cancer model was selected, while other quantal data were modeled using the multistage model (both have the same model form and yield the same result). For multidose continuous data, the linear model was selected for all datasets, as it is the simplest model form for continuous data. For both quantal and continuous datasets, the goodness-of-fit criteria were used to evaluate model fit. If the model did not provide adequate fit to the data,

high-dose groups were sequentially eliminated in an effort to achieve adequate fit, except when truncating the data would result in the loss of datapoints at response levels in the range of the benzo[a]pyrene response. The focus of the modeling effort is on the low dose and response region, so doses and responses much higher than the benchmark response (BMR) are not as informative and can be eliminated to improve model fit. If dose-group elimination did not improve the model fit, a point-estimate ratio approach was used (see Section 5.4). The BMD modeling outputs for all datasets that were successfully modeled are shown in Appendix D.

Selection of BMR: Multidose data for both PAH and benzo[a]pyrene. For tumor incidence data, the BMR used in estimating the point of departure was a 10% increase in tumor incidence over controls (extra risk form). For cancer-related endpoints such as frequency of mutations, endpoint-specific points of departure were selected based on the background/control frequency of the endpoint and the detection limit of the assay. For example, a 1% frequency was selected for a control mutation frequency of 1/10,000 and a detection limit of two- to threefold above background.

For multidose continuous data, the BMR used in estimating the point of departure was a change of 1 standard deviation (1 SD) from the control mean. In the event that multiple-dose continuous data were reported in the absence of SD values, a point estimate ratio approach was employed to calculate the slope (see Section 5.4).

Selection of BMR: Multidose data for PAH, single dose benzo[a]pyrene. Some studies included only one dose of benzo[a]pyrene as a positive control, while providing multiple-dose data for a selected PAH. In these cases, dose-response modeling was performed for the selected PAH and the BMR used for modeling was the observed response for benzo[a]pyrene adjusted for background response. For tumor incidence data, for example, if the benzo[a]pyrene dose was associated with a 60% extra risk for tumors, the BMR chosen for modeling the data for the PAH was 60% extra risk. RPFs were then calculated using a ratio of the slope factors calculated with equivalent points of departure (e.g., BMD_{60}). The goal of this approach was to compare PAH potencies at similar response locations on the dose-response curve. There is uncertainty associated with relative potency estimates calculated at the high end of the dose-response curves and using the resultant RPF for low-exposure scenarios, because the relative potency relationship between any two PAHs may be different at the low end, compared with the high end, of the dose-response curves. The uncertainties and limitations associated with the use of high-dose data to estimate relative potency are further discussed in Chapter 7. Data sets for which tumor incidence was ≥90% in the lowest dose group were not used to calculate potency estimates and RPFs, because the response is near plateau and such data provide insufficient information on the slope of the dose-response relationship.

For continuous data, when a point estimate was used to estimate the slope for benzo[a]pyrene and modeling was used to estimate the slope for a given PAH, the BMR used for BMD modeling was a point value set at the response (e.g., mean number of tumors per animal

for tumor multiplicity data) observed in the benzo[a]pyrene group, adjusted for response in the control group. This approach is consistent with the BMR used for quantal data when only a single benzo[a]pyrene dose group was available. Provided that a linear model is fit to continuous data, the choice of a higher BMR would not appreciably change the RPF.

Selection of point of departure. The point of departure selected for slope estimation was the BMD estimate rather than the lower confidence limit on the BMD. The BMD, as the central or "best" estimate of the dose associated with the selected BMR, was considered a more stable basis for comparison between the potency of the selected PAH and benzo[a]pyrene, and thus for calculation of relative potency, than the lower confidence limit.

Extrapolation from point of departure. The slopes of the dose-response curves in the low-dose regions were calculated by linear extrapolation to the origin from the model-predicted points of departure. Equation 5-2 below shows the calculation of slope from multidose quantal data.

$$\text{Slope} = [0.1/\text{BMD}_{10}] \quad (5\text{-}2)$$

Equation 5-3 below shows the calculation of slope from multidose continuous data.

$$\text{Slope} = [1\text{SD change}]/[\text{BMD}_{1\text{SD}}] \quad (5\text{-}3)$$

5.4. RPF CALCULATION FOR SINGLE DOSE DATASETS

A number of studies reported data for only single doses of benzo[a]pyrene and other PAHs; for these studies, a point estimate approach was used to calculate the RPF. A point estimate approach was also used to calculate RPFs for multidose datasets when model fit was not achieved, when variance data were not available for continuous data, or when problems with model implementation were encountered.

Selection of point of departure. When only one dose of each compound was used, there was only one choice for the point of departure. However, when multidose data were available, but a point estimate approach was used, the point of departure was chosen as follows. For tumor bioassay data, the lowest dose associated with a statistically significant increase in tumor incidence or multiplicity over control values was selected as the point of departure. Variance was not reported for tumor multiplicity data in any of the dermal studies and for some of the intraperitoneal studies, so the corresponding incidence data were used to determine the dose at which a significant difference from control was observed.

The benzo[a]pyrene dose chosen in most instances was the lowest dose associated with a significant increase in tumor count or incidence. For tumor multiplicity data, the PAH dose chosen for the point estimate RPF calculation was the lowest dose associated with a tumor count similar to that observed at the selected benzo[a]pyrene dose (similar to selecting a BMR similar

to the benzo[a]pyrene incidence). In the case of two dermal initiation studies conducted by Cavalieri et al. (1991), however, the tumor count at the lowest dose of dibenzo[a,l]pyrene was much higher than the tumor count at the lowest benzo[a]pyrene dose associated with statistical significance. In order to compare the doses associated with similar tumor counts (i.e., at a similar place on the dose-response curve), a higher benzo[a]pyrene dose was chosen for the RPF calculation. A comparison of the RPFs calculated using this approach with RPFs calculated using the lowest dose associated with a statistically significant increase over controls for both dibenzo[a,l]pyrene and benzo[a]pyrene showed only small differences in the RPF values (9 versus 10 in the 16-week study and 39 versus 42 in the 27-week study). A similar approach was used to calculate the RPF for BjAC using the intraperitoneal multiplicity data from Mass et al. (1993).

For cancer-related endpoint data, statistical analysis was not always available for each dose group. For these data, the lowest dose that produced a near maximal change in the assay of concern was selected as the point of departure. That is, the highest dose in the linear portion of the dose-response curve (identified by visual display of the data) was selected in these cases.

Extrapolation from point of departure. As with multiple dose slope estimations, point estimate slope calculations also used the extra risk form. Thus, for single dose quantal data, the slope was calculated by linear extrapolation to the origin after an extra risk adjustment of the observed response (Equation 5-4):

$$\text{Slope} = [(\text{response at dose} - \text{control response}) \div (1 - \text{control response})] \div \text{dose} \qquad (5\text{-}4)$$

For single dose continuous data, the slope was calculated by linear extrapolation to the origin after adjustment of the observed response in the PAH-treated animals for the control response (Equation 5-5).

$$\text{Slope} = [(\text{value of variable at dose}) - (\text{value of variable})_{\text{control}}] \div \text{dose} \qquad (5\text{-}5)$$

5.5. DOSE CONVERSION FOR RPF CALCULATION

Some of the studies used to calculate RPFs reported doses or test concentrations on a molar basis (e.g., µmol per mouse, µmol/L), rather than a mass basis (mg or µg). The molar ratio differs from the mass ratio for any PAH with a molecular weight that differs from that of benzo[a]pyrene; thus, for these compounds, an RPF expressed on a mass basis will differ from that expressed on a molar basis. Table 5-1 shows a hypothetical example for fluoranthene, a PAH with a molecular weight that differs from benzo[a]pyrene by 20%. As the table shows, the RPF differs depending on which dose units are used.

Table 5-1. Comparison between molar and mass-based RPF

	Response	Dose in mol	Molecular weight (g/mol)	Dose in g	Molar RPF	Mass RPF
FA	0.1	5	202.26	1,011	0.20	0.25
BaP	0.1	1	252.32	252	1	1

In order to ensure that comparisons across endpoints used consistent units, the doses used to calculate RPFs were converted to mass-based units using the molecular weight of the relevant PAH prior to estimating the RPF. While the RPF ratio is nominally unitless, it should be interpreted as the ratio of the dose of PAH to the dose of benzo[a]pyrene. Since RPFs will be used in conjunction with a PAH dose and benzo[a]pyrene cancer potency in mass units (oral slope factors and inhalation unit risks reported in units of $[mg/kg\text{-}day]^{-1}$ and $[\mu g/m^3]^{-1}$, respectively); it is important to use mass-based RPFs. Alternatively, if a molar RPF ratio were to be used, it would be applied with PAH doses and benzo[a]pyrene cancer potency values estimated on a molar basis; this would require a significant shift in the way PAH risks are calculated compared to other carcinogens. Therefore, the mass-based RPF was selected to be consistent with dose metrics used to calculate cancer risk.

5.6. SPECIAL CONSIDERATIONS FOR RPF CALCULATION USING TUMOR BIOASSAY DATA

Several dermal bioassays reported significant mortality prior to the appearance of the first skin tumor. For these data sets, an assumption was made that the number of animals at risk for tumor development was equal to the total number of animals alive at the time of the appearance of the first tumor. Benign and malignant tumor types within the same target organ were combined for calculation of the RPF. The total incidence of animals with either a benign or malignant lesion was directly reported in each study (i.e., the number of animals with adenoma or carcinoma).

Tumor incidence data reported for different target organs within the same group of animals were analyzed separately unless the joint incidence (incidence of either tumor type in each dose group) was reported in the publication. Liver and lung tumors were reported in newborn mice exposed to PAHs by intraperitoneal injection (LaVoie et al., 1994, 1987; Busby et al., 1989, 1984; Weyand and LaVoie, 1988; Wislocki et al., 1986). In most studies, tumor incidence was reported separately for the different target organs and could not be combined as the joint incidence was unknown. A gender difference was observed in the newborn mouse studies, with liver tumors observed in male mice only, and lung tumors reported for both male and female mice. The tumor incidence data were, therefore, evaluated separately for male and

female mice. RPF values were calculated separately for male and female mice and for lung tumor incidence and liver tumor incidence in these studies.

5.7. SPECIAL CONSIDERATIONS FOR RPF CALCULATION USING CANCER-RELATED ENDPOINT DATA

The in vitro studies of cancer-related endpoints included measurements of bacterial mutagenicity, mammalian mutagenicity, morphological/malignant cell transformation, DNA adduct formation, DNA damage or repair, and clastogenicity or sister chromatid exchange frequency. Many of the studies describing in vitro cancer-related endpoints provide dose-response data under varying study conditions. For example, bacterial mutagenesis studies used multiple strains, different metabolic activation processes, and/or varying assay systems. In order to limit the number of datasets used for dose-response analysis of in vitro mutagenicity studies, and to provide a consistent basis for comparing RPFs for different PAHs, data associated with the conditions that maximized the benzo[a]pyrene response within a particular study were used for the dose-response assessment of PAHs. It should be noted that in several studies, test conditions that were optimal for benzo[a]pyrene were not necessarily optimal for the selected PAH (see Appendix C for specific studies). The uncertainties and limitations associated with this approach are discussed further in Chapter 8.

For time-course studies of DNA adducts, results were reported as either AUC or peak formation of adducts. AUC was considered preferable for dose-response assessment, because this measure considers both adduct formation and repair. Adducts measured in more than one organ were summed to derive a total measure of adduct formation (standardized per unit amount of DNA).

The data for bacterial and mammalian cell mutagenicity and malignant cell transformation were sometimes expressed as a mutation or transformation frequency (i.e., mutants/total cell count or transformed cells/total cells). For multiple-dose studies, these quantal variables were evaluated using the multistage model as described above. Problems were sometimes encountered when using the multistage model for incidence data of this type. In some cases, modifying the initial parameters in the multistage algorithm facilitated convergence. In a select few cases, the quantal linear model was used when the multistage model would not converge. If neither the multistage nor quantal linear models provided adequate fit, a point estimate approach was used. If possible, the point estimates for both benzo[a]pyrene and the target PAH were chosen at a comparable response level (e.g., the doses of benzo[a]pyrene and the target PAH that both gave two mutants in 10^5 cells). However, in many cases, a comparable response rate was not available. In these instances, the RPF was derived from slopes calculated by linear extrapolation from the peak response.

As noted earlier, for studies that included only one dose of benzo[a]pyrene and multiple dose data for a selected PAH, the BMR selected for dose-response modeling for the selected

PAH was the benzo[a]pyrene response with the background or control response subtracted. In some instances, when the benzo[a]pyrene response level greatly exceeded the response at the highest dose of the selected PAH, the software would fail to calculate the BMD at the benzo[a]pyrene response level. In these instances, a point estimate approach using the peak response for the selected PAH was used.

The individual study RPFs calculated for each PAH were used in a weight of evidence evaluation to select PAHs for inclusion in the RPF approach (see Chapter 6) and in the derivation of a final RPF for each compound (Chapter 7).

6. SELECTION OF PAHs FOR INCLUSION IN RELATIVE POTENCY APPROACH

The selection of PAHs to be included in the RPF approach began with an evaluation of whether the available data were adequate to assess the carcinogenicity of each compound. At least one RPF value was calculated for each of 51 PAHs. For 16 of these compounds, only a single RPF value derived from an in vitro cancer-related endpoint (primarily mutagenicity assays) was available. These PAHs are shown in Table 6-1. Due to the limited data available for these 16 compounds, no further evaluation of these PAHs was conducted, and they were not selected for inclusion in the RPF approach.

Table 6-1. PAHs with only one RPF from a single in vitro cancer-related endpoint study and excluded from RPF approach

PAH	CASRN	Abbreviation
Aceanthrylene	202-03-09	ACEA
Acenaphthene	83-32-9	AN
Acenaphthylene	208-96-8	ANL
Acephenanthrylene	201-06-9	APA
Benzo[a]perylene	191-85-5	BaPery
Benz[b]anthracene	92-24-9	BbA
Benzo[b]perylene	197-70-6	BbPery
Benzo[c]phenanthrene	195-19-7	BcPH
Cyclopent[h,i]aceanthrylene	131581-33-4	CPhiACEA
Cyclopent[h,i]acephenanthrylene	114959-37-4	CPhiAPA
Dibenzo[a,f]fluoranthene	203-11-2	DBafF
Dibenz[a,j]anthracene	224-41-9	DBajA
Dibenzo[b,e]fluoranthene	2997-45-7	DBbeF
Dibenzo[e,l]pyrene	192-51-8	DBelP
Dibenz[k,mno]acephenanthrylene	153043-81-3	DBkmnoAPH
Naphtho[2,3-a]pyrene	196-42-9	N23aP

The remaining 35 PAHs had RPF values calculated from at least one in vivo dataset or at least two in vitro cancer-related endpoint datasets. For these compounds, a weight of evidence approach was used to determine whether the available data (including the calculated RPFs as well as nonpositive studies that met selection criteria) were adequate to include each compound in the RPF approach. Using the calculated RPFs in the weight of evidence evaluation allowed consideration of the magnitude of calculated RPFs in assessing carcinogenicity. When data were not considered adequate, the PAH was excluded from the RPF approach. When data were considered adequate for a given PAH, it was selected for inclusion.

A PAH with adequate evidence to suggest no carcinogenicity was selected for inclusion in the RPF approach and assigned an RPF of zero. While there is little quantitative difference

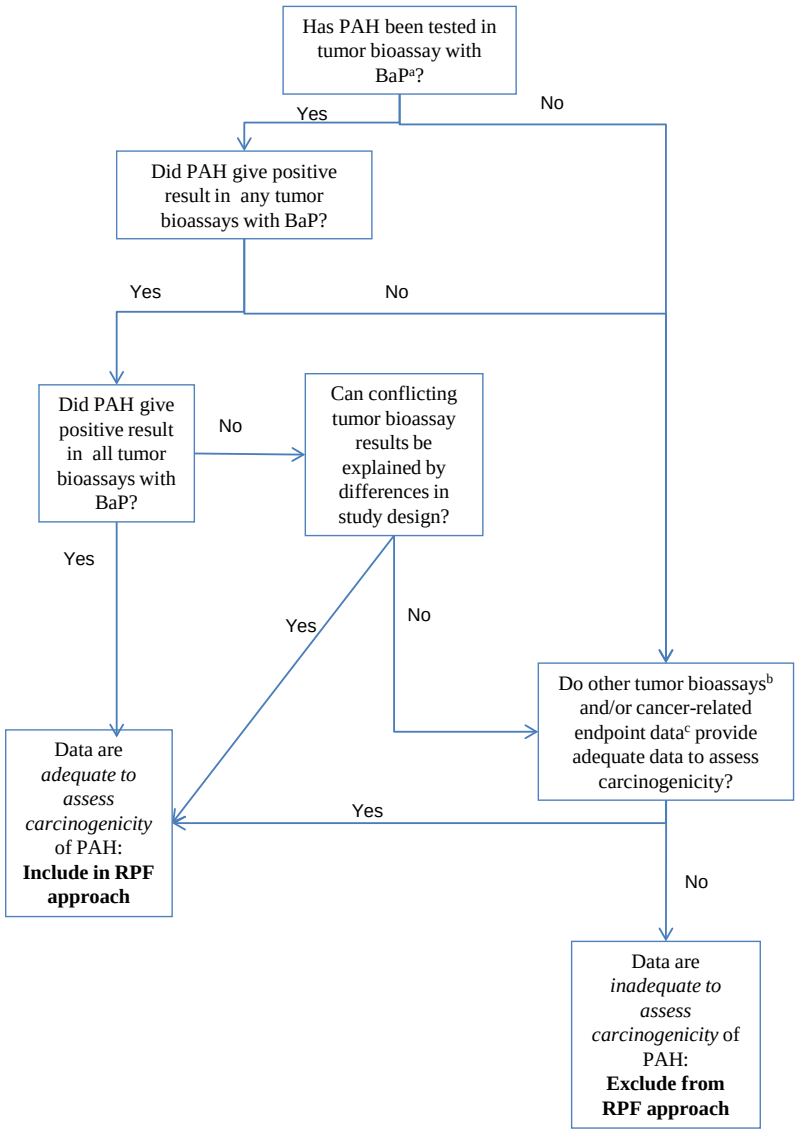
between selecting a final RPF of zero for a given PAH and excluding that PAH from the RPF approach, this is an important distinction for uncertainty analysis. There is substantial uncertainty in the risk associated with a PAH that is excluded from the RPF approach due to inadequate data; this compound could be of low or high potency. However, for a PAH with an RPF of zero, there is evidence to suggest that this compound is not carcinogenic, and the uncertainty associated with the cancer risk is markedly reduced. For anthracene, phenanthrene, and pyrene, it has been determined that the available data support a practical RPF of zero. The weight of evidence analysis is outlined in Section 6.1 and the results are described in narratives for each of the 35 individual PAHs (Section 6.2). Chapter 7 describes how the RPFs from multiple datasets were used to derive final RPFs for those PAHs selected for inclusion in the approach, and reports the final RPF information for each PAH.

6.1. METHOD FOR SELECTING PAHs FOR INCLUSION IN RELATIVE POTENCY APPROACH

For each of the 35 PAHs, a weight of evidence evaluation was conducted to assess the evidence that each PAH could induce a carcinogenic response. For the purposes of this analysis, PAHs were assumed to be carcinogenic by inferring toxicological similarity to the indicator compound, benzo[a]pyrene. The weight of evidence approach was developed to determine whether the available information for each PAH was adequate for inclusion of the PAH in the RPF approach. Figure 6-1 shows the decision tree that was used to evaluate the data for each PAH and to determine whether it should be included in the RPF approach. The weight of evidence evaluation concluded with one of two possible outcomes:

(1) The data reviewed are adequate to evaluate carcinogenicity and the PAH should be included in the RPF analysis, or

(2) The data reviewed are inadequate to assess carcinogenicity and the PAH should be excluded from the RPF analysis.



[a]Bioassays with benzo[a]pyrene that met study quality criteria (includes studies with nonpositive results).
[b]Other bioassays include those that did not test benzo[a]pyrene and/or those that were not suitable for RPF derivation (e.g., incidence at lowest dose exceeded 90%).
[c]Cancer-related endpoint data examined in this process included studies of DNA adducts, clastogenicity or sister chromatid exchange, mutagenicity, morphological transformation, DNA damage, unscheduled DNA synthesis, etc. that included the selected PAH and benzo[a]pyrene.

Figure 6-1. Weight of evidence analysis of for selection of PAHs to be included in the RPF approach.

In vivo tumor bioassays that included benzo[a]pyrene were given the greatest weight in assessing the carcinogenicity of a given PAH; data from other bioassays and cancer-related endpoint studies were used to supplement the weight of evidence when the bioassay data that included benzo[a]pyrene were conflicting or nonpositive. Structural alerts for PAH carcinogenicity or mutagenicity (specifically, at least four aromatic rings, or the presence of a classic bay or fjord region formed entirely by aromatic rings) were noted in the evaluation for each PAH, but were not used explicitly in the weight of evidence evaluation.

When there were bioassays including benzo[a]pyrene with positive findings, and none with nonpositive findings for a given PAH, that compound was selected for inclusion in the RPF approach, and no further evaluation of cancer-related endpoint data was conducted. However, the cancer-related endpoint findings for these compounds were noted in the individual PAH narratives (Section 6.2). Among the PAHs included in this analysis, there were none with positive bioassay data and robust nonpositive cancer-related endpoint data. Were this instance to arise, it would require special consideration, as it might imply a different mode of carcinogenic action than the PAHs addressed herein.

Bioassays that met selection criteria (see Section 4.3) were included in the weight of evidence analysis, regardless of whether positive or nonpositive results were found. However, the weight of evidence evaluation assumed that a given compound may be active in one system (e.g., newborn mouse) and inactive or weakly active in another (e.g., dermal initiation). Thus, when conflicting results were observed in different test systems, different species, or different genders, the PAH was assumed to be carcinogenic based on the positive findings and was included in the RPF approach.

In order to evaluate the results of bioassays with positive and nonpositive results in the same test system, an "RPF detection limit" was conceptualized as a means of approximating the minimum RPF that could be determined with respect to the design of the study. The "RPF detection limit" was defined as the RPF determined by the lowest response that would have been statistically significant for the subject PAH and the actual benzo[a]pyrene response. The lowest statistically significant response was calculated using the incidence of tumors in the control group, number of animals in the group treated with the subject PAH, and Fisher's exact test[5] (employing a one-sided p-value ≤ 0.05). Appendix F provides an example calculation of an "RPF detection limit." The utility of this concept is in weighing positive and nonpositive bioassay results. If all of the nonpositive studies for a subject PAH had "RPF detection limits" in excess of or in the range of what is observed in the positive studies, then it is plausible that the nonpositive studies may not have been sufficiently sensitive to estimate the RPF appropriate to the subject PAH. In this event, the PAH was considered carcinogenic and was included in the RPF approach.

[5]This calculation was implemented using trial and error within the Fisher's exact test in the online statistical calculator, GraphPad©.

If there were no bioassays with benzo[a]pyrene for a given compound, all of the selected bioassays gave nonpositive results, or inconsistent results could not be explained by test system or "RPF detection limit", then the results of other bioassays (those without benzo[a]pyrene, or those rejected from dose-response assessment exclusively because of concerns associated with benzo[a]pyrene) and cancer-related endpoint data were evaluated. The weight of evidence analysis then considered all of the following information: bioassays with benzo[a]pyrene, other bioassays, and cancer-related endpoint data. If these data were determined to be inadequate to assess the carcinogenicity for a given PAH, then that compound was excluded from the RPF approach. If the data were considered adequate to assess the carcinogenicity, the compound was retained and a final RPF was derived. Section 6.2 below describes the weight of evidence evaluation for each of the 35 PAHs. Section 7.1 describes how final RPFs were derived for the 27 PAHs selected for inclusion in the RPF approach.

6.2. WEIGHT OF EVIDENCE EVALUATION FOR 35 INDIVIDUAL PAHs

For each PAH, the structure is shown along with a brief reference to any structural alerts for carcinogenicity (specifically, more than three aromatic rings and/or bay or fjord region in alternant PAH). Next, a brief narrative describing the weight of evidence evaluation is given, with a graphical representation of the data that were available for RPF calculation (Figures 6-2 to 6-35). The graph for each compound provides a visual representation of the database of studies that included both the subject PAH and benzo[a]pyrene. The solid bars show the values of the RPFs calculated from all studies with positive findings. The x-axis label shows the reference for the pertinent study. The RPFs are color-coded to distinguish among in vivo tumor bioassays based on incidence data, in vivo tumor bioassays based on multiplicity data, in vivo cancer-related endpoint studies, and in vitro cancer-related endpoint studies. Within these categories, the RPFs are ordered (left to right in the graph) from highest to lowest, with positive results shown before nonpositive results.

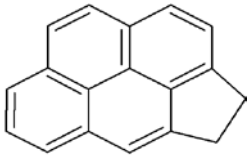
For each nonpositive bioassay, an empty, dotted bar shows what is termed the "RPF detection limit" (see Section 6.1 for description). Missing bars designate cancer-related studies that resulted in nonpositive findings. An RPF detection limit for nonpositive cancer-related studies was not included, because comparisons between nonpositive and positive studies were complicated by the wide variety of study conditions (e.g., test species and strains, metabolic activation sources, assay systems).

Each narrative concludes with a statement as to whether the subject PAH was selected for inclusion in the PAH RPF approach. The weight of evidence evaluation for the 35 PAHs with at least one in vivo RPF or at least two in vitro cancer-related endpoint RPFs resulted in the selection of 27 PAHs for inclusion in the RPF approach (see Table 6-2) and the exclusion of 8 PAHs from the approach.

Table 6-2. Results of weight of evidence evaluation for 27 PAHs selected for inclusion in the RPF approach

Adequate data: selected for inclusion in RPF approach					
PAH	**CASRN**	**Abbreviation**	**PAH**	**CASRN**	**Abbreviation**
Benzo[a]pyrene	50-32-8	BaP	Cyclopenta[c,d]pyrene	27208-37-3	CPcdP
Anthanthrene	191-26-4	AA	Cyclopenta[d,e,f]chrysene, 4H-	202-98-2	CPdefC
Anthracene	120-12-7	AC	Dibenz[a,c]anthracene	215-58-7	DBacA
Benz[a]anthracene	56-55-3	BaA	Dibenzo[a,e]fluoranthene	5385-75-1	DBaeF
Benz[b,c]aceanthrylene, 11H-	202-94-8	BbcAC	Dibenzo[a,e]pyrene	192-65-4	DBaeP
Benzo[b]fluoranthene	205-99-2	BbF	Dibenz[a,h]anthracene	53-70-3	DBahA
Benzo[c]fluorene	205-12-9	BcFE	Dibenzo[a,h]pyrene	189-64-0	DBahP
Benz[e]aceanthrylene	199-54-2	BeAC	Dibenzo[a,i]pyrene	189-55-9	DBaiP
Benzo[g,h,i]perylene	191-24-2	BghiP	Dibenzo[a,l]pyrene	191-30-0	DBalP
Benz[j]aceanthrylene	202-33-5	BjAC	Fluoranthene	206-44-0	FA
Benzo[j]fluoranthene	205-82-3	BjF	Indeno[1,2,3-c,d]pyrene	193-39-5	IP
Benzo[k]fluoranthene	207-08-9	BkF	Naphtho[2,3-e]pyrene	193-09-9	N23eP
Benz[l]aceanthrylene	211-91-6	BlAC	Phenanthrene	85-01-8	PH
Chrysene	218-01-9	CH	Pyrene	129-00-0	Pyr
Inadequate data					
PAH	**CASRN**	**Abbreviation**	**PAH**	**CASRN**	**Abbreviation**
Acepyrene, 2,3-	25732-74-5	ACEP	Coronene	191-07-1	CO
Benzo[b]fluorene, 11H-	243-17-4	BbFE	Fluorene	86-73-7	FE
Benzo[e]pyrene	192-97-2	BeP	Perylene	198-55-0	Pery
Benzo[g,h,i]fluoranthene	203-12-3	BghiF	Triphenylene	217-59-4	Tphen

2,3-Acepyrene (ACEP)



2,3-Acepyrene (CASRN 25732-74-5) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. 2,3-Acepyrene does not contain a classic bay or fjord region in its structure.

Five datasets for 2,3-acepyrene met selection criteria and included benzo[a]pyrene (shown in Figure 6-2). Dermal initiation and complete carcinogenicity bioassays in mice resulted in nonpositive findings (both published by Cavalieri et al., 1981b). RPF detection limits for these studies were 0.09 and 0.02, respectively. The limited cancer-related data are mixed, with one positive dataset for in vivo DNA adduct formation, one positive bacterial mutagenicity dataset (both published by Cavalieri et al., 1981a), and one nonpositive mammalian mutagenicity dataset (Barfknecht et al., 1982). There are no bioassays of 2,3-acepyrene without benzo[a]pyrene. Overall, the database for 2,3-acepyrene is both limited and inconsistent. The database for 2,3-acepyrene does not provide adequate information with which to assess carcinogenicity; this PAH was not selected for inclusion in the RPF approach.

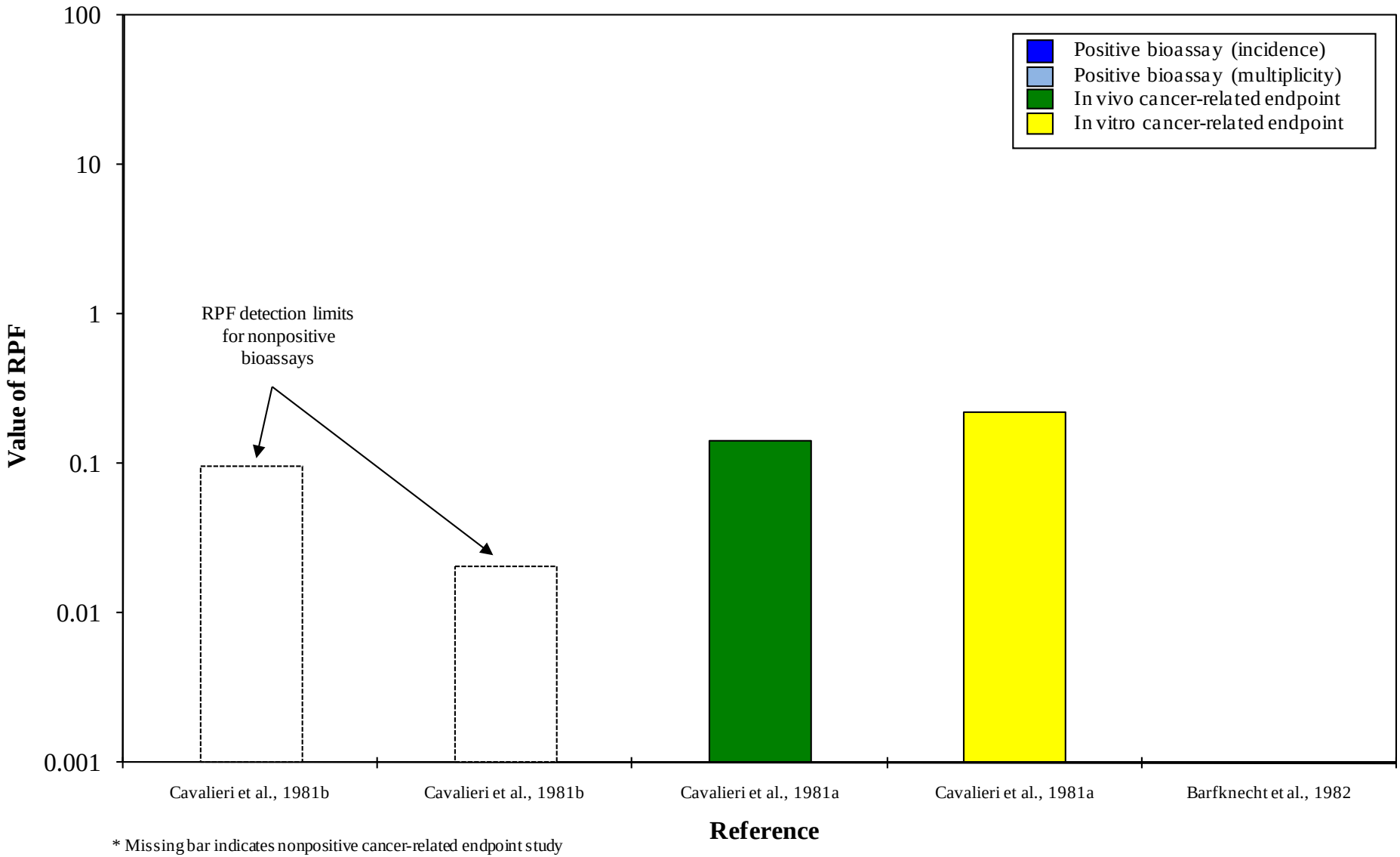
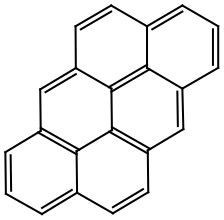


Figure 6-2. 2,3-Acepyrene (ACEP) RPFs*.

Anthanthrene (AA)



Anthanthrene (CASRN 191-26-4) is an alternant PAH comprised of six fused aromatic rings. Anthanthrene does not have a bay or fjord region in its structure.

There are seven datasets for anthanthrene that met selection criteria and included benzo[a]pyrene (Figure 6-3). The database includes three in vivo tumor bioassays, three bacterial mutagenicity datasets, and one in vitro DNA damage dataset. Statistically increased tumor incidences were reported in both a rat lung implantation bioassay (Deutsch-Wenzel et al., 1983) and a dermal complete carcinogenicity bioassay in mice (Cavalieri et al., 1977). No increase over control tumor incidence was reported in a dermal initiation study (Hoffmann and Wynder, 1966), but the RPF detection limit for this study was 0.3. All of the cancer-related endpoint studies gave positive results. Because conflicting bioassay data can be explained by differences in study design (initiation versus complete dermal carcinogenicity), anthanthrene was considered carcinogenic and selected for inclusion in the RPF approach.

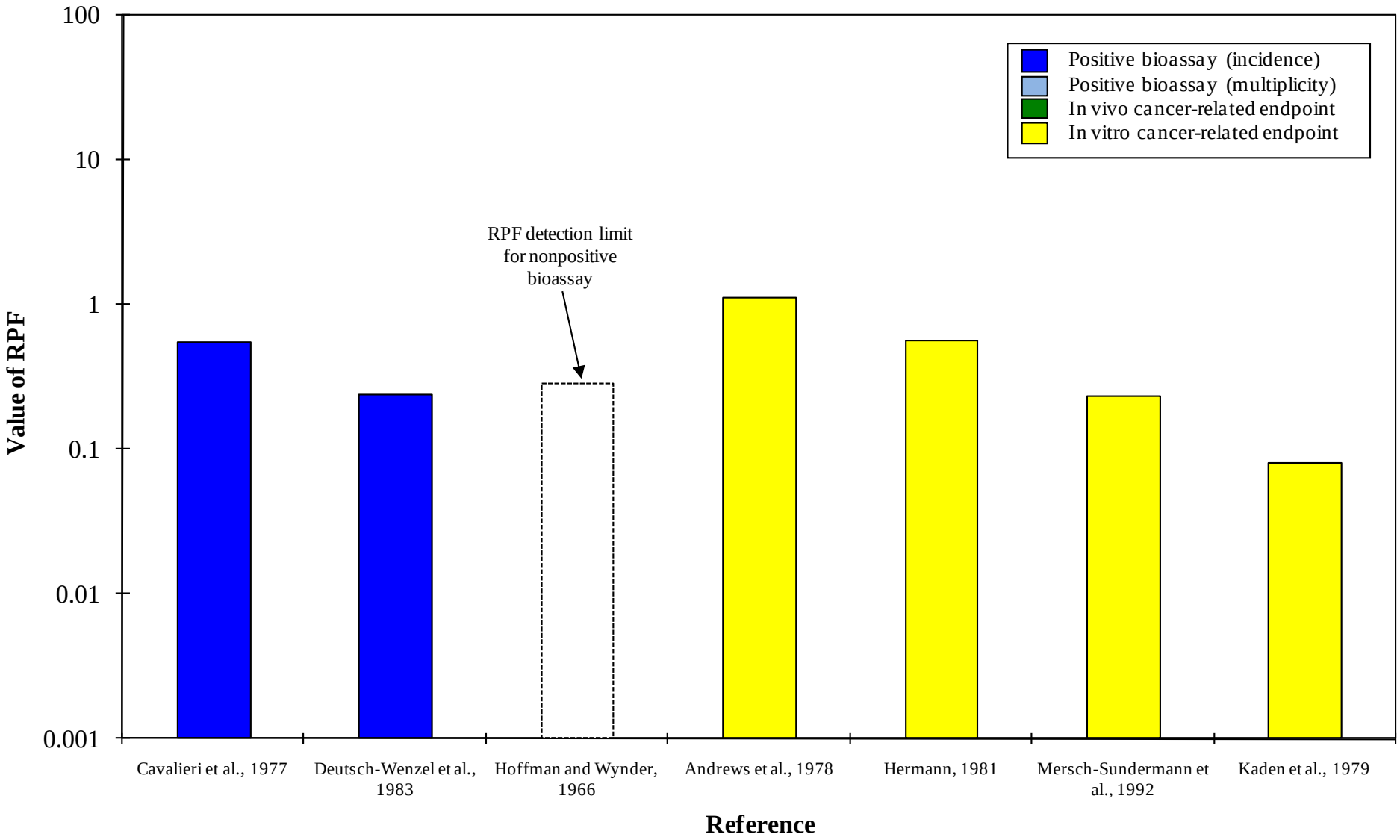
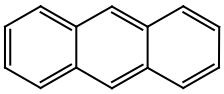


Figure 6-3. Anthanthrene (AA) RPFs.

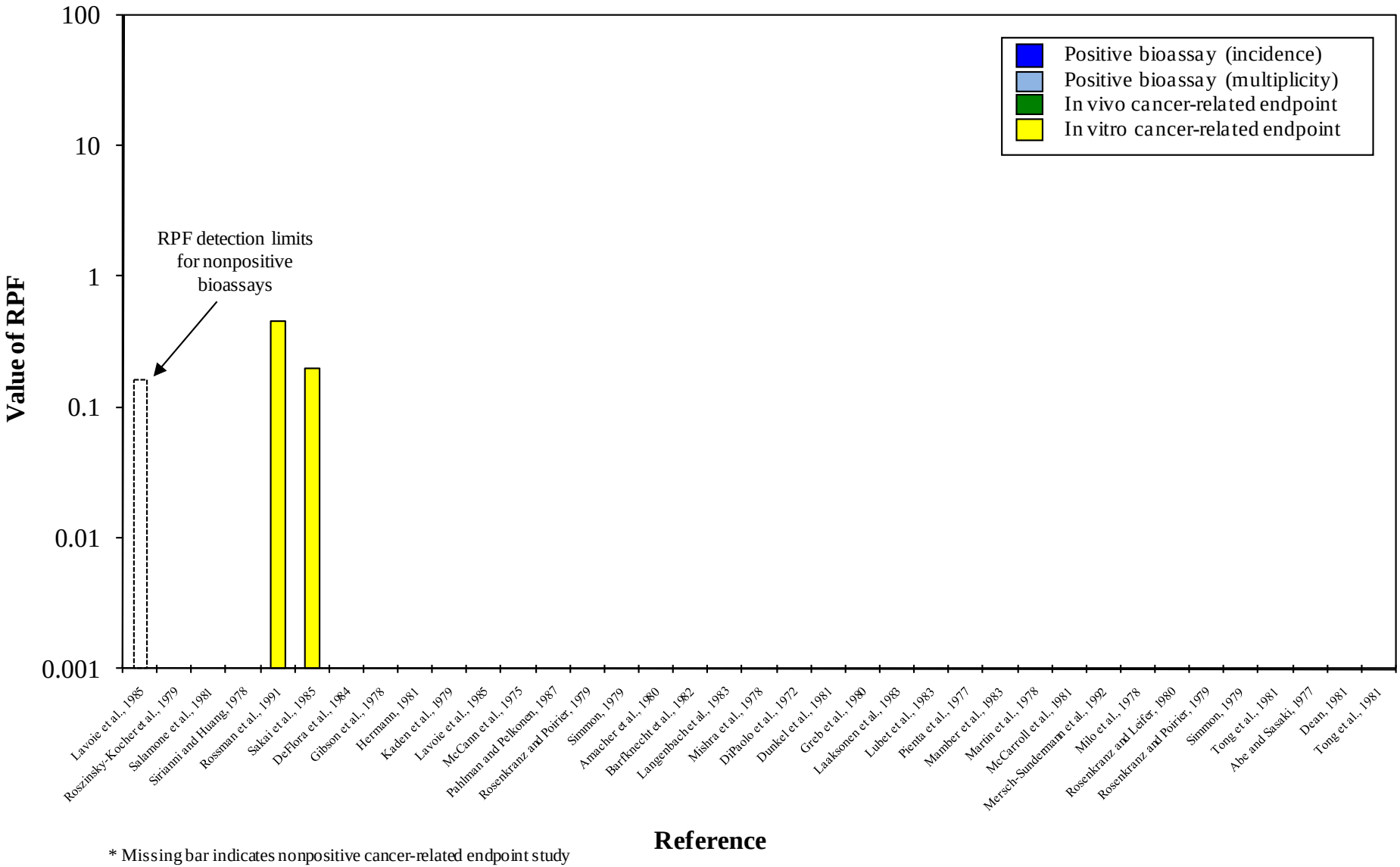
Anthracene (AC)



Anthracene (CASRN 120-12-7) is an alternant PAH comprised of three fused aromatic rings. Anthracene does not have a bay or fjord region in its structure, and contains less than four aromatic rings.

Thirty-seven datasets for anthracene met selection criteria and included benzo[a]pyrene, including 1 dermal initiation tumor bioassay, 3 in vivo clastogenicity or sister chromatid exchange datasets, 10 bacterial mutagenicity datasets, 4 mammalian mutagenicity datasets, 6 morphological/malignant cell transformation datasets, and 13 in vitro DNA adduct, DNA damage, or clastogenicity datasets (Figure 6-4). The single dermal initiation bioassay gave a nonpositive result, with an RPF detection limit of 0.2 (LaVoie et al., 1985). Only two datasets gave positive results: an in vitro bacterial mutagenicity assay and an in vitro study of DNA damage. The remaining 35 datasets reported nonpositive findings. To confirm the nonpositive findings in the one tumor bioassay that included benzo[a]pyrene, other bioassays and cancer-related endpoint data for anthracene were considered in the weight of evidence evaluation. In bioassays without benzo[a]pyrene, anthracene did not induce a statistically significant increase in tumor incidence in two dermal initiation studies (LaVoie et al., 1983; Salaman and Roe, 1956) and a lung implantation bioassay (Stanton, 1972). Scribner (1973) reported a weak tumorigenic response in a dermal initiation study in mice (4/28 mice developed papillomas by week 35 after dermal treatment with 10 µmol anthracene in benzene followed by twice weekly treatment with TPA, as compared with 0/30 control mice, $p = 0.048$).

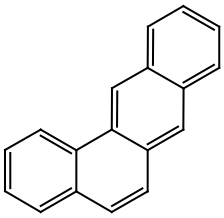
In vitro assays of mutagenicity (both bacterial and mammalian) are nearly all nonpositive for anthracene (13/14 studies). Studies of morphological/malignant cell transformation were all nonpositive. Finally, in numerous in vitro studies of DNA damage or clastogenicity, anthracene has given nonpositive results (12/13). Sakai et al. (1985) reported a mutagenic response in bacteria treated with anthracene, and Rossman et al. (1991) observed evidence of unscheduled DNA synthesis in *Escherichia coli* treated with anthracene. Overall, the weight of evidence suggests that anthracene is not carcinogenic. In addition, anthracene lacks all three known structural alerts (at least four rings, bay or fjord region) for PAH carcinogenicity and/or mutagenicity. Because the weight of evidence evaluation suggests that the data are adequate to assess the carcinogenicity of anthracene, this compound was selected for inclusion in the RPF approach and assigned an RPF of zero.



* Missing bar indicates nonpositive cancer-related endpoint study

Figure 6-4. Anthracene (AC) RPFs*.

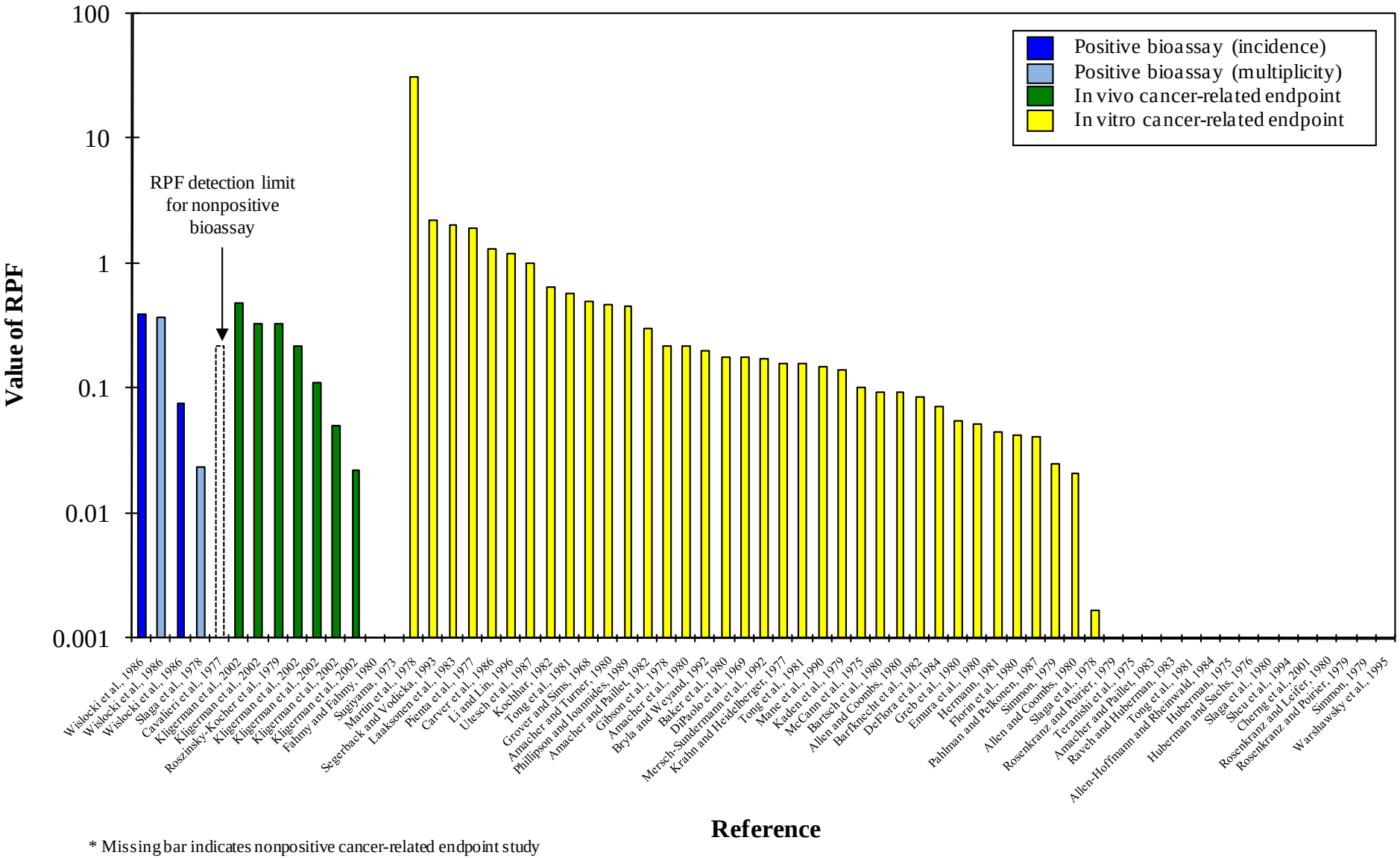
Benz[a]anthracene (BaA)



Benz[a]anthracene (CASRN 56-55-3) is an alternant PAH comprised of four fused aromatic rings. Benz[a]anthracene contains a bay region but no fjord region in its structure.

There are 65 datasets for benz[a]anthracene that met selection criteria and included benzo[a]pyrene (Figure 6-5). Included in the database are tumor bioassays (5), in vivo DNA adduct studies (4), in vivo clastogenicity studies (4), an in vivo mutagenicity study (1), bacterial mutagenicity (15), mammalian mutagenicity (14), morphological/malignant cell transformation assays (6), and in vitro studies of DNA damage, adducts, or clastogenicity (16). There are five tumor bioassay datasets of benz[a]anthracene that included benzo[a]pyrene; four gave positive results and one gave a nonpositive result. The positive findings were in different genders tested in a newborn mouse study using intraperitoneal injection (Wislocki et al., 1986); the datasets included both tumor incidence and multiplicity data for both sexes. Positive results were also reported in a dermal initiation study (Slaga et al., 1978). The one nonpositive bioassay (Cavalieri et al., 1977) was a dermal complete carcinogenicity study with an RPF detection limit of 0.2. Benz[a]anthracene was shown to form DNA adducts when administered in vivo in both rats and mice via injection and gavage (Kligerman et al., 2002). Mutagenicity and morphological/ malignant cell transformation assays of benz[a]anthracene were predominantly positive, as were studies of other cancer-related endpoints.

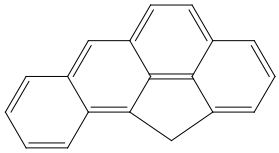
Given that the differing bioassay results can be attributed to different test systems and study design, benz[a]anthracene was considered carcinogenic and was selected for inclusion in the RPF approach.



* Missing bar indicates nonpositive cancer-related endpoint study

Figure 6-5. Benz[a]anthracene (BaA) RPFs*.

11H-Benz[b,c]aceanthrylene (BbcAC)



11H-Benz[b,c]aceanthrylene (CASRN 202-94-8) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. 11H-Benz[b,c]aceanthrylene does not contain a classic bay or fjord region in its structure.

There was only one dataset for benz[b,c]aceanthrylene that met selection criteria and included benzo[a]pyrene (Figure 6-6). This multidose dermal initiation study resulted in an RPF estimate of 0.05 (Rice et al., 1988). Benz[b,c]aceanthrylene has not been tested in any bioassay without benzo[a]pyrene. There are no cancer-related endpoint data for benz[b,c]aceanthrylene. As the only available bioassay of this PAH was positive, benz[b,c]aceanthrylene was considered carcinogenic and was selected for inclusion in the RPF approach.

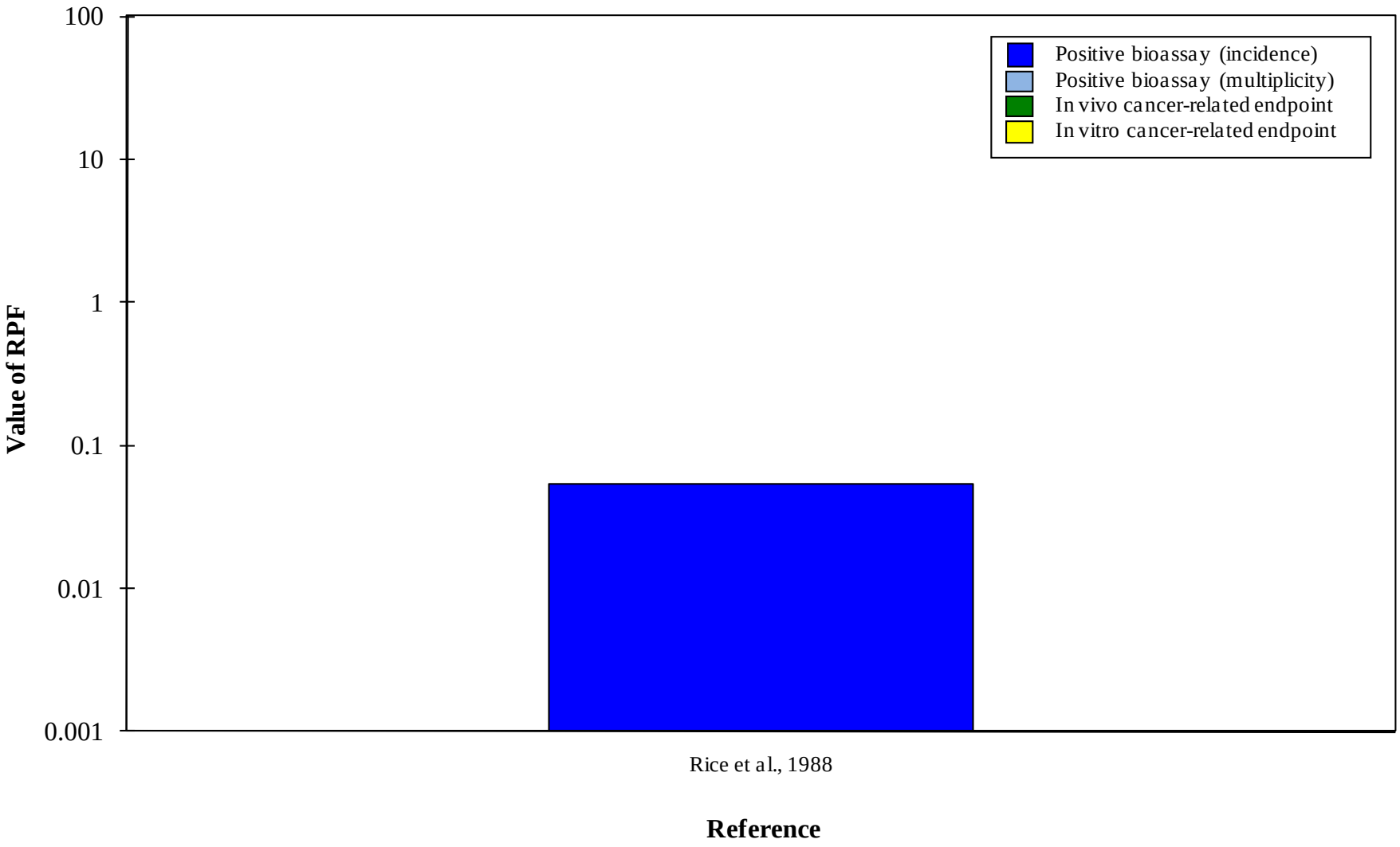
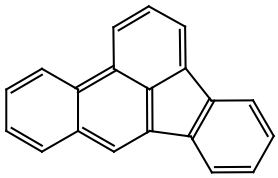


Figure 6-6. 11H-Benz[b,c]aceanthrylene (BbcAC) RPFs.

Benzo[b]fluoranthene (BbF)



Benzo[b]fluoranthene (CASRN 205-99-2) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benzo[b]fluoranthene contains one classic bay region but no fjord region in its structure.

There were 22 datasets of benzo[b]fluoranthene that met selection criteria and included benzo[a]pyrene (Figure 6-7). Included in the database are in vivo tumor bioassay datasets (8), in vivo DNA adduct datasets (7), in vivo clastogenicity datasets (3), mutagenicity and morphological/malignant cell transformation datasets (3), and an in vitro DNA damage dataset (1). Statistically significant increases in tumor incidence and/or multiplicity were reported in male mice tested in two newborn mouse bioassays using intraperitoneal injection (Nesnow et al., 1998b; LaVoie et al., 1987), in dermal initiation (LaVoie et al., 1982) and dermal complete carcinogenicity (Habs et al., 1980) bioassays, and in a rat lung implantation bioassay (Deutsch-Wenzel et al., 1983). The one nonpositive result was in female mice tested in the newborn mouse bioassay; the RPF detection limit was 0.8 (LaVoie et al., 1987). A number of studies showed that benzo[b]fluoranthene forms DNA adducts when administered in vivo to rats or mice via injection or gavage (Kligerman et al., 2002; Nesnow et al., 1998b, 1993b). One mutagenicity assay and two morphological/malignant cell transformation assays of benzo[b]fluoranthene were positive, as were studies of other cancer-related endpoints; there were no nonpositive studies of cancer-related endpoints. Given that the differing bioassay results can be attributed to different genders, benz[a]anthracene was considered carcinogenic and was selected for inclusion in the RPF approach.

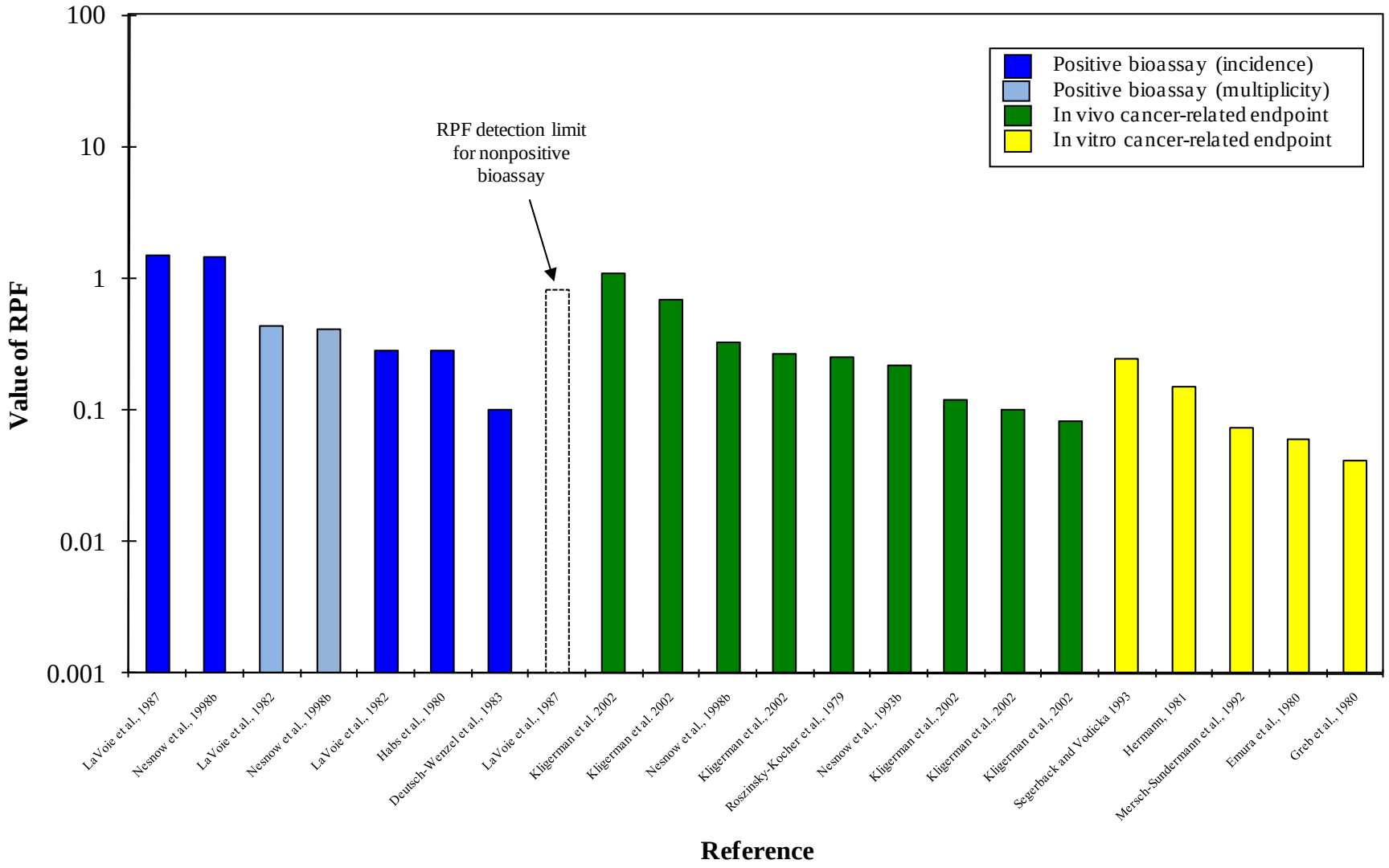
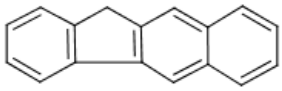


Figure 6-7. Benzo[b]fluoranthene (BbF) RPFs.

11H-Benzo[b]fluorene (BbFE)



11H-Benzo[b]fluorene (CASRN 243-17-4) is a nonalternant PAH comprised of three aromatic rings and one five-membered ring. 11H-Benzo[b]fluorene does not contain a classic bay or fjord region in its structure.

There were three datasets for 11H-benzo[b]fluorene that met selection criteria and included benzo[a]pyrene (Figure 6-8): two mutagenicity datasets and an in vitro DNA damage dataset. There are no bioassays of 11H-benzo[b]fluorene that included benzo[a]pyrene, so bioassays without benzo[a]pyrene and cancer-related endpoint data were considered. LaVoie et al. (1981) conducted a study of skin tumor initiation in mice treated with 1 mg 11H-benzo[b]-fluorene followed by 20 weeks of treatment with TPA. The incidence of tumor-bearing animals (4/20) was not significantly increased over controls (1/20) (LaVoie et al., 1981). The limited cancer-related endpoint data were mixed, with one positive mutagenicity study (Kaden et al., 1979), one nonpositive mutagenicity study (Hermann, 1981), and one positive in vitro study of DNA damage (Mersch-Sundermann et al., 1992). Overall, the database for 11H-benzo[b]-fluorene is both limited and inconsistent. Because the database for 11H-benzo[b]fluorene does not provide adequate information with which to assess carcinogenicity, this PAH was not selected for inclusion in the RPF approach.

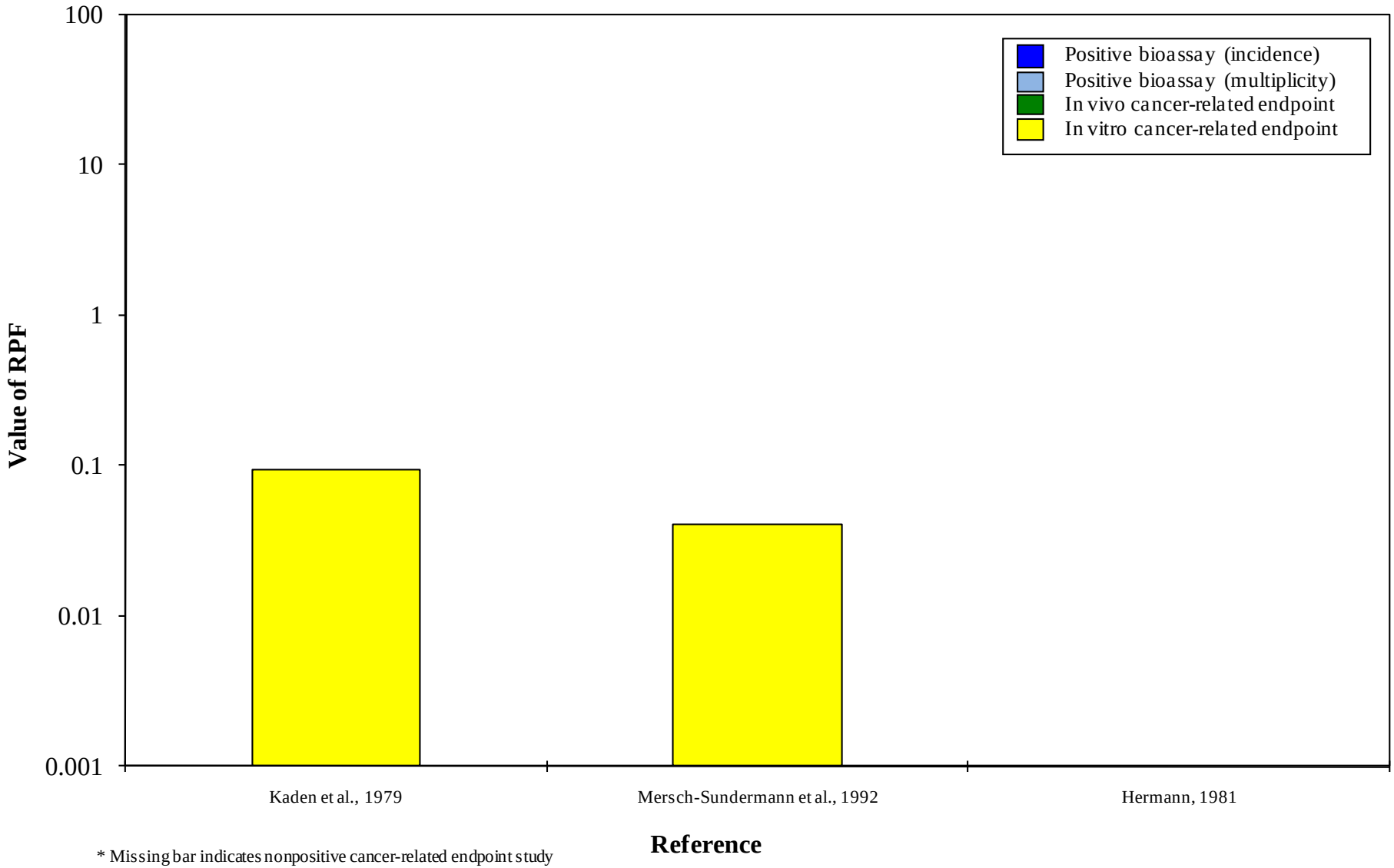
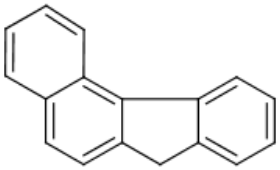


Figure 6-8. 11H-Benzo[b]fluorene (BbFE) RPFs*.

Benzo[c]fluorene (BcFE).



Benzo[c]fluorene (CASRN 205-12-9) is a nonalternant PAH comprised of three aromatic rings and one five-membered ring. Benzo[c]fluorene does not contain a classic bay or fjord region in its structure.

There were six datasets for benzo[c]fluorene that met selection criteria and included benzo[a]pyrene (Figure 6-9); all gave positive results. The database includes oral and intraperitoneal in vivo tumor bioassays (each reporting both incidence and multiplicity) and in vivo DNA adduct data. Significantly increased lung tumor incidence and tumor multiplicity were reported after both oral and intraperitoneal exposure (Weyand et al., 2004). As the available bioassays that included benzo[a]pyrene were positive, benzo[c]fluorene was considered carcinogenic and was selected for inclusion in the RPF approach.

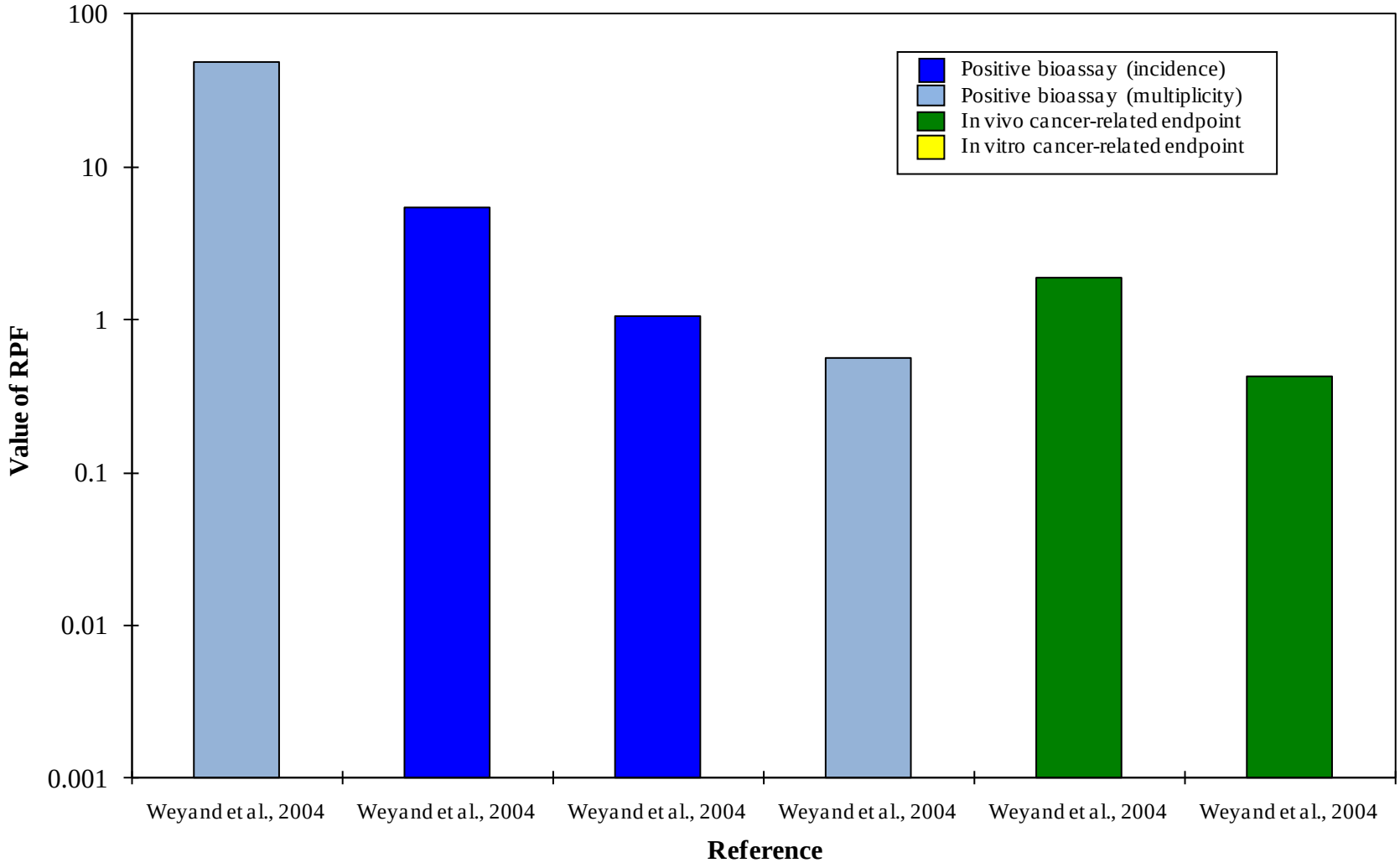
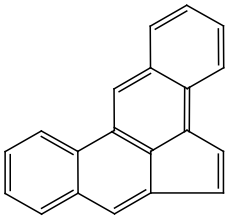


Figure 6-9. Benzo[c]fluorene (BcFE) RPFs.

Benz[e]aceanthrylene (BeAC).



Benz[e]aceanthrylene (CASRN 199-54-2) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benz[e]aceanthrylene contains a classic bay region but no fjord region in its structure.

There were six datasets for benz[e]aceanthrylene that met selection criteria and included benzo[a]pyrene (Figure 6-10); all gave positive results. The database includes an in vivo tumor bioassay in two sexes (each reporting both incidence and multiplicity), a mammalian mutagenicity study, and a morphological/malignant cell transformation study. Significantly increased tumor incidence and tumor multiplicity were reported for both male and female mice in a dermal initiation bioassay in mice (Nesnow et al., 1984). As the available bioassay that included benzo[a]pyrene was positive, benz[e]aceanthrylene was considered carcinogenic and was selected for inclusion in the RPF approach.

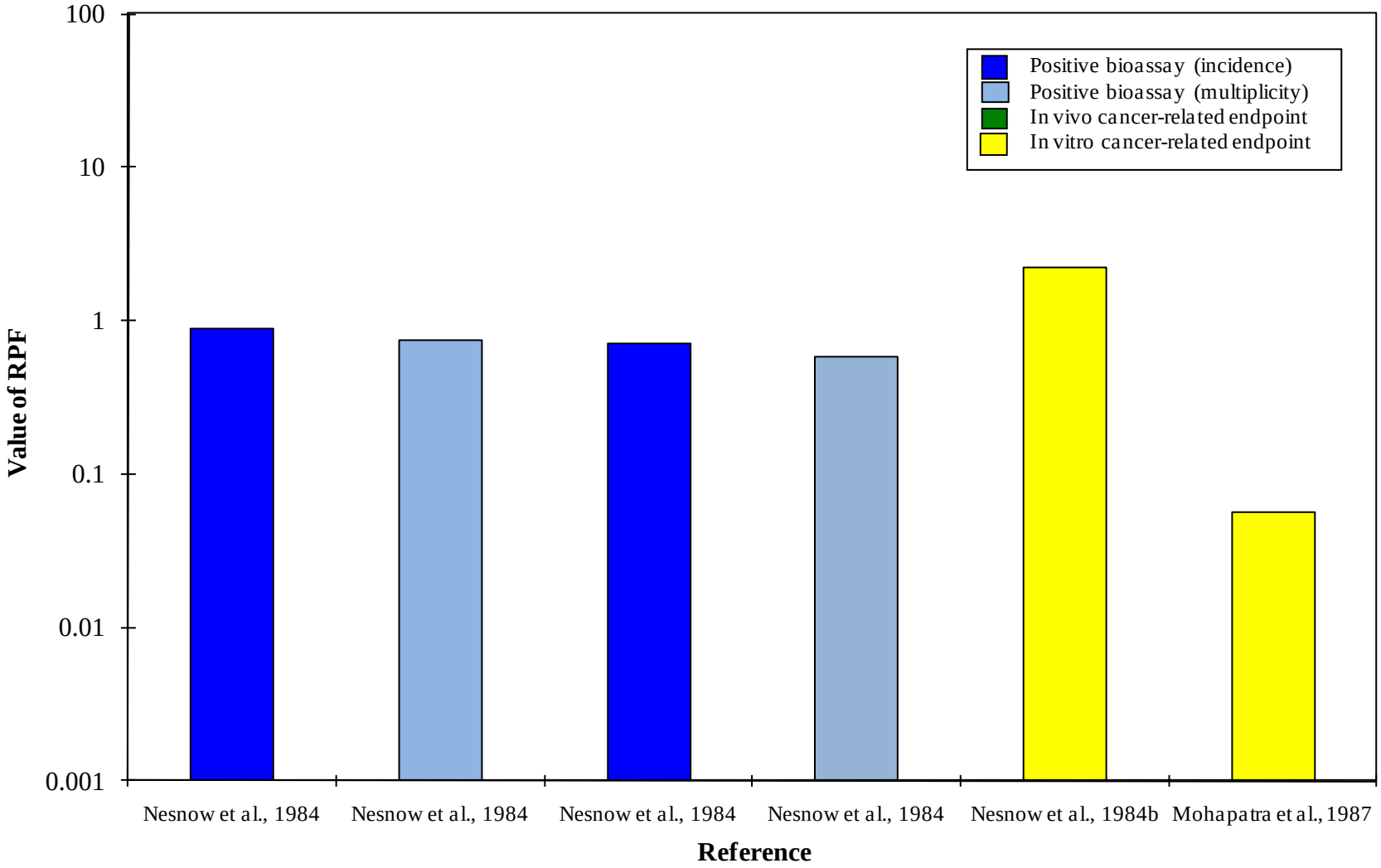
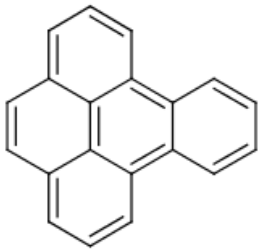


Figure 6-10. Benz[e]aceanthrylene (BeAC) RPFs.

Benzo[e]pyrene (BeP)

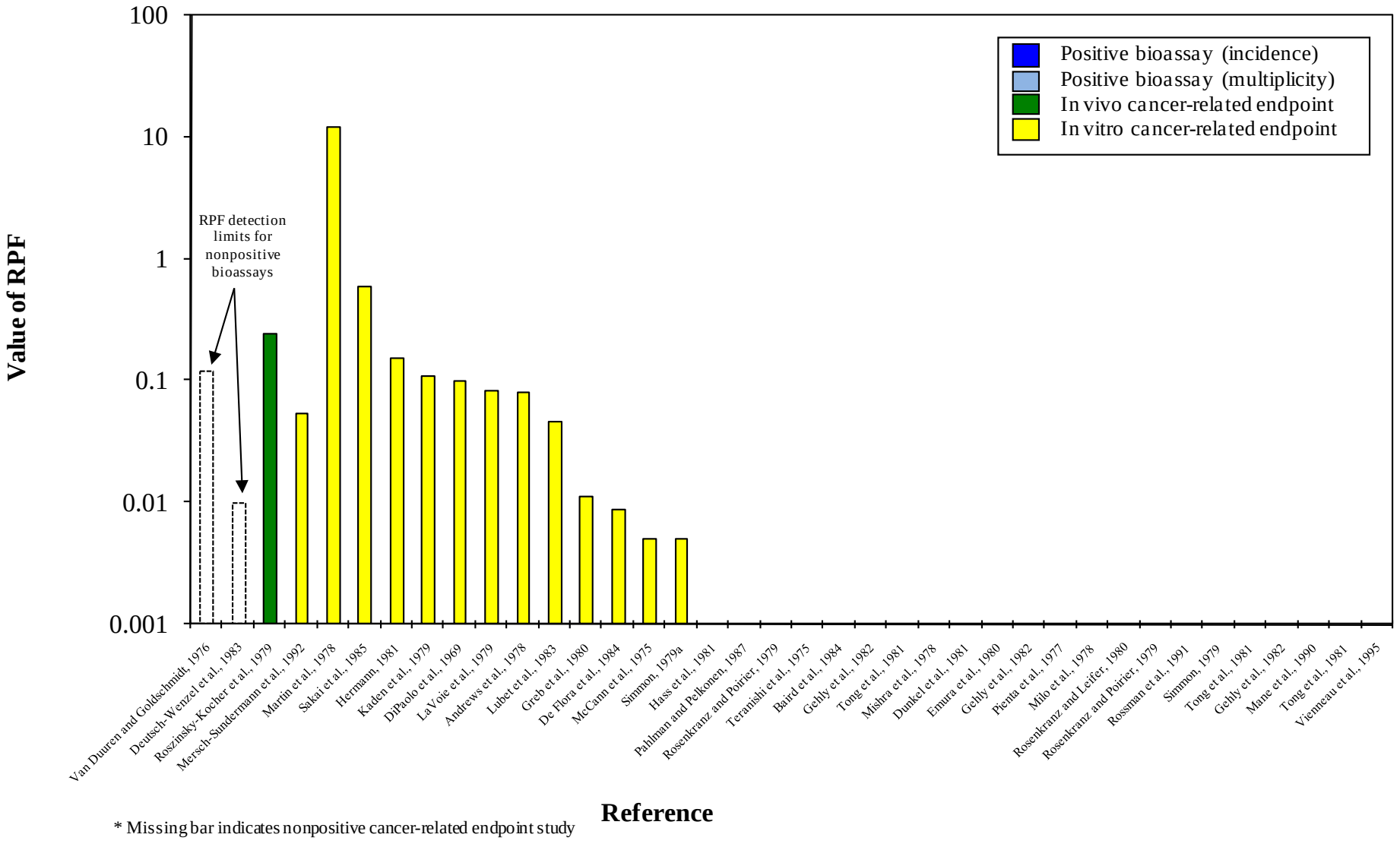


Benzo[e]pyrene (192-97-2) is an alternant PAH comprised of five fused aromatic rings. Benzo[e]pyrene contains two bay regions but no fjord region in its structure.

Thirty-seven datasets for benzo[e]pyrene met selection criteria and included benzo[a]pyrene: 2 tumor bioassays, 1 in vivo clastogenicity dataset, 12 bacterial mutagenicity datasets, 4 mammalian mutagenicity datasets, 7 morphological/malignant cell transformation datasets, and 11 in vitro DNA damage or clastogenicity datasets (Figure 6-11). No increase in tumor incidence was observed when benzo[e]pyrene was tested alone as part of a dermal cocarcinogenicity bioassay (Van Duuren and Goldschmidt, 1976). When tested in a lung implantation bioassay in rats, benzo[e]pyrene exposure did not result in a significant increase in tumor incidence (Deutsch-Wenzel et al., 1983). The RPF detection limits of these studies were approximately 0.01 and 0.1. To confirm the nonpositive findings in the available tumor bioassays that included benzo[a]pyrene, other bioassays and cancer-related endpoint data were considered. In bioassays without benzo[a]pyrene, benzo[e]pyrene gave nonpositive results in a dermal initiation bioassay (1 mg/mouse; Van Duuren et al., 1968) and a newborn mouse bioassay (0.7 µmol; Chang et al., 1981). A significant increase in tumor incidence was reported in a single-concentration dermal initiation study in mice; 11/13 surviving mice (20 were treated) had papillomas by week 35 after dermal treatment with 10 µmol benzo[e]pyrene in benzene ($p < 0.0001$), followed by twice weekly treatment with TPA; no control mice had papillomas (Scribner, 1973).

In vitro assays of mutagenicity (both bacterial and mammalian) and morphological/ malignant cell transformation give inconsistent results for benzo[e]pyrene; 11/23 studies were positive and the rest were nonpositive. Positive studies include a mix of bacterial mutagenicity and morphological/malignant cell transformation assays; four mammalian mutagenicity assays were nonpositive. One study of in vivo clastogenicity and two studies of in vitro DNA damage were positive, while nine studies of in vitro DNA damage or clastogenicity were nonpositive.

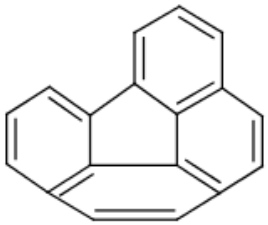
While the database for benzo[e]pyrene is quite large, the results are inconsistent; as a result, no conclusion can be drawn as to carcinogenicity. This PAH was not selected for inclusion in the RPF approach.



* Missing bar indicates nonpositive cancer-related endpoint study

Figure 6-11. Benzo[e]pyrene (BeP) RPFs*.

Benzo[g,h,i]fluoranthene (BghiF)



Benzo[g,h,i]fluoranthene (CASRN 203-12-3) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benzo[g,h,i]fluoranthene does not contain a classic bay or fjord region in its structure.

There were six datasets for benzo[g,h,i]fluoranthene that met selection criteria and included benzo[a]pyrene (Figure 6-12). A dermal initiation bioassay in mice (Van Duuren et al., 1966) did not result in a statistically significant increase in tumor incidence; the RPF detection limit was 0.06. There were no other bioassays that met selection criteria. There were three positive bacterial mutagenicity studies (Chang et al., 2002; Lafleur et al., 1993; Carver et al., 1986), one positive study of in vitro DNA damage (Mersch-Sundermann et al., 1992), and a mammalian mutagenicity study with nonpositive results (Lafleur et al., 1993). The RPF values for the positive cancer-related endpoint datasets ranged from 0.6 to 1. Overall, the database for benzo[g,h,i]fluroanthene is both limited and inconsistent. Because the database for benzo[g,h,i]fluoranthene does not provide adequate information with which to assess carcinogenicity, this PAH was not selected for inclusion in the RPF approach.

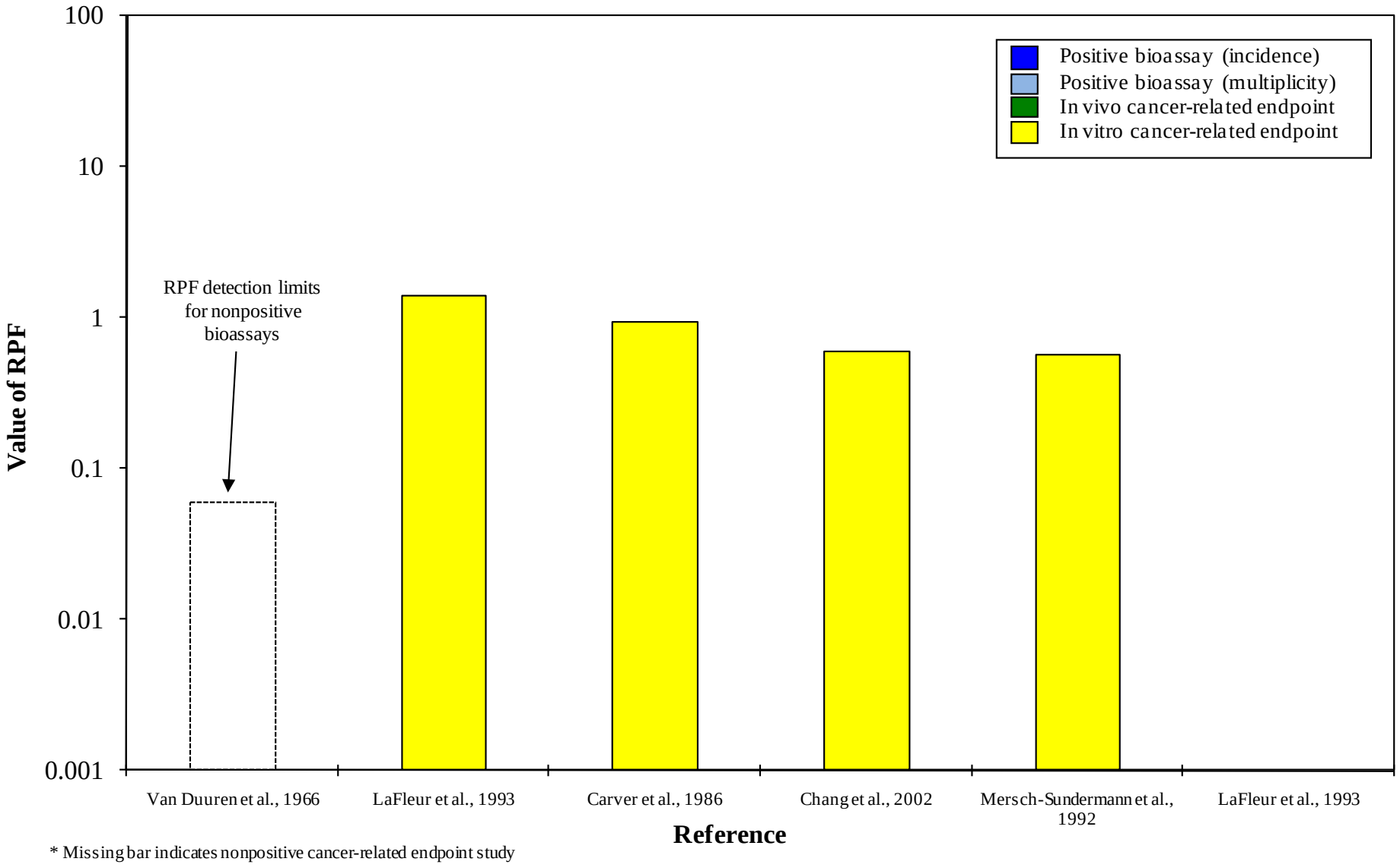
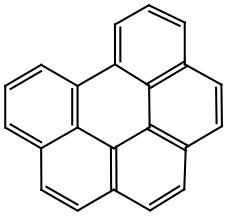


Figure 6-12. Benzo[g,h,i]fluoranthene (BghiF) RPFs*.

Benzo[g,h,i]perylene (BghiP)



Benzo[g,h,i]perylene (CASRN 191-24-2) is an alternant PAH comprised of six fused aromatic rings. Benzo[g,h,i]perylene contains a bay region but no fjord region in its structure.

There were 10 datasets for benzo[g,h,i]perylene that met selection criteria and included benzo[a]pyrene (Figure 6-13). The database includes three in vivo tumor bioassays, four bacterial mutagenicity datasets, an in vitro DNA damage dataset, and two in vitro DNA adduct datasets. Of the three bioassays, positive findings were only reported in one: a rat lung implantation bioassay (Deutsch-Wenzel et al., 1983) that resulted in an RPF estimate of 0.009. In a dermal initiation bioassay (Hoffmann and Wynder, 1966) and a dermal cocarcinogenicity bioassay (Van Duuren and Goldschmidt, 1976), there was no statistically significant increase in tumor incidence, but these studies had relatively insensitive RPF detection limits (around 0.1) compared with the positive study. There were four positive mutagenicity studies; all were conducted in bacterial systems. Studies of in vitro DNA adducts and DNA damage were positive. Because the inconsistent bioassay results can be attributed to different test systems (different species and route), benzo[g,h,i]perylene was considered carcinogenic and was selected for inclusion in the RPF approach.

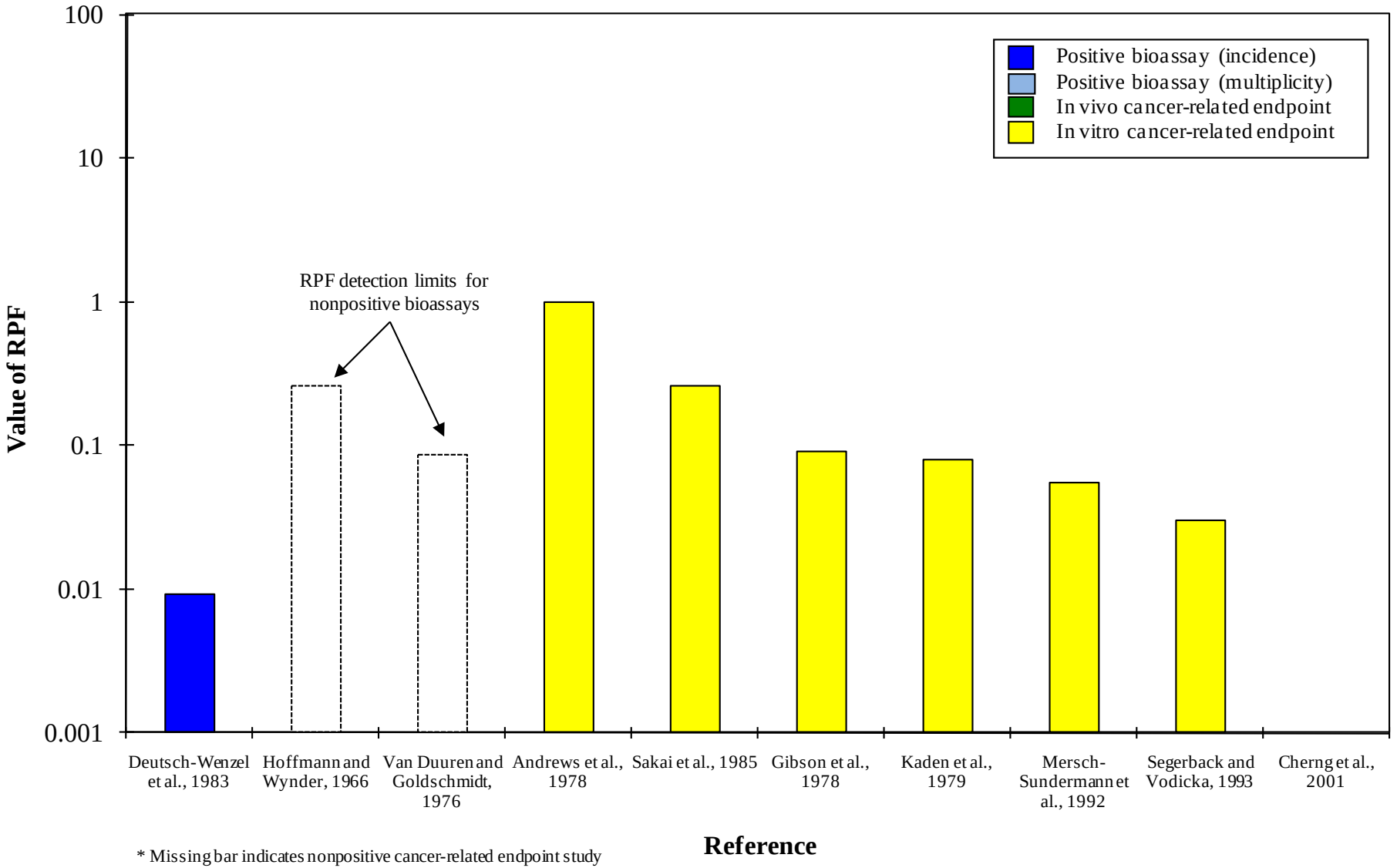
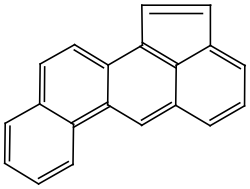


Figure 6-13. Benzo[g,h,i]perylene (BghiP) RPFs*.

Benz[j]aceanthrylene (BjAC)



Benz[j]aceanthrylene (CASRN 202-33-5) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benz[j]aceanthrylene contains a classic bay region but no fjord region in its structure.

There were 12 datasets for benz[j]aceanthrylene that met selection criteria and included benzo[a]pyrene (Figure 6-14); all of the studies gave positive results. The database includes one in vivo tumor bioassay dataset, one in vivo DNA adduct dataset, four mutagenicity or morphological/malignant cell transformation datasets, and six in vitro DNA damage or DNA adduct datasets. In a bioassay of benz[j]aceanthrylene that used intraperitoneal injection in an A/J mouse system (Mass et al., 1993), all mice treated with benz[j]aceanthrylene developed tumors (incidence of 100% at doses of 20–100 mg/kg; incidence for benzo[a]pyrene was 63–100% across the same dose range), precluding the derivation of an RPF using incidence data. However, tumor multiplicity (average number of tumors per animal) data were available for dose-response modeling and resulted in an RPF estimate of 60. Benz[j]aceanthrylene treatment resulted in a pronounced increase in the average number of tumors per animal (59.45 tumors per animal at 20 mg/kg), much higher than benzo[a]pyrene treatment (5.05 tumors per animal at 100 mg/kg), indicating that this compound is very potent in this test system. In a dermal initiation bioassay that did not include benzo[a]pyrene, benz[j]aceanthrylene induced papillomas in 90% of mice treated with an initiating dose of 40 µg (compared with 5% incidence in controls). As the available bioassay that included benzo[a]pyrene was positive and suggested that this compound is very potent, benz[j]aceanthrylene was considered carcinogenic and was selected for inclusion in the RPF approach.

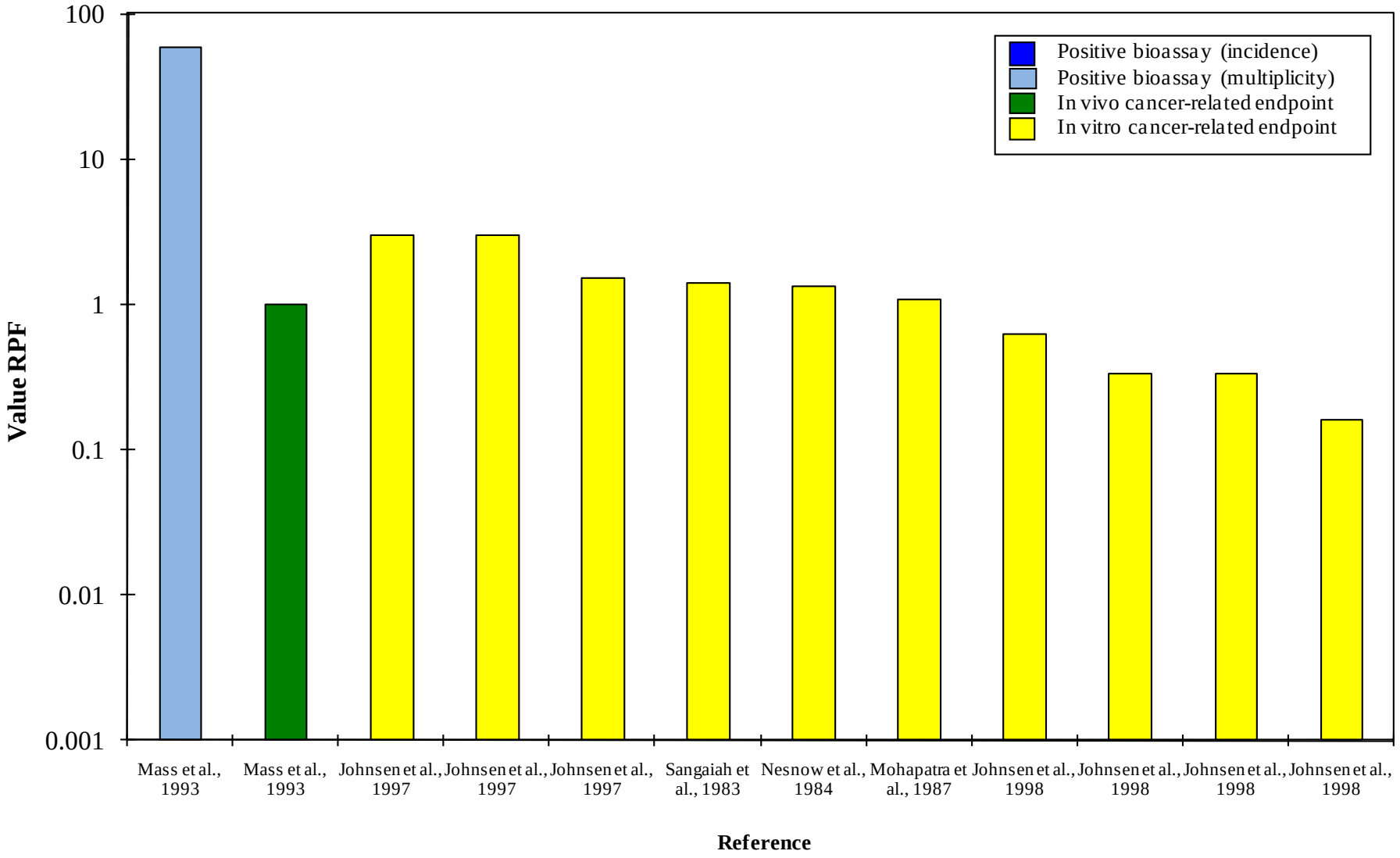
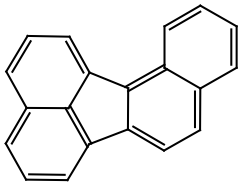


Figure 6-14. Benz[j]aceanthrylene (BjAC) RPFs.

Benzo[j]fluoranthene (BjF)



Benzo[j]fluoranthene (CASRN 205-82-3) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benzo[j]fluoranthene does not contain a classic bay or fjord region in its structure.

There were eight datasets for benzo[j]fluoranthene that met selection criteria and included benzo[a]pyrene (Figure 6-15): seven in vivo tumor bioassay datasets and one in vitro study of DNA damage. Of the seven bioassay datasets, significant increases in tumor incidence or count were observed in all but one. Significant increases in tumor incidence were reported in both male and female mice tested in a newborn mouse bioassay using intraperitoneal injection of single doses (LaVoie et al., 1987), a mouse dermal initiation study (LaVoie et al., 1982), and a rat lung implantation bioassay (Deutsch-Wenzel et al., 1983). Significant increases in tumor multiplicity were reported in two mouse dermal initiation studies (Weyand et al., 1992; LaVoie et al., 1982). The one nonpositive bioassay was a mouse dermal complete carcinogenicity bioassay with an RPF detection limit of 0.1 (Habs et al., 1980). The in vitro study of DNA damage gave positive results (Mersch-Sundermann et al., 1992). Because the inconsistent bioassay results can be attributed to different test systems or study design, benzo[j]fluroanthene was considered carcinogenic and was selected for inclusion in the RPF approach.

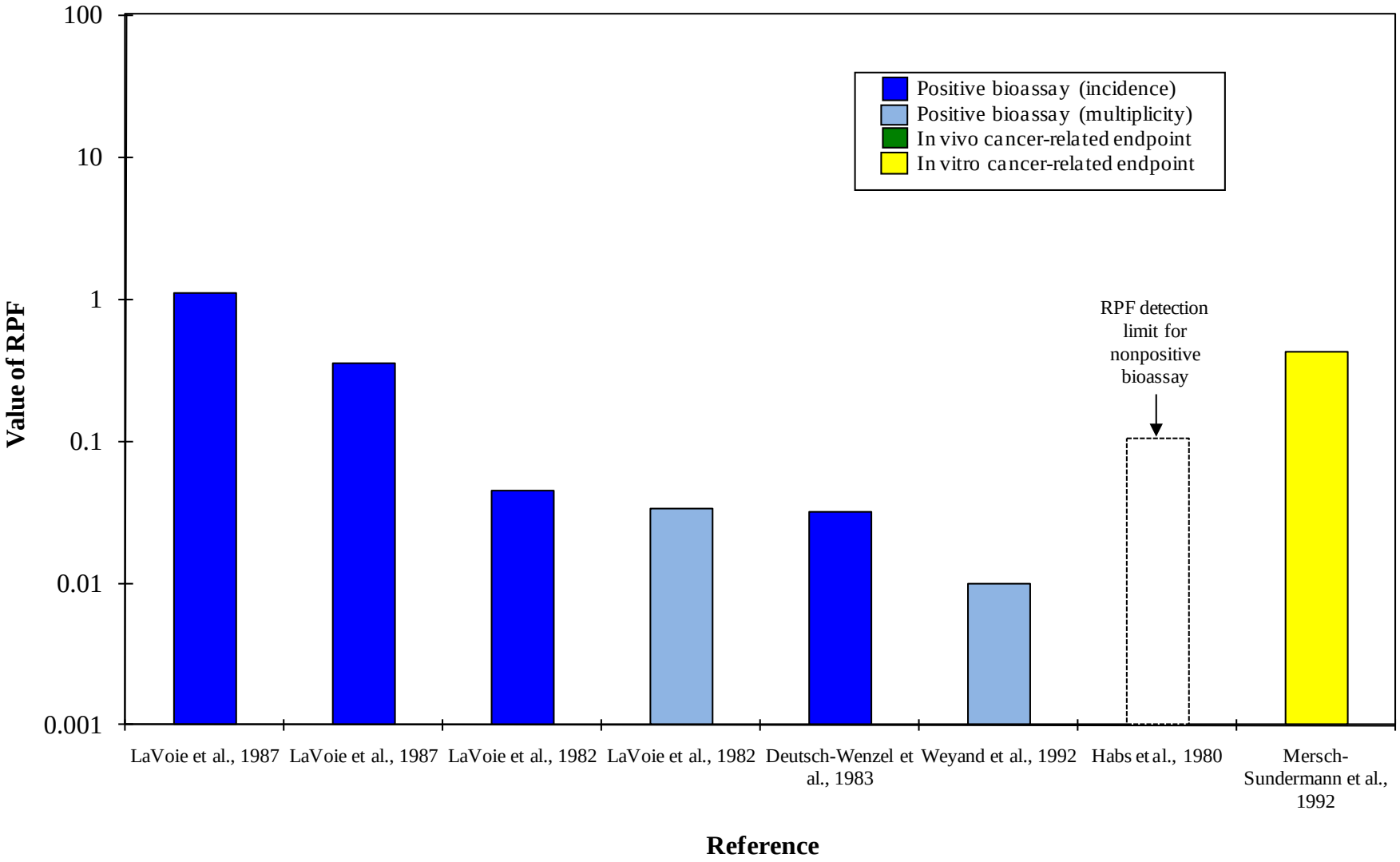
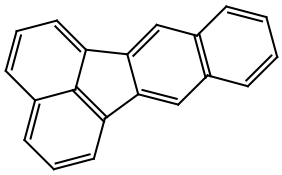


Figure 6-15. Benzo[j]fluoranthene (BjF) RPFs.

Benzo[k]fluoranthene (BkF)



Benzo[k]fluoranthene (CASRN 207-08-9) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benzo[j]fluoranthene does not contain a classic bay or fjord region in its structure.

There were five datasets for benzo[k]fluoranthene that met selection criteria and included benzo[a]pyrene (Figure 6-16). The database includes four in vivo tumor bioassay datasets and one morphological/malignant cell transformation dataset. Statistically significant increases in tumor incidence and tumor count were reported in a mouse dermal initiation study (LaVoie et al., 1982) and increased tumor incidence was reported in a rat lung implantation bioassay (Deutsch-Wenzel et al., 1983). No significant increase in tumor incidence was observed in a dermal complete carcinogenicity study with an RPF detection limit of 0.1 (Habs et al., 1980). The morphological/malignant cell transformation study (Emura et al., 1980) was nonpositive. Because the inconsistent bioassay results can be attributed to different test systems or study design (dermal initiation versus dermal complete carcinogenicity), benzo[k]fluroanthene was considered carcinogenic and was selected for inclusion in the RPF approach.

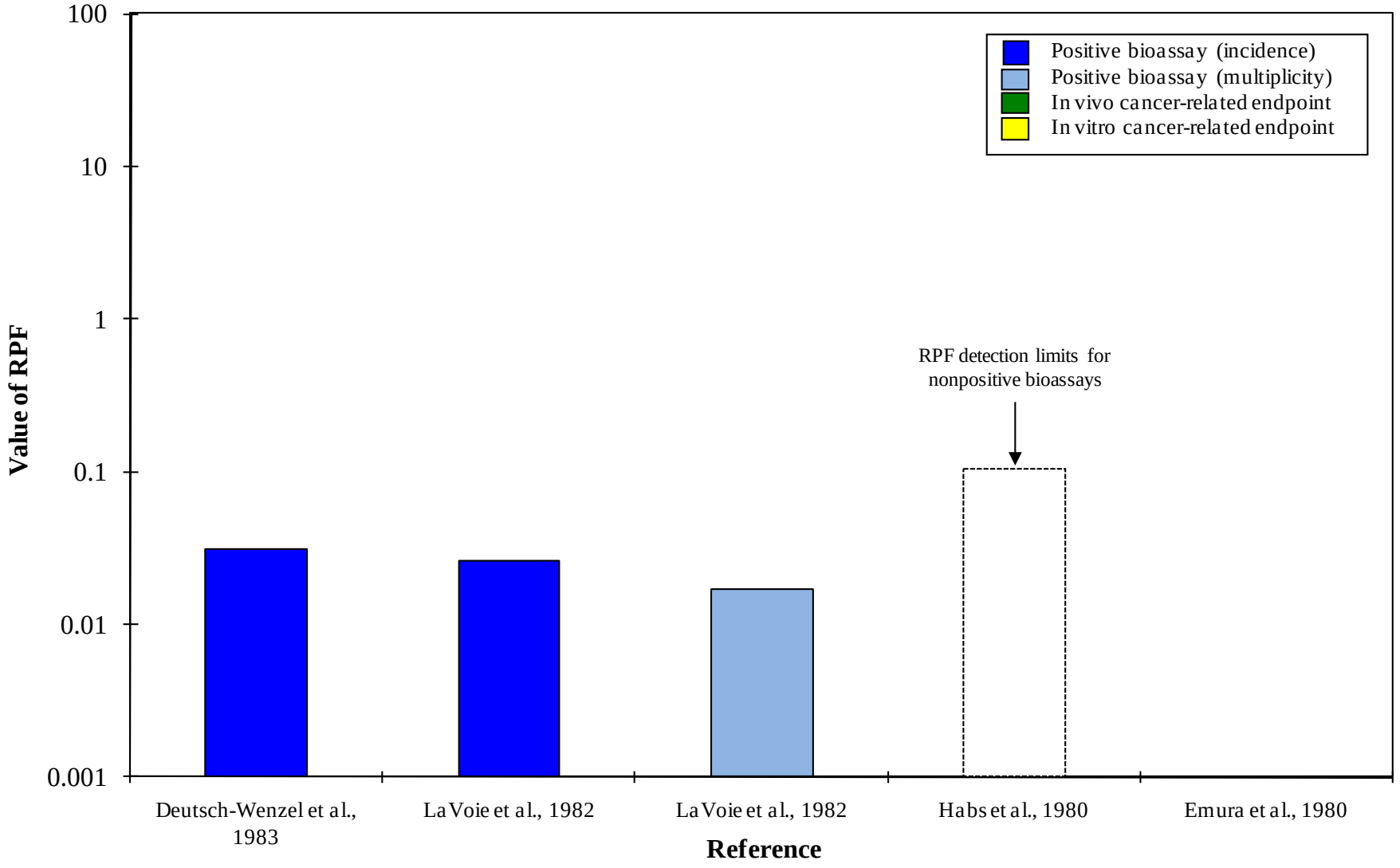
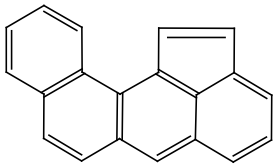


Figure 6-16. Benzo[k]fluoranthene (BkF) RPFs*.

Benz[l]aceanthrylene (BlAC)



Benz[l]aceanthrylene (CASRN 211-91-6) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Benz[l]aceanthrylene does not contain a classic bay or fjord region in its structure.

There were 16 datasets for benz[l]aceanthrylene that met selection criteria and included benzo[a]pyrene (Figure 6-17); all of the studies gave positive results. The database includes four in vivo tumor bioassay datasets, five mutagenicity or morphological/malignant cell transformation datasets, one in vivo clastogenicity dataset, and six in vitro DNA adduct or DNA damage datasets. Significant increases in tumor count and multiplicity were reported in both male and female mice in a dermal initiation bioassay (Nesnow et al., 1984). All of the cancer-related endpoint studies were positive as well. Relative potency estimates for most of the available datasets were ≥1.0, suggesting equivalent or greater potency than benzo[a]pyrene. As the available bioassays that included benzo[a]pyrene were positive, benz[l]aceanthrylene was considered carcinogenic and was selected for inclusion in the RPF approach.

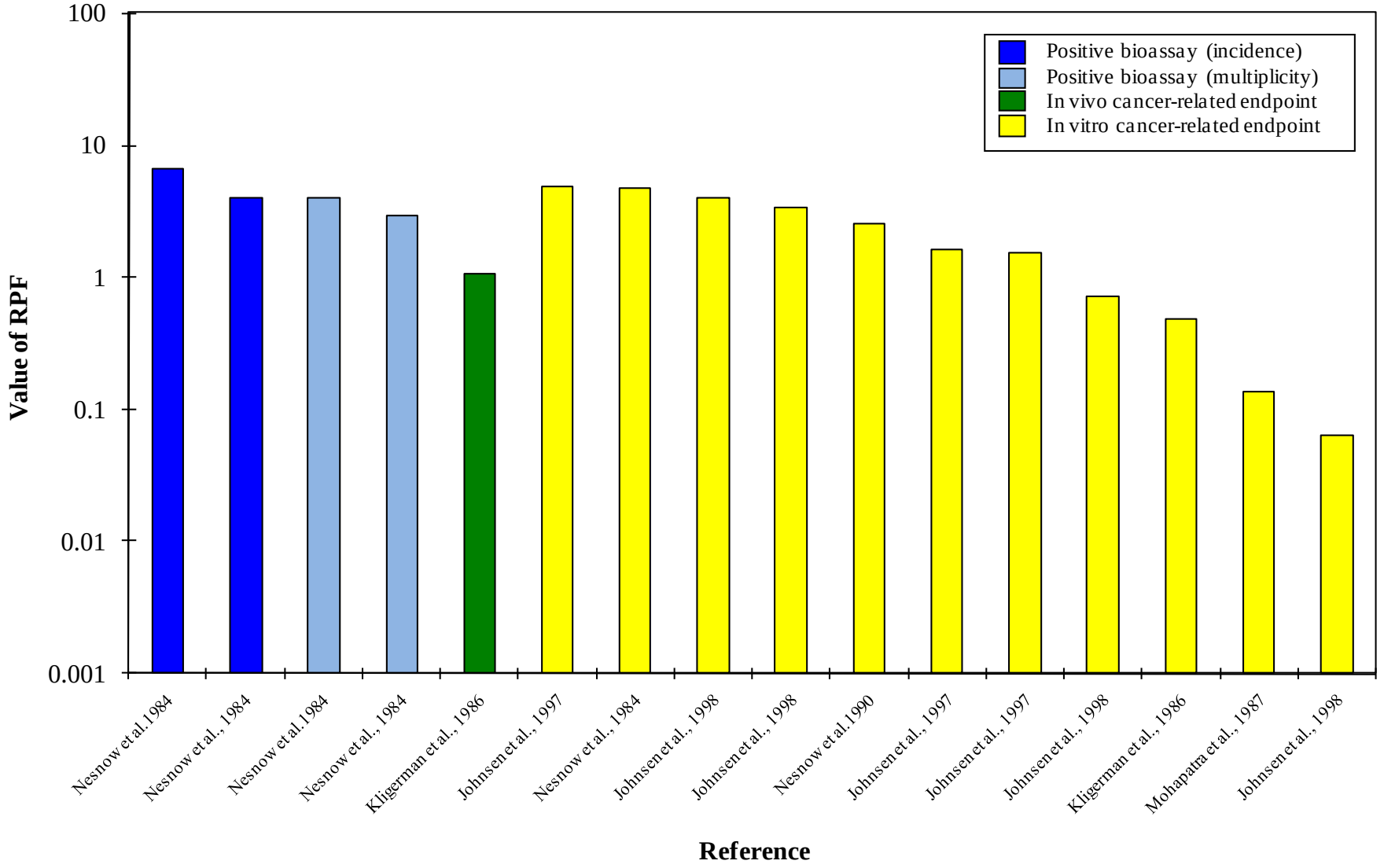
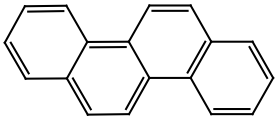


Figure 6-17. Benz[l]aceanthrylene (BlAC) RPFs.

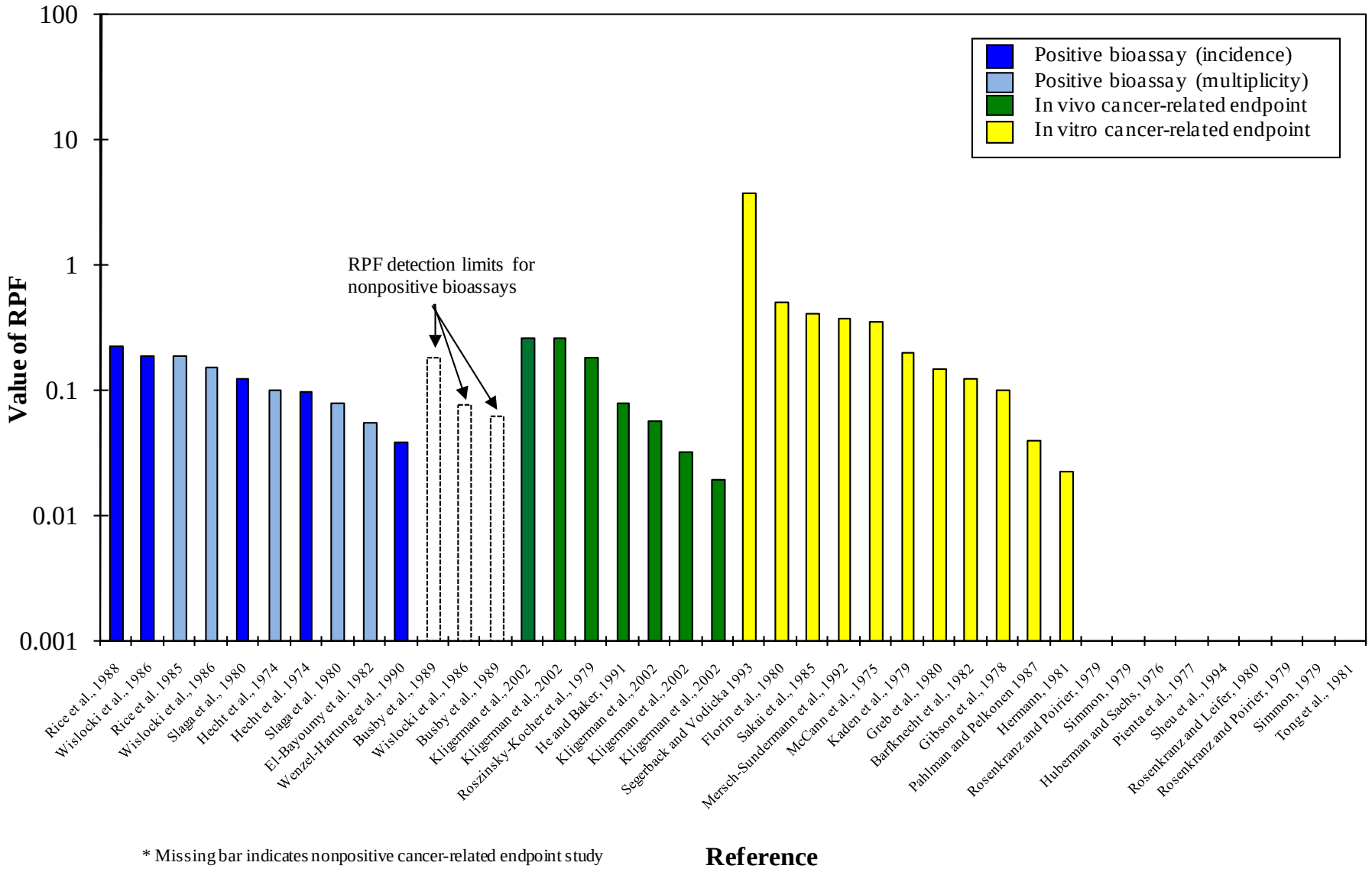
Chrysene (CH)



Chrysene (CASRN 218-01-9) is an alternant PAH comprised of four fused aromatic rings. Chrysene contains two bay regions but no fjord region in its structure.

There were 40 datasets for chrysene that met selection criteria and included benzo[a]pyrene (Figure 6-18). Included in the database are 13 in vivo tumor bioassay datasets, 4 in vivo DNA adduct datasets, 3 in vivo clastogenicity datasets, 11 mutagenicity datasets, 3 morphological/malignant cell transformation datasets, and 6 in vitro studies of DNA damage, adducts, or clastogenicity. Among the bioassays that included benzo[a]pyrene, 11 reported significant increases in tumor incidence or tumor multiplicity, and 3 did not. Significant increases in tumor incidence and/or multiplicity were reported in three dermal initiation studies in mice (Rice et al., 1988; Slaga et al., 1980; Hecht et al., 1974), a newborn mouse study in males (Wislocki et al., 1986), and a rat lung implantation bioassay (Wenzel-Hartung et al., 1990). Female mice tested in the newborn mouse assay published by Wislocki et al. (1986) did not have a significant increase in tumor incidence, resulting in one of the three nonpositive studies. The other two nonpositive findings were in males and females tested in another newborn mouse bioassay (Busby et al., 1989). The bioassays with nonpositive findings had RPF detection limits between 0.06 and 0.2. Conflicting results in male mice were reported in the two newborn mouse bioassays (Busby et al., 1989; Wislocki et al., 1986). The major difference between the two studies is the duration of follow-up; Busby et al. (1989) sacrificed the mice at 26 weeks, while Wislocki et al. (1986) followed the mice for a full year. LaVoie et al. (1994) observed that liver tumor induction in the newborn mouse bioassay is not fully realized until the mice have reached 1 year of age, and the positive findings by Wislocki et al. (1986) indeed reflect liver tumors in the male mice. Chrysene was shown to form DNA adducts when administered in vivo in both rats and mice via injection and gavage (Kligerman et al., 2002). Bacterial and mammalian mutagenicity and morphological/malignant cell transformation assays of chrysene were all positive, as were studies of clastogenicity tested in vivo. In contrast, results from in vitro studies of DNA adducts, DNA damage, and clastogenicity were not consistent.

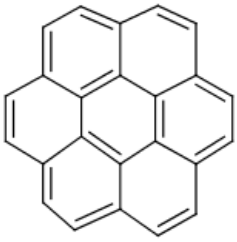
Because the inconsistent bioassay results can be attributed to different study designs (gender, follow-up time), chrysene was considered carcinogenic and was selected for inclusion in the RPF approach.



* Missing bar indicates nonpositive cancer-related endpoint study

Figure 6-18. Chrysene (CH) RPFs*.

Coronene (CO)



Coronene (CASRN 191-07-1) is an alternant PAH comprised of seven fused aromatic rings. Coronene contains no bay or fjord regions in its structure.

There were six datasets for coronene that met selection criteria and included benzo[a]pyrene (Figure 6-19). A dermal complete carcinogenicity bioassay in mice did not result in a statistically significant increase in tumor incidence (Habs et al., 1980); the RPF detection limit was 0.06. To confirm the nonpositive findings in the one tumor bioassay that included benzo[a]pyrene, other bioassays and cancer-related endpoint data were considered. There was one bioassay of coronene that did not include benzo[a]pyrene. Van Duuren et al. (1968) conducted a dermal initiation bioassay of coronene using groups of 20 mice (0.5 mg coronene in 0.5 mL benzene, followed by croton resin treatment until death). Although the authors characterized coronene as a weak tumor initiator, the incidence of tumors was not significantly increased over concurrent controls. The limited cancer-related endpoint data were mixed, with three positive bacterial mutagenicity studies (with RPFs ranging from 0.01 to 0.5), one nonpositive bacterial mutagenicity study, and a nonpositive in vitro DNA damage study.

Overall, the database for coronene is both limited and inconsistent. Because the database for coronene does not provide adequate information with which to assess carcinogenicity, this PAH was not selected for inclusion in the RPF approach.

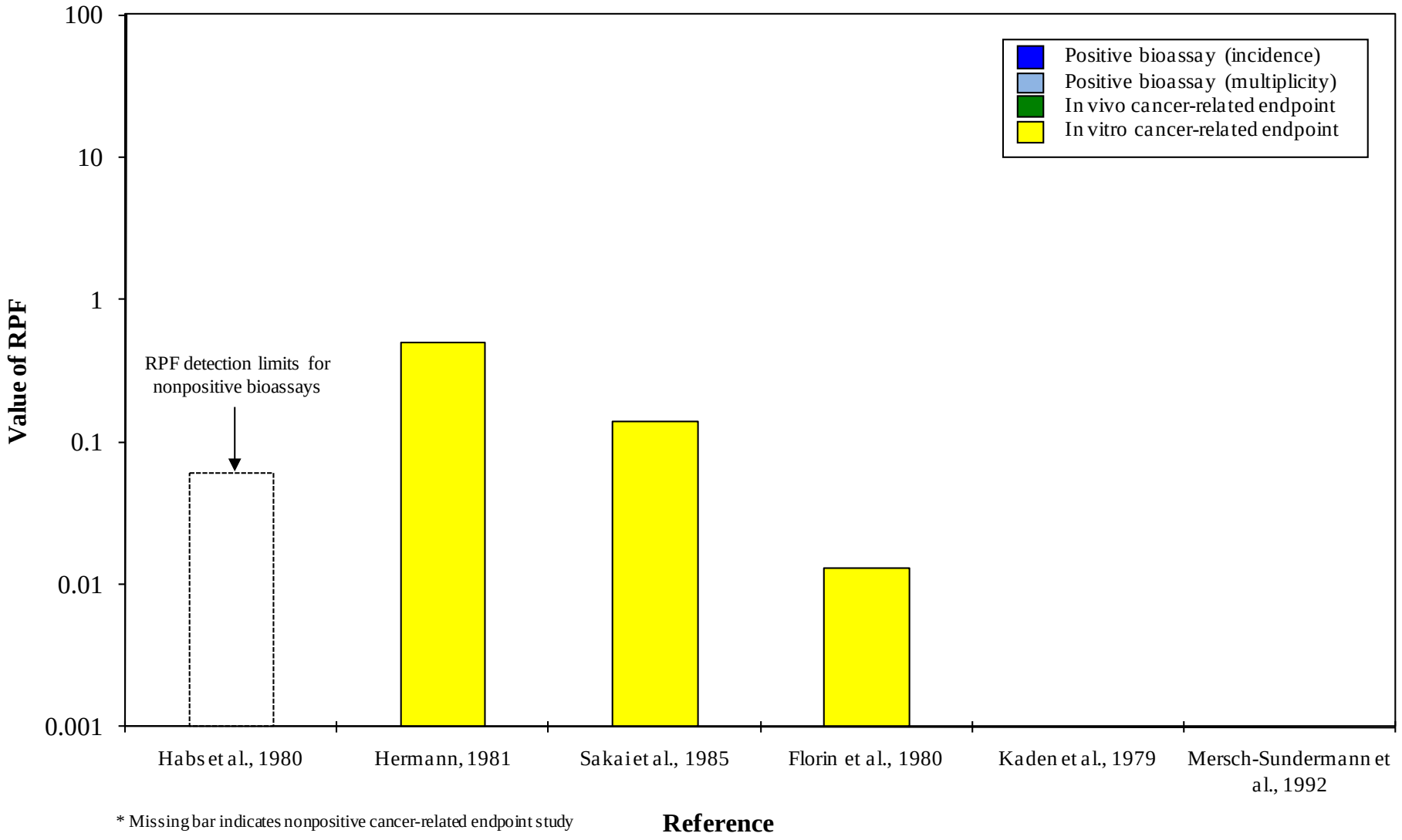
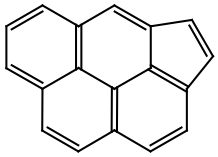


Figure 6-19. Coronene (CO) RPFs*.

Cyclopenta[c,d]pyrene (CPcdP)



Cyclopenta[c,d]pyrene (CASRN 27208-37-3) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. Cyclopenta[c,d]pyrene does not contain a classic bay or fjord region in its structure.

There were 25 datasets for cyclopenta[c,d]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-20). The database includes 11 in vivo tumor bioassay datasets, 2 in vivo DNA adduct datasets, 11 studies of mutagenicity or morphological/malignant cell transformation, and a single study of in vitro clastogenicity. Nine of the 11 tumor bioassay datasets and all of the cancer-related endpoint studies gave positive results. Statistically significant increases in tumor incidence and/or multiplicity were reported in two dermal complete carcinogenicity bioassay (Cavalieri et al., 1983, 1981b), two dermal initiation bioassays (Raveh et al., 1982; Cavalieri et al., 1981b), and an intraperitoneal study using adult A/J mice (Nesnow et al., 1998b). Bioassays in which no significant increase in tumorigenicity was observed included a dermal initiation (Wood et al., 1980) and complete carcinogenicity study (Habs et al., 1980); these studies had RPF detection limits of 0.1 and 0.03, respectively. After obtaining nonpositive results for low initiating doses of cyclopenta[c,d]pyrene, Wood et al. (1980) repeated their experiment with higher doses and observed statistically significant increases in tumor incidence. In the latter experiment, benzo[a]pyrene was not included, so an RPF could not be calculated from these data. The study design of the nonpositive complete carcinogenicity bioassay was quite similar to that of the two positive studies of this type, with the exception of the mouse strain used; Habs et al. (1980) used NMRI mice, while Cavalieri et al. (1983, 1981b) used Swiss mice. Although the differing results in dermal complete carcinogenicity studies may be explained by slight differences in strain susceptibility, these two strains are of common origin, which argues against this explanation.

The available cancer-related endpoint data indicate that cyclopenta[c,d]pyrene is mutagenic and capable of morphological/malignant cell transformation in vitro; a single study of in vitro clastogenicity was also positive. Overall, the data supporting a finding of carcinogenicity for cyclopenta[c,d]pyrene are very consistent, and this compound was selected for inclusion in the RPF approach.

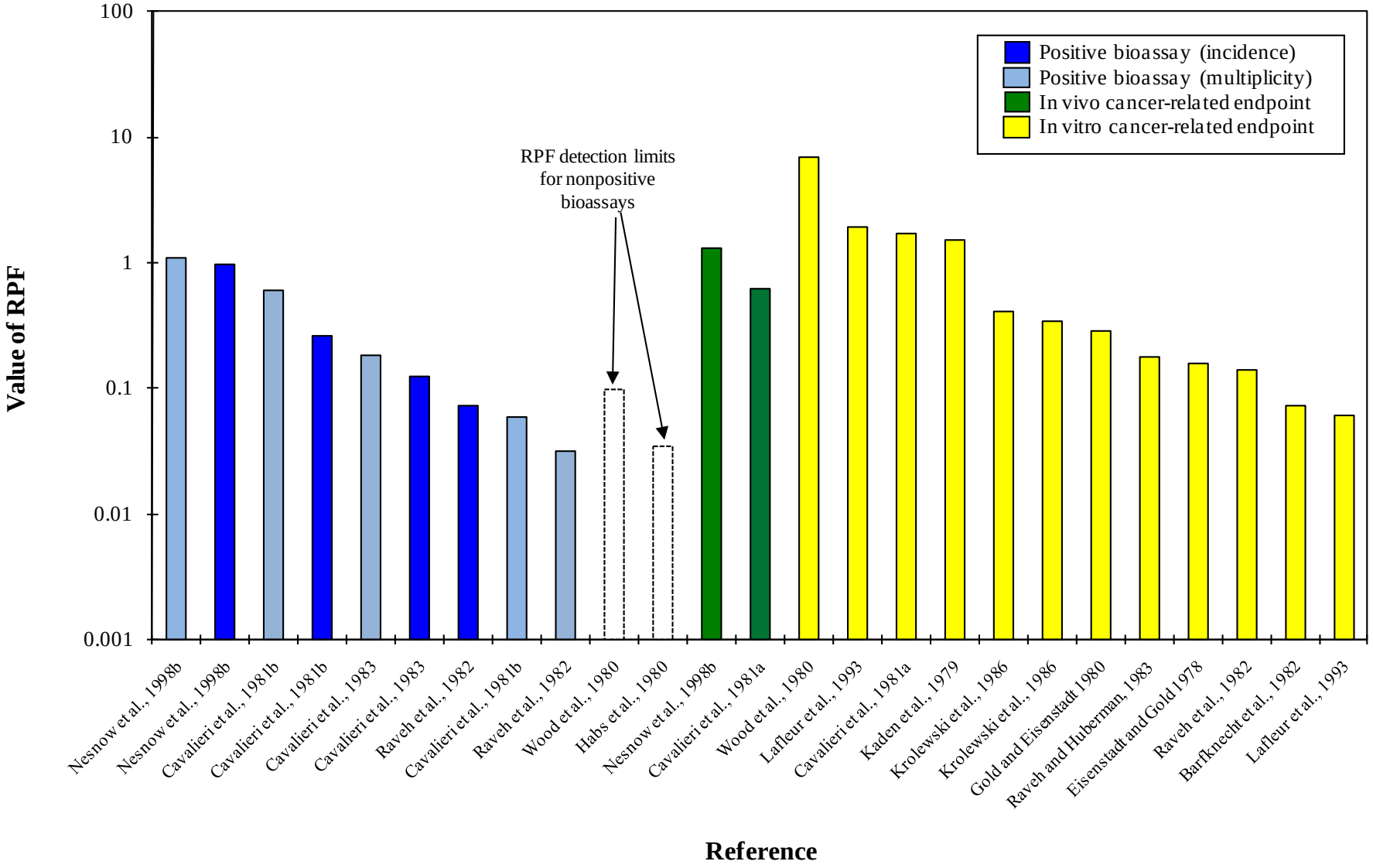
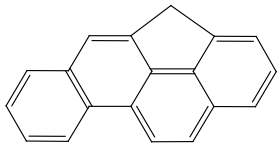


Figure 6-20. Cyclopenta[c,d]pyrene (CPcdP) RPFs.

4H-Cyclopenta[d,e,f]chrysene (CPdefC)



4H-Cyclopenta[d,e,f]chrysene (CASRN 202-98-2) is a nonalternant PAH comprised of four aromatic rings and one five-membered ring. 4H-Cyclopenta[d,e,f]chrysene contains a classic bay region but no fjord region in its structure.

There were two datasets for 4H-cyclopenta[d,e,f]chrysene that met selection criteria and included benzo[a]pyrene (Figure 6-21); both were multidose dermal initiation datasets (Rice et al., 1988, 1985). Rice et al. (1988) reported a statistically significant increase in tumor incidence in a multidose dermal initiation study. In the second study, the incidence of tumors after treatment with cyclopenta[d,e,f]chrysene exceeded 90%, precluding RPF derivation from incidence data, but tumor multiplicity data were available for RPF calculation (Rice et al., 1985). Cyclopenta[d,e,f]chrysene has not been tested in a bioassay without benzo[a]pyrene; however, sterically hindered diol epoxides of this compound have given positive results in a newborn mouse assay (Amin et al., 1995). Because the bioassay of cyclopenta[d,e,f]chrysene was positive, this PAH was considered carcinogenic and was selected for inclusion in the RPF approach.

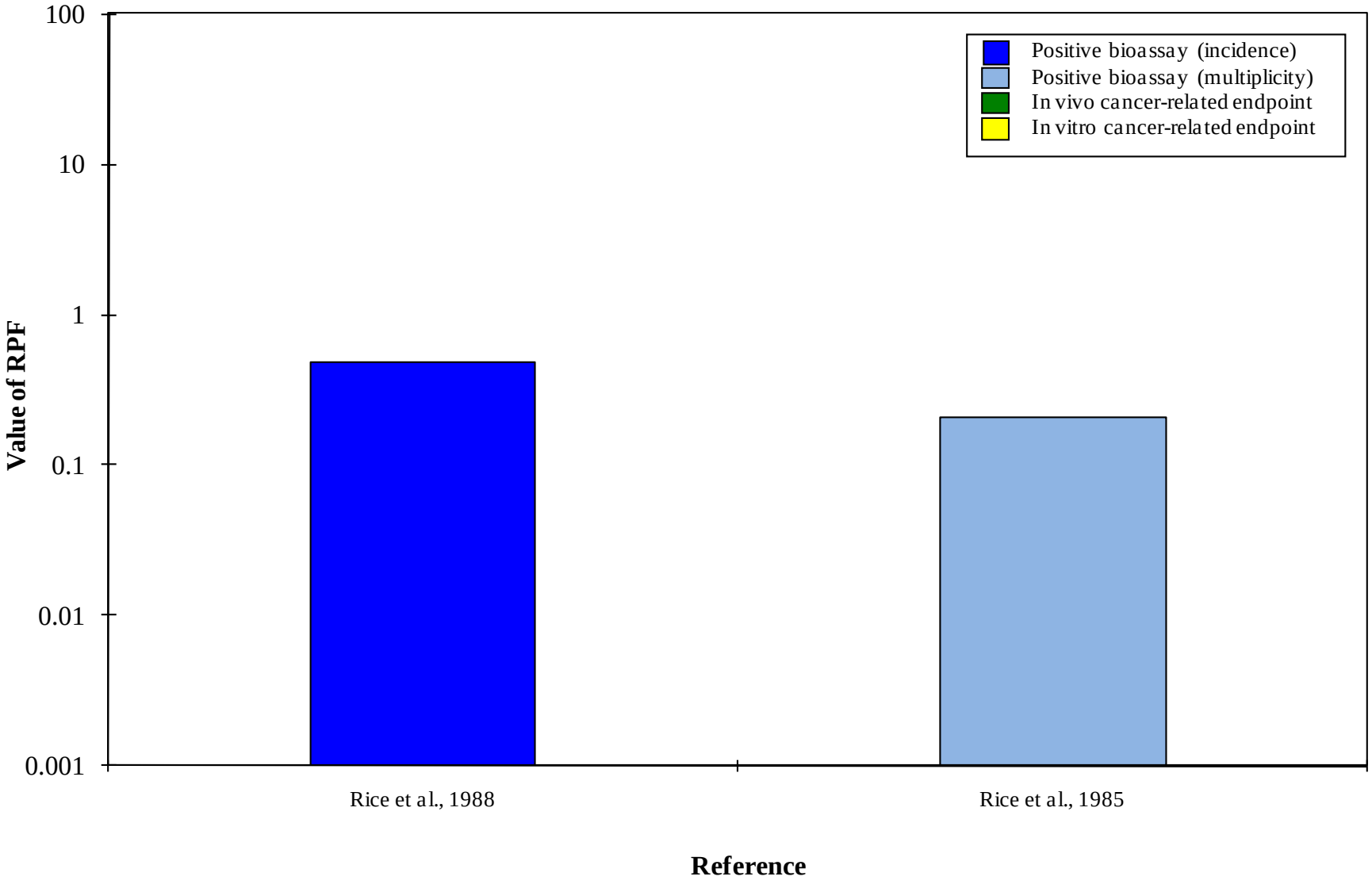
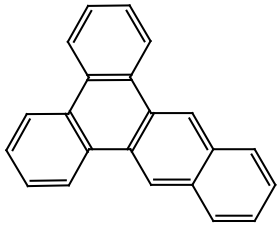


Figure 6-21. Cyclopenta[d,e,f]chrysene (CPdefC) RPFs.

Dibenz[a,c]anthracene (DBacA)



Dibenz[a,c]anthracene (CASRN 215-58-7) is an alternant PAH comprised of five fused aromatic rings. Dibenz[a,c]anthracene contains three bay regions but no fjord region in its structure.

There were 15 datasets for dibenz[a,c]anthracene that met selection criteria and included benzo[a]pyrene (Figure 6-22). The database includes a single in vivo study of DNA adducts, nine mutagenicity or morphological/malignant cell transformation studies, and five studies of in vitro DNA damage or adducts. One morphological/malignant cell transformation assay gave nonpositive results, while the remaining studies were positive. In the absence of positive bioassays with benzo[a]pyrene, other bioassays and cancer-related data were considered to evaluate the carcinogenicity of dibenz[a,c]anthracene.

Conflicting results were reported in three dermal initiation bioassays of dibenz[a,c]anthracene in which benzo[a]pyrene was not included. Van Duuren et al. (1970) observed a tumor incidence of 95% (19/20, compared to 1/20 controls) when mice were treated with an initiating dose of 1 mg dibenz[a,c]anthracene in benzene followed by thrice weekly treatment with phorbol myristate acetate. In contrast, there was no significant increase in tumor formation when the same initiating dose was followed by thrice weekly application of croton resin (Van Duuren et al., 1968); however, the latency to first tumor was substantially reduced (65 versus 150 days in controls). Latency was also substantially reduced in the study by Van Duuren et al. (1970), in which the first tumor appeared after 74 days, compared with 338 days in controls.

Cancer-related endpoint data for dibenz[a,c]anthracene are predominantly positive (8/9 mutagenicity or morphological/malignant cell transformation studies and 5/5 studies of in vitro DNA adducts or DNA damage). Although the conflicting bioassay data are not easily explained, the high incidence of tumors (19/20) in the study by Van Duuren et al. (1970) and the reduced latency to tumor formation in both studies, coupled with predominantly positive cancer-related endpoint data, suggest that dibenz[a,c]anthracene is carcinogenic. Contributing to this conclusion is the observation that dibenz[a,c]anthracene is an alternant PAH with known structural alerts for carcinogenicity (more than three rings, and three bay regions). Thus, dibenz[a,c]anthracene was selected for inclusion in the RPF approach.

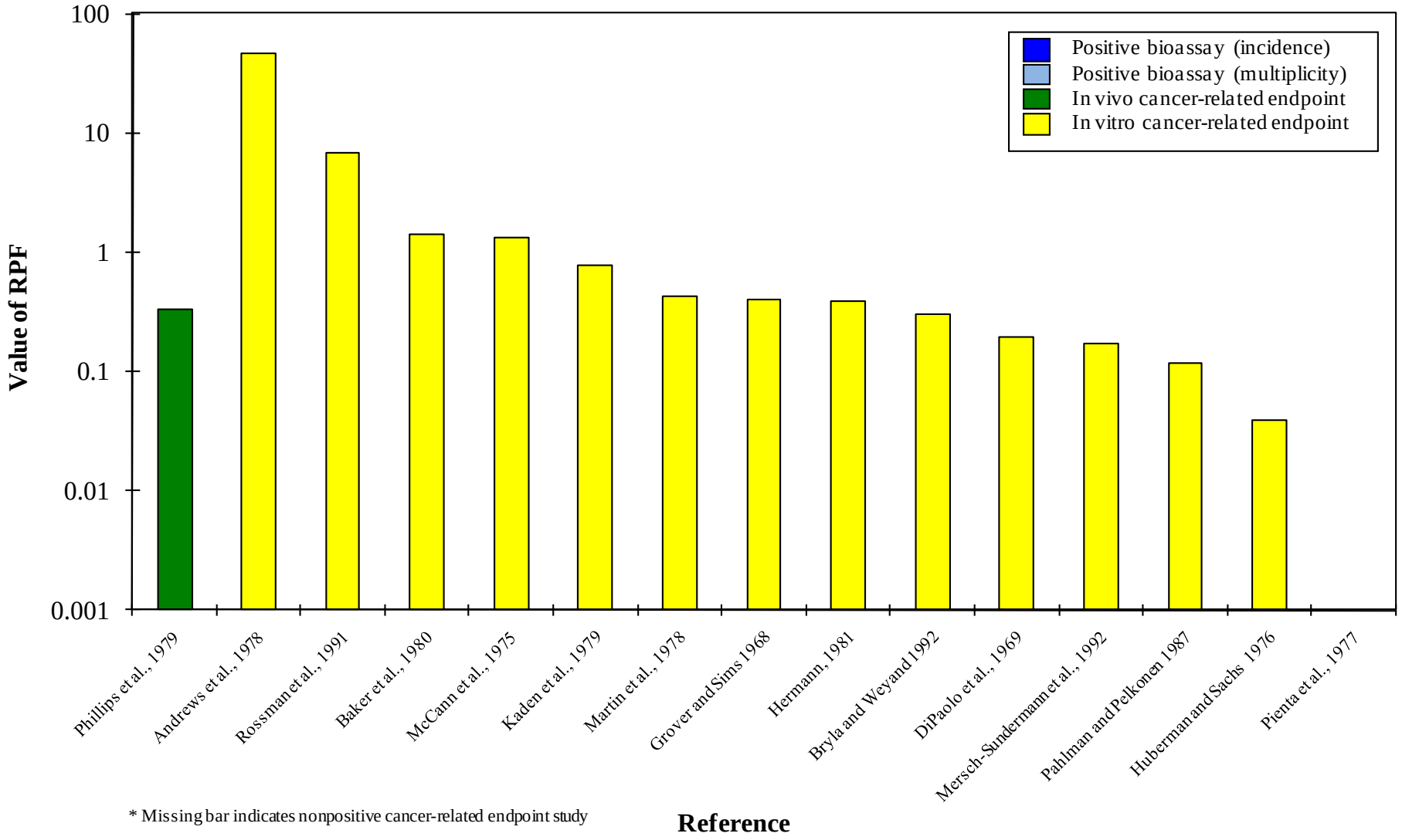
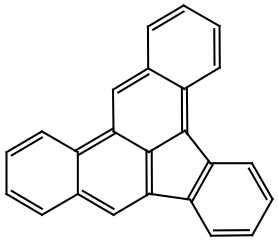


Figure 6-22. Dibenz[a,c]anthracene (DBacA) RPFs*.

Dibenzo[a,e]fluoranthene (DBaeF)



Dibenzo[a,e]fluoranthene (CASRN 5385-75-1) is a nonalternant PAH comprised of five aromatic rings and one five-membered ring. Dibenzo[a,e]fluoranthene contains a classic bay region but no fjord region in its structure.

There were three datasets for dibenzo[a,e]fluoranthene that met selection criteria and included benzo[a]pyrene (Figure 6-23); all gave positive results. The database includes two in vivo tumor bioassays and one mammalian mutagenicity study. Statistically significant increases in tumor incidence were reported in dermal initiation and complete carcinogenicity bioassays in mice (both reported by Hoffmann and Wynder, 1966). As the available bioassays for dibenzo[a,e]fluoranthene were positive, this compound was considered carcinogenic and was selected for inclusion in the RPF approach.

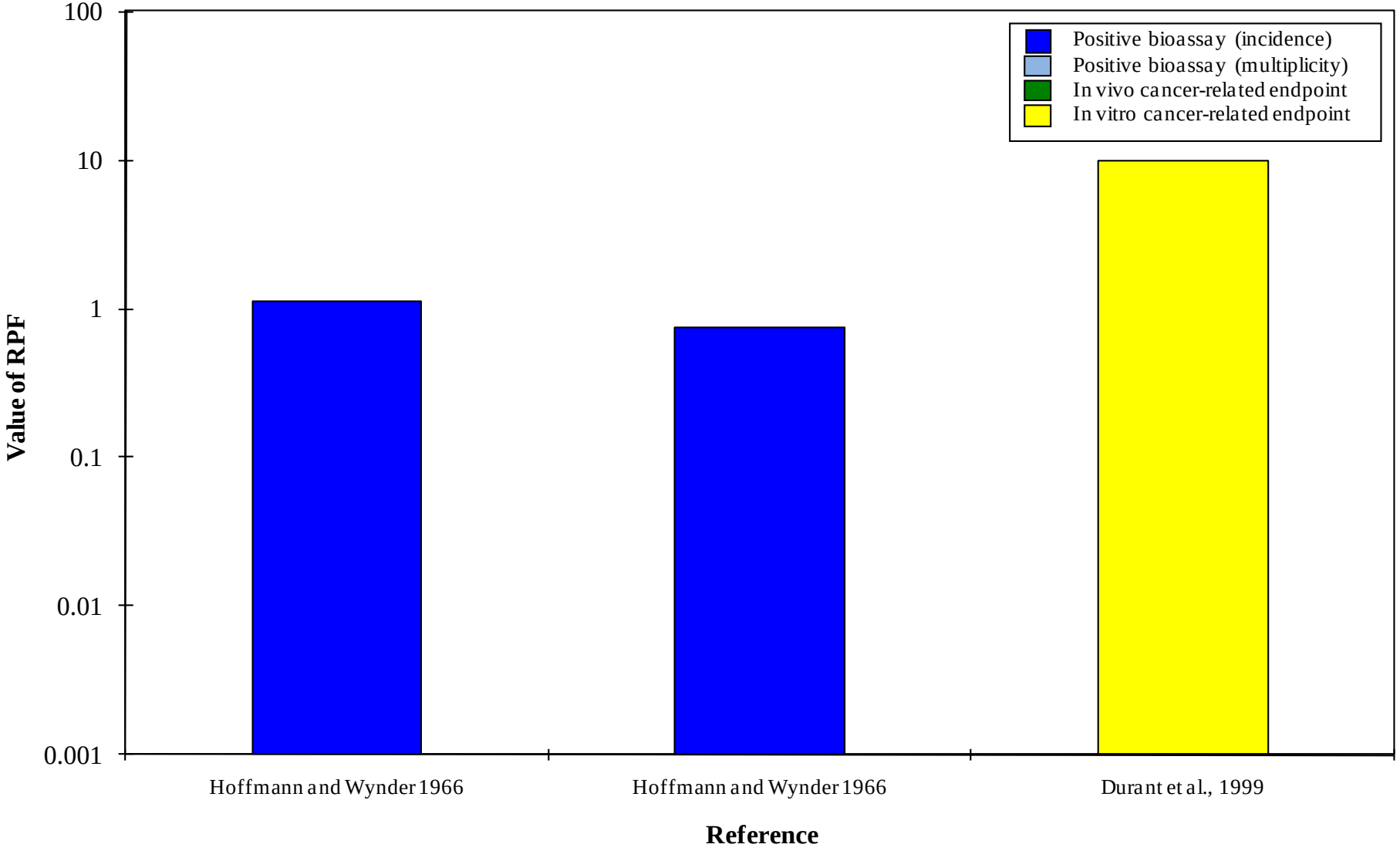
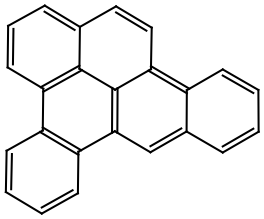


Figure 6-23. Dibenzo[a,e]fluoranthene (DBaeF) RPFs.

Dibenzo[a,e]pyrene (DBaeP)



Dibenzo[a,e]pyrene (CASRN 192-65-4) is an alternant PAH comprised of six fused aromatic rings. Dibenzo[a,e]pyrene contains three bay regions but no fjord region in its structure.

There were three datasets for dibenzo[a,e]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-24). The database includes two in vivo tumor bioassay datasets and one in vitro bacterial mutagenicity dataset, all of which gave positive results. Statistically significant increases in tumor incidence were reported in dermal initiation and complete carcinogenicity bioassays in mice (Hoffmann and Wynder, 1966). The complete carcinogenicity bioassay was confounded by significant toxicity-related mortality unrelated to tumors (Hoffmann and Wynder, 1966). The one bacterial mutagenicity study reported positive results. Because the available bioassays with benzo[a]pyrene were both positive, dibenzo[a,e]pyrene was considered carcinogenic and was selected for inclusion in the RPF approach.

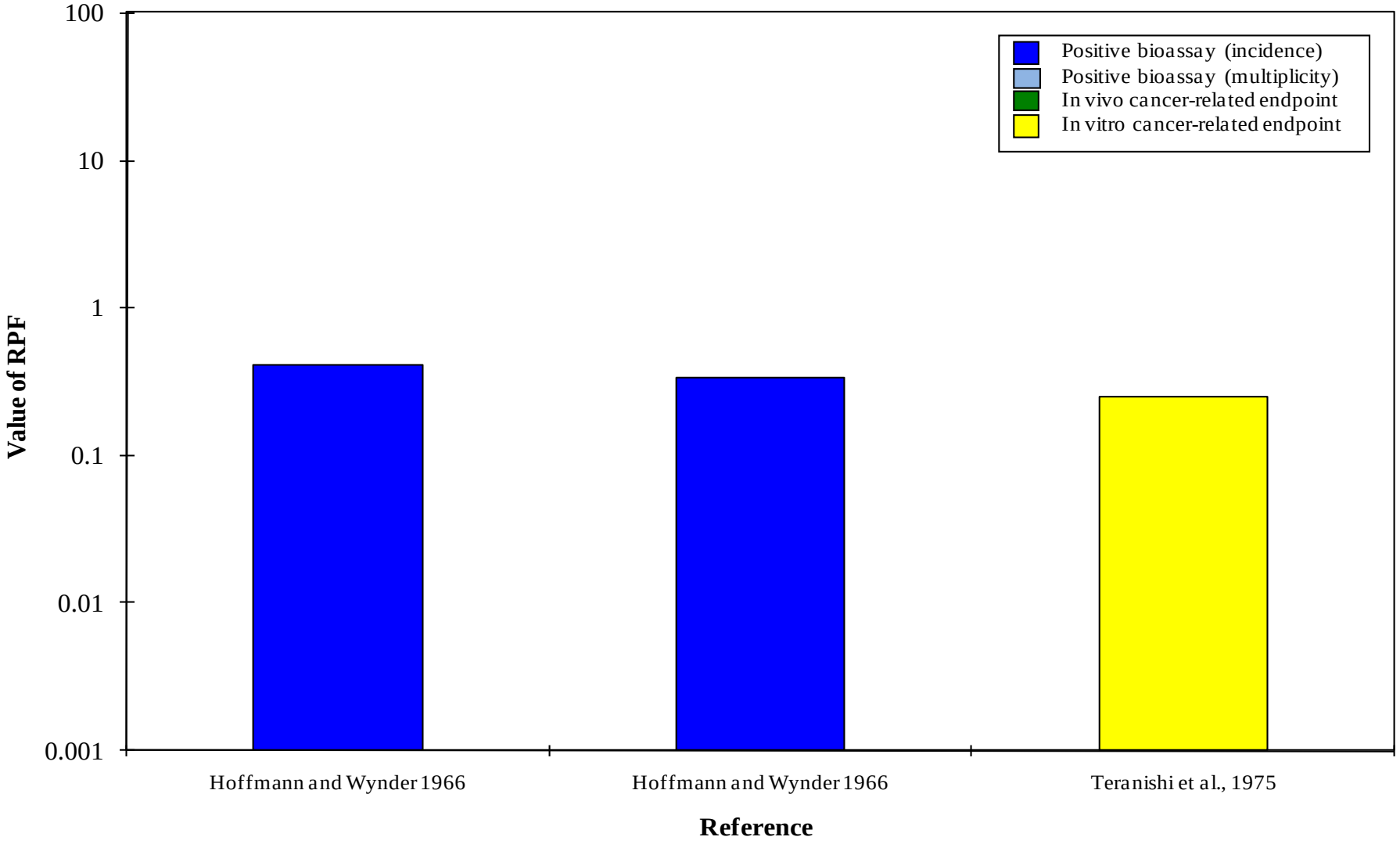
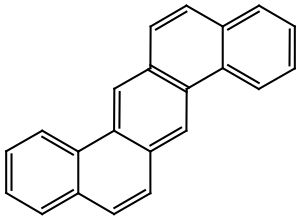


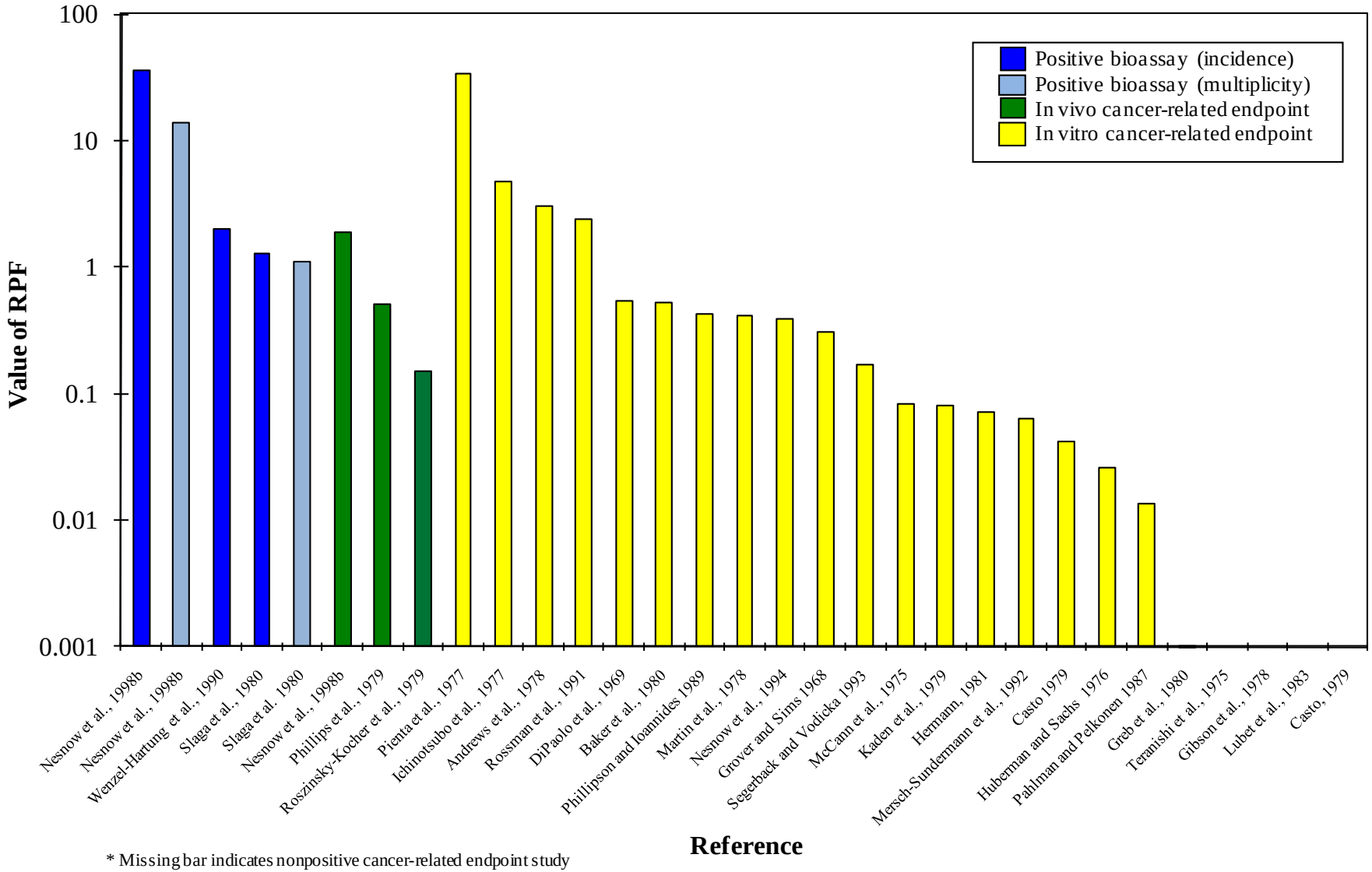
Figure 6-24. Dibenzo[a,e]pyrene (DBaeP) RPFs.

Dibenz[a,h]anthracene (DBahA)



Dibenz[a,h]anthracene (CASRN 53-70-3) is an alternant PAH comprised of five fused aromatic rings. Dibenz[a,h]anthracene contains two bay regions but no fjord region in its structure.

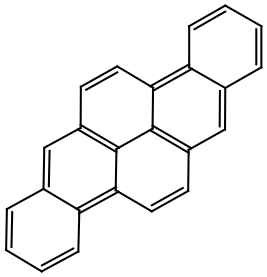
There were 31 datasets for dibenz[a,h]anthracene that met selection criteria and included benzo[a]pyrene (Figure 6-25). Included in the database are in vivo tumor bioassay datasets (5), in vivo DNA adduct datasets (2), an in vivo clastogenicity dataset, mutagenicity datasets (10), morphological/malignant cell transformation datasets (6), and in vitro DNA damage, adducts, or clastogenicity datasets (7). There were three tumor bioassays for dibenz[a,h]anthracene that included benzo[a]pyrene, and all resulted in statistically significant increases in tumor incidence and/or multiplicity. The bioassays were in three different test systems: a rat lung implantation study (Wenzel-Hartung et al., 1990), a mouse dermal initiation study reporting both incidence and multiplicity (Slaga et al., 1980), and an intraperitoneal study in A/J mice (Nesnow et al., 1998b). Dibenz[a,h]anthracene was shown to form DNA adducts when administered in vivo to mice via intraperitoneal injection (Nesnow et al., 1998b) and dermal application (Phillips et al., 1979). Mutagenicity and morphological/malignant cell transformation assays of dibenz[a,h]anthracene were predominantly positive (13/16), as were studies of other cancer-related endpoints. Because the available bioassays with benzo[a]pyrene were positive, dibenz[a,h]anthracene was considered carcinogenic and was selected for inclusion in the RPF approach.



* Missing bar indicates nonpositive cancer-related endpoint study

Figure 6-25. Dibenz[a,h]anthracene (DBahA) RPFs*.

Dibenzo[a,h]pyrene (DBahP)



Dibenzo[a,h]pyrene (CASRN 189-64-0) is an alternant PAH comprised of six fused aromatic rings. Dibenzo[a,h]pyrene contains two bay regions but no fjord region in its structure.

There were five datasets for dibenzo[a,h]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-26); all gave positive results. The database includes one in vivo bioassay dataset, one in vivo DNA adduct dataset, two in vitro mammalian mutagenicity datasets, and one in vitro DNA damage dataset. A statistically significant increase in tumor incidence was reported in a dermal initiation bioassay in mice (Hoffmann and Wynder, 1966). In addition, two dermal studies of complete carcinogenicity that included benzo[a]pyrene gave positive results, but no RPF could be calculated because the incidence of tumors in the mice exposed to dibenzo[a,h]pyrene was ≥90% at the lowest dose tested (Cavalieri et al., 1977; Hoffmann and Wynder, 1966) and tumor multiplicity was not reported. As all of the available bioassays that included benzo[a]pyrene showed exposure-related tumorigenic responses, dibenzo[a,h]pyrene was considered carcinogenic and was selected for inclusion in the RPF approach.

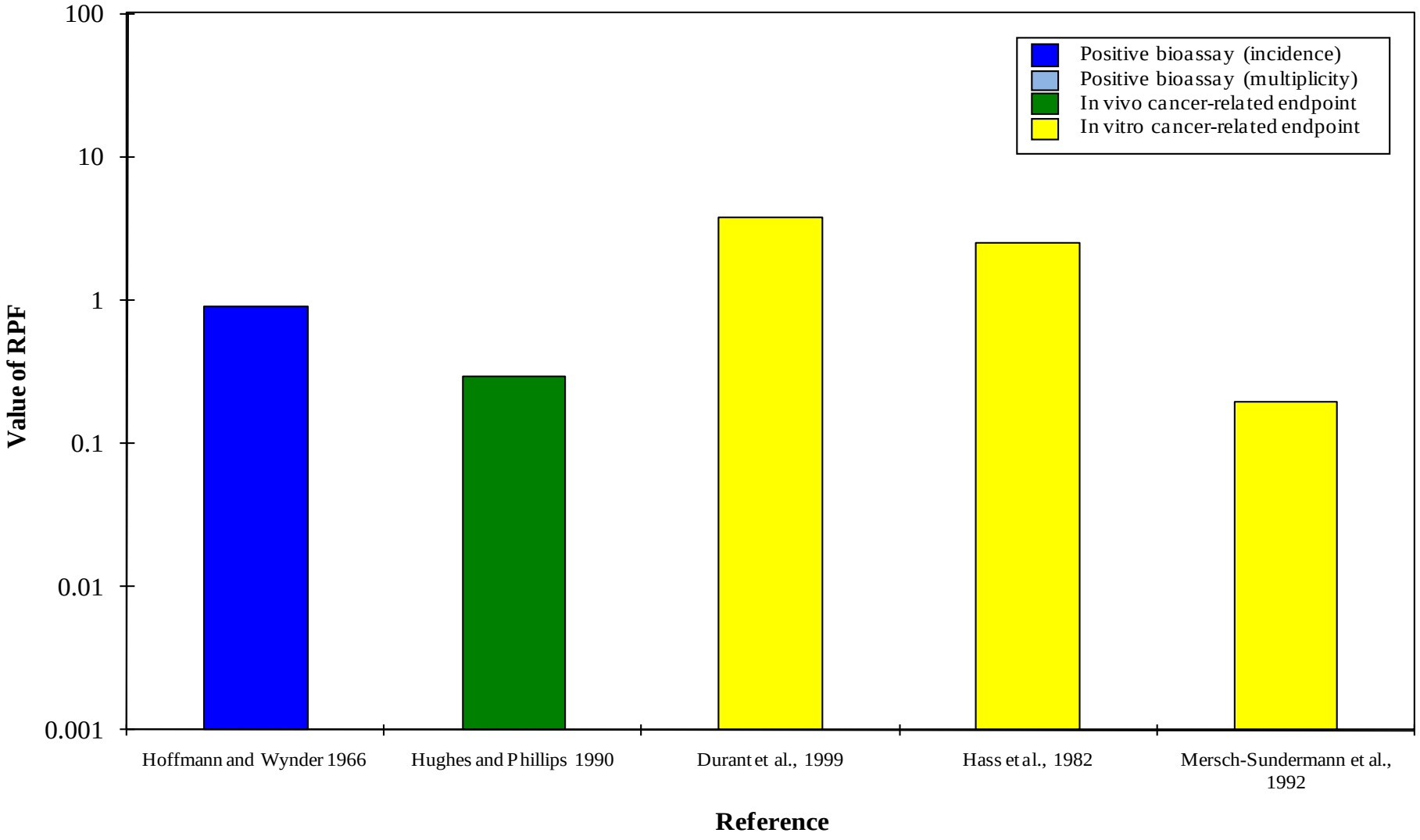
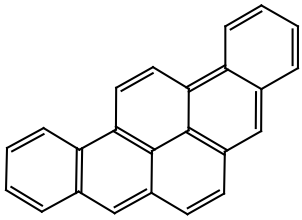


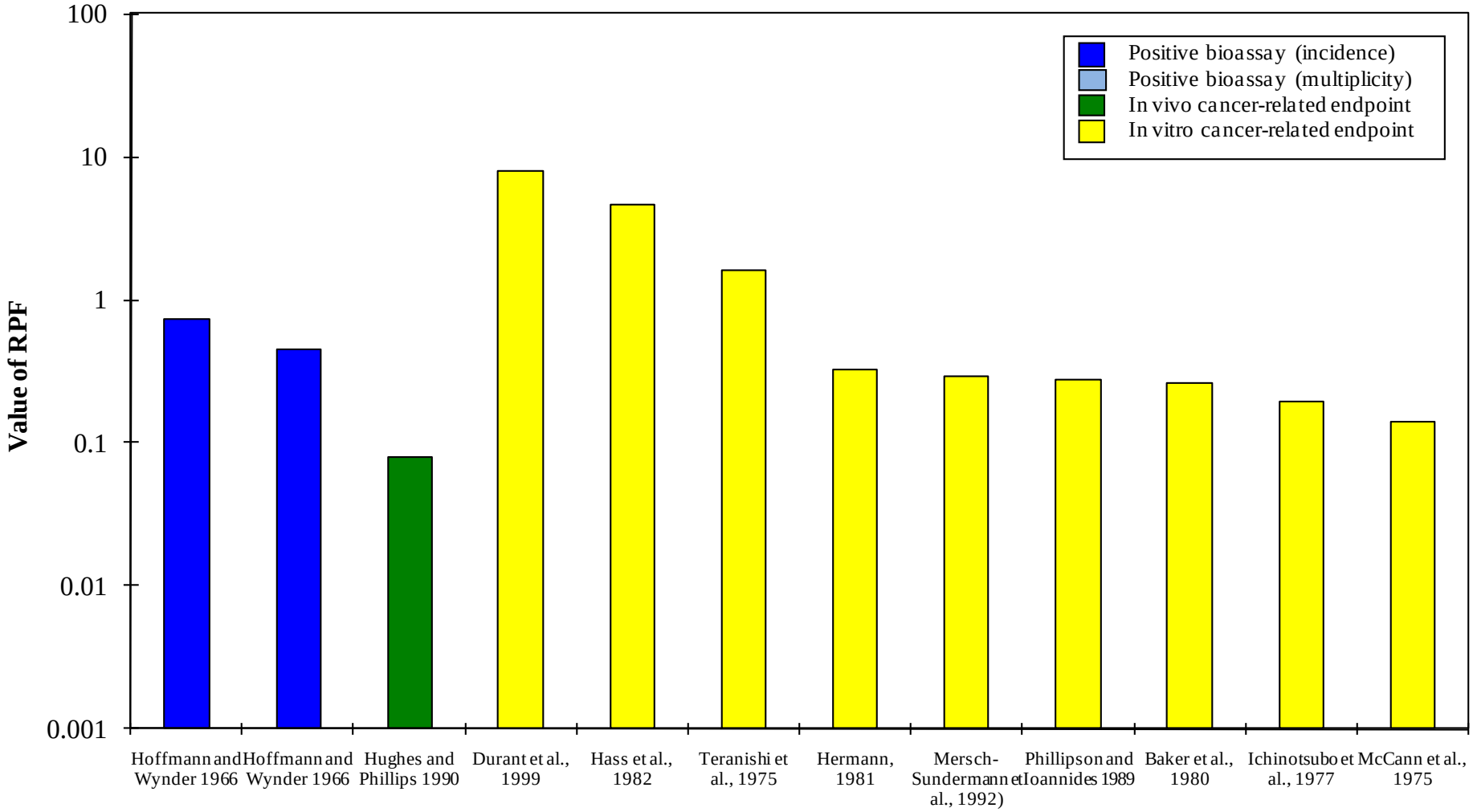
Figure 6-26. Dibenzo[a,h]pyrene (DBahP) RPFs.

Dibenzo[a,i]pyrene (DBaiP)



Dibenzo[a,i]pyrene (CASRN 189-55-9) is an alternant PAH comprised of six fused aromatic rings. Dibenzo[a,i]pyrene contains two bay regions but no fjord region in its structure.

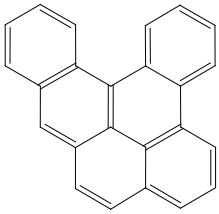
There were 12 datasets for dibenzo[a,i]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-27); all gave positive results. The database includes two in vivo bioassay datasets, one in vivo DNA adduct dataset, seven in vitro mutagenicity datasets, and two in vitro DNA damage datasets. Statistically significant increases in tumor incidence were reported in dermal initiation and complete carcinogenicity bioassays in mice, both published by Hoffmann and Wynder (1966). The cancer-related endpoint studies were all positive. As the available bioassays that included benzo[a]pyrene were both positive, dibenzo[a,i]pyrene was considered carcinogenic and was selected for inclusion in the RPF approach.



* Missing bar indicates nonpositive genotoxicity study

Figure 6-27. Dibenzo[a,i]pyrene (DbaiP) RPFs*.

Dibenzo[a,l]pyrene (DBalP).



Dibenzo[a,l]pyrene (CASRN 191-30-0) is an alternant PAH comprised of six fused aromatic rings. Dibenzo[a,l]pyrene contains both a bay region and a fjord region in its structure.

There were 16 datasets for dibenzo[a,l]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-28); all of the studies gave positive results. The database includes four in vivo tumor bioassay datasets, three in vivo DNA adduct datasets, one bacterial mutagenicity dataset, one morphological/malignant cell transformation dataset, four in vivo clastogenicity datasets, and three in vitro DNA adduct or DNA damage datasets.

In three bioassays of dibenzo[a,l]pyrene included benzo[a]pyrene, RPFs could not be calculated using incidence data, because the incidence of tumors associated with the lowest dose of dibenzo[a,l]pyrene exceeded 90% (two dermal initiation experiments in mice and an intramammilary injection study in rats, both reported by Cavalieri et al., 1991); however, tumor multiplicity data were reported for the dermal initiation experiments and were used to calculate RPFs of 10 and 40. Nesnow et al. (1998b) provided tumor multiplicity and incidence data[6] in A/J mice exposed intraperitoneally; both endpoints indicated an RPF of ~30. Because the available studies indicated that dibenzo[a,l]pyrene may be much more potent benzo[a]pyrene, other studies were also examined to confirm the potency of this compound.

Dibenzo[a,l]pyrene treatment resulted in significant increases in tumor incidence in seven bioassays that did not include benzo[a]pyrene, including two dermal initiation studies (Gill et al., 1994; Cavalieri et al., 1989), a dermal complete carcinogenicity study (Nakatsuru et al., 2004), an intramammilary injection study in rats (Cavalieri et al., 1989), a newborn mouse bioassay (Platt et al., 2004), an intraperitoneal bioassay using A/J mice (Prahalad et al., 1997), and a gavage bioassay comparing the responses of cyp1B1 wild-type and null mice (Buters et al., 2002). In several of these studies, there was significant toxicity associated with dibenzo[a,l]-pyrene treatment. Tumor incidences were very high in most of the studies, including the gavage study (Buters et al., 2002), which reported an overall tumor incidence of 100% in cyp1B1 wild-type mice treated with a single dose of dibenzo[a,l]pyrene. A recent study examining in utero and/or lactational exposure to dibenzo[a,l]pyrene showed that mouse pups exposed during late gestation develop T-cell lymphomas between 3 and 6 months of age, as well multiple lung and liver tumors (Castro et al., 2008). All of the cancer-related data for dibenzo[a,l]pyrene were positive and resulted in high RPF estimates, including in vivo and in vitro studies of DNA

[6]Data were obtained courtesy of S. Nesnow.

adducts, in vivo clastogenicity studies, morphological/malignant cell transformation studies, bacterial mutagenicity studies, and in vitro DNA damage or DNA adduct studies.

The weight of evidence supporting a finding of carcinogenicity for dibenzo[a,l]pyrene is strong and suggests that this compound is very potent; thus, it was selected for inclusion in the RPF approach.

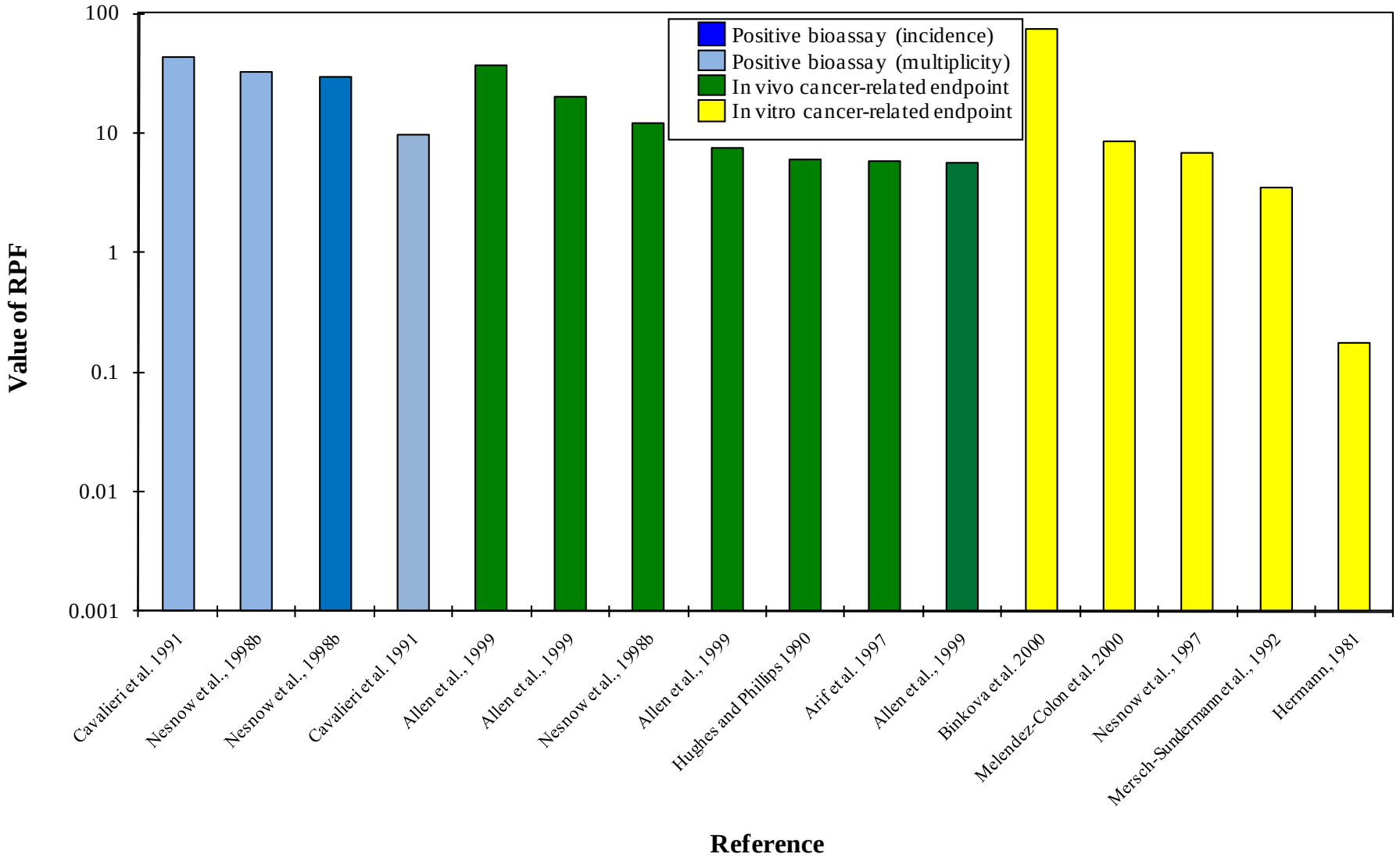
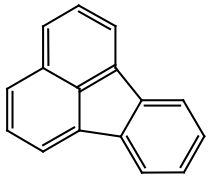


Figure 6-28. Dibenzo[a,l]pyrene (DBalP) RPFs.

Fluoranthene (FA)



Fluoranthene (CASRN 206-44-0) is a nonalternant PAH comprised of three aromatic rings and one five-membered ring. Fluoranthene does not contain a classic bay or fjord region in its structure.

There were 21 datasets for fluoranthene that met selection criteria and included benzo[a]pyrene (Figure 6-29). Included in the database are in vivo tumor bioassay datasets (11), bacterial and mammalian mutagenicity datasets (5), a morphological/malignant cell transformation assay, and in vitro studies of DNA damage, DNA adducts, or clastogenicity (4). Of the bioassay datasets that included benzo[a]pyrene, nine gave positive results and two gave nonpositive results. Statistically significant increases in tumor incidence and tumor multiplicity were reported in newborn mouse bioassays (in male and female mice [LaVoie et al., 1994] and in female mice [Busby et al., 1989]). The tumor incidence was not significantly increased by fluoranthene in a mouse dermal initiation study with an RPF detection limit of 0.01 (Hoffman et al., 1972) and when fluoranthene was tested alone in a dermal cocarcinogenicity bioassay with an RPF detection limit of 0.1 (Van Duuren and Goldschmidt, 1976). In another newborn mouse bioassay (Busby et al., 1984) that reported both incidence and multiplicity, the lowest dose of benzo[a]pyrene resulted in a tumor incidence of >90%, precluding RPF calculation from the incidence data; however, multiplicity data were available. Statistical analysis of the data for fluoranthene demonstrated positive findings for both incidence and multiplicity in male mice, but the results for the two endpoints were inconsistent in females. In female mice exposed at the high dose of fluoranthene in a newborn mouse bioassay reported by Busby et al. (1984), the lung tumor count was significantly increased (albeit borderline, $p = 0.0343$) while the incidence was not ($p > 0.05$), and neither was statistically significantly increased at the lower dose. For the purpose of this analysis, the multiplicity data were treated as an independent measure of carcinogenic potency, and an RPF was calculated for the statistically increased tumor count in female mice.

The mutagenicity studies of fluoranthene were all positive, but in vitro studies of DNA damage, DNA adducts, and clastogenicity gave inconsistent results. Because the inconsistent bioassay results can be attributed to different test systems (different exposure route and/or gender) or study design, fluoranthene was considered carcinogenic and was selected for inclusion in the RPF approach.

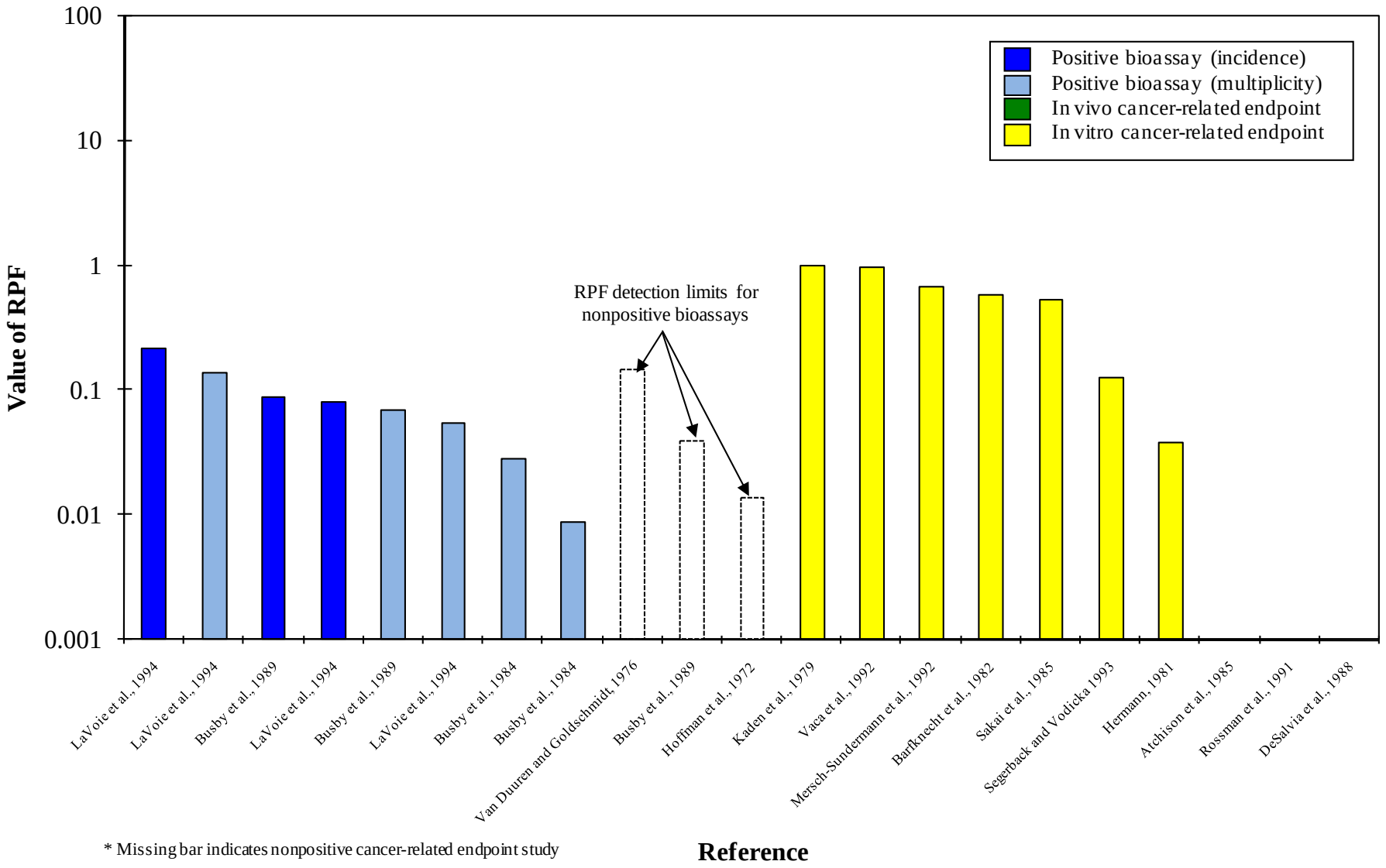
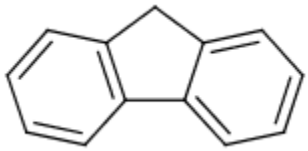


Figure 6-29. Fluoranthene (FA) RPFs*.

Fluorene (FE)



Fluorene (CASRN 86-73-7) is a nonalternant PAH comprised of two aromatic rings and one five-membered ring. Fluorene does not contain a classic bay or fjord region in its structure.

There were nine datasets for fluorene that met selection criteria and included benzo[a]pyrene (Figure 6-30). There were no tumor bioassays of fluorene that included benzo[a]pyrene, so other bioassays and cancer-related endpoint data were considered. LaVoie et al. (1980) conducted a study of skin tumor initiation in mice treated with 1 mg fluorene followed by 20 weeks of treatment with TPA; the study did not include benzo[a]pyrene. The incidence of tumor-bearing animals (5%) was not significantly increased over controls (0%) (LaVoie et al., 1980). The limited cancer-related endpoint data were mixed, with three positive and four nonpositive mutagenicity datasets, and two nonpositive in vitro DNA damage datasets. Overall, the database for fluorene is both limited and inconsistent. Because the database for fluorene does not provide adequate information with which to assess carcinogenicity, this PAH was not selected for inclusion in the RPF approach.

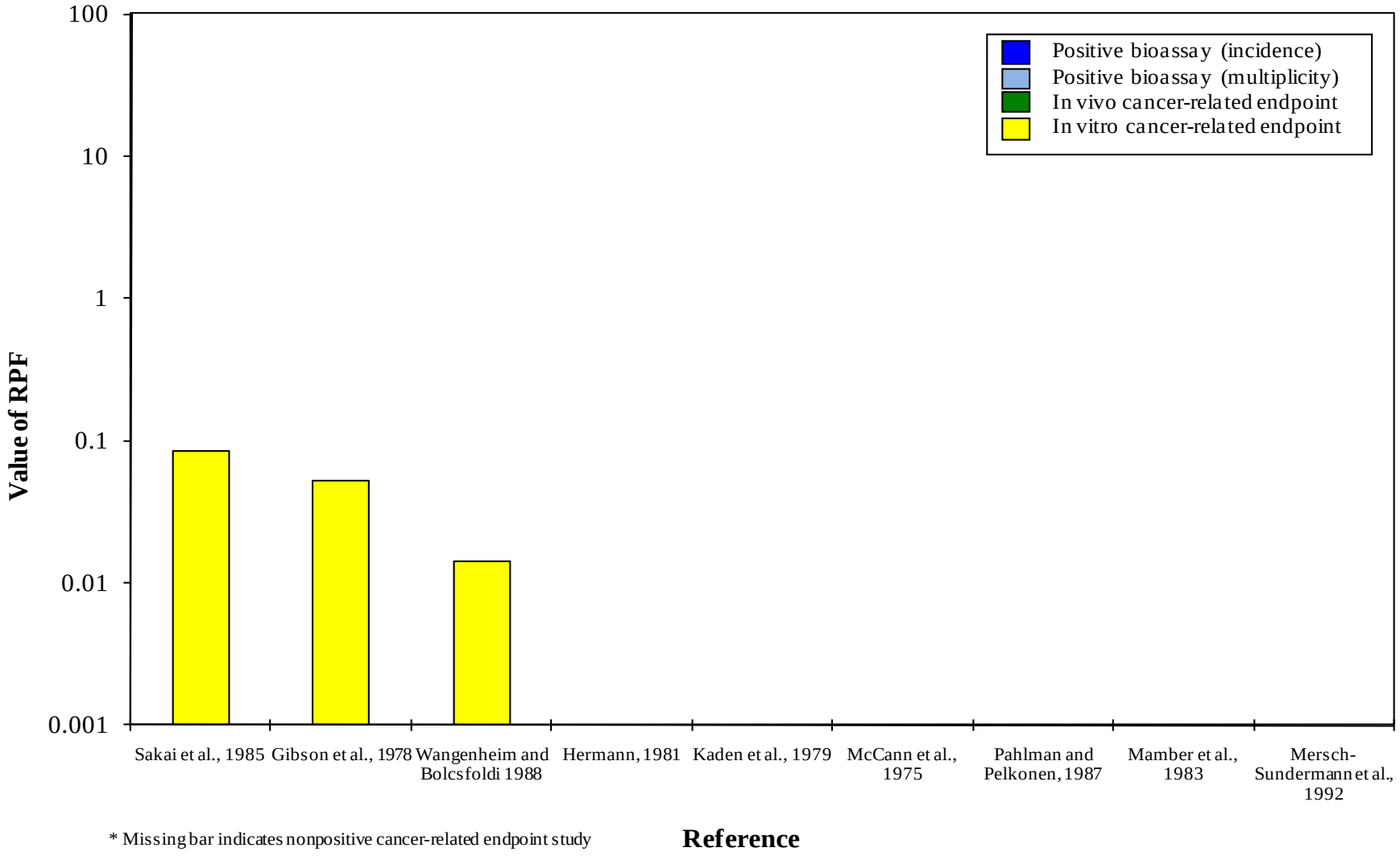
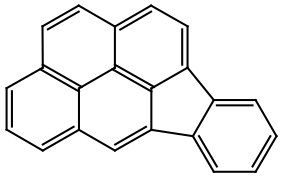


Figure 6-30. Fluorene (FE) RPFs*.

Indeno[1,2,3-c,d]pyrene (IP)



Indeno[1,2,3-c,d]pyrene (CASRN 193-39-5) is a nonalternant PAH comprised of five aromatic rings and one five-membered ring. Indeno[1,2,3-c,d]pyrene does not contain a classic bay or fjord region in its structure.

There were five datasets for indeno[1,2,3-c,d]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-31). There are three tumor bioassays, one in vitro study of morphological/malignant cell transformation (Emura et al., 1980), and one in vitro study of DNA damage (Mersch-Sundermann et al., 1992). Of the three tumor bioassays, only one, a rat lung implantation study (Deutsch-Wenzel et al., 1983), reported a statistically significant increase in tumor incidence or multiplicity; the RPF was 0.07. Nonpositive findings were reported in mouse dermal initiation (Hoffmann and Wyner, 1966) and complete carcinogenicity (Habs et al., 1980) studies with RPF detection limits in the range of 0.1–0.3. Because the inconsistent bioassay results can be attributed to different test systems (different species and route), and the nonpositive studies may not have been sufficiently sensitive to detect an effect, indeno-[1,2,3-c,d]pyrene was considered carcinogenic and was selected for inclusion in the RPF approach.

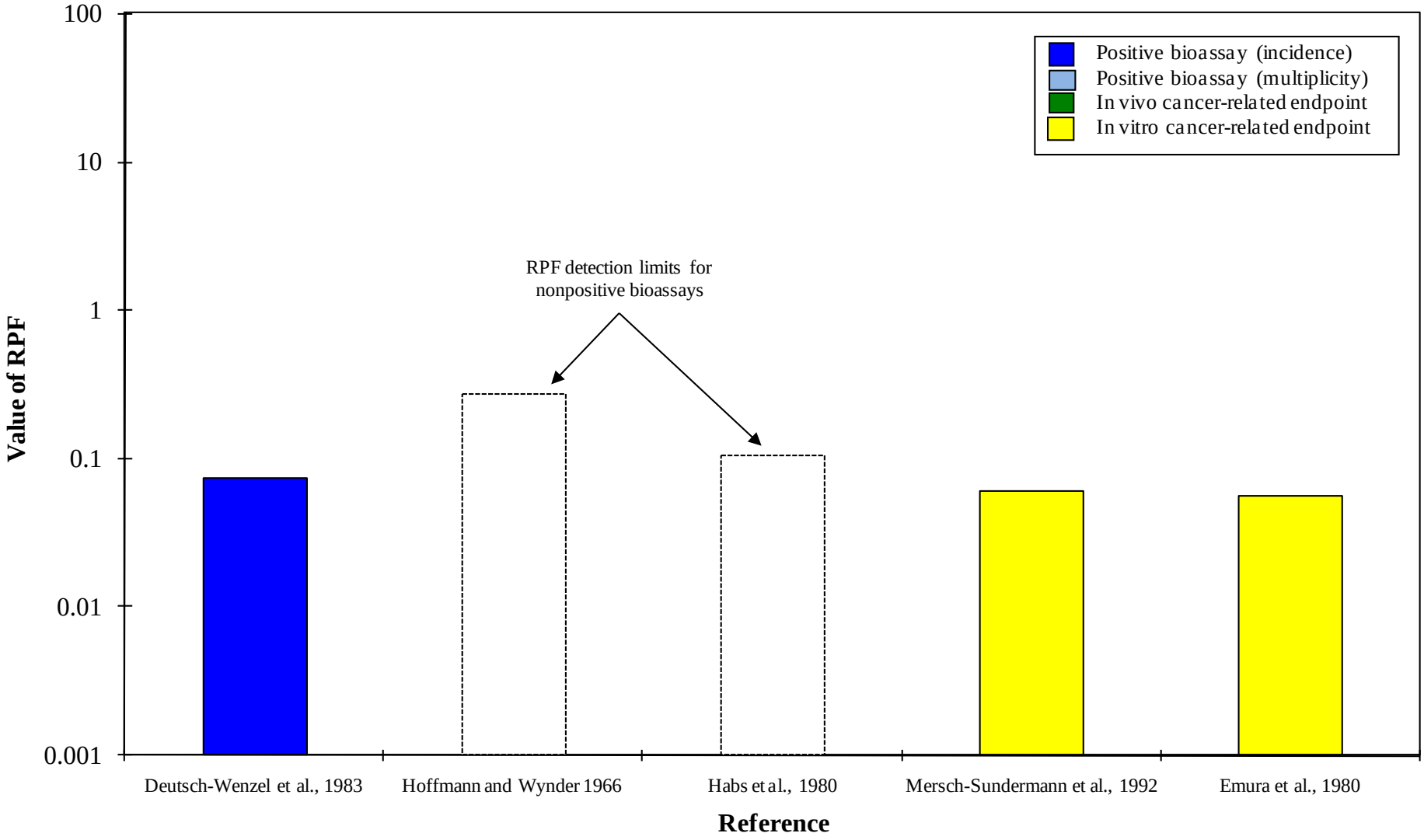
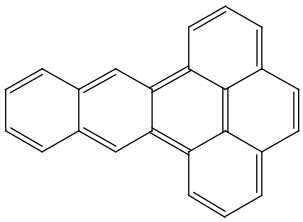


Figure 6-31. Indeno[1,2,3-c,d]pyrene (IP) RPFs.

Naphtho[2,3-e]pyrene (N23eP)



Naphtho[2,3-e]pyrene (CASRN 193-09-9) is an alternant PAH comprised of six fused aromatic rings. Naphtho[2,3-e]contains two bay regions but no fjord region in its structure.

There were two datasets for naphtho[2,3-e]pyrene that met selection criteria and included benzo[a]pyrene (Figure 6-32): a tumor bioassay dataset and an in vitro mammalian mutagenicity dataset (both were positive). The tumor bioassay was a single dose dermal initiation bioassay (Hoffmann and Wynder, 1966). As the available bioassay reported a statistically significant increase in tumor incidence, naphtho[2,3-e]pyrene was considered carcinogenic, and was selected for inclusion in the RPF approach.

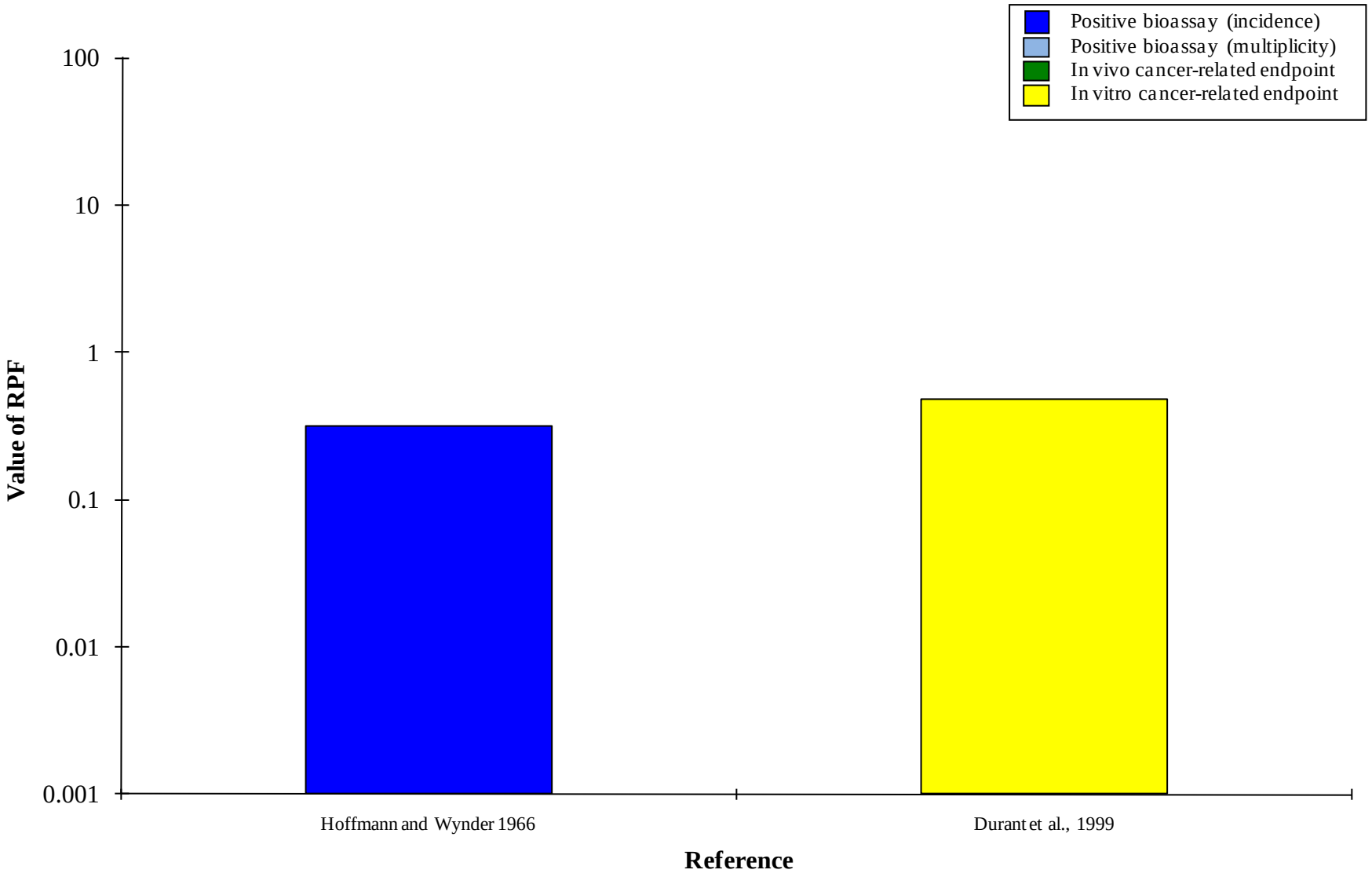
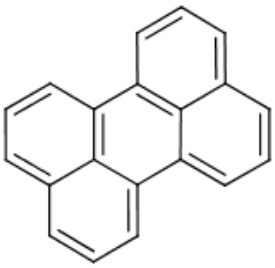


Figure 6-32. Naphtho[2,3-e]pyrene (N23eP) RPFs.

Perylene (Pery)



Perylene (CASRN 198-55-0) is an alternant PAH comprised of five fused aromatic rings. Perylene contains two bay regions but no fjord region in its structure.

There were 11 datasets for perylene that met selection criteria and included benzo[a]pyrene (Figure 6-33). The database includes an in vivo tumor bioassay dataset, an in vivo clastogenicity dataset, eight bacterial mutagenicity datasets, and an in vitro DNA damage dataset. The single tumor bioassay, a dermal initiation study, gave nonpositive results for perylene (El-Bayoumy et al., 1982); the RPF detection limit was 0.01. To confirm the nonpositive bioassay findings, other bioassays and cancer-related endpoint data were considered. In a study that did not include benzo[a]pyrene, Van Duuren et al. (1970) did not observe an increase in tumor incidence over controls when mice were treated by dermal application with an initiating dose of 0.8 mg perylene in benzene followed by thrice weekly treatment with phorbol myristate acetate for 58 weeks. However, seven of the eight bacterial mutagenicity studies gave positive results, while perylene tested nonpositive in one bacterial mutagenicity study, the clastogenicity study, and the DNA damage study. Overall, the database for perylene is both limited and inconsistent. Because the database for perylene does not provide adequate information with which to assess carcinogenicity, this PAH was not selected for inclusion in the RPF approach.

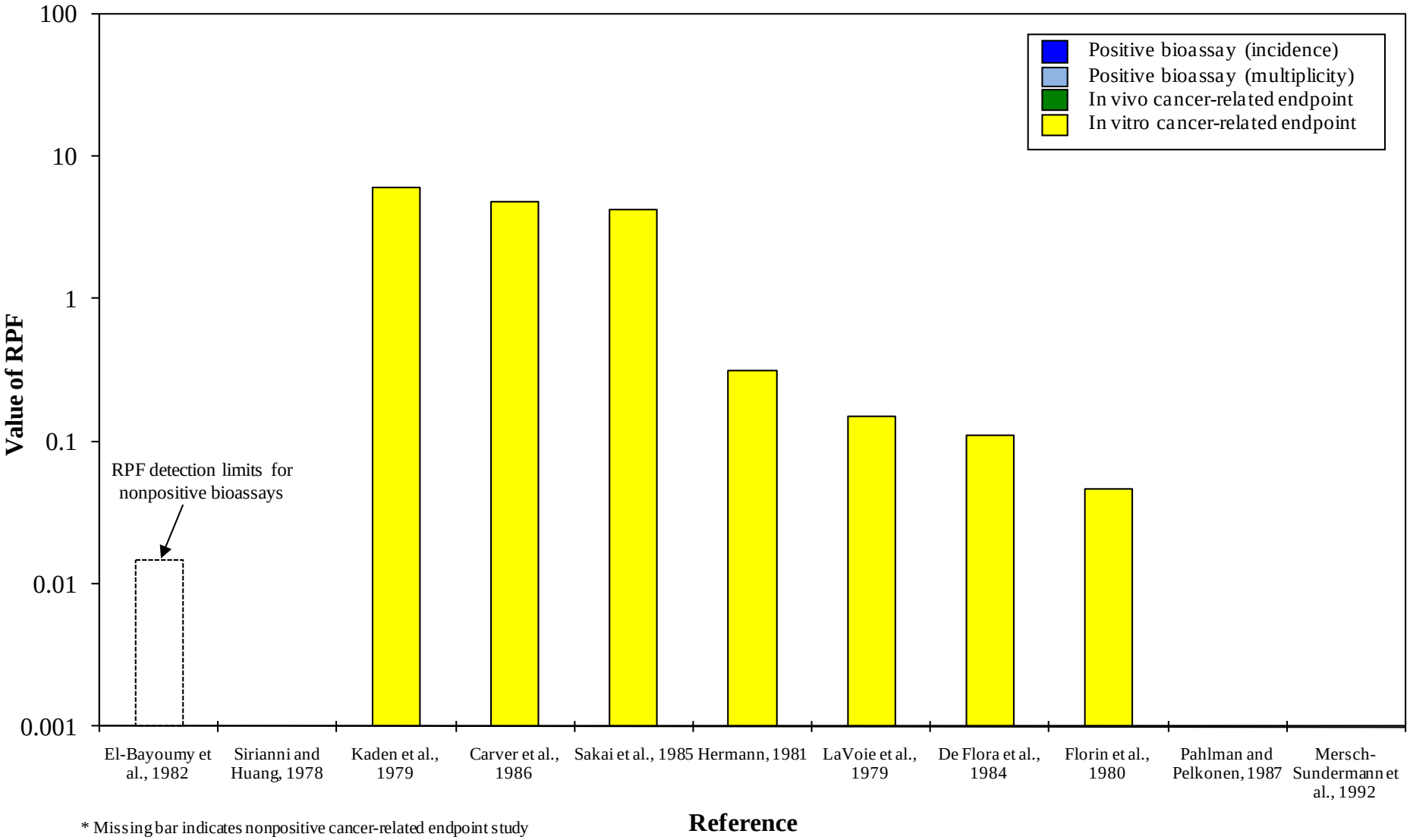
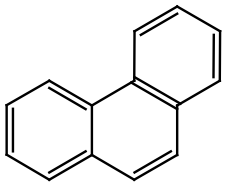


Figure 6-33. Perylene (Pery) RPFs*.

Phenanthrene (PH)



Phenanthrene (CASRN 85-01-8) is an alternant PAH comprised of three fused aromatic rings. Phenanthrene contains a bay region in its structure, but has less than four aromatic rings.

There were 34 datasets for phenanthrene that met selection criteria and included benzo[a]pyrene, including 3 in vivo tumor bioassay datasets, 2 in vivo clastogenicity datasets, 11 mutagenicity datasets, 6 morphological/malignant cell transformation datasets, and 12 in vitro studies of DNA adducts, DNA damage, or clastogenicity (Figure 6-34). Only 7 studies reported positive results; the remaining 27 studies reported nonpositive findings, including all 3 bioassays. Nonpositive findings were reported in the three bioassays that included benzo[a]pyrene, including a lung implantation study in rats (Wenzel-Hartung et al., 1990), a dermal initiation study in mice (LaVoie et al., 1981), and a subcutaneous study in mice (Grant and Roe, 1963). To confirm the nonpositive findings, other bioassays and cancer-related endpoint data were considered. In bioassays without benzo[a]pyrene, phenanthrene did not induce significant increases in tumors in a newborn mouse assay using a total dose of 1.4 µmol (Buening et al., 1979) or in two dermal initiation assays (Wood et al., 1979; Salaman and Roe, 1956) using doses of 10 µmol and 540 mg, respectively. However, 12/30 mice developed papillomas by week 35 after dermal treatment with 10 µmol phenanthrene (in benzene) followed by twice weekly treatment with TPA; no control mice had papillomas (Scribner, 1973). The response was statistically significantly increased over controls ($p < 0.01$).

In vitro assays of mutagenicity and morphological/malignant cell transformation were predominantly nonpositive for phenanthrene. One of the two positive studies (Sakai et al., 1988) reported a poor dose-response relationship for phenanthrene. Two studies found evidence of clastogenicity after in vivo administration of phenanthrene (Roszinsky-Kocher et al., 1979; Bayer, 1978). However, in the study by Bayer (1978), only the high dose gave a significant response, and there was not a significant dose-response trend. When phenathrene was tested in in vitro studies of DNA adducts, DNA damage, and clastogenicity, the results were predominantly nonpositive (9/12 studies). Overall, the database for phenanthrene is substantial, and the weight of evidence suggests that this PAH is not carcinogenic. Based on the large number of nonpositive bioassays and the abundant evidence that phenanthrene lacks genotoxic action, this compound was selected for inclusion in the RPF approach and assigned an RPF of zero.

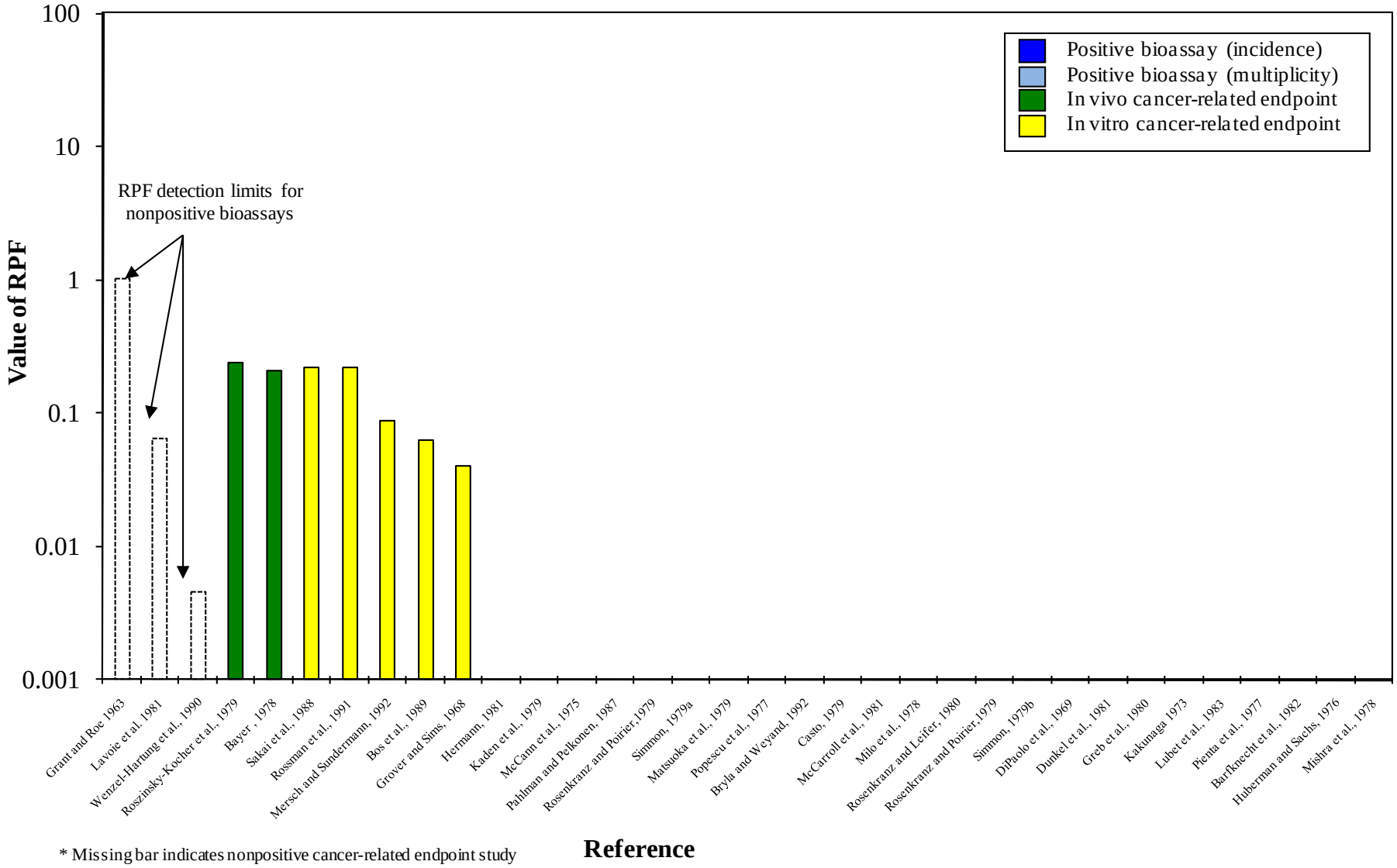
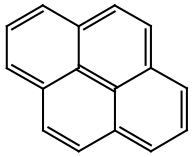


Figure 6-34. Phenanthrene (PH) RPFs*.

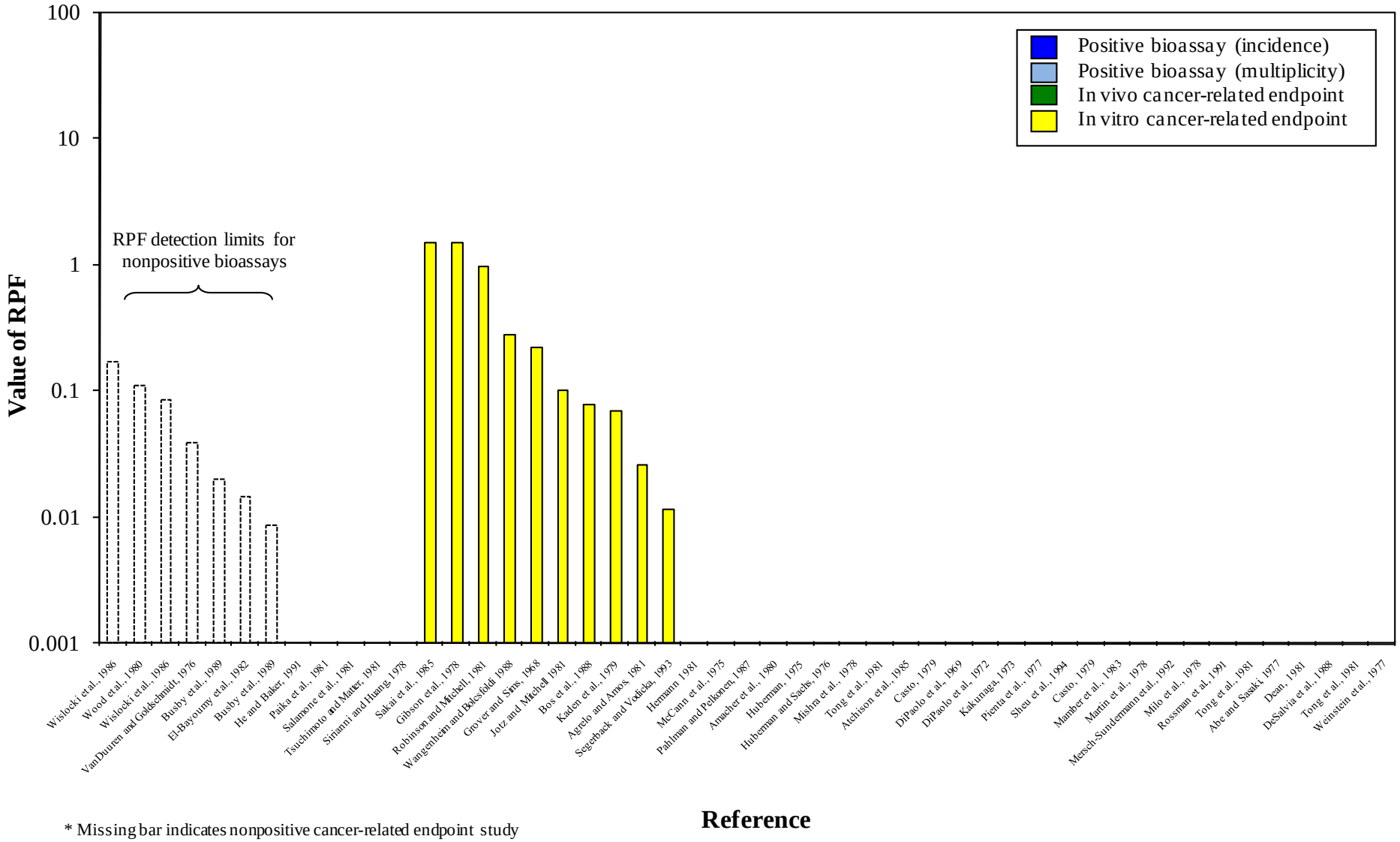
Pyrene (Pyr)



Pyrene (CASRN 129-00-0) is an alternant PAH comprised of four fused aromatic rings. Pyrene does not contain a bay or fjord region in its structure.

There were 49 datasets for pyrene that met study quality criteria and included benzo[a]pyrene (Figure 6-35). Included in the database are in vivo tumor bioassay datasets (7), in vivo clastogenicity datasets (5), bacterial and mammalian mutagenicity datasets (14), morphological/malignant cell transformation datasets (7), and in vitro DNA damage, DNA adducts, or clastogenicity datasets (16). There were seven bioassays of pyrene that included benzo[a]pyrene; all gave nonpositive results. Nonpositive results were reported in two newborn mouse bioassays in which both males and females were tested (Busby et al., 1989; Wislocki et al., 1986), two studies of dermal initiation (El-Bayoumy et al., 1982; Wood et al., 1980), and a dermal cocarcinogenesis bioassay (Van Duuren and Goldschmidt, 1976). RPF detection limits in these studies ranged from about 0.01 to 0.1 (see Figure 6-35). In an intraperitoneal bioassay using A/J mice that included benzo[a]pyrene, the authors reported that pyrene treatment did not induce lung adenomas (Ross et al., 1995); data were not reported, so an RPF detection limit could not be estimated. In bioassays without benzo[a]pyrene, pyrene did not induce a significant increase in tumors in a dermal initiation bioassay (Salaman and Roe, 1956). Scribner (1973) reported a weak tumorigenic response in a dermal initiation study in mice (5/29 mice developed papillomas 35 weeks after dermal treatment with 10 µmol pyrene in benzene followed by twice weekly treatment with TPA as compared with 0/30 control mice, $p = 0.02$).

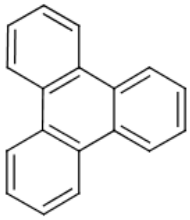
In vitro assays of bacterial and mammalian mutagenicity and morphological/malignant cell transformation were predominantly nonpositive for pyrene. In five studies of clastogenicity in animals exposed in vivo to pyrene, no evidence of clastogenic effects was reported. Further, in vitro studies of DNA adducts, DNA damage, and clastogenicity using pyrene also largely reported nonpositive results. Overall, the database for pyrene is substantial, and the weight of evidence suggests that this PAH is not carcinogenic. Based on the large number of nonpositive bioassays and the abundant evidence that pyrene lacks genotoxic action, this compound was selected for inclusion in the RPF approach and assigned an RPF of zero.



* Missing bar indicates nonpositive cancer-related endpoint study

Figure 6-35. Pyrene (Pyr) RPFs*.

Triphenylene (TPhen)



Triphenylene (CASRN 217-59-4) is an alternant PAH comprised of four fused aromatic rings. Triphenylene contains several bay regions but no fjord region in its structure.

There were six datasets for triphenylene that met selection criteria and included benzo[a]pyrene (Figure 6-36); all but one of the studies gave positive results. The database includes five mutagenicity studies (four positive and one nonpositive) and a study of in vitro DNA damage. There were no bioassays of triphenylene that met selection criteria, and no bioassays without benzo[a]pyrene. Although all of the available cancer-related endpoint studies for triphenylene gave positive results, the database is very limited, consisting of only a few in vitro mutagenicity and DNA damage studies. The RPFs for cancer-related endpoints ranged from 0.02 to 0.4. Because the database for triphenylene does not provide adequate information with which to assess carcinogenicity, this PAH was not selected for inclusion in the RPF approach.

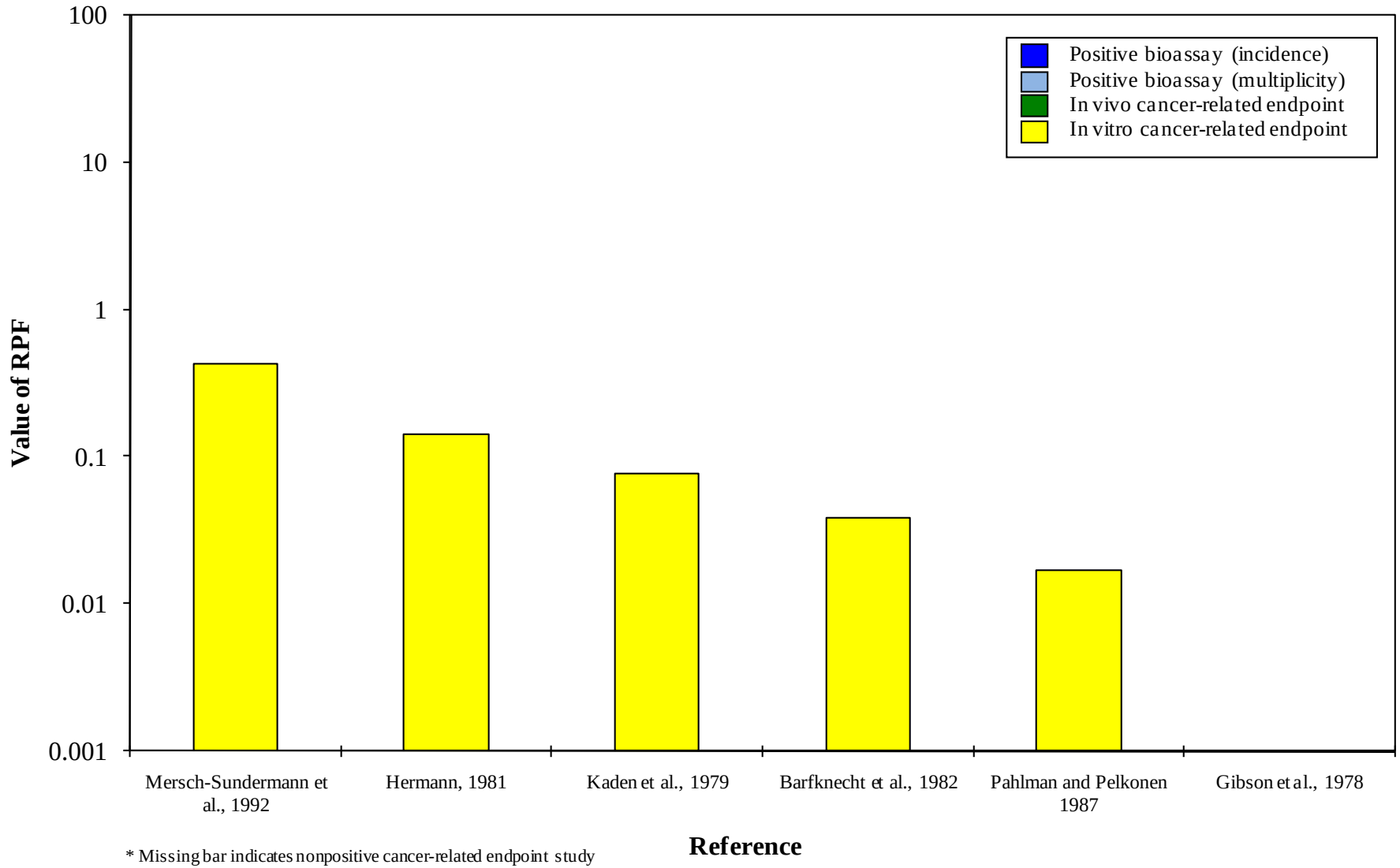


Figure 6-36. Triphenylene (Tphen) RPFs*.

7. DERIVATION OF FINAL RPFs FOR SELECTED PAHs

The weight of evidence evaluation (Chapter 6) indicates that the available data are adequate to suggest that 24 of the 27 PAHs are carcinogenic, 3 PAHs (anthracene, phenanthrene, and pyrene) exhibited no carcinogenicity, and data are inadequate to evaluate the carcinogenicity of eight PAHs. The 8 PAHs with inadequate data are excluded from the RPF analysis.

For the three PAHs for which there were sufficient data to conclude that they were not carcinogenic (i.e., robust nonpositive tumor bioassay data and cancer-related endpoint data), a final RPF of zero was recommended. While there is little quantitative difference between selecting a final RPF of zero for a given PAH and excluding that PAH from the RPF approach, this is an important distinction for uncertainty analysis. There is substantial uncertainty in the risk associated with PAHs that are excluded from the RPF analysis due to inadequate data, as these compounds could be of low or high potency. However, for PAHs with an RPF of zero, there is evidence to suggest that these compounds are not carcinogenic, and the uncertainty associated with the cancer risk for these compounds is markedly reduced.

For each of the remaining 24 compounds, a final nonzero RPF was derived. A number of options were considered for deriving a final RPF from among the numerous values calculated for each individual PAH. These options included: prioritizing bioassay RPFs from different exposure routes based on environmentally relevant routes; prioritizing bioassay RPFs based on target organs considered relevant to human susceptibility to PAH carcinogenesis; prioritizing RPFs based on quality of the underlying study; prioritizing cancer-related endpoints by their correlation with bioassay potency (i.e., ability to predict bioassay potency); and combining (i.e., averaging) RPFs across all bioassays, across all cancer-related endpoints, or across all endpoints. Appendix G details analyses that were undertaken to assess various options for ranking or prioritizing RPFs. It was concluded that the available data did not provide a basis for prioritizing RPFs except for a preference for bioassay data over cancer-related endpoints. As a consequence, final RPFs were derived from bioassay data for any PAH that had at least one RPF based on a bioassay. For carcinogenic PAHs without bioassay data, final RPFs were calculated from all cancer-related endpoint datasets with positive results (see next section).

7.1. METHODS FOR DERIVING FINAL RPFs

For each carcinogenic PAH with bioassay data, the average RPF was calculated from bioassay datasets with positive results (nonpositive bioassay results were not included in the calculation). For those PAHs that did not have any RPF based on a bioassay, but for which the weight of evidence evaluation indicated a carcinogenic response (e.g., dibenz[a,c]anthracene), the average RPF was calculated from all cancer-related endpoint datasets with positive results (again, nonpositive results were not included in the calculation). The range of RPF values was

also reported. Presenting the average and the range provides an average and maximum estimate for each PAH that has data from multiple studies.

Several options were considered for the estimation of a final RPF, including arithmetic mean, geometric mean, weighted average, maximum, or order of magnitude estimates. The arithmetic mean and range were chosen as a simple approach to describing the calculated RPF values available for each PAH. Other estimates were not considered due to the limited number of individual RPF values calculated for most PAHs and the variability in the RPF estimates. There were usually not enough data (3 or fewer RPFs for 17/23 PAHs with nonzero RPFs) to assess the shape of the RPF distribution for any given PAH; thus, a geometric mean was not considered. Further, the range of RPF values from tumor bioassays was greater than an order of magnitude for several compounds (6/23 PAHs). The variability in RPF estimates is likely due to differences in study design parameters (e.g., route, species/strain, exposure duration, exposure during sensitive time periods, initiation versus complete carcinogenesis protocol, tumor incidence versus tumor multiplicity reporting) and dose-response methods (modeled versus point estimates). Calculation of a weighted average was considered, but without a rationale for assigning weights among study types or among tumor data outcomes, using a weighting approach might increase uncertainty.

Several previous approaches for generating RPF values for PAHs have used order-of-magnitude estimates (Collins et al., 1998; Malcolm and Dobson, 1994; U.S. EPA, 1993; Nisbet and LaGoy, 1992, see Chapter 3). The presentation of the arithmetic mean (and range) of RPFs for each PAH reflects the available data better than an order-of-magnitude approach.

The range was reported as a measure of variability instead of a confidence interval on the average RPF. The input data for each average RPF (bioassay RPFs of different route, species, sex, and target organ, or cancer-related endpoint data across a wide variety of assays and test conditions) reflect such heterogeneity in study design that confidence limits would not provide the statistical precision that they typically convey. All tumor bioassay RPFs (across all exposure routes, species, and sexes, and including both tumor incidence and tumor multiplicity RPFs) were combined to estimate the mean and range for each PAH, except as follows. Only nonzero RPFs were included in the calculation of the final RPF and range for each PAH

While tumor multiplicity data from tumor bioassays are not generally used to estimate *cancer potency*, these data were included in the dose-response assessment in order to determine whether they could serve as a reliable measure of *relative cancer potency*. Several bioassays reported data on both tumor incidence and tumor number, providing information that was used to compare relative potencies estimated from these two endpoints. The comparison between RPFs calculated from incidence and tumor multiplicity data from the same experiment showed these values to be highly correlated ($r^2 = 0.76$; see further discussion in Chapter 8), indicating that multiplicity RPFs are reasonably predictive of incidence RPFs. When both incidence and multiplicity RPFs were calculated for the same group of animals, the results for each endpoint

could not be considered independent, so the higher of the two values was included in the average and the lower value was excluded. As discussed further in Chapter 8, in 70% of the cases where data for both incidence and multiplicity were used to calculate RPFs, the RPF associated with incidence was the higher of the two (or the two values were equal) and was therefore included in the average, omitting the corresponding multiplicity RPF.

When separate RPFs were calculated for different target organs in the same group of animals, the higher value of the two RPFs was included in the average and range, and the lower value was dropped from the combined data. Different RPFs were calculated for liver and lung tumors in male mice (females did not develop liver tumors) in newborn mouse studies. This occurrence applied only to benz[a]anthracene, chrysene, and fluoranthene tested in studies reported by LaVoie et al. (1994) and Wislocki et al. (1986).

When separate RPFs were calculated for male and female animals in the same study (generally, these were also newborn mouse studies), both sex-specific RPFs were included in the aggregation, as these were two separate groups of animals. In the one dermal study that included both sexes (Nesnow et al., 1984), the male and female RPFs differed by only ~50% for both benz[c]aceanthrylene and benz[l]aceanthrylene. In the newborn mouse studies that resulted in nonzero RPFs for both males and females (LaVoie et al., 1994, 1987; Wislocki et al., 1986), the male RPF was typically three- to fivefold higher than the female RPF. Final RPFs that included both male and female values from the same study were calculated for three PAHs: benzo[j]fluoranthene, benz[a]anthracene, and fluoranthene.

Table 7-1 shows the average RPFs based on tumor bioassay data with their associated range, and an overview of the tumor bioassay database (total number of studies, exposure routes tested, species tested, and sexes tested) for each PAH. Table 7-2 shows the average RPF for dibenz[a,c]anthracene, the only RPF based on cancer-related endpoint data, with its associated range, and an overview of the database for this compound.

Table 7-1. Final RPFs based on tumor bioassay data

PAH	Average RPF	Range of RPFs	Number of datasets	Exposure routes tested	Species tested	Sexes tested
Anthanthrene	0.4	0.2–0.5	2	Dermal, lung implantation	Mouse, rat	Female
Anthracene	0	0	1 (nonpositive)	Dermal	Mouse	Female
Benz[a]anthracene	0.2	0.02–0.4	3	Dermal, intraperitoneal	Mouse	Female, male
Benz[b,c]aceanthrylene, 11H-	0.05	0.05	1	Dermal	Mouse	Female
Benzo[b]fluoranthene	0.8	0.1–2	5	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Benzo[c]fluorene	20	1–50	2	Oral, intraperitoneal	Mouse	Female
Benz[e]aceanthrylene	0.8	0.6–0.9	2	Dermal	Mouse	Female, male
Benzo[g,h,i]perylene	0.009	0.009	1	Lung implantation	Rat	Female
Benz[j]aceanthrylene	60	60	1	Intraperitoneal	Mouse	Male
Benzo[j]fluoranthene	0.3	0.01–1	5	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Benzo[k]fluoranthene	0.03	0.03–0.03	2	Dermal, lung implantation	Mouse, rat	Female
Benz[l]aceanthrylene	5	4–7	2	Dermal	Mouse	Female, male
Chrysene	0.1	0.04–0.2	7	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Cyclopenta[c,d]pyrene	0.4	0.07–1	5	Dermal, intraperitoneal	Mouse	Female, male
Cyclopenta[d,e,f]chrysene, 4H-	0.3	0.2–0.5	2	Dermal	Mouse	Female
Dibenzo[a,e]fluoranthene	0.9	0.7–1	2	Dermal	Mouse	Female
Dibenzo[a,e]pyrene	0.4	0.3–0.4	2	Dermal	Mouse	Female
Dibenz[a,h]anthracene	10	1–40	3	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Dibenzo[a,h]pyrene	0.9	0.9	1	Dermal	Mouse	Female
Dibenzo[a,i]pyrene	0.6	0.5–0.7	2	Dermal	Mouse	Female
Dibenzo[a,l]pyrene	30	10–40	3	Dermal, intraperitoneal	Mouse	Female, male
Fluoranthene	0.08	0.009–0.2	5	Intraperitoneal	Mouse	Female, male
Indeno[1,2,3-c,d]pyrene	0.07	0.07	1	Lung implantation	Rat	Female
Naphtho[2,3-e]pyrene	0.3	0.3	1	Dermal	Mouse	Female
Phenanthrene	0	0	3 (nonpositive)	Dermal, intraperitoneal, lung implantation	Mouse, rat	Female, male
Pyrene	0	0	7 (nonpositive)	Dermal, intraperitoneal	Mouse	Female, male

Table 7-2. Final RPFs based on cancer-related endpoint data (no tumor bioassay data available)

PAH	Average RPF	Range of RPFs	Types of studies	Multiple dose studies
Dibenz[a,c]anthracene	4	0.04–50	Total = 14 studies One in vivo DNA adduct Six in vitro bacterial mutagenicity One in vitro mammalian mutagenicity One in vitro morphological/ malignant transformation Three in vitro DNA damage Two in vitro DNA adducts	Total = 6 studies Four in vitro bacterial mutagenicity One in vitro DNA damage One in vitro DNA adduct

7.2. CONFIDENCE RATINGS FOR FINAL RPFs

Once a final RPF was derived for a given PAH, the resulting value was assigned a relative confidence rating of *high, medium, low,* or *very low*. The relative confidence rating characterized the nature of the database upon which the final RPF was based. Confidence rankings were based on the robustness of the database. For final RPFs based on tumor bioassay data, confidence ratings considered both the available tumor bioassays and the availability of supporting data for cancer-related endpoints. The most important factors that were considered included the availability of in vivo data and whether multiple exposure routes were represented. Other database characteristics that were considered included the availability of more than one in vivo study, and whether effects were evident in more than one sex or species. The database characteristics of exposure route, species, and gender are somewhat related (i.e., not independent variables). For example, intraperitoneal injection studies were generally performed in both male and female mice while lung implantation studies were conducted in rats only. An increase in the number of exposure routes tested also results in generation of data for multiple species and genders. The factors that were considered in the relative confidence rating for each RPF are illustrated in Table 7-3.

Table 7-3. Relative confidence ratings for RPFs

PAH	Relative confidence	Tumor bioassay data					Supporting data for cancer-related endpoints
		In vivo data	>1 Exposure route	>2 Exposure routes	>1 Species	>1 Gender	
Benzo[b]fluoranthene	High	✓	✓	✓	✓	✓	✓
Benzo[j]fluoranthene	High	✓	✓	✓	✓	✓	✓
Chrysene	High	✓	✓	✓	✓	✓	✓
Dibenz[a,h]anthracene	High	✓	✓	✓	✓	✓	✓
Phenanthrene	High	✓	✓	✓	✓	✓	✓
Anthanthrene	Medium	✓	✓		✓		✓
Anthracene	Medium	✓	✓[a]		✓[a]		✓
Benz[a]anthracene	Medium	✓	✓			✓	✓
Benzo[c]fluorene	Medium	✓	✓				✓
Benzo[k]fluoranthene	Medium	✓	✓		✓		
Cyclopenta[c,d]pyrene	Medium	✓	✓			✓	✓
Dibenzo[a,l]pyrene	Medium	✓	✓			✓	✓
Pyrene	Medium	✓	✓			✓	✓
Benz[b,c]aceanthrylene, 11H-	Low	✓					
Benz[e]aceanthrylene	Low	✓				✓	✓
Benzo[g,h,i]perylene	Low	✓					✓
Benz[j]aceanthrylene	Low	✓					✓
Benz[l]aceanthrylene	Low	✓				✓	✓
Cyclopenta[d,e,f]chrysene, 4H-	Low	✓					
Dibenzo[a,e]fluoranthene	Low	✓					✓
Dibenzo[a,e]pyrene	Low	✓					✓
Dibenzo[a,h]pyrene	Low	✓					✓
Dibenzo[a,i]pyrene	Low	✓					✓
Fluoranthene	Low	✓				✓	✓
Indeno[1,2,3-c,d]pyrene	Low	✓					✓
Naphtho[2,3-e]pyrene	Low	✓					✓
Dibenz[a,c]anthracene	Very low						✓

[a]Bioassays of anthracene without benzo[a]pyrene included dermal studies in mice and a lung implantation study in rats.

Very low relative confidence was used to describe final RPFs based on cancer-related endpoint data only (e.g., dibenz[a,c]anthracene).

For RPFs of zero, the confidence rating considered both the available tumor bioassays (with and without benzo[a]pyrene) and the size and consistency of the cancer-related endpoint database. An RPF of zero was only applied if the data implied *high* or *medium relative confidence*. For anthracene, phenanthrene, and pyrene, the available data support a practical RPF of zero.

7.3. APPLICATION OF RPFs FOR ASSESSING CANCER RISKS FROM EXPOSURE TO PAH MIXTURES

In the proposed RPF approach, the cancer risk associated with exposure to a particular mixture of PAHs is assumed to equal the sum of the risks associated with exposure to individual carcinogenic components. Because quantitative cancer risk values are available only for benzo[a]pyrene, exposure units (either concentrations or doses, in units of mass) for other PAHs found in the mixture are expressed in terms of benzo[a]pyrene equivalents. These are summed with benzo[a]pyrene to obtain an estimate of the total benzo[a]pyrene equivalents (in concentration or dose) presented by the mixture. Benzo[a]pyrene equivalents for PAH components in a particular mixture are calculated by multiplying the concentration (or dose) of a particular PAH component in the mixture by its RPF. The total benzo[a]pyrene equivalents for a particular mixture of PAHs is calculated as follows:

$$E = \sum RPF_j C_j + X$$

where:

E = the benzo[a]pyrene equivalent exposure presented by the mixture
RPF_j = relative potency factor of the jth PAH detected in the mixture
C_j = dose or concentration of the jth PAH detected in the mixture
X = dose or concentration of benzo[a]pyrene in the mixture.

The cancer risk for the PAH mixture is determined by multiplying the benzo[a]pyrene equivalent dose or concentration by the benzo[a]pyrene cancer toxicity value (e.g., oral slope factor). The proposed RPF approach considers each of the bioassay types used for RPF derivation to be equivalent for the purpose of determining relative potency to benzo[a]pyrene. The uncertainty associated with using a single RPF to derive benzo[a]pyrene equivalents for multiple exposure routes is discussed in Section 8.6.

7.4. SUSCEPTIBILITY FROM EARLY LIFE EXPOSURE TO CARCINOGENS

According to the *Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005b), benzo[a]pyrene is carcinogenic by a mutagenic

mode of action. For example, an acute dosing study using benzo[a]pyrene suggests that early-lifestage exposure would lead to an increased incidence of tumors compared with adult exposures of a similar dose and duration (EPA, 2005b). Mice that were treated with benzo[a]pyrene (75 or 150 μg/g body weight intraperitoneal) within 24 hours of birth or at 15 days of age developed hepatomas at a higher incidence than similarly treated animals at 42 days of age (Vesselinovitch et al., 1975, as cited in EPA 2005b).

The *Supplemental Guidance* establishes age-dependent adjustment factors (ADAFs) for three specific age groups. The ADAFs and their age groupings are 10 for <2 years, 3 for 2–<16 years, and 1 for ≥16 years (U.S. EPA, 2005b). The 10- and 3-fold adjustments in slope factor are to be combined with age-specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to PAHs.

Because a mutagenic mode of action for benzo[a]pyrene carcinogenicity is sufficiently supported in laboratory animals and relevant to humans, and in the absence of chemical-specific data to evaluate differences in susceptibility, increased early-life susceptibility is assumed and the ADAFs should be applied, as appropriate. A common mutagenic mode of action for carcinogenic PAHs is hypothesized based on information available for the indicator chemical, benzo[a]pyrene (U.S. EPA, 2005b). In the absence of chemical-specific data to evaluate differences in susceptibility, increased early-life susceptibility to the 24 PAHs (for which RPFs were derived) in this analysis is assumed and the ADAFs should be applied, along with exposure information, as appropriate (see Table 7-4 for example).

Some of the studies used to derive RPFs for the PAHs were conducted in newborn mice. The RPFs calculated from the newborn mouse studies reflect only the potency of the tested PAH *relative to that of benzo[a]pyrene*, and do not take into account the potency of the PAH administered in newborn or young animals *relative to the potency of the same PAH* administered to adult animals. The ADAF should be applid to account for the latter difference.

Table 7-4. Sample calculation of estimated cancer risk for benz[a]anthracene with the application of ADAFs

Age group	ADAF	Benzo[a]pyrene oral slope factor (per mg/kg-d)	Adjusted benzo[a]pyrene cancer risk estimate	RPF	Benz[a]anthracene estimated cancer risk (per mg/kg-d)
0–<2	10	7.3	73	0.2	15
2–<16	3	7.3	24	0.2	4.8
≥16	1	7.3	7.3	0.2	1.5

8. UNCERTAINTIES AND LIMITATIONS ASSOCIATED WITH THE RPF APPROACH

A description of uncertainties and limitations is an important component of the RPF approach for PAH mixtures risk assessment. Many of the general uncertainties related to chemical-specific risk assessment are also applicable to the proposed RPF approach for PAHs. These include issues related to selection of an appropriate animal model, low-dose and interspecies extrapolation, and variability within the human population. Use of a component-based approach to mixtures risk assessment leads to additional uncertainties, e.g., the lack of experimental data on potential interactions among individual components within the mixture (i.e., among PAHs and with other chemicals).

The feasibility of conducting a robust component-based approach for PAH mixtures (RPF approach) was evaluated by a PAH mixtures peer consultation workshop (U.S. EPA, 2002). Included in the discussion was a general evaluation of U.S. EPA's *Provisional Guidance* (U.S. EPA, 1993). Workshop participants highlighted the following limitations of the 1993 guidance:

(1) The approach only considered a small subset of PAHs (i.e., unsubstituted PAHs only, no heterocyclic compounds or nitro- or alkyl- substituted PAHs);

(2) There are no human toxicity data for any individual PAH;

(3) The assumption of additivity may not be valid, and there may be interactions among PAHs or between PAHs and other components of a mixture (e.g., metals);

(4) PAHs may generally have a common mode of action (i.e., mutagenicity), but multiple modes of action for carcinogenesis are possible; and

(5) The EOPP approach was limited to the oral exposure route (i.e., a recommendation was made not to apply the factors to dermal and inhalation exposures).

The current analysis represents a significant improvement upon the previous component-based approach for PAH mixtures risk assessment. One of the most important improvements is a comprehensive review of the scientific literature dating from the 1950s through 2009 on the carcinogenicity and genotoxicity of PAHs. The search identified over 900 individual publications for a target list of 74 PAHs that had been identified in environmental media or for which toxicological data were available. Review of these publications resulted in the identification of more than 600 papers that included carcinogenicity or cancer-related endpoint data on at least one PAH and benzo[a]pyrene tested at the same time. Dose-response data were extracted, and individual RPFs were calculated from over 300 data sets representing

51 individual PAHs. For 35 PAHs, a weight of evidence evaluation was conducted to select compounds for inclusion in the RPF approach; data were inadequate to conduct such an evaluation for the remaining 16 compounds. A final RPF was derived for each PAH based on tumor bioassay data (if available) or cancer-related endpoint data if no tumor bioassay RPFs were available. Final RPFs were derived for 27 PAHs (see Table 7-2), significantly increasing the number of PAHs that can be addressed through this approach. Each RPF was assigned a relative confidence rating reflecting the size and diversity of the tumor bioassay or cancer-related endpoint database that was used to derive the final RPF for that PAH.

Despite these improvements, many of the uncertainties highlighted during the 2002 peer consultation workshop (U.S. EPA, 2002) also apply to the current analysis. The following sections describe some specific uncertainties and limitations associated with the development and use of RPFs for PAHs. The uncertainties that are specific to the approach presented herein are discussed below in Sections 8.1 and 8.2. Sections 8.3–8.6 discuss the general uncertainties associated with a component-based approach to PAH mixtures risk assessment. These include the number of PAHs included in the approach, human relevance of animal data, assumptions regarding mode of action and dose additivity, and cross-route extrapolation.

8.1. DOSE-RESPONSE ASSESSMENT FOR INDIVIDUAL PAHs

Several uncertainties and limitations are specifically associated with the selection of data and dose-response assessment methodology used in this analysis to derive RPFs for PAHs. Uncertainties are associated with the following decisions:

- Inclusion of data from studies reporting the occurrence of benign tumors in derivation of RPFs;
- Use of a single dose-response model for quantal or continuous data;
- Use of varying BMR levels;
- Use of tumor incidence data at the upper end of the dose-response curve (e.g., >75% incidence) to calculate some RPFs;
- Use of tumor multiplicity data to calculate some RPFs;
- Use of single-dose point estimates[7] to calculate some RPFs;
- Reliance on data from cancer-related endpoint studies in the absence of bioassays; and

[7]In this report, the term "point estimate RPF" is used to describe an RPF calculated from a single point on the dose-response curve for both the PAH of interest and benzo[a]pyrene. This term distinguishes the RPF from one calculating using a BMD modeling result from multidose data.

- Use of cancer-related data from assay conditions that maximize the benzo[a]pyrene response, even though these conditions were not necessarily optimal for other PAHs.

The decision was made to employ a single dose-response model for either quantal or continuous data due to the large number of data sets that needed be analyzed from the PAH database. The multistage model for incidence data and the linear model for continuous data were considered to be broadly applicable to different types of data as simple curve-fitting models. In some cases, the goodness-of-fit criteria indicated that the selected model did not fit the data. In these cases, high-dose groups were sequentially eliminated until an adequate fit was achieved, but other model structures (e.g., gamma, probit, logistic, etc.) were not considered.

Tumor bioassay data were modeled at a BMR of 10% in order to target the low end of the dose-response curve as the point of departure for slope estimation. When this was not feasible, usually because only a single dose was used for benzo[a]pyrene, an attempt was made to match individual target PAH response levels to the benzo[a]pyrene response chosen for the point estimate. This assumes that the shape of the dose-response curve is similar for the target PAH and benzo[a]pyrene (also a necessary assumption of dose additivity) and that the slope is constant across the dose-response curve. These assumptions may not hold, especially in studies of tumor incidence where the point estimate benzo[a]pyrene response was very high or near maximal. In many cases, the dose of benzo[a]pyrene selected as the positive control produced near maximal tumor incidence in exposed animals (i.e., >75%). There is uncertainty associated with comparing potency estimates at the high end of the dose-response curves and using the resultant RPF to estimate risks associated with low environmental exposures. The relative potency relationship between any two PAHs may be different at the low end, compared with the high end, of the dose-response curves.

It is not clear whether relative potency values estimated at the high end of the dose-response curve are reasonably predictive of relative potency at low environmental exposure levels. For this reason, additional uncertainty is involved in using RPFs that are not based on a BMR of 10% (especially those RPFs that are based on responses exceeding 75%) to estimate risks associated with low exposures.

If model fit was not achieved, then a point-estimate ratio approach was used. Point estimate ratios were also used for several other reasons:

(1) Only a single dose group was tested;

(2) When the standard deviation or number of replicates were not reported for continuous data sets; or

(3) High-dose groups from multiple dose data sets were not usable due to a saturated tumor response (>90% incidence in the lowest exposure group).

The point estimate approach is most reliable when the chosen point is in the linear portion of the dose-response curve. In many cases, however, especially for single-dose data, it was not possible to determine whether the chosen point was in a linear or nonlinear portion of the dose-response curve. The dose-response relationship observed in many studies of cancer-related endpoints was nonlinear at high doses. Whenever possible, the point estimate was chosen from the linear portion of the dose-response curve (i.e., before the response plateau that occurs at high doses). Of 50 individual RPFs calculated from tumor incidence data, 21 were calculated using a point of departure incidence ≤25%, 19 were calculated using a point of departure incidence between 25 and 75%, and the remaining 10 were calculated using a point of departure incidence between 75 and 90%. Thus, only 20% of the individual RPFs for tumor incidence data were calculated from a point high (>75 and <90% incidence) on the dose-response curve.

For a few PAHs tested in older dermal bioassays, the authors reported mortality prior to the appearance of the first tumor. For these data sets, an assumption was made that the number of animals at risk for tumor development was equal to the total number of animals alive at the time of the appearance of the first tumor. This approach ensures that the incidence is not underestimated by including animals that did not survive long enough to develop tumors. As this assumption applied to a small number of RPFs (specifically, individual RPFs for chrysene, dibenzo[a,e]pyrene, dibenzo[a,e]fluoranthene, and dibenzo[a,h]pyrene calculated from data reported by Hecht et al. [1974] and Hoffmann and Wynder [1966]), it had little impact on the overall analysis.

RPFs were also calculated for many cancer-related endpoints. Many of the studies describing in vitro cancer-related endpoints provided dose-response data under varying study conditions. For example, bacterial mutagenesis studies utilized multiple strains, different metabolic activation processes, and varying assay systems. In order to minimize the amount of data used for dose-response analysis of in vitro mutagenicity studies, and to provide a consistent basis for comparing RPFs for different PAHs, the data from conditions that maximize the benzo[a]pyrene response within a particular study were used for the dose-response assessment. In several studies, the conditions that were optimal for benzo[a]pyrene were not necessarily optimal for the target PAH. For example, the concentration of S9 mix that produced the highest mutation rate for benzo[a]pyrene did not produce a maximal response for perylene or cyclopenta[c,d]pyrene (Carver et al., 1986; Eisenstadt and Gold, 1978). In vitro data were only used in the derivation of a single final RPF (for dibenz[a,c]anthracene; see Table 7-2); thus, the uncertainties associated with the use of cancer-related endpoint data are important for dibenz[a,c]anthracene, but have minimal impact on the proposed RPFs for the other 26 PAHs.

8.2. SELECTION OF PAHs FOR INCLUSION IN RPF APPROACH

One of the uncertainties highlighted by the peer consultation workshop (U.S. EPA, 2002) stemmed from the fact that U.S. EPA's 1993 provisional EOPP approach only considered a small

subset of PAHs (i.e., unsubstituted PAHs only, no heterocyclic compounds or nitro- or alkyl-substituted PAHs), and EOPPs were available for only seven PAHs. Although the present report considered a larger number of PAHs than previous analyses (the toxicological literature was searched for data on 74 individual PAHs identified in environmental media or for which there were toxicological data), the focus of this analysis remains limited to unsubstituted PAHs with three or more fused aromatic rings containing only carbon and hydrogen atoms. Thus, the RPF analysis presented here does not account for the possible carcinogenicity of substituted or heterocyclic PAHs that may be present in complex mixtures. This may result in an underestimation of PAH mixture cancer risk.

Of the 74 unsubstituted PAHs with three or more aromatic rings, there were studies including benzo[a]pyrene that were suitable for RPF calculation for 51 compounds. The methodology for selecting PAHs for inclusion in the RPF approach from among these 51 PAHs is described in Chapter 6. At the outset, 16 PAHs were excluded because only one or two in vitro cancer-related endpoint RPFs were available. The remaining 35 PAHs were evaluated using a weight of evidence approach. The primary uncertainties associated with the selection process relate to:

(1) The use of a weight of evidence approach that focused on tumor bioassays including benzo[a]pyrene as opposed to a comprehensive cancer assessment to select PAHs for inclusion in the approach; and

(2) The exclusion of PAHs with limited or inconclusive data.

The weight of evidence approach was used due to the large number of compounds that were under consideration. The approach was structured as a decision tree that focused primarily on cancer bioassays that included benzo[a]pyrene, and only considered other data (e.g., bioassays that did not include benzo[a]pyrene, or cancer-related data) when cancer bioassays with benzo[a]pyrene were unavailable, nonpositive, or inconsistent (see Figure 6-1). The data collection for this analysis was centered on studies that included benzo[a]pyrene, as these studies would be most useful for RPF calculation. Consequently, information from bioassays that included benzo[a]pyrene were readily available for use in the weight of evidence determinations. Bioassays that did not include benzo[a]pyrene and cancer-related endpoint data were considered only when there were conflicting or nonpositive results in the studies that did include benzo[a]pyrene. There is uncertainty in drawing conclusions as to carcinogenicity based on a narrow subset of the available database. Other elements of a more comprehensive weight of evidence determination that were not considered include: cancer-related endpoint data from studies that did not include benzo[a]pyrene; information on tumorigenicity of metabolites; information on formation of reactive metabolites; other mechanistic data (e.g., AhR reactivity, inhibition of gap junction intercellular communication, etc.); and QSAR assessment.

A number of PAHs (24 of 51 PAHs that had at least one RPF value) were excluded from the relative potency approach because the available data were inadequate to draw a conclusion as to carcinogenicity (see Tables 6-1 and 6-2). All of these PAHs had at least one RPF, indicating that the compounds were active in at least one cancer-related endpoint assay. Excluding these PAHs from the approach increases the uncertainty in assessing risks from a mixture that includes them, particularly if the excluded PAHs constitute a large fraction of the mixture.

In summary, RPFs were proposed for only 27 of the 74 PAHs initially considered, because the remaining 47 compounds did not have adequate data. Thus, even among the subset of PAHs upon which this analysis was focused, RPFs were only recommended for only about one-third of the compounds. Because only a fraction of any given PAH mixture can be evaluated using the RPF approach, it is important to note as part of the uncertainty evaluation of a risk assessment using these RPFs that there is some proportion of the total mixture (i.e., mass fraction) that is comprised of compounds that are not considered in the component-based approach.

8.3. DERIVATION OF A FINAL RPF FOR EACH PAH

The methodology for deriving a final RPF value and assigning a relative confidence rating is described in Sections 7.1 and 7.2. The primary uncertainties associated with RPF derivation relate to:

(1) Combining RPFs across multiple exposure routes, species, sexes, tumor types, and studies;

(2) Inclusion of RPFs based on tumor multiplicity data in the combined data;

(3) Inclusion of RPFs from female newborn mice when male RPF values were demonstrably higher;

(4) Use of an arithmetic mean to derive final RPFs; and

(5) Use of cancer-related endpoint data to derive final RPFs for compounds without tumor bioassay RPFs.

A variety of options were considered for prioritizing and/or combining RPFs. Appendix G describes analyses that were undertaken to assess options for prioritizing RPFs. As the appendix indicates, the current state of knowledge does not suggest a clear biological basis for prioritizing RPFs. As a result, RPFs were combined across exposure routes, species, sexes, tumor types, dose-response methods, and studies.

In addition to tumor incidence data, tumor multiplicity data were used to calculate RPFs. The relationship between tumor incidence RPFs and tumor multiplicity RPFs is not known; however, this analysis resulted in the calculation of both incidence and multiplicity RPFs for

24 individual datasets. These data were plotted, and a linear regression analysis was performed to assess the correlation between these two relative potency estimates. Figure 8-1 shows the results.

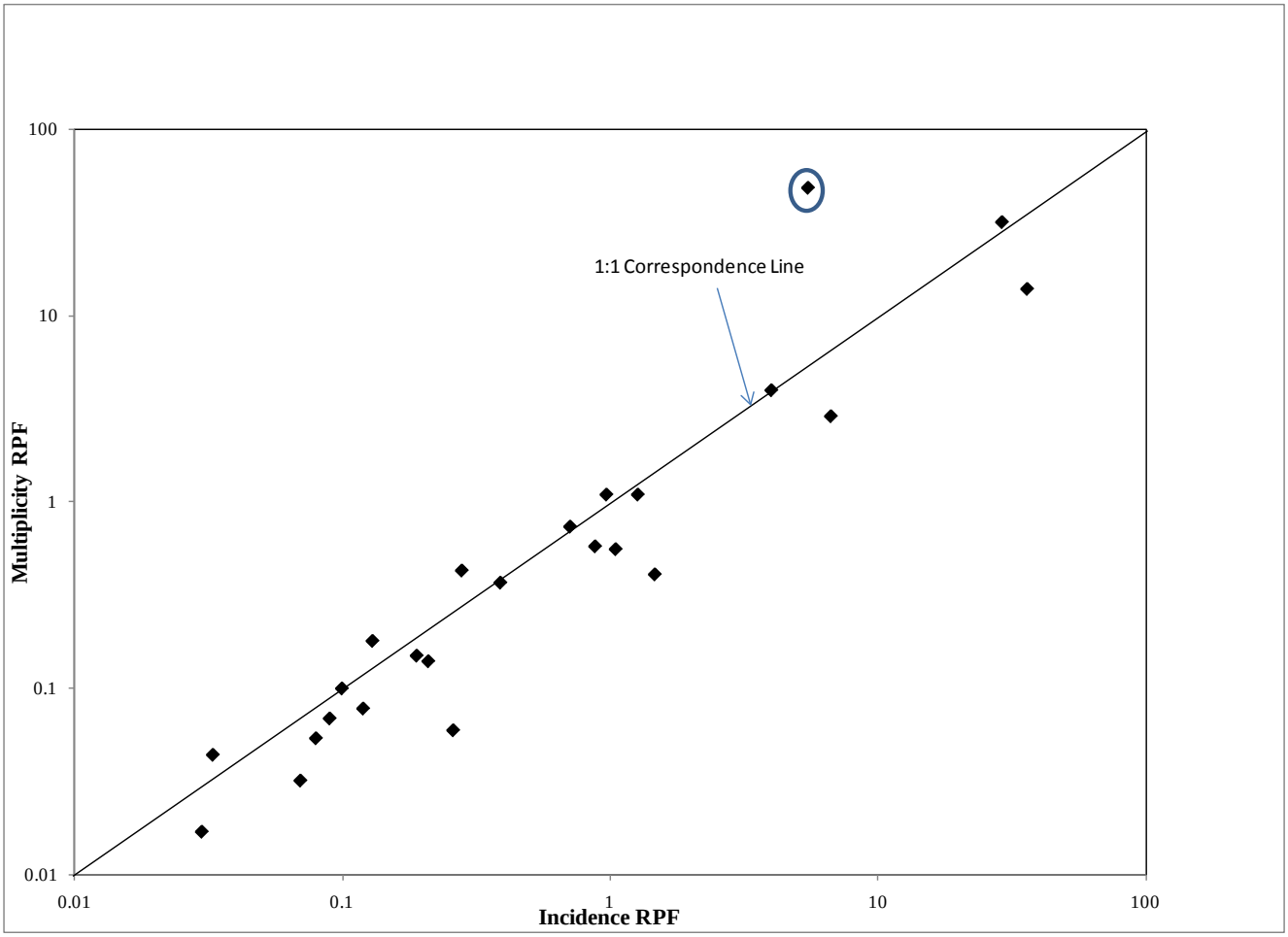


Figure 8-1. Correlation between incidence and multiplicity RPFs.

As shown in Figure 8-1, there is a high degree of correspondence between incidence and multiplicity RPFs calculated from results in the same animals, with one exception (see circled data point). The regression analysis indicated an r^2 of 0.76 for the correlation when the outlier was excluded, or only 0.28 when it was included. The outlier datapoint reflects the incidence and multiplicity RPFs for benzo[c]fluorene calculated for the one oral study (Weyand et al., 2004). All of the other datapoints reflect incidence and multiplicity RPFs for dermal or intraperitoneal exposure studies; thus, one possible explanation for the outlier is that the relationship between incidence and multiplicity after oral exposure differs from the relationship after exposure via other routes. However, there was good correspondence between incidence and multiplicity in dermal and intraperitoneal studies, despite the marked differences in absorption, distribution, and metabolism of PAHs administered by these two exposure routes.

Compound-specific differences in the association between incidence and multiplicity RPFs also seem unlikely; the dataset shown in Figure 8-1 also includes a comparison between incidence and multiplicity RPFs for benzo[c]fluorene in an intraperitoneal exposure study, and there is good correspondence between the two (RPF = 1 for incidence and RPF = 0.6 for multiplicity). The most plausible explanation for the outlier is that the basis for the multiplicity RPF in the oral study of benzo[c]fluorene (RPF = 50) was estimated using a point high on the dose-response curve (incidence was 100%), at which a large mean number of tumors per animal (46 ± 2.8) was recorded, while the incidence RPF (RPF = 5) for the same study was estimated using BMD modeling at a response point lower on the curve (BMR of 0.7). All of the other comparisons between incidence and multiplicity RPFs from the same set of animals were based on multiplicity responses <10 tumors per animal. Although there is little information with which to explore this hypothesis, it is possible that RPFs for multiplicity that are calculated using unusually high tumor number are not reliable measures of relative incidence potency. This could result from changes in the slope of the tumor number versus dose curve at high tumor number, or from methodology limitations that hamper accurate measurement of high tumor numbers.

Notwithstanding the one outlier, as the remaining incidence and multiplicity RPFs from the same study were highly correlated, only one of the two metrics (the higher of the incidence or multiplicity RPF from the same study) was included in the average and range. Figure 8-1 shows that multiplicity RPFs exhibit a slight tendency to underestimate the RPF from incidence data (more points are to the right of the 1:1 correspondence line); thus, the higher value was usually calculated from incidence data. Specifically, 15/24 incidence RPFs were higher than the corresponding multiplicity RPF from the same study, and 2/24 of the incidence and multiplicity RPFs were identical. Thus, only 7/24 multiplicity RPFs were higher than their corresponding incidence RPFs.

As discussed in Section 7.1, in newborn mouse studies that resulted in nonzero RPFs for both males and females (LaVoie et al., 1994, 1987; Wislocki et al., 1986), the male RPF was typically three- to fivefold higher than the female RPF, but both were included in the final RPF calculation. Final RPFs that included both male and female values from the same study were calculated for three PAHs: benzo[a]anthracene, benzo[j]fluoranthene, and fluoranthene. An alternative approach would be to select the RPF associated with the most sensitive sex (i.e., males) and to omit the female RPF from the final calculation. The net effect of including female RPFs for these three compounds is to reduce the average RPF and, in some cases, to reduce the lower limit of the range of RPFs. For benzo[a]anthracene and benzo[j]fluoranthene, the final RPF is unchanged whether or not the female RPF is included. For fluoranthene, inclusion of the female RPFs yields a final RPF of 0.08, while excluding the female RPFs would result in a final RPF of 0.1.

Final RPFs were calculated as the arithmetic mean and range of RPFs from tumor bioassay data when such data were available. Presenting the average and the range provides both

an average and a maximum estimate for each PAH that has data from multiple studies. Other options for deriving a central tendency RPF include geometric mean, median, weighted average, and order of magnitude estimates. The arithmetic mean represents a simple approach to describing the calculated RPF values available for each PAH. There were usually not enough data (≤3 RPFs for 18/24 PAHs with nonzero RPFs) to assess the shape of the RPF distribution for any given PAH, so a geometric mean was not considered. Calculation of a weighted average was considered, but without a clear biological rationale for assigning weights among study types or tumor data outcomes, using a weighting approach might increase uncertainty. Finally, the use of simple means and ranges of estimated RPFs rather than order of magnitude estimates, as has been previously done for estimating RPFs for PAHs, was considered to better reflect the available data and provide a clearer characterization of uncertainty.

Cancer-related endpoint data were relied upon for the derivation of an RPF for only one PAH (dibenz[a,c]anthracene). For this compound, there were no tumor bioassay data suitable for the determination of an RPF. However, cancer-related endpoint data provided qualitative support for the finding of carcinogenicity for this compound (see individual narrative for this compound in Section 6.2). Although the mutagenic mode of action for benzo[a]pyrene (U.S. EPA, 2005b) suggests that, in general, these endpoints may be relevant to PAH carcinogenicity, the predictive value of a positive response in these tests has not been conclusively demonstrated. Thus, there is considerable uncertainty in an RPF based on cancer-related endpoint data. Appendix G includes analysis of the correlation between average RPFs calculated from cancer-related endpoint data and tumor bioassay data. As shown in Table 8-1, and further discussed in Appendix G, cancer-related endpoint RPFs are reasonably predictive of tumor bioassay RPFs; however, the relationship between these RPFs and the relative potency of a given PAH in humans exposed via environmentally relevant routes is unknown.

Table 8-1. Results of simple linear regression of log-transformed average tumor bioassay RPF versus log average genotoxicity RPF

Genotoxicity endpoint	r^2	Slope	*p*-Value	n
All in vivo DNA adducts	0.64	1.22	<0.01	10
All in vivo nonbioassays	0.55	1.16	<0.01	11
All nonbioassay endpoints (in vitro and in vivo)	0.40	1.10	<0.01	20
All in vitro nonbioassays	0.39	0.91	<0.01	19
All in vivo micronuclei and sister chromatid exchanges	0.39	0.81	>0.05 (nonsignificant)	6
All in vitro mutagenicity	0.032	0.33	>0.05 (nonsignificant)	17

For three PAHs (anthracene, phenanthrene, and pyrene), a final RPF of zero was recommended. As noted earlier in Chapter 6, there is little quantitative difference between selecting a final RPF of zero for a given PAH and excluding that PAH from the RPF approach. However, excluding PAHs from the RPF approach implies substantial uncertainty (these

compounds could be of low or high potency), while assigning an RPF of zero suggests lower uncertainty because there is evidence to suggest that these compounds are not carcinogenic. Nevertheless, there remains uncertainty in the RPFs for these three compounds, as all of them included one or more studies suggesting activity in cancer-related endpoint assays. In addition, it is possible that available bioassay studies for these compounds may not provide sufficient sensitivity to allow for a potency comparison with benzo[a]pyrene; thus, the RPF of zero should not be considered a characterization of the inherent carcinogenicity of anthracene, phenanthrene, or pyrene.

In the present analysis, RPFs for individual PAHs were based on data of varying quality and reproducibility, so there is additional uncertainty in risks estimated for mixtures containing differing concentrations of individual PAHs. Confidence ratings were assigned to each RPF to qualitatively characterize the uncertainty in each individual RPF. Table 8-2 shows the distribution of PAHs with RPFs of each confidence rating. As the table indicates, there are 5 PAHs with RPFs of high confidence, 8 PAHs with RPFs of medium confidence, 13 PAHs with RPFs of low confidence, and 1 PAH with an RPF of very low confidence. The confidence ratings assigned to the RPFs may be used to qualitatively assess the uncertainty in a mixtures risk assessment that utilizes the RPFs. For example, if a high proportion of the total cancer risk predicted for a given mixture is attributable to benzo[a]pyrene and other PAHs with RPFs of high or medium confidence, then the confidence in the overall cancer risk assessment will be relatively high. If, in contrast, benzo[a]pyrene contributes a relatively small fraction of the overall risk, and/or the mixture consists primarily of PAHs with RPFs of low confidence, then the confidence in the overall cancer risk assessment will be correspondingly lower. Thus, it will be important to consider the relative contribution of benzo[a]pyrene to the total risk, as well as the relative confidence ratings of the RPF values for component PAHs, in the uncertainty evaluation for cancer risk assessments that employ these RPFs.

Table 8-2. PAHs with RPFs of varying relative confidence

High confidence RPF	Medium confidence RPF	Low confidence RPF	Very low confidence RPF
Benzo[b]fluoranthene Benzo[j]fluoranthene Chrysene Dibenz[a,h]anthracene Phenanthrene	Anthanthrene Anthracene Benz[a]anthracene Benzo[c]fluorene Benzo[k]fluoranthene Cyclopenta[c,d]pyrene Dibenzo[a,l]pyrene Pyrene	Benz[b,c]aceanthrylene, 11H- Benz[e]aceanthrylene Benzo[g,h,i]perylene Benz[j]aceanthrylene Benz[l]aceanthrylene Cyclopenta[d,e,f]chrysene, 4H- Dibenzo[a,e]fluoranthene Dibenzo[a,e]pyrene Dibenzo[a,h]pyrene Dibenzo[a,i]pyrene Fluoranthene Indeno[1,2,3-c,d]pyrene Naphtho[2,3-e]pyrene	Dibenz[a,c]anthracene

8.4. USE OF ANIMAL DATA TO PREDICT HUMAN CANCER RISK FOR PAHs

Section 4.2 briefly summarizes the epidemiology and human biomarker data related to exposure to PAH mixtures and carcinogenicity. Exposure to certain PAH mixtures is clearly associated with cancer in humans. Epidemiology studies evaluating emissions from coke production, coal gasification, aluminum production, iron and steel founding, coal tars, coal tar pitches, and soot have demonstrated associations between exposure and increased risk of lung cancer in humans (see review of Bostrom et al., 2002). Skin and scrotal cancers have been associated with exposure to coal tar, coal tar pitches, nonrefined mineral oils, shale oils, and soot (Larsen and Larsen, 1998; WHO, 1998; ATSDR, 1995). While human epidemiology data may be sufficient for the purpose of quantifying the cancer risks associated with exposure to a few PAH mixtures, there are no data for many mixtures; hence the need for other approaches including surrogate-mixture and component-based approaches. As noted by the peer consultation workshop (U.S. EPA, 2002), there are no human data on cancer response to individual PAHs that could be used as the basis for, or as a supplement to, a component-based approach. As a result, the RPF approach relies on animal bioassay data to predict human cancer risk associated with individual PAHs.

The use of animal bioassays in predicting relative carcinogenic potency in humans represents a source of uncertainty in this approach. As there are no human data on cancer response to individual PAHs, including benzo[a]pyrene, there can be no quantitative evaluation of uncertainty in extrapolating from RPFs based on animal bioassay data to relative potency in humans. Possible species differences in toxicokinetics, toxicodynamics, and mode of action contribute to the uncertainty. Cancer-related endpoint data are available using human cells (e.g., epidermal keratinocytes, lymphoblasts, human epithelial cells) for the evaluation of mutagenicity, DNA adducts, unscheduled DNA synthesis, DNA damage, and clastogenicity or sister chromatid exchange frequency (see Section 4.3). Findings in human cells were generally consistent with those in other mammalian cells; however, whether this finding of consistency extends to effects in vivo, and specifically to formation of tumors, is not known.

In addition, animal bioassays use various routes of administration (e.g., intraperitoneal and subcutaneous injection), which may not be directly relevant to expected routes of exposure for humans. It is difficult to determine whether the relative potency based on animal bioassays using injection routes of exposure is predictive of relative potency that would be observed in humans exposed through environmentally relevant exposure routes (see further discussion of exposure-route uncertainties in Section 8.6). An additional source of uncertainty in the use of animal bioassay data stems from differences in the doses used in animal bioassays as compared with low doses received by humans exposed in the environment. Mechanistic data, primarily obtained using benzo[a]pyrene, provide support for the human relevance of PAH tumorigenicity in animals. There is evidence linking three pathways activating benzo[a]pyrene to DNA-reactive agents [(+)-anti-BPDE, radical cations, benzo[a]pyrene-7,8-dione, and reactive oxygen species]

with key mutational events in genes (p53 tumor suppressor gene and H-ras or K-ras oncogenes) that can lead to tumor initiation. Results in support of mutagenic modes of action via the diol epoxide and radical cation pathways include in vivo results in animals. All of these activation pathways occur in human tissues, and associations have been made between spectra of mutations in the p53 tumor suppressor gene or ras oncogenes induced by benzo[a]pyrene metabolites with spectra of mutations in these genes in tumor tissue from benzo[a]pyrene-exposed animals or tumor tissue in humans.

Support for the association between the diol epoxide pathway and tumor initiation includes observation that: (+)-anti-BPDE activated the H-ras-1 proto-oncogene to transform NIH/3T3 cells via G→T point mutations in the 12th codon (Marshall et al., 1984); (+)-anti-BPDE reacts with the p53 tumor suppressor gene at several hotspots mutated in lung cancer patients (Denissenko et al., 1996; Puisieux et al., 1991); the spectra of p53 and K-ras mutations in lung tumors of nonsmoking patients, chronically exposed to smoky coal emissions, was consistent with (+)-anti-BPDE mutations in these genes (DeMarini et al., 2001); elevated BPDE-DNA adducts have been observed in coke oven workers and chimney sweepers (Pavanello et al., 1999); and the spectra of mutation in the K-ras, H-ras, and p53 genes in forestomach tumors of mice fed benzo[a]pyrene in the diet for 2 years were consistent with (+)-anti-BPDE DNA reactions (Culp et al., 2000).

Support for the radical cation pathway includes observations that depurinated adducts, (expected products from reactions of benzo[a]pyrene radical cations with DNA) accounted for 74% of identified DNA adducts in mouse skin exposed to benzo[a]pyrene (Rogan et al., 1993) and 9/13 examined tumors from mice exposed to dermal applications of benzo[a]pyrene had H-ras oncogene mutations attributed to depurinated DNA adducts from benzo[a]pyrene radical cations (Chakravarti et al., 1995).

Support for the aldo-keto reductase pathway includes in vitro demonstration that several types of DNA damage can occur from o-quinones and reactive oxygen species (Park et al., 2006; Balu et al., 2004; McCoull et al., 1999; Flowers-Geary et al., 1997, 1996), benzo[a]pyrene-7,8-dione can induce mutations in the p53 tumor suppressor gene using an in vitro yeast reporter gene assay (Park et al., 2008; Shen et al., 2006; Yu et al., 2002), and dominant p53 mutations induced by benzo[a]pyrene,7,8-dione in this system corresponded with p53 mutation hotspots observed in human lung cancer tissue (Park, 2008).

All three activation pathways are expected to occur in human tissues (Jiang et al., 2007), and associations have been made between spectra of mutations in the p53 tumor suppressor gene or ras oncogenes induced by benzo[a]pyrene metabolites with spectra of mutations in these genes in tumor tissue from benzo[a]pyrene-exposed animals or humans. In particular, DeMarini et al. (2001) demonstrated mutations in the p53 tumor suppressor gene and the K-ras oncogene in the lung tumors of nonsmokers, whose tumors were associated with exposure to smoky coal.

The available information supporting these actions for benzo[a]pyrene is consistent with what is known about the mode of action for other PAHs demonstrated to induce cancer in animals, including cyclopenta[cd]pyrene, dibenz[a,h]anthracene, and dibenzo[a,l]pyrene (Cogliano et al., 2008; Straif et al., 2005). All PAHs that have been studied require metabolic activation to produce carcinogenic responses in animals, and there is evidence for activation to DNA reactive intermediates via several pathways (Straif et al., 2005; Xue and Warshawsky, 2005; WHO, 1998; Cavalieri and Rogan, 1995). For example, incubation of rat liver microsomes with dibenzo[a,l]pyrene, a PAH that is more tumorigenically potent than benzo[a]pyrene in mouse skin and rat mammary tissue, formed depurinated DNA adducts from the radical cation pathway, as well as DNA adducts from the diol epoxide pathway (Cavalieri and Rogan, 1995).

In summary, the relevance of animal bioassay data to the prediction of human carcinogenic potency remains a significant area of uncertainty in the use of this and other approaches to PAH cancer risk assessment. However, mechanistic data on benzo[a]pyrene and other PAHs provide evidence that the molecular events leading to PAH-induced tumor formation in animals are relevant to humans.

8.5. ASSUMPTIONS OF A COMMON MODE OF ACTION AND DOSE ADDITIVITY

A discussion of the potential modes of action for PAH carcinogenicity is presented in Section 2.4. Individual carcinogenic PAHs are linked by a common effect (i.e., tumorigenicity), which may occur through multiple mechanisms. Reactive metabolites produced during metabolic transformations of PAHs include diol epoxides, reactive oxygen species, radical cations, and o-quinones. The formation of these metabolites is not mutually exclusive, and the carcinogenic process for PAHs is likely to be related to some combination of molecular events resulting from formation of several reactive species. Reactive metabolites of PAHs interact with DNA to form adducts and produce DNA damage resulting in mutations in cancer-related genes such as tumor suppressor genes or oncogenes. These events appear to reflect the initiation potency of an individual PAH (e.g., strong mutagens are generally potent initiators) (Sjogren et al., 1996). Certain PAHs exhibit promotional effects that may be related to cytotoxicity and the formation of reactive oxygen species, AHR affinity, and the upregulation of genes related to biotransformation (i.e., induction of CYP1A1), growth, and differentiation (Bostrom et al., 2002). The inhibition of gap junctional intracellular communication is also related to tumor promotion by PAHs (Bostrom et al., 2002). The ability of certain PAHs to act as tumor promoters as well as initiators may increase their carcinogenic potency in animal bioassays conducted at high doses. Initiation potency may be more relevant to low-level environmental exposure in humans (Bostrom et al., 2002; Sjogren et al., 1996); however, the proposed RPF approach is not unduly affected by this as it relies largely on high-dose animal bioassay data for

selecting RPF values. This represents an uncertainty in the use of the RPF approach in estimating human cancer risks from PAHs.

Conceptually, the uncertainty related to relative potency for initiation versus promotion could be reduced by using separate RPF schemes for each part of the carcinogenic process. This would require selection of indicator compounds that best represent the initiation and promotion processes, and use of mechanistic data to determine relative potency for each process (i.e., mutagenicity for initiation, AhR binding, or enzyme induction for promotion). There are several problems with this approach, including the lack of data to support the selection of indicator compounds and the complete carcinogenic nature of many PAHs (i.e., they act as both initiators and promoters). The initiation and promotion potency of an individual PAH is determined by its chemical structure. Some PAHs are strong mutagens, but have low affinity for the AhR (e.g., fjord-region PAHs) (Bostrum et al., 2002; Sjogren et al., 1996). Other PAHs are complete carcinogens, with initiating properties (i.e., mutagenesis) and AhR affinity leading to tumor promotion (e.g., benzo[a]pyrene, dibenz[a,h]anthracene) (Bostrum et al., 2002; Sjogren et al., 1996). Benzo[a]pyrene is considered a good indicator compound for similar PAHs with complete carcinogenic activity. However, the relative potency of other PAHs, especially those that act primarily via either initiation or promotion, may be over- or underestimated.

There is evidence that an assumption of similar toxicological action is reasonable for PAHs; however, the carcinogenic process for individual PAHs is likely to be related to some unique combination of multiple molecular events resulting from formation of several reactive species. The absence of a clearly-defined common mode of action increases the level of uncertainty associated with the use of an RPF approach. It is not possible to determine whether cancer risks would be under- or overestimated by using a PAH RPF approach that assumes a common mode of action. The assumption that interactions among PAH mixture components do not occur at low levels of exposure cannot be conclusively demonstrated using experimental approaches. The experimental data relating to dose additivity for PAH carcinogenicity are discussed in Section 2.8. It appears that interactions may occur at higher doses of PAH mixtures given in combination. This remains a significant uncertainty in the proposed RPF approach.

8.6. EXTRAPOLATION OF RPFs ACROSS EXPOSURE ROUTES

The peer consultation workshop (U.S. EPA, 2002) also identified uncertainty in extrapolation of RPFs across exposure routes. As with the 1993 *Provisional Guidance*, RPFs proposed in this analysis are also based on in vivo bioassay data collected using various routes of administration (e.g., dermal, intraperitoneal, subcutaneous, intramammillary, intramuscular, or intravenous injection, as well as lung implantation, tracheal implantation, and transplacental exposure after subcutaneous injection). The RPF approach considers each bioassay type equivalent for the purpose of determining relative potency to benzo[a]pyrene.

Table 8-3 compares the average RPFs (calculated from raw numbers and rounded to one significant digit) based on tumor bioassay data for each PAH across exposure routes. Dermal studies are shown collectively as well as separated by study type (complete or initiation). Likewise, intraperitoneal studies are shown grouped as well as separated by target organ (lung and liver).

Table 8-3. Comparisons among average tumor bioassay RPF values by exposure route and target organ

PAH	Dermal		Dermal complete		Dermal initiation		Intraperitoneal		Intraperitoneal, target organ = lung		Intraperitoneal, target organ = liver		Lung implantation		Oral	
	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average
AA	1	0.5	1	0.5	–	–	–	–	–	–	–	–	1	0.2	–	–
AC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
BaA	1	0.02	–	–	1	0.02	2	0.2[a]	1	0.08	2	0.4	–	–	–	–
BbcAC (1,12-MBA)	1	0.05	–	–	1	0.05	–	–	–	–	–	–	–	–	–	–
BbF	2	0.4	1	0.3	1	0.4	2[b]	1[c]	1	1	–	–	1	0.1	–	–
BcFE	–	–	–	–	–	–	1	1[d]	1	1	–	–	–	–	1	50
BeAC	2	0.8	–	–	2	0.8	–	–	–	–	–	–	–	–	–	–
BghiP	–	–	–	–	–	–	–	–	–	–	–	–	1	0.009	–	–
BjAC	–	–	–	–	–	–	1	60[d]	1	60	–	–	–	–	–	–
BjF	2	0.03	–	–	2	0.03	2[b]	0.7[a]	1	0.4	1	1	1	0.03	–	–
BkF	1	0.03	–	–	1	0.03	–	–	–	–	–	–	1	0.03	–	–
BlAC	2	5	–	–	2	5	–	–	–	–	–	–	–	–	–	–
CH	5	0.1	–	–	5	0.1	1	0.2[a]	–	–	1	0.2	1	0.04	–	–
CPcdP	4	0.3	2	0.4	2	0.2	1	1[d]	1	1	–	–	–	–	–	–
CPdefC	2	0.3	–	–	2	0.3	–	–	–	–	–	–	–	–	–	–
DBacA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
DBaeF	2	0.9	1	1	1	0.7	–	–	–	–	–	–	–	–	–	–
DBaeP	2	0.4	1	0.3	1	0.4	–	–	–	–	–	–	–	–	–	–
DBahA	1	1	–	–	1	1	1	40[d]	1	40	–	–	1	2	–	–
DBahP	1	0.9	–	–	1	0.9	–	–	–	–	–	–	–	–	–	–
DBaiP	2	0.6	1	0.7	1	0.5	–	–	–	–	–	–	–	–	–	–
DBalP	2	30	–	–	2	30	1	30[d]	1	30	–	–	–	–	–	–
FA	–	–	–	–	–	–	5	0.08[a]	4	0.05	1	0.2	–	–	–	–
IP	–	–	–	–	–	–	–	–	–	–	–	–	1	0.07	–	–
N23eP	1	0.3	–	–	1	0.3	–	–	–	–	–	–	–	–	–	–

Table 8-3. Comparisons among average tumor bioassay RPF values by exposure route and target organ

PAH	Dermal		Dermal complete		Dermal initiation		Intraperitoneal		Intraperitoneal, target organ = lung		Intraperitoneal, target organ = liver		Lung implantation		Oral	
	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average
PH	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pyr	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

[a]Newborn mouse model.
[b]Number of intraperitoneal RPFs includes those calculated for combined lung and liver incidence; these are not included in numbers of RPFs with lung or liver tumors.
[c]Includes both newborn mouse and adult A/J mouse models.
[d]Adult A/J mouse model.

The table shows a marked difference between the oral and intraperitoneal RPFs for benzo[c]fluorene (BcFE) (RPF = 50 for oral multiplicity and RPF = 1 for intraperitoneal incidence). However, as discussed earlier, this difference may result more from the use of a high tumor number to calculate the oral multiplicity RPF for this compound than route differences; if the oral incidence RPF is used for comparison, the two routes are more similar (RPF = 1 for intraperitoneal incidence versus RPF = 5 for oral incidence). Based on the latter comparison, which represents the only data with which to compare oral RPFs with those calculated from other routes, there appears to be fairly good correspondence between intraperitoneal and oral RPFs; however, this is based on only one PAH.

Based on the comparisons in the table, RPFs based on initiation and complete dermal carcinogenicity studies are similar (within a factor of 2). However, there are few PAHs with both types of dermal studies.

With respect to other route comparisons, the table generally shows that RPFs calculated from lung implantation and dermal studies are of the same order of magnitude, while RPFs calculated from intraperitoneal studies are higher for most compounds. The intraperitoneal RPF for dibenzo[a,l]pyrene is similar to its dermal RPF. At first glance, one might attribute the higher intraperitoneal RPFs calculated from newborn mouse assays (footnoted "a" in the table) to greater sensitivity of the newborn mouse, compared with an adolescent or adult mouse, to the carcinogenic action of PAHs. However, since the RPFs reflect potency of the PAH relative to benzo[a]pyrene, and not potency of the newborn mouse relative to other systems, the higher RPF cannot reflect a greater sensitivity of the animal model, since both the PAH of interest and benzo[a]pyrene have been tested in the same model. There is little information to evaluate whether RPFs from newborn mouse studies tend to be higher or lower than the adult A/J mouse model when both are exposed via intraperitoneal injection. Only one compound, benzo[b]fluoranthene (BbF), had RPFs calculated from both newborn mouse and adult A/J mouse models, and the values were similar; the newborn mouse RPF was 2, while the A/J mouse RPF was 1. In summary, it is not clear whether the intraperitoneal RPFs are higher than dermal or lung implantation RPFs due to route-specific differences or animal model differences (for example, differential metabolism in various animal systems).

Cross-route extrapolation of relative potency estimates is a necessary, though uncertain, aspect of the RPF approach. It is difficult to determine which of the available study types (e.g., dermal, intraperitoneal, intratracheal) is most predictive of potential risks from oral and inhalation exposure in humans. In order to prioritize bioassays by exposure route, robust data are needed on relative potencies for oral and inhalation exposures for comparison with relative potencies based on other exposure routes.

The inhalation RPF scheme used by the California EPA (2004) employed a hierarchy of bioassay data based on exposure route (inhalation studies were preferred, followed by

intratracheal or intrapulmonary instillation, oral administration, skin-painting, and subcutaneous or intraperitoneal injection). Apart from the obvious preference for exposure routes that targeted the respiratory tract (inhalation, intratracheal, intrapulmonary), the basis for prioritizing the other exposure routes is not evident. Pufulete et al. (2004), who were also focused on PAHs as air contaminants, suggested that the clearance of PAHs after intratracheal instillation may be similar to clearance after inhalation exposure. The authors acknowledged that the high concentrations of PAHs used in intratracheal and intrapulmonary instillation studies may lead to major differences in pharmacokinetics, compared with inhalation exposure (Pufulete et al., 2004). Nevertheless, the authors suggested that intratracheal instillation of low doses of PAHs might be an appropriate surrogate exposure model for assessing relative potency of inhalation exposure. It is important to note that no intratracheal instillation studies were identified in the search for studies from which to calculate RPFs; thus, the information provided by Pufulete et al. (2004) is not directly useful for suggesting route-specific RPFs. Pufulete et al. (2004) did not provide any specific information on the relevance of intrapulmonary administration (a route used in several of the bioassays used to calculate RPFs) to inhalation exposure.

As noted by U.S. EPA (2004), cross-route extrapolation would be contraindicated if there were convincing toxicokinetic evidence that absorption of PAHs does not occur by one or more exposure routes. Available data on the absorption of PAHs indicate that, in general, PAHs are readily absorbed via ingestion, inhalation, and dermal exposure routes; however, the rate of uptake varies with route and other factors (e.g., matrix, intake of fats and oils) (ATSDR, 1995). Evidence for absorption of PAHs through these routes includes measurement of PAH-DNA adducts at sites distal from the route of entry, measurement of urinary metabolites, and radiotracer studies in animals (ATSDR, 1995). U.S. EPA (2004) indicated that demonstration of any degree of uptake for each of the routes of interest is sufficient to allow the qualitative judgment to apply the route-to-route extrapolation; thus, cross-route extrapolation is supported by current data on the bioavailability of PAHs across several exposure routes.

U.S. EPA (2004, 1994) also noted that point-of-entry toxicity may be considered contrary evidence for cross-route extrapolation. With respect to PAHs, available information on this issue is mixed. The one inhalation bioassay of benzo[a]pyrene (Thyssen et al., 1981) identified the upper respiratory tract as the site of tumor formation, suggesting a point-of-entry effect; however, the authors did not specify the organs that were examined histologically in the study. Dermal bioassays of benzo[a]pyrene have generally evaluated only skin tumors, precluding their use in determining whether distal tumors are induced. A number of early oral cancer bioassays of benzo[a]pyrene suggested that tumor formation was limited to the forestomach (Rigdon and Neal, 1969, 1966; Neal and Rigdon, 1967). In oral carcinogenicity bioassays of MGP residue (Weyand et al., 1995) and coal tar preparations (Culp et al., 1998; Gaylor et al., 1998) that included separate groups exposed to benzo[a]pyrene, there were significant differences in target organ distribution of tumors between benzo[a]pyrene and the complex mixtures.

Benzo[a]pyrene-induced tumors were observed primarily at the point of contact (i.e., the forestomach), while MGP residue and coal tar produced tumors in the lung, liver, forestomach, skin, and other organs. Other PAHs (e.g., benzo[c]fluorene) were proposed as the primary compounds responsible for tumors at distal sites such as the lung (Koganti et al., 2000; Culp et al., 1998). However, a gavage study in rats (Kroese et al., 2001) and a dietary study in A/J mice (Weyland et al., 2004) each demonstrated that oral exposure to benzo[a]pyrene could induce tumors at distal sites, including the lung, liver, and auditory canal. Tissue-specific differences in metabolic activation and DNA binding of PAHs may contribute to the observed differences in target organ sensitivity (Weyand and Wu, 1995; Culp and Beland, 1994).

In summary, available information provides some support for cross-route extrapolation. Absorption of PAHs across oral, inhalation, and dermal routes is evident and, while many of the cancer bioassays of benzo[a]pyrene suggested tumor formation limited to the point-of-entry, at least one recent study (Kroese et al., 2001) suggests that tumors may also be induced at distal sites. Furthermore, there is evidence that other PAHs (e.g., benzo[c]fluorene) may induce tumors at distal sites after oral exposure (Weyand et al., 2004; Koganti et al., 2000; Culp et al., 1998). However, cross-route extrapolation of RPFs is a significant source of uncertainty in this approach.

Another approach to the issue of route-to-route extrapolation would be to prefer RPFs derived from particular target tissues deemed relevant to the exposure route of interest. For example, RPFs based on lung tumor data might be preferred for use in inhalation risk assessment. To examine whether lung tumor RPFs were consistent across routes, RPFs calculated from lung tumor potency in intraperitoneal studies (both newborn mouse and adult A/J mouse models) were compared with RPFs from lung implantation studies in Table 8-3. RPFs for both intraperitoneal-lung and lung implantation studies were available for only four compounds (benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, and dibenz[a,h]anthracene); for each of these, the intraperitoneal lung tumor RPF exceeded the lung implantation RPF. No information assessing the concordance between lung tumor potency after intraperitoneal administration and inhalation cancer potency was identified in the literature. The use of the final RPFs derived in this analysis across all routes of exposure is recommended given the information outlined above and in the absence of data to indicate otherwise.

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APPENDIX B. BIBLIOGRAPHY OF STUDIES WITHOUT BENZO[A]PYRENE AS A REFERENCE COMPOUND

Table B-1. Bioassays with and without benzo[a]pyrene by PAH

		Bioassays with benzo[a]pyrene						Bioassays without benzo[a]pyrene					
		Dermal		Intra-	Sub-			Dermal		Intra-	Sub-		
PAH[a]	CASRN	Initiation	Complete	peritoneal	cutaneous	Oral	Other	Initiation	Complete	peritoneal	cutaneous	Oral	Other
Aceanthrylene	202-03-09												
Acenaphthene	83-32-9												
Acenaphthylene	208-96-8												
Acephenanthrylene	201-06-9												
Acepyrene, 2,3-	25732-74-5	x	x										
Anthanthrene	191-26-4	x	x				x	x	x				
Anthracene	120-12-7	x	x		x			x	x	x	x	x	x
Benz[a]anthracene	56-55-3	x	x	x	x	x	x	x	x	x	x	x	x
Benz[b]anthracene	92-24-9												
Benz[b,c]aceanthrylene, 11H-	202-94-8	x											
Benz[e]aceanthrylene	199-54-2												
Benz[j]aceanthrylene	202-33-5			x				x					
Benz[l]aceanthrylene	211-91-6	x											
Benzacenaphthylene	76774-50-0												
Benzo[a]fluoranthene	203-33-8							x					
Benzo[a]fluorene	238-84-6 or 30777-18-5							x					
Benzo[a]perylene	191-85-5												
Benzo[b]chrysene	214-17-5							x					
Benzo[b]fluoranthene	205-99-2	x	x	x			x	x		x			x
11H-Benzo[b]fluorene	243-17-4 or 30777-19-6							x					
Benzo[b]perylene	197-70-6												
Benzo[c]chrysene	194-69-4												
Benzo[c]fluorene	205-12-9 or 30777-20-9							x					
Benzo[c]phenanthrene	195-19-7							x	x	x	x		
Benzo[e]pyrene	192-97-2	x	x				x	x		x			
Benzo[g]chrysene	196-78-1												
Benzo[g,h,i]fluoranthene	203-12-3	x	x										
Benzo[g,h,i]perylene	191-24-2	x	x				x	x					
Benzo[j]fluoranthene	205-82-3	x	x	x			x	x		x			x
Benzo[k]fluoranthene	207-08-9	x	x	x			x	x					
Benzophenanthrene	65777-08-4												
Chrysene	218-01-9	x	x	x	x		x	x	x	x	x		
Coronene	191-07-1		x					x					
Cyclopenta[c,d]pyrene	27208-37-3	x	x	x						x			
Cyclopenta[d,e,f]chrysene, 4H-	202-98-2	x								x			
Cyclopenta[d,e,f]phenanthrene, 4H-	203-64-5												
Cyclopenta[h,i]acephenanthrylene	114959-37-4												

Table B-1. Bioassays with and without benzo[a]pyrene by PAH

		Bioassays with benzo[a]pyrene							Bioassays without benzo[a]pyrene					
		Dermal		Intra-	Sub-				Dermal		Intra-	Sub-		
PAH[a]	CASRN	Initiation	Complete	peritoneal	cutaneous	Oral	Other		Initiation	Complete	peritoneal	cutaneous	Oral	Other
Cyclopenta[h,i]aceanthrylene	131581-33-4													
Cyclopentaphenanthrene	219-08-9													
Cyclopenteno-1,2-benzanthracene, 5,6-	7099-43-6											x		
Dibenz[a,c]anthracene	215-58-7	x	x						x	x	x	x		
Dibenzo[a,e]fluoranthene	5385-75-1	x	x						x					
Dibenz[a,j]anthracene	224-41-9								x					
Dibenzo[b,e]fluoranthene	2997-45-7													
Dibenzo[a,c]fluorene, 13H-	201-65-0													
Dibenzo[a,e]pyrene	192-65-4	x	x						x					
Dibenzo[a,f]fluoranthene	203-11-2	x	x						x	x				
Dibenzo[a,g]fluorene, 13H-	207-83-0									x				
Dibenz[a,h]anthracene	53-70-3	x	x	x	x	x	x		x	x	x	x	x	x
Dibenzo[a,h]pyrene	189-64-0	x	x						x		x			
Dibenzo[a,i]pyrene	189-55-9	x	x						x	x	x	x		x
Dibenzo[a,l]pyrene	191-30-0	x	x	x					x	x	x	x	x	
Dibenzo[e,l]pyrene	192-51-8	x	x											
Dibenzo[h,rst]pentaphene	192-47-2													
Dibenz[k,mno]acephenanthrylene	153043-81-3													
Dibenzo[j,mno]acephenanthrylene	153043-82-4													
Dihydroaceanthrylene, 1,2-	641-48-5											x		
Fluoranthene	206-44-0	x	x	x							x			x
Fluorene	86-73-7								x	x				
Indeno[1,2,3-c,d]fluoranthene	193-43-1													
Indeno[1,2,3-c,d]pyrene	193-39-5	x	x	x			x		x					
Naphtho[1,2-b]fluoranthene	111189-32-3								x					
Naphtho[1,2,3,-mno]acephenanthrylene	113779-16-1													
Naphtho[2,1-a]fluoranthene	203-20-3								x					
Naphtho[2,3-a]pyrene	196-42-9													
Naphtho[2,3-e]pyrene	193-09-9	x	x											
Pentacene	135-48-8													
Pentaphene	222-93-5													
Perylene	198-55-0	x	x						x					
Phenanthrene	85-01-8	x	x	x	x	x	x		x	x	x	x		x
Picene	213-46-7								x	x	x	x		
Pyrene	129-00-0	x	x	x			x		x					x
Tribenzofluoranthene 3,4-10,11-12,13-	13579-05-0													
Triphenylene	217-59-4		x											

[a]PAHs in bold have at least one bioassay without benzo[a]pyrene and no bioassays with benzo[a]pyrene.

B.1. BIBLIOGRAPHY OF BIOASSAYS WITHOUT BENZO[A]PYRENE

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B.2. BIBLIOGRAPHY OF STUDIES ON CANCER-RELATED ENDPOINTS WITHOUT BENZO[A]PYRENE

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APPENDIX C. DOSE-RESPONSE DATA FOR POTENCY CALCULATIONS

Table C-1. Dermal bioassays: dose-response information for incidence data

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	Comments
Complete carcinogenicity studies															
600	Habs et al., 1980	Complete	Mice	Sum of Papilloma, carcinoma, sarcoma	Acetone	F	0	µg/animal	0	35	0				
					DMSO	F	0	µg/animal	0	36	0				
					BaP	F	1.7	µg/animal	8	34	24		1.92×10^{-3}		
					BaP	F	2.8	µg/animal	24	35	69		1.67×10^{-11}		
					BaP	F	4.6	µg/animal	22	36	61		2.1×10^{-9}	2.15×10^{-9}	
					BbF	F	3.4	µg/animal	2	38	5		2.6×10^{-1}		
					BbF	F	5.6	µg/animal	5	34	15		2.3×10^{-2}		
					BbF	F	9.2	µg/animal	20	37	54		3.7×10^{-8}	1.33×10^{-9}	
					BjF	F	3.4	µg/animal	1	38	3		5.1×10^{-1}		
					BjF	F	5.6	µg/animal	1	35	3		4.9×10^{-1}		
					BjF	F	9.2	µg/animal	2	38	5		2.6×10^{-1}	1.77×10^{-1}	
					BkF	F	3.4	µg/animal	1	39	3		5.2×10^{-1}		
					BkF	F	5.6	µg/animal	0	38	0				
					BkF	F	9.2	µg/animal	0	38	0				
					CPcdP	F	1.7	µg/animal	0	34	0				
					CPcdP	F	6.5	µg/animal	0	35	0				
					CPcdP	F	27.2	µg/animal	3	38	8		1.3×10^{-1}	6.36×10^{-2}	
					IP	F	3.4	µg/animal	1	36	3		5×10^{-1}		
					IP	F	5.6	µg/animal	0	37	0				
					IP	F	9.2	µg/animal	0	37	0				
					CO	F	5.6	µg/animal	1	39	3		0.52		
					CO	F	15	µg/animal	2	40	5		0.27	1.83×10^{-1}	
13640	Cavalieri et al., 1983	Complete	Mice	Papilloma, adenoma, carcinoma	Acetone	F	0	nmol	0	29	0				
					BaP	F	2.2	nmol	2	30	7		0.25		
					BaP	F	6.6	nmol	2	28	7		0.24		

Table C-1. Dermal bioassays: dose-response information for incidence data

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	Comments
					BaP	F	20	nmol	17	30	57		4.32×10^{-7}	2.96×10^{-1}	
					CPcdP	F	22.2	nmol	2	29	7		0.25		
					CPcdP	F	66.6	nmol	2	29	7		0.25		
					CPcdP	F	200	nmol	24	29	83		9.25×10^{-12}	1.39×10^{-16}	
620	Hoffmann and Wynder 1966	Complete	Mice	Papilloma	Dioxane	F	0	%	0	20	0				
					BaP	F	0.05	%	17	20	85		1.28×10^{-8}		
					BaP	F	0.1	%	19	20	95		1.5×10^{-10}	8.7×10^{-10}	
					DBaeP	F	0.05	%	16	30	53		3.31×10^{-5}		
					DBaeP	F	0.1	%	9	17	53		1.95×10^{-4}	5.69×10^{-4}	
					DBahP	F	0.05	%	16	17	94		1.32×10^{-9}		
					DBahP	F	0.1	%	15	18	83		5.27×10^{-8}	1.29×10^{-7}	
					DBaiP	F	0.05	%	16	19	84		2.58×10^{-9}		
					DBaiP	F	0.1	%	16	19	84		2.58×10^{-9}	9.81×10^{-8}	
					DBaeF	F	0.05	%	17	19	89		3.35×10^{-9}		
					DBaeF	F	0.1	%	18	19	95		3.05×10^{-10}	1.13×10^{-9}	
17660	Cavalieri et al., 1977	Complete	Mice	Papilloma, kerato-acanthoma, carcinoma	Acetone	F	0	µmol/ap-plication	0	29	0				
					BaP	F	0.396	µmol/ap-plication	30	38	79		4.9×10^{-12}		
					DBahP	F	0.396	µmol/ap-plication	35	39	90		2.98×10^{-15}		
					AA	F	0.396	µmol/ap-plication	18	38	47		3.59×10^{-6}		
					BaA	F	0.396	µmol/ap-plication	1	39	3		0.66		

Table C-1. Dermal bioassays: dose-response information for incidence data

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	Comments
Initiation studies															
630	LaVoie et al., 1982	Initiation	Mice	Primarily squamous cell papilloma	Acetone/ TPA	F	0	µg/mouse	0	20	0				
					BaP	F	30	µg/mouse	17	20	85		1.28×10^{-8}		
					BbF	F	10	µg/mouse	9	20	45		6.14×10^{-4}		
					BbF	F	30	µg/mouse	12	20	60		2.25×10^{-5}		
					BbF	F	100	µg/mouse	16	20	80		7.7×10^{-8}	1.46×10^{-5}	
					BjF	F	30	µg/mouse	6	20	30		0.01		
					BjF	F	100	µg/mouse	11	20	55		7.27×10^{-5}		
					BjF	F	1,000	µg/mouse	19	20	95		1.52×10^{-10}	4.67×10^{-8}	
					BkF	F	30	µg/mouse	1	20	5		0.01		
					BkF	F	100	µg/mouse	5	20	25		0.02		
					BkF	F	1,000	µg/mouse	15	20	75		3.85×10^{-7}	4.51×10^{-9}	
18570	Hecht et al., 1974	Initiation	Mice	Unspeci-fied	Acetone	F	0	mg/mouse	0	20	0				Number of surviving not reported for controls; initial group size used here
					BaP	F	0.05	mg/mouse	6	20	30		0.01		
					CH	F	1	mg/mouse	11	19	58		4.51×10^{-5}		
24800	Nesnow et al., 1984	Initiation	Mice	Papilloma	Acetone	M	0	nmol	0	20	0				Data at 30 wks
					Acetone	F	0	nmol	1	19	5				
					BaP	M	200	nmol	13	18	67	<0.005			
					BaP	F	200	nmol	10	19	53	<0.005			
					BlAC	M	50	nmol	12	20	60	<0.005			
					BlAC	M	100	nmol	16	17	94	<0.005			
					BlAC	M	250	nmol	21	21	100	<0.005			
					BlAC	M	500	nmol	16	16	100	<0.005			

Table C-1. Dermal bioassays: dose-response information for incidence data

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	Comments
					BlAC	M	1,000	nmol	19	20	95	<0.005			
					BlAC	F	50	nmol	13	20	65	<0.005			
					BlAC	F	100	nmol	18	19	95	<0.005			
					BlAC	F	250	nmol	19	21	91	<0.005			
					BlAC	F	500	nmol	20	21	95	<0.005			
					BlAC	F	1,000	nmol	20	20	100	<0.005			
					BeAC	M	50	nmol	4	20	20				
					BeAC	M	100	nmol	4	20	20				
					BeAC	M	250	nmol	12	20	60	<0.005			
					BeAC	M	500	nmol	15	20	75	<0.005			
					BeAC	M	1,000	nmol	16	18	89	<0.005			
					BeAC	F	50	nmol	4	20	20				
					BeAC	F	100	nmol	7	19	37	<0.005			
					BeAC	F	250	nmol	10	19	53	<0.005			
					BeAC	F	500	nmol	8	18	44	<0.005			
					BeAC	F	1,000	nmol	18	20	90	<0.005			
21420	Slaga et al., 1980	Initiation	Mouse	Papilloma	Control	F	0	nmol	2	30	6				Different controls used for each chemical except DBacA and BeP
					Control	F	0	µmol	3	30	10				
					Control	F	0	µmol	3	30	10				
					Control	F	0	nmol	2	29	6				
					Control pooled	F	0	nmol	10	119	8				
					BaP	F	200	nmol	20	30	67		1.41×10^{-6}		
					BeP	F	2,000	nmol	5	29	17		0.33		
					CH	F	2,000	nmol	21	29	73		8.38×10^{-7}		
					DBacA	F	2,000	nmol	8	28	27		0.07		
					DBahA	F	100	nmol	15	29	50		3.52×10^{-6}		

Table C-1. Dermal bioassays: dose-response information for incidence data

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	Comments
15640	Raveh et al., 1982	Initiation	Mice	Papilloma	Control	F	0	µg	3	29	10				
					BaP	F	10	µg	17	29	58		1.11×10^{-4}		
					BaP	F	25	µg	21	28	76		5.96×10^{-7}		
					BaP	F	50	µg	24	28	87		5.43×10^{-9}		
					BaP	F	100	µg	27	27	100		5.50×10^{-13}		
					BaP	F	200	µg	26	26	100		1.03×10^{-12}	2.78×10^{-10}	
					CPcdP	F	10	µg	3	30	11		0.65		
					CPcdP	F	100	µg	11	29	39		0.01		
					CPcdP	F	200	µg	16	28	57		1.90×10^{-4}	2.75×10^{-6}	
620	Hoffmann and Wynder 1966	Initiation	Mice	Papilloma	Croton oil control	F	0	mg/mouse	2	30	7				
					BaP	F	0.25	mg/mouse	24	30	80		3.80×10^{-9}		
					DBaeF	F	0.25	mg/mouse	18	30	60		9.40×10^{-6}		
					DBaeP	F	0.25	mg/mouse	10	27	37		0.006		
					DBelP	F	0.25	mg/mouse	0	29	0		0.25		
					DBahP	F	0.25	mg/mouse	21	29	72		1.30×10^{-7}		
					DBaiP	F	0.25	mg/mouse	12	30	40		0.002		
					AA	F	0.25	mg/mouse	2	29	7		0.68		
					BghiP	F	0.25	mg/mouse	2	27	7		0.65		
					N23eP	F	0.25	mg/mouse	9	30	30		0.02		
					IP	F	0.25	mg/mouse	5	30	17		0.21		
13650	Cavalieri et al., 1981b	Initiation	Mice	Papilloma	Acetone/ TPA	F	0	µmol	3	29	10				
					BaP	F	0.2	µmol	12	30	40		0.009		
					CPcdP	F	0.2	µmol	1	30	3		0.29		
					CPcdP	F	0.6	µmol	9	29	31		0.05		
					CPcdP	F	1.8	µmol	6	29	21		0.24	0.14	
					ACEP	F	0.2	µmol	0	30	0		0.11		
					ACEP	F	0.6	µmol	1	30	3		0.29		

Table C-1. Dermal bioassays: dose-response information for incidence data

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	Comments
					ACEP	F	1.8	µmol	4	30	13		0.52	0.18	
15700	Rice et al., 1988	Initiation	Mice	Unspeci-fied	Acetone	F	0	µmol	1	20	5				
					BaP	F	0.1	µmol	17	19	89	<0.005			
					CH	F	0.15	µmol	5	20	25	<0.05			
					CH	F	0.5	µmol	18	20	90	<0.005			
					CH	F	1.5	µmol	19	20	95	<0.005		6.39×10^{-9}	
					CPdefC (4,5-MC)	F	0.15	µmol	13	20	65	<0.005			
					CPdefC (4,5-MC)	F	0.5	µmol	19	19	100	<0.005			
					CPdefC (4,5-MC)	F	1.5	µmol	19	19	100	<0.005		1.90×10^{-7}	
					BbcAC (1,12-MBA)	F	0.5	µmol	15	20	75	<0.005			
					BbcAC (1,12-MBA)	F	2	µmol	18	20	90	<0.005			
					BbcAC (1,12-MBA)	F	4	µmol	18	20	90	<0.005		3.03×10^{-6}	

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Table C-2. Dermal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis Fisher's exact *p*-value	Mean number tumors/ animal	Comments
Complete carcinogenicity															
13640	Cavalieri et al., 1983	Complete	Mice	Papilloma, adenoma, carcinoma	Acetone	F	0	nmol	0	29	0			0	Number tumors per animal at risk calculated
					BaP	F	2.2	nmol	2	30	7		>0.05	0.07	
					BaP	F	6.6	nmol	2	28	7		>0.05	0.07	
					BaP	F	20	nmol	17	30	57		<0.001	1.5	
					CPcdP	F	22.2	nmol	2	29	7		>0.05	0.07	
					CPcdP	F	66.6	nmol	2	29	7		>0.05	0.07	
					CPcdP	F	200	nmol	24	29	83		<0.001	2.45	
13650	Cavalieri et al., 1981b	Complete	Mice	Primarily squamous cell carcinoma	Acetone	US	0	µmol/ application	0	30	0			0	Number tumors per animal at risk calculated
					BaP	US	0.2	µmol/ application	30	30	100		<0.001	1.5	
					CPcdP	US	0.2	µmol/ application	17	30	57		<0.001	0.8	
					CPcdP	US	0.6	µmol/ application	11	30	37		<0.001	0.5	
					CPcdP	US	1.8	µmol/ application	7	30	23		0.0053	0.4	
					ACEP	US	0.2	µmol/ application	0	30	0		>0.05	0	
					ACEP	US	0.6	µmol/ application	1	30	3		>0.05	0.03	
					ACEP	US	1.8	µmol/ application	1	30	3		>0.05	0.03	
Initiation															
630	LaVoie et al., 1982	Initiation	Mice	Primarily squamous cell papilloma	Acetone/ TPA	F	0	µg/mouse	0	20	0			0	
					BaP	F	30	µg/mouse	17	20	85		<0.001	4.9	
					BbF	F	10	µg/mouse	9	20	45		<0.001	0.9	
					BbF	F	30	µg/mouse	12	20	60		<0.001	2.3	
					BbF	F	100	µg/mouse	16	20	80		<0.001	7.1	

Table C-2. Dermal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis Fisher's exact *p*-value	Mean number tumors/ animal	Comments
					BjF	F	30	µg/mouse	6	20	30		0.01	0.6	
					BjF	F	100	µg/mouse	11	20	55		<0.001	1.9	
					BjF	F	1,000	µg/mouse	19	20	95		<0.001	7.2	
					BkF	F	30	µg/mouse	1	20	5		>0.05	0.1	
					BkF	F	100	µg/mouse	5	20	25		0.02	0.4	
					BkF	F	1,000	µg/mouse	15	20	75		<0.001	2.8	
18570	Hecht et al., 1974	Initiation	Mice	Unspecified	Acetone	F	0	mg/animal	0	20	0			0	Number surviving not reported for controls; initial group size used here; number tumors per animal at risk calculated
					BaP	F	0.05	mg/animal	6	20	30		0.01	0.5	
					CH	F	1	mg/animal	11	19	61		<0.001	1	
21420	Slaga et al., 1980	Initiation	Mouse	Papilloma	Control	F	0	nmol	2	29	6			0.1	Different controls used for each chemical except DBacA and BeP
					Control	F	0	nmol	3	30	10			0.2	
					Control	F	0	nmol	3	30	10			0.1	
					Control	F	0	nmol	2	29	6			0.1	
					Control pooled	F	0	nmol	10	119	8			0.13	
					BaP	F	200	nmol	20	30	67		<0.001	2.2	
					BeP	F	2,000	nmol	5	29	17		>0.05	0.2	
					CH	F	2,000	nmol	21	29	73		<0.001	1.6	
					DBacA	F	2,000	nmol	8	28	27		>0.05	0.5	
					DBahA	F	100	nmol	15	29	50		<0.001	1.4	
15640	Raveh et al., 1982	Initiation	Mice	Papilloma	Control	F	0	µg	3	29	10			0.2	
					BaP	F	10	µg	17	29	58		<0.001	1.3	
					BaP	F	25	µg	21	28	76		<0.001	3.8	
					BaP	F	50	µg	24	28	87		<0.001	6.2	
					BaP	F	100	µg	27	27	100		<0.001	8.8	
					BaP	F	200	µg	26	26	100		<0.001	9	
					CPcdP	F	10	µg	3	30	11		>0.05	0.1	

Table C-2. Dermal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis Fisher's exact *p*-value	Mean number tumors/ animal	Comments
					CPcdP	F	100	µg	11	29	39		0.01	0.4	
					CPcdP	F	200	µg	16	28	57		<0.001	0.9	
13650	Cavalieri et al., 1981	Initiation	Mice	Papilloma	Acetone/ TPA	F	0	µmol	3	29	10			0.14	
					BaP	F	0.2	µmol	12	30	40		0.009	1.2	
					CPcdP	F	0.2	µmol	1	30	3		>0.05	0.03	
					CPcdP	F	0.6	µmol	9	29	31		0.05	0.31	
					CPcdP	F	1.8	µmol	6	29	21		>0.05	0.31	
					ACEP	F	0.2	µmol	0	30	0		>0.05	0	
					ACEP	F	0.6	µmol	1	30	3		>0.05	0.03	
					ACEP	F	1.8	µmol	4	30	13		>0.05	0.13	
21410	Slaga et al., 1978	Initiation	Mice	Papilloma	Acetone/ TPA	F	0	µmol	2	29	6			0.1	
					BaP	F	0.2	µmol	27	29	92		<0.001	5.3	
					BaA	F	2	µmol	17	30	57		<0.001	1.2	
16310	Weyand et al., 1992	Initiation	Mice	Unspecified	Acetone	US	0	µmol	1	21	5			0.05	
					BaP	US	0.01	µmol	24	24	100	<0.01		4.08	
					BjF	US	0.3	µmol	11	20	55	<0.01		1.75	
					BjF	US	1	µmol	21	24	88	<0.01		4.08	
					BjF	US	2	µmol	24	24	100	<0.01		7.17	
10200	El-Bayoumy et al., 1982	Initiation	Mice	Primarily squamous cell papilloma	Acetone	F	0	mg/mouse	1	20	5			0.1	
					BaP	F	0.05	mg/mouse	18	20	90	<0.01		7.1	
					CH	F	1	mg/mouse	20	20	100	<0.01		7.7	
					Pery	F	1	mg/mouse	1	20	5			0.1	
					Pyr	F	1	mg/mouse	4	20	20			0.2	
24300	Rice et al., 1985	Initiation	Mice	Unspecified	Acetone	F	0	mg/mouse	2	25	8			0.12	Mean number of tumors/animal digitally estimated from Figure 2 and rounded to even number tumors
					BaP	F	0.3	mg/mouse	24	25	96		<0.001	8.04	
					CH	F	1	mg/mouse	23	25	92		<0.001	5	

Table C-2. Dermal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis Fisher's exact *p*-value	Mean number tumors/ animal	Comments
					CPdefC	F	1	mg/mouse	24	24	100		<0.001	5.63	Number reported in text
13660	Cavalieri et al., 1991	Initiation	Mice	Primarily papilloma	Acetone	F	0	nmol	0	24	0			0	16-Wk experiment
					BaP	F	33.3	nmol	10	23	43		<0.001	0.65	
					BaP	F	100	nmol	17	24	71		<0.001	2.75	
					BaP	F	300	nmol	21	23	91		<0.001	5.22	
					DBalP	F	33.3	nmol	23	24	96		<0.001	6.75	
					DBalP	F	100	nmol	22	24	92		<0.001	7.92	
					DBalP	F	300	nmol	24	24	100		<0.001	8.5	
13660	Cavalieri et al., 1991	Initiation	Mice	Primarily papilloma	Acetone	F	0	nmol	0	24	0			0	27-Wk experiment
					BaP	F	4	nmol	1	24	4		>0.05	0.04	
					BaP	F	20	nmol	10	24	42		<0.001	0.75	
					BaP	F	100	nmol	22	24	92		<0.001	3.42	
					DBalP	F	4	nmol	22	24	92		<0.001	6.96	
					DBalP	F	20	nmol	20	24	83		<0.001	5.29	
					DBalP	F	100	nmol	20	24	83		<0.001	3.29	
16440	Wood et al., 1980	Initiation	Mice	Papilloma	Acetone	F	0	µmol	3	30	10			0.1	Number tumors per animal at risk calculated
					BaP	F	0.1	µmol	20	30	68	<0.05		2	
					BaP	F	0.4	µmol	22	30	73	<0.05		4.6	
					Pyr	F	0.1	µmol	4	30	14	>0.05		0.14	
					Pyr	F	0.4	µmol	3	30	10	>0.05		0.1	
					CPcdP	F	0.1	µmol	3	30	10	>0.05		0.1	
					CPcdP	F	0.4	µmol	6	30	21	>0.05		0.29	
18680	Hoffmann et al., 1972	Initiation	Mice	Papilloma	Acetone	F	0	mg	1	30	3			0.03	
					BaP	F	0.05	mg	19	29	66		<0.001	2.3	
					FA	F	1	mg	1	29	3		>0.05	0.03	
24800	Nesnow et al., 1984	Initiation	Mice	Papilloma	Acetone	M	0	nmol	0	20	0			0	
					Acetone	F	0	nmol	1	19	5			0.05	
					BaP	M	200	nmol	12	18	67		<0.001	1.4	
					BaP	F	200	nmol	10	19	53		0.0015	1.5	
					BeAC	M	50	nmol	4	20	20		>0.05	0.25	
					BeAC	F	50	nmol	4	20	20		>0.05	0.25	

Table C-2. Dermal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Study type	Species	Tumor type	PAH	Sex	Dose of PAH	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis Fisher's exact *p*-value	Mean number tumors/ animal	Comments
					BeAC	M	100	nmol	4	20	20		>0.05	0.4	
					BeAC	F	100	nmol	7	19	37		0.02	0.53	
					BeAC	M	250	nmol	12	20	60		<0.001	1.3	
					BeAC	F	250	nmol	10	19	53		<0.001	1.1	
					BeAC	M	500	nmol	15	20	75		<0.001	1.9	
					BeAC	F	500	nmol	8	18	44		0.007	1.2	
					BeAC	M	1,000	nmol	16	18	89		<0.001	3.1	
					BeAC	F	1,000	nmol	18	20	90		<0.001	2.2	
					BlAC	M	50	nmol	12	20	60		<0.001	1.4	
					BlAC	F	50	nmol	13	20	65		<0.001	1.1	
					BlAC	M	100	nmol	16	17	94		<0.001	2.3	
					BlAC	F	100	nmol	18	19	95		<0.001	3.1	
					BlAC	M	250	nmol	21	21	100		<0.001	8.4	
					BlAC	F	250	nmol	19	21	91		<0.001	4.7	
					BlAC	M	500	nmol	16	16	100		<0.001	10.8	
					BlAC	F	500	nmol	20	21	95		<0.001	6.6	
					BlAC	M	1,000	nmol	19	20	95		<0.001	8.7	
					BlAC	F	1,000	nmol	20	20	100		<0.001	10.8	

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Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bearing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
17560	Busby et al., 1989	Mice	Intraperitoneal	Lung	Adenoma + adenocarcinoma	DMSO	M	0	µg (total)	13	91	0.14				Stats reported for combined M and F only for each dose and treatment compared to control not individual sexes
				Lung	Adenoma + adenocarcinoma	DMSO	F	0	µg (total)	7	101	0.07				
				Lung	Adenoma + adenocarcinoma	BaP	M	59.5	µg (total)	13	28	0.46		7.2×10^{-4}		
				Lung	Adenoma + adenocarcinoma	BaP	F	59.5	µg (total)	19	27	0.70		3.96×10^{-11}		
				Lung	Adenoma + adenocarcinoma	Pyr	M	86.1	µg (total)	4	23	0.17		4.60×10^{-1}		
				Lung	Adenoma + adenocarcinoma	Pyr	F	86.1	µg (total)	1	28	0.04		4.50×10^{-1}		
				Lung	Adenoma + adenocarcinoma	Pyr	M	1,750	µg (total)	2	27	0.07		2.80×10^{-1}	3.13×10^{-1}	
				Lung	Adenoma + adenocarcinoma	Pyr	F	1,750	µg (total)	3	26	0.12		3.30×10^{-1}	3.50×10^{-1}	
				Lung	Adenoma + adenocarcinoma	FA	M	257.6	µg (total)	5	23	0.22		2.80×10^{-4}		
				Lung	Adenoma + adenocarcinoma	FA	F	257.6	µg (total)	9	29	0.31		1.65×10^{-3}		

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Expo-sure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bear-ing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Lung	Adenoma + adeno-carcinoma	CH	M	6.3	µg (total)	2	27	0.07		2.80×10^{-1}		
				Lung	Adenoma + adeno-carcinoma	CH	F	6.3	µg (total)	3	29	0.10		3.90×10^{-1}		
				Lung	Adenoma + adeno-carcinoma	CH	M	210	µg (total)	3	20	0.15		5.85×10^{-1}	8.03×10^{-1}	
				Lung	Adenoma + adeno-carcinoma	CH	F	210	µg (total)	0	29	0.00		1.60×10^{-1}	1.28×10^{-1}	
640	LaVoie et al., 1987	Mice	Intra-periton-eal	Lung	Adenoma	DMSO	M	0	µmol/ mouse	0	17	0				
				Lung	Adenoma	DMSO	F	0	µmol/ mouse	0	18	0				
				Lung	Adenoma	BaP	M	1.1	µmol/ mouse	14	17	0.82	<0.005			
				Lung	Adenoma	BaP	F	1.1	µmol/ mouse	9	14	0.64				
				Lung	Adenoma	BbF	M	0.5	µmol/ mouse	2	15	0.13	>0.05			
				Lung	Adenoma	BbF	F	0.5	µmol/ mouse	3	17	0.18	>0.05			
				Lung	Adenoma	BjF	M	1.1	µmol/ mouse	11	21	0.52	<0.005			
				Lung	Adenoma	BjF	F	1.1	µmol/ mouse	4	18	0.22	<0.05			
				Lung	Adenoma	BkF	M	2.1	µmol/ mouse	1	16	0.06	>0.05			
				Lung	Adenoma	BkF	F	2.1	µmol/ mouse	3	18	0.17	>0.05			

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Expo-sure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bear-ing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Lung	Adenoma	IP	M	2.1	µmol/ mouse	1	11	0.09				
				Lung	Adenoma	IP	F	2.1	µmol/ mouse	0	9	0				
				Liver	Adenoma + hepatoma	DMSO	M	0	µmol/ mouse	1	17	0.06				Adenoma and hepatoma also reported separately; none of animals surviving 35 wks
				Liver	Adenoma + hepatoma	DMSO	F	0	µmol/ mouse	0	18	0				
				Liver	Adenoma + hepatoma	BaP	M	1.1	µmol/ mouse	13	17	0.76	<0.005			
				Liver	Adenoma + hepatoma	BaP	F	1.1	µmol/ mouse	0	14	0				
				Liver	Adenoma + hepatoma	BbF	M	0.5	µmol/ mouse	8	15	0.53	<0.005			
				Liver	Adenoma + hepatoma	BbF	F	0.5	µmol/ mouse	0	17	0				
				Liver	Adenoma + hepatoma	BjF	M	1.1	µmol/ mouse	11	21	0.52	<0.005			
				Liver	Adenoma + hepatoma	BjF	F	1.1	µmol/ mouse	0	18	0				
				Liver	Adenoma + hepatoma	BkF	M	2.1	µmol/ mouse	3	16	0.19	>0.05			
				Liver	Adenoma + hepatoma	BkF	F	2.1	µmol/ mouse	0	18	0				
				Liver	Adenoma + hepatoma	IP	M	2.1	µmol/ mouse	0	11	0				
				Liver	Adenoma + hepatoma	IP	F	2.1	µmol/ mouse	0	9	0				
				Liver or lung	Adenoma + hepatoma	DMSO	M	0	µmol/ mouse	1	17	0.06				

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bearing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Liver or lung	Adenoma + hepatoma	DMSO	F	0	µmol/ mouse	0	18	0				
				Liver or lung	Adenoma + hepatoma	BaP	M	1.1	µmol/ mouse	13	17	0.76				
				Liver or lung	Adenoma + hepatoma	BaP	F	1.1	µmol/ mouse	9	14	0.64				
				Liver or lung	Adenoma + hepatoma	BbF	M	0.5	µmol/ mouse	8	15	0.53				
				Liver or lung	Adenoma + hepatoma	BbF	F	0.5	µmol/ mouse	3	17	0.18				
				Liver or lung	Adenoma + hepatoma	BjF	M	1.1	µmol/ mouse	17	21	0.81				
				Liver or lung	Adenoma + hepatoma	BjF	F	1.1	µmol/ mouse	4	18	0.22				
				Liver or lung	Adenoma + hepatoma	BkF	M	2.1	µmol/ mouse	3	16	0.19				
				Liver or lung	Adenoma + hepatoma	BkF	F	2.1	µmol/ mouse	3	18	0.17				
				Liver or lung	Adenoma + hepatoma	IP	M	2.1	µmol/ mouse	1	11	0.09				
				Liver or lung	Adenoma + hepatoma	IP	F	2.1	µmol/ mouse	0	9	0				
7510	LaVoie et al., 1994	Mice	Intraperitoneal	Lung	Total	DMSO	M	0	µmol/ mouse	5	29	0.17				Survival to 1 yr
				Lung	Total	DMSO	F	0	µmol/ mouse	4	34	0.12				
				Lung	Total	BaP	M	1.1	µmol/ mouse	24	32	0.75	<0.001			
				Lung	Total	BaP	F	1.1	µmol/ mouse	17	20	0.85	<0.001			

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Expo-sure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bear-ing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Lung	Total	FA	M	3.46	µmol/ mouse	12	28	0.43	<0.05			
				Lung	Total	FA	F	3.46	µmol/ mouse	11	31	0.35	<0.05			
				Lung	Total	FA	M	17.3	µmol/ mouse	11	17	0.65	<0.005		2.84×10^{-3}	
				Lung	Total	FA	F	17.3	µmol/ mouse	25	29	0.86	<0.001		2.18×10^{-9}	
				Liver	Foci + adenoma + carcinoma	DMSO	M	0	µmol/ mouse	5	29	0.17				Foci, adenomas, carcinomas also reported separately
				Liver	Foci + adenoma + carcinoma	DMSO	F	0	µmol/ mouse	2	34	0.06				
				Liver	Foci + adenoma + carcinoma	BaP	M	1.1	µmol/ mouse	27	32	0.84	<0.001			
				Liver	Foci + adenoma + carcinoma	BaP	F	1.1	µmol/ mouse	2	20	0.10	>0.05			
				Liver	Foci + adenoma + carcinoma	FA	M	3.46	µmol/ mouse	18	28	0.64	<0.001			
				Liver	Foci + adenoma + carcinoma	FA	F	3.46	µmol/ mouse	0	31	0				
				Liver	Foci + adenoma + carcinoma	FA	M	17.3	µmol/ mouse	17	17	1.00	<0.001		5.10×10^{-7}	
				Liver	Foci + adenoma + carcinoma	FA	F	17.3	µmol/ mouse	2	29	0.07			5.47×10^{-1}	

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bearing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
24590	Nesnow et al., 1998b	Mice	Intraperitoneal	Lung	NS	Control	M	0	mg/kg	6	20	0.30				Data provided by S. Nesnow
				Lung	NS	BaP	M	5	mg/kg	6	20	0.30		>0.05		
				Lung	NS	BaP	M	10	mg/kg	7	17	0.41		>0.05		
				Lung	NS	BaP	M	50	mg/kg	19	19	1.00		<0.001		
				Lung	NS	BaP	M	100	mg/kg	16	16	1.00		0.0018		
				Lung	NS	BaP	M	200	mg/kg	24	24	1.00		<0.001		
				Lung	NS	BbF	M	10	mg/kg	9	18	0.50		>0.05		
				Lung	NS	BbF	M	50	mg/kg	16	20	0.80		>0.05		
				Lung	NS	BbF	M	100	mg/kg	20	20	1.00		<0.001		
				Lung	NS	BbF	M	200	mg/kg	19	19	1.00		<0.001		
				Lung	NS	CPcdP	M	10	mg/kg	8	20	0.40		>0.05		
				Lung	NS	CPcdP	M	50	mg/kg	20	20	1.00		<0.001		
				Lung	NS	CPcdP	M	100	mg/kg	19	19	1.00		<0.001		
				Lung	NS	CPcdP	M	200	mg/kg	19	19	1.00		<0.001		
				Lung	NS	DBahA	M	1.25	mg/kg	12	18	0.67		<0.05		
				Lung	NS	DBahA	M	2.5	mg/kg	18	19	0.95		0.0053		
				Lung	NS	DBahA	M	5	mg/kg	20	20	1.00		<0.001		
				Lung	NS	DBahA	M	10	mg/kg	19	19	1.00		<0.001		
24590	Nesnow et al., 1998b	Mice	Intraperitoneal	Lung	NS	Control	M	0	mg/kg	15	30	0.50				Data provided by S. Nesnow
				Lung	NS	DBalP	M	0.3	mg/kg	13	33	0.39		>0.05		
				Lung	NS	DBalP	M	1.5	mg/kg	33	34	0.97		<0.001		
				Lung	NS	DBalP	M	3	mg/kg	35	35	1.00		<0.001		
				Lung	NS	DBalP	M	6	mg/kg	30	30	1.00		<0.001		
24801	Weyand et al., 2004	Mouse	Intraperitoneal	Lung	Adenoma	Tricaprylin	F	0	mg/kg	14	29	0.48				

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bearing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
						BaP	F	100	mg/kg	27	30	0.90		0.0005		
						BcFE	F	100	mg/kg	26	28	0.92		0.0002		
22510	Wislocki et al., 1986	Mice	Intraperitoneal	Liver	Adenoma + carcinoma	DMSO	M	0	nmol	2	28	0.07				Animals surviving through weaning
				Liver	Adenoma + carcinoma	DMSO	F	0	nmol	0	31	0				0
				Liver	Adenoma + carcinoma	DMSO	M	0	nmol	5	45	0.11				This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	DMSO	F	0	nmol	0	34	0				This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	DMSO pooled	M	0	nmol	7	73	0.09				
				Liver	Adenoma + carcinoma	DMSO pooled	F	0	nmol	0	65	0				
				Liver	Adenoma + carcinoma	BaP	M	560	nmol	18	37	0.49	<0.05			
				Liver	Adenoma + carcinoma	BaP	F	560	nmol	0	27	0				
				Liver	Adenoma + carcinoma	CH	M	700	nmol	10	35	0.29	<0.05			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	CH	F	700	nmol	0	33	0				This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	CH	M	2,800	nmol	14	34	0.41	<0.05		6×10^{-3}	
				Liver	Adenoma + carcinoma	CH	F	2,800	nmol	0	24	0			1	
				Liver	Adenoma + carcinoma	BaA	M	2,800	nmol	31	39	0.79	<0.05			

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Expo-sure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bear-ing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Liver	Adenoma + carcinoma	BaA	F	2,800	nmol	0	32	0				
				Lung	Adenoma + carcinoma	DMSO	M	0	nmol	1	28	0.04				
				Lung	Adenoma + carcinoma	DMSO	F	0	nmol	0	31	0				
				Lung	Adenoma + carcinoma	DMSO	M	0	nmol	4	45	0.09				This group started 10 wks after other groups
				Lung	Adenoma + carcinoma	DMSO	F	0	nmol	2	34	0.06				This group started 10 wks after other groups
				Lung	Adenoma + carcinoma	DMSO pooled	M	0	nmol	5	73	0.07				
				Lung	Adenoma + carcinoma	DMSO pooled	F	0	nmol	2	65	0.03				
				Lung	Adenoma + carcinoma	BaP	M	560	nmol	13	37	0.35	<0.05			
				Lung	Adenoma + carcinoma	BaP	F	560	nmol	13	27	0.48	<0.05			
				Lung	Adenoma + carcinoma	CH	M	700	nmol	6	35	0.17				This group started 10 wks after other groups
				Lung	Adenoma + carcinoma	CH	F	700	nmol	2	33	0.06				This group started 10 wks after other groups
				Lung	Adenoma + carcinoma	CH	M	2,800	nmol	7	34	0.21	<0.05		1.1×10^{-1}	
				Lung	Adenoma + carcinoma	CH	F	2,800	nmol	1	24	0.04			5.6×10^{-1}	
				Lung	Adenoma + carcinoma	BaA	M	2,800	nmol	6	39	0.15				

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bearing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Lung	Adenoma + carcinoma	BaA	F	2,800	nmol	6	32	0.19	<0.05			
				Lymphatic system	Lymphoma	DMSO	M	0	nmol	1	28	0.04				
				Lymphatic system	Lymphoma	DMSO	F	0	nmol	1	31	0.03				
				Lymphatic system	Lymphoma	DMSO	M	0	nmol	0	45	0				This group started 10 wks after other groups
				Lymphatic system	Lymphoma	DMSO	F	0	nmol	0	34	0				This group started 10 wks after other groups
				Lymphatic system	Lymphoma	BaP	M	560	nmol	2	37	0.05				
				Lymphatic system	Lymphoma	BaP	F	560	nmol	4	27	0.15				
				Lymphatic system	Lymphoma	CH	M	700	nmol	3	35	0.09	<0.05			This group started 10 wks after other groups
				Lymphatic system	Lymphoma	CH	F	700	nmol	1	33	0.03				This group started 10 wks after other groups
				Lymphatic system	Lymphoma	CH	M	2,800	nmol	0	34	0			2.2×10^{-1}	
				Lymphatic system	Lymphoma	CH	F	2,800	nmol	0	24	0			3.9×10^{-1}	

Table C-3. Intraperitoneal bioassays: dose-response information for incidence data

Record number	Reference	Species	Expo-sure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor bear-ing animals	Results of authors' statistical analysis (*p*-value)	SRC Statistical Analysis		Comments
														Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
				Lymph-atic system	Adenoma + carcinoma	BaA	M	2,800	nmol	1	39	0.03				
				Lymph-atic system	Adenoma + carcinoma	BaA	F	2,800	nmol	3	32	0.09				

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Table C-4. Intraperitoneal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis (Fisher's exact *p*-value)	Mean number tumors/ animal	SD of mean	Results of SRC statistical analysis (t-test *p*-value)	Comments
17560	Busby et al., 1989	Mice	Intra-peritoneal	Lung	Adenoma+ adeno-carcinoma	DMSO	M	0	µg (total)	13	91	0.14			0.15	0.38		Stats reported for combined M and F
				Lung	Adenoma+ adeno-carcinoma	DMSO	F	0	µg (total)	7	101	0.07			0.08	0.30		
				Lung	Adenoma+ adeno-carcinoma	BaP	M	59.5	µg (total)	13	28	0.46		<0.001	0.71	1.01	<0.001	
				Lung	Adenoma+ adeno-carcinoma	BaP	F	59.5	µg (total)	19	27	0.70		<0.001	1.19	1.09	<0.001	
				Lung	Adenoma+ adeno-carcinoma	Pyr	M	86.1	µg (total)	4	23	0.17		>0.05	0.17	0.38	>0.05	
				Lung	Adenoma+ adeno-carcinoma	Pyr	F	86.1	µg (total)	1	28	0.04		>0.05	0.04	0.21	>0.05	
				Lung	Adenoma+ adeno-carcinoma	Pyr	M	1,750	µg (total)	2	27	0.07		>0.05	0.07	0.26	>0.05	
				Lung	Adenoma+ adeno-carcinoma	Pyr	F	1,750	µg (total)	3	26	0.12		>0.05	0.12	0.31	>0.05	
				Lung	Adenoma+ adeno-carcinoma	FA	M	257.6	µg (total)	5	23	0.22		>0.05	0.22	0.43	>0.05	
				Lung	Adenoma+ adenocarcinoma	FA	F	257.6	µg (total)	9	29	0.31		0.00165	0.41	0.70	<0.0001	
				Lung	Adenoma+ adeno-carcinoma	CH	M	6.3	µg (total)	2	27	0.07		>0.05	0.07	0.26	>0.05	
				Lung	Adenoma+ adeno-carcinoma	CH	F	6.3	µg (total)	3	29	0.10		>0.05	0.1	0.32	>0.05	
				Lung	Adenoma+ adeno-carcinoma	CH	M	210	µg (total)	3	20	0.15		>0.05	0.15	0.36	>0.05	
				Lung	Adenoma+ adeno-carcinoma	CH	F	210	µg (total)	0	29	0.00		>0.05	0	0.00	>0.05	
7510	LaVoie et al., 1994	Mice	Intra-peritoneal	Lung	Total	DMSO	M	0	µmol/mouse	5	29	0.17			0.17			Survived to 1 yr
				Lung	Total	DMSO	F	0	µmol/mouse	4	34	0.12			0.15			
				Lung	Total	BaP	M	1.1	µmol/mouse	24	32	0.75	<0.001		4.3			
				Lung	Total	BaP	F	1.1	µmol/mouse	17	20	0.85	<0.001		3.55			
				Lung	Total	FA	M	3.46	µmol/mouse	12	28	0.43	<0.05		0.64			

Table C-4. Intraperitoneal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis (Fisher's exact *p*-value)	Mean number tumors/ animal	SD of mean	Results of SRC statistical analysis (t-test *p*-value)	Comments
				Lung	Total	FA	F	3.46	µmol/mouse	11	31	0.35	<0.05		0.35			
				Lung	Total	FA	M	17.3	µmol/mouse	11	17	0.65	<0.005		1.12			
				Lung	Total	FA	F	17.3	µmol/mouse	25	29	0.86	<0.001		2.45			
				Liver	Foci + adenoma + carcinoma	DMSO	M	0	µmol/mouse	5	29	0.17			0.41			
				Liver	Foci + adenoma + carcinoma	DMSO	F	0	µmol/mouse	2	34	0.06			0.06			Tumor count appears to be error in publication
				Liver	Foci + adenoma + carcinoma	BaP	M	1.1	µmol/mouse	27	32	0.84	<0.001		4.53			
				Liver	Foci + adenoma + carcinoma	BaP	F	1.1	µmol/mouse	2	20	0.10	>0.05		0.3			
				Liver	Foci + adenoma + carcinoma	FA	M	3.46	µmol/mouse	18	28	0.64	<0.001		1.86			
				Liver	Foci + adenoma + carcinoma	FA	F	3.46	µmol/mouse	0	31	0			0			
				Liver	Foci + adenoma + carcinoma	FA	M	17.3	µmol/mouse	17	17	1.00	<0.001		7.53			
				Liver	Foci + adenoma + carcinoma	FA	F	17.3	µmol/mouse	2	29	0.07			0.07			
22510	Wislocki et al., 1986	Mice	Intra-peritoneal	Liver	Adenoma + carcinoma	DMSO	M	0	nmol	2	28	0.07			0.07			Animals surviving through weaning
				Liver	Adenoma + carcinoma	DMSO	F	0	nmol	0	31	0			0			
				Liver	Adenoma + carcinoma	DMSO	M	0	nmol	5	45	0.11			0.11			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	DMSO	F	0	nmol	0	34	0			0			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	DMSO pooled	M	0	nmol	7	73	0.09			0.096			
				Liver	Adenoma + carcinoma	DMSO pooled	F	0	nmol	0	65	0			0			
				Liver	Adenoma + carcinoma	BaP	M	560	nmol	18	37	0.49	<0.05		1.46			

Table C-4. Intraperitoneal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis (Fisher's exact *p*-value)	Mean number tumors/ animal	SD of mean	Results of SRC statistical analysis (t-test *p*-value)	Comments
				Liver	Adenoma + carcinoma	BaP	F	560	nmol	0	27	0	>0.05		0			
				Liver	Adenoma + carcinoma	Pyr	M	200	nmol	0	29	0	>0.05		0			
				Liver	Adenoma + carcinoma	Pyr	F	200	nmol	0	31	0	>0.05		0			
				Liver	Adenoma + carcinoma	Pyr	M	700	nmol	3	25	0.12	>0.05		0.12			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	Pyr	F	700	nmol	0	49	0	>0.05		0			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	Pyr	M	2,800	nmol	3	14	0.21	>0.05		0.21			
				Liver	Adenoma + carcinoma	Pyr	F	2,800	nmol	0	18	0	>0.05		0			
				Liver	Adenoma + carcinoma	CH	M	700	nmol	10	35	0.29	<0.05		0.86			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	CH	F	700	nmol	0	33	0	>0.05		0			This group started 10 wks after other groups
				Liver	Adenoma + carcinoma	CH	M	2,800	nmol	14	34	0.41	<0.05		1.03			
				Liver	Adenoma + carcinoma	CH	F	2,800	nmol	0	24	0	>0.05		0			
				Liver	Adenoma + carcinoma	BaA	M	2,800	nmol	31	39	0.79	<0.05		2.38			
				Liver	Adenoma + carcinoma	BaA	F	2,800	nmol	0	32	0	>0.05		0			
13610	Busby et al., 1984	Mice	Intra-peritoneal	Lung	Adenoma + carcinoma	DMSO	M	0	mg (total)	1	27	0.04			0.04	0.21		
				Lung	Adenoma + carcinoma	DMSO	F	0	mg (total)	4	28	0.14			0.14	0.37		
				Lung	Adenoma + carcinoma	BaP	M	0.28	mg (total)	24	25	0.96		<0.001	4.32	3.5	<0.001	
				Lung	Adenoma + carcinoma	BaP	F	0.28	mg (total)	25	27	0.93		<0.001	3.7	3.10	<0.001	
				Lung	Adenoma + carcinoma	BaP	M	1.4	mg (total)	16	20	0.80		<0.001	10.15	13.0	<0.001	No model fit
				Lung	Adenoma + carcinoma	BaP	F	1.4	mg (total)	21	24	0.88		<0.001	4.25	4.70	<0.001	No model fit
				Lung	Adenoma + carcinoma	FA	M	0.7	mg (total)	7	31	0.23		0.0412	0.29	0.84	>0.05	
				Lung	Adenoma + carcinoma	FA	F	0.7	mg (total)	3	20	0.15		>0.05	0.15	0.49	>0.05	

Table C-4. Intraperitoneal bioassays: dose-response information for tumor multiplicity

Record number	Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis (Fisher's exact *p*-value)	Mean number tumors/ animal	SD of mean	Results of SRC statistical analysis (t-test *p*-value)	Comments
				Lung	Adenoma + carcinoma	FA	M	3.5	mg (total)	20	27	0.74		<0.001	1.52	1.66	<0.001	Nonconstant variance
				Lung	Adenoma + carcinoma	FA	F	3.5	mg (total)	8	21	0.38		>0.05	0.52	0.82	0.0343	NS incidence; nonconstant variance
24590	Nesnow et al., 1998b	Mice	Intra-peritoneal	Lung	NS	Control	M	0	mg/kg	6	20	0.30			0.53	0.72		Pooled controls from data provided by Nesnow
				Lung	NS	BaP	M	5	mg/kg	6	20	0.30		>0.05	0.45	0.80	>0.05	
				Lung	NS	BaP	M	10	mg/kg	7	17	0.41		>0.05	0.53	0.78	>0.05	
				Lung	NS	BaP	M	50	mg/kg	19	19	1.00		<0.001	4.37	2.74	<0.001	
				Lung	NS	BaP	M	100	mg/kg	16	16	1.00		0.0018	12.75	4.28	<0.001	
				Lung	NS	BaP	M	200	mg/kg	24	24	1.00		<0.001	32.96	10.23	<0.001	
				Lung	NS	BbF	M	10	mg/kg	9	18	0.50		>0.05	0.67	0.75	>0.05	
				Lung	NS	BbF	M	50	mg/kg	16	20	0.80		<0.05	2.00	1.82	0.0022	
				Lung	NS	BbF	M	100	mg/kg	20	20	1.00		<0.001	5.30	3.21	<0.001	
				Lung	NS	BbF	M	200	mg/kg	19	19	1.00		<0.001	6.95	3.52	<0.001	
				Lung	NS	CPcdP	M	10	mg/kg	8	20	0.40		>0.05	0.55	0.80	>0.05	
				Lung	NS	CPcdP	M	50	mg/kg	20	20	1.00		<0.001	4.75	2.12	<0.001	
				Lung	NS	CPcdP	M	100	mg/kg	19	19	1.00		<0.001	32.21	15.15	<0.001	
				Lung	NS	CPcdP	M	200	mg/kg	19	19	1.00		<0.001	97.68	28.68	<0.001	
				Lung	NS	DBahA	M	1.25	mg/kg	12	18	0.67		<0.05	1.44	1.46	0.0229	
				Lung	NS	DBahA	M	2.5	mg/kg	18	19	0.95		0.0053	3.05	1.90	<0.001	
				Lung	NS	DBahA	M	5	mg/kg	20	20	1.00		<0.001	13.05	5.99	<0.001	
				Lung	NS	DBahA	M	10	mg/kg	19	19	1.00		<0.001	32.16	10.78	<0.001	
24590	Nesnow et al., 1998b	Mice	Intra-peritoneal	Lung	NS	Control	M	0	mg/kg	15	30	0.50			0.67	0.80		
				Lung	NS	DBalP	M	0.3	mg/kg	13	33	0.39		>0.05	0.42	0.56	>0.05	
				Lung	NS	DBalP	M	1.5	mg/kg	33	34	0.97		<0.001	4.32	2.86	<0.001	
				Lung	NS	DBalP	M	3	mg/kg	35	35	1.00		<0.001	7.49	3.79	<0.001	
				Lung	NS	DBalP	M	6	mg/kg	30	30	1.00		<0.001	16.10	7.26	<0.001	
11190	Mass et al., 1993	Mice	Intra-peritoneal	Lung	NS	Control	M	0	mg/kg	19	34	0.56			0.85	0.9		
					NS	BaP	M	20	mg/kg	10	16	0.63		>0.05	1	1	>0.05	
					NS	BaP	M	50	mg/kg	15	16	0.94		0.0065	3.9	2.9	<0.001	
					NS	BaP	M	100	mg/kg	14	14	1.00		0.0017	5.9	3.3	<0.001	
					NS	BjAC	M	20	mg/kg	12	12	1.00		0.0036	60.3	14.6	<0.001	
					NS	BjAC	M	50	mg/kg	13	13	1.00		0.0025	140.6	21.5	<0.001	
					NS	BjAC	M	100	mg/kg	14	14	1.00		0.0017	97.6	28.2	<0.001	
24801	Weyand et al., 2004	Mice	Intra-peritoneal	Lung	Adenoma	Tri-caprylin	F	0	mg/kg	14	29	0.48			0.6	0.75		
				Lung	Adenoma	BaP	F	100	mg/kg	27	30	0.9		0.0005	6.7	5.26	<0.01	
				Lung	Adenoma	BcFE	F	100	mg/kg	26	28	0.92		0.0002	4	2.8	<0.01	

Table C-5. Lung implantation bioassays: dose-response information for incidence data

Record number	Reference	Species	Target organ	Tumor type	PAH	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	SRC statistical analysis		Comments
											Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
17940	Deutsch-Wenzel et al., 1983	Rat	Lung	Epidermoid carcinoma	Untreated control	0	mg	0	35	0.00			
					Vehicle control	0	mg	0	35	0.00			
					BaP	0.1	mg	4	35	0.11	5.70×10^{-2}		
					BaP	0.3	mg	21	35	0.60	6.02×10^{-9}		
					BaP	1	mg	33	35	0.94	5.93×10^{-18}	1.57×10^{-17}	
					BbF	0.1	mg	0	35	0.00			
					BbF	0.3	mg	1	35	0.03	5×10^{-1}		
					BbF	1	mg	9	35	0.26	1×10^{-3}	5.12×10^{-7}	
					BeP	0.2	mg	0	35	0.00			
					BeP	1	mg	0	30	0.00			
					BeP	5	mg	1	35	0.03	5×10^{-1}	9.49×10^{-2}	
					BjF	0.2	mg	1	35	0.03	5×10^{-1}		
					BjF	1	mg	3	35	0.09	1.2×10^{-1}		
					BjF	5	mg	18	35	0.51	1.96×10^{-7}	1.28×10^{-11}	
					BkF	0.16	mg	0	35	0.00			
					BkF	0.83	mg	3	31	0.10	1×10^{-1}		
					BkF	4.15	mg	12	27	0.44	8.05×10^{-6}	1.03×10^{-9}	
					IP	0.16	mg	3	35	0.09	1.20×10^{-1}		
					IP	0.83	mg	8	35	0.23	2×10^{-3}		
					IP	4.15	mg	21	35	0.60	6.02×10^{-9}	2.09×10^{-10}	
					AA	0.16	mg	1	35	0.03	5×10^{-1}		
					AA	0.83	mg	19	35	0.54	6.4×10^{-8}	1.13×10^{-10}	
					BghiP	0.16	mg	0	35	0.00			
					BghiP	0.83	mg	1	35	0.03	1.2×10^{-1}		
					BghiP	4.15	mg	4	34	0.12	5.4×10^{-2}	2.47×10^{-3}	
			Lung	Pleomorphic sarcoma	Untreated control	0	mg	0	35	0.00			
					Vehicle control	0	mg	0	35	0.00			

Table C-5. Lung implantation bioassays: dose-response information for incidence data

Record number	Reference	Species	Target organ	Tumor type	PAH	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	SRC statistical analysis		Comments
											Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
					BaP	0.1	mg	6	35	0.17	1.2×10^{-2}		
					BaP	0.3	mg	2	35	0.06	2.5×10^{-1}		
					BaP	1	mg	0	35	0.00		1.36×10^{-1}	
					BbF	0.1	mg	1	35	0.03	1.2×10^{-1}		
					BbF	0.3	mg	2	35	0.06	2.5×10^{-1}		
					BbF	1	mg	4	35	0.11	$6. \times 10^{-2}$	7.55×10^{-3}	
					BeP	0.2	mg	0	35	0.00			
					BeP	1	mg	1	30	0.03			
					BeP	5	mg	0	35	0.00			
					BjF	0.2	mg	0	35	0.00			
					BjF	1	mg	0	35	0.00			
					BjF	5	mg	0	35	0.00			
					BkF	0.16	mg	0	35	0.00			
					BkF	0.83	mg	0	31	0.00			
					BkF	4.15	mg	0	27	0.00			
					IP	0.16	mg	1	35	0.03	1.2×10^{-1}		
					IP	0.83	mg	0	35	0.00			
					IP	4.15	mg	0	35	0.00			
					AA	0.16	mg	0	35	0.00			
					AA	0.83	mg	0	35	0.00			
					BghiP	0.16	mg	0	35	0.00			
					BghiP	0.83	mg	0	35	0.00			
					BghiP	4.15	mg	0	34	0.00			
			Lung	Carcinoma+ sarcoma	Untreated control	0	mg	0	35	0.00			
					Vehicle control	0	mg	0	35	0.00			
					BaP	0.1	mg	10	35	0.29	4.63×10^{-4}		
					BaP	0.3	mg	23	35	0.66	4.7×10^{-10}		
					BaP	1	mg	33	35	0.94	5.9×10^{-19}	3.66×10^{-9}	

Table C-5. Lung implantation bioassays: dose-response information for incidence data

Record number	Reference	Species	Target organ	Tumor type	PAH	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	SRC statistical analysis		Comments
											Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
					BbF	0.1	mg	1	35	0.03	1.2×10^{-1}		
					BbF	0.3	mg	3	35	0.09	1.2×10^{-1}		
					BbF	1	mg	13	35	0.37	3.1×10^{-5}	9.63×10^{-8}	
					BeP	0.2	mg	0	35	0.00			
					BeP	1	mg	1	30	0.03			
					BeP	5	mg	1	35	0.03	1.2×10^{-1}	3.23×10^{-1}	
					BjF	0.2	mg	1	35	0.03	1.2×10^{-1}		
					BjF	1	mg	3	35	0.09	1.20×10^{-1}		
					BjF	5	mg	18	35	0.51	1.96×10^{-7}	1.28×10^{-11}	
					BkF	0.16	mg	0	35	0.00			
					BkF	0.83	mg	3	31	0.10	1×10^{-1}		
					BkF	4.15	mg	12	27	0.44	8.05×10^{-4}	1.03×10^{-9}	
					IP	0.16	mg	4	35	0.11	6×10^{-2}		
					IP	0.83	mg	8	35	0.23	2×10^{-3}		
					IP	4.15	mg	21	35	0.60	6.02×10^{-9}	7.56×10^{-10}	
					AA	0.16	mg	1	35	0.03			
					AA	0.83	mg	19	35	0.54	6.4×10^{-8}	1.13×10^{-10}	
					BghiP	0.16	mg	0	35	0.00			
					BghiP	0.83	mg	1	35	0.03			
					BghiP	4.15	mg	4	34	0.12	5.4×10^{-2}	2.47×10^{-3}	
22000	Wenzel-Hartung et al., 1990	Rat	Lung	Carcinoma	Untreated control	0	mg/ animal	0	35	0.00			ED_{10}, relative potencies reported
					Vehicle control	0	mg/ animal	0	35	0.00			
					BaP	0.03	mg/ animal	3	35	0.09	1.2×10^{-1}		
					BaP	0.1	mg/ animal	11	35	0.31	1.93×10^{-4}		
					BaP	0.3	mg/ animal	27	35	0.77	$1.29E \times 10^{-12}$	8.85×10^{-15}	

Table C-5. Lung implantation bioassays: dose-response information for incidence data

Record number	Reference	Species	Target organ	Tumor type	PAH	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	SRC statistical analysis		Comments
											Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
					PH	1	mg/ animal	0	35	0.00			
					PH	3	mg/ animal	0	35	0.00			
					PH	10	mg/ animal	1	35	0.03	5×10^{-1}	1	
					CH	1	mg/ animal	5	35	0.14	2.7×10^{-2}		
					CH	3	mg/ animal	10	35	0.29	4.63×10^{-4}	7.96×10^{-4}	
					DBahA	0.1	mg/ animal	20	35	0.57	2.01×10^{-8}		

1
2

1

Table C-6. Oral bioassays: dose-response information for incidence data

Record number	Reference	Species	Target organ	Tumor type	PAH	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	SRC statistical analysis		Comments
											Fisher's exact *p*-value	Cochran-Armitage trend test *p*-value	
24801	Weyand et al., 2004	Mouse	Lung	Adenoma	Control	0	µg/mouse/day	7	29	0.24			
					BaP	230	µg/mouse/day	21	27	0.77	>0.0001		
					BcFE	13.6	µg/mouse/day	13	28	0.46	0.0684		
					BcFE	197	µg/mouse/day	29	29	1	>0.0001		
			Fore-stomach	Squamous cell carcinoma	Control	0	µg/mouse/day	0	29	0			
					BaP	230	µg/mouse/day	10	27	0.36			
					BcFE	13.6	µg/mouse/day	0	28	0			
					BcFE	197	µg/mouse/day	0	29	0			

2

Table C-7. Oral bioassays: dose-response information for tumor multiplicity

Reference	Species	Exposure route	Target organ	Tumor type	PAH	Sex	Dose	Dose units	Number of animals with tumors	Number of animals in group	% Tumor-bearing animals	Results of authors' statistical analysis (*p*-value)	Results of SRC statistical analysis (Fisher's exact *p*-value)	Mean number tumors/animal	SD of mean	Results of SRC statistical analysis (t-test *p*-value)	Comments
24801	Weyand et al., 2004	Mouse	Lung	Adenoma	Control	F	0	µg/mouse/day	7	29	0.24			0.31	0.59		
					BaP	F	230	µg/mouse/day	21	27	0.77		>0.0001	1.4	1.14	>0.0001	
					BcFE	F	13.6	µg/mouse/day	13	28	0.46		0.0684	0.57	0.69	0.13	
					BcFE	F	197	µg/mouse/day	29	29	1		>0.0001	46	15.1	>0.0001	

Table C-8. In vitro bacterial mutagenicity: data use

Record number	Reference	Data source	Data points	Basis for RPF approach	Comments
17030	Andrews et al., 1978	Figure 1	Dose (µg) and number of revertant colonies for DBacA, DBajA, DBahA, AA, BghiP, BeP, BaP	Point estimate	TA100 with Ar S9
23830	Baker et al., 1980	Table 2	Use data for guinea pig-MC S9 only (column D); dose in µg/plate and number of revertant colonies; BaP, DBaiP, BaA, DBacA, DBahA	Point estimate Table 2	TA100 with guinea pig-MC S9; Table 1 data not used, different S9 mix used for each of three experiments
23660	Bartsch et al., 1980	Appendix table	Use data for BaA and BaP; dose in µmol/plate and mutagenic activity in revertants/µmol	Point estimate	TA100 rat MC S9
17380	Bos et al., 1988	Table 1	Use TA100 strain only; dose (µg/plate) and number of revertant colonies/plate for PH, Pyr, BaP	Derive point estimate for BaP (use PH control as background); continuous model PH and Pyr using the BaP response as the BMR	TA100 with rat Ar S9
17590	Carver et al., 1986	Figure 1	Use curves for BaP, BaA, BghiF, and Pery; use 400 µL S9 per plate (last data point on x-axis); each curve is different dose in µg/plate, use hamster data; revertants per plate is y-axis	Point estimate; use highest dose in hamster, except for perylene (use 10 µg/plate); this is maximal response in hamsters	TA100 with hamster Ar S9; multidose data but not SD was reported
17630	Cavalieri et al., 1981a	Figure 1	Dose-response curves for BaP, CPcdP (CPEP in figure), and ACEP (CPAP in figure); dose as µM, response as mutant fraction x 105	Model as quantal data (mutant fraction reported)	TM677 with Ar S9
9620	Chang et al., 2002	Figure 7	Dose-response curves for BghiF, BcPH, and BaP; dose (µg/plate) and revertants/plate	Point estimate; use 5 µg/plate dose for BghiF and BaP; use 10 µg/plate for BcPH	TA100 with rat Ar S9; SD not available from graph (reported for some data points, but not all)
24030	De Flora et al., 1984	Table 2	Table provides potency estimates as revertants/nmol for BaA, Pery, BaP, and BeP	Calculate the RPF ratio using the potency estimates provided	Determine strain used to calculate potencies; rat Ar S9
18050	Eisenstadt and Gold, 1978	Figure 2B	Use TA100 data for BaP and CPcdP (open circles); dose is 1 µg for CPcdP and 2 µg for BaP (legend); use the same S9 concentration (20 µL/plate)	Point estimate; single point data (20 µL S9/plate)	TA100 with rat Ar S9; µL S9 that maximizes the BaP response does not produce maximal response for CPcdP

Table C-8. In vitro bacterial mutagenicity: data use

Record number	Reference	Data source	Data points	Basis for RPF approach	Comments
18180	Florin et al., 1980	Table III	Use TA100 data for BaA, CH, and BaP, use TA98 data for Pery, CO, and BaP; dose is indicated as optimal dose (µmol/plate) and number revertants/plate	Point estimate; please note that reported response includes subtraction of spontaneous revertants (control); need to use formula for added risk; make sure to flag in comments	Note that data for both TA100 and TA98 strains were used; BaP results were provided for each; rat MC S9
24080	Gibson et al., 1978	Table 1 (BaP) Table 3 (PAHs)	Use data for TA98; in Table 1 use Expt. No.1 for BaP; in Table 3 use data for DBahA, Tphen, BaA, BghiP, CH, FE, Pyr; dose as µg/plate, response as increase in revertants	Point estimate; use the dose associated with the max-imum response (if reported as a range, do not use); controls were reported as negative (no mutagenic or toxic response)	TA98 with non-enzymatic induction (gamma irradiation); multidose data but not SD reported
14080	Gold and Eisenstadt, 1980	Table 2	Use data for 3-MC induction at 50 µL S9/plate; dose is 4 nmol for BaP and CPcdP, results as revertants/plate	Point estimate	TA100 using 50 µL of rat MC S9; important to note that maximal response for CPcdP occurred at much lower dose of S9 (5 µL/plate)
18650	Hermann, 1981	Table 1	Table provides potency estimates as revertants/nmol for BbA, BaA, CH, FA, Tphen, BeP, DBacA, DBahA, BbF, Pery, DBalP, DBaiP, AA, CO; potency of BaP in legend as 100 revertants/nmol	Calculate the RPF ratio using the potency estimates provided	TA98 with rat Ar S9; potency estimates were calculated from the linear portion of the dose-response curve
10670	Johnsen et al., 1997	Figure 2	Use data for PCB microsomes for BaP, BjAC, BlAC; dose as µg/plate, response as revertants	Model to derive BMDsd1; need to extract SDs from graph; control response is 113 ± 9 revertants per plate (see legend); add control response to each response for modeling (it was subtracted prior to graphing)	TA98 with PCB microsomes
19000	Kaden et al., 1979	Table 1	RPFs calculated for AN, ANL, Pyr, BbFE, CPcdP, BaA, CH, Tphen, FA, BeP, Pery, BghiP, AA, DBacA, DBahA, DBbeF	Not applicable	TM677 with Ar S9 and PB S9
24680	Lafleur et al., 1993	Figures 3 and 4	Use dose-response curves for BaP, BghiF, CPcdP, CPhiACEA (CPAA), ACEA (AA), CPhiAPA (CPAP), APA (AP); dose as µg/mL, response as mutant fraction ($\times 10^5$)	Model as quantal data (mutant fraction reported)	Forward mutation to 8-azaguanine resistance in TM677 with rat AR S9
19320	LaVoie et al., 1979	Table VI	Use data for TA98 for BaP, BeP, and Pery; 10 µg dose and response as revertants/plate	Point estimate; use 20 µg for BaP; 10 µg for BeP; and 20 µg for Pery	TA98 with rat Ar S9; for BeP and Pery the maximal response was in TA100

Table C-8. In vitro bacterial mutagenicity: data use

Record number	Reference	Data source	Data points	Basis for RPF approach	Comments
23650	McCann et al., 1975	Table 1	Table provides potency estimates as revertants/nmol for DBaiP, BaP, BeP, DBacA, DBahA, CH, BaA	Calculate the RPF ratio using the potency estimates provided	Multiple strains, rat Ar S9
20220	Pahlman and Pelkonen, 1987	Table 1	Use data for rat-MC induced (last column); potency estimates are provided as revertants/nmol for BaA, CH, Tphen, DBacA, DBahA	Calculate the RPF ratio using the potency estimates provided	TA100 with rat MC S9
20450	Phillipson and Ioannides, 1989	Figures 2 and 3	Use the curve for hamster S9 (open triangles); data for BaP, DBaiP, BaA, and DBahA, dose as µg/plate, revertants/plate	Point estimate; use 10 µg/plate for BaP, DBahA; 20 µg/plate BaA, DBaiP	TA100 with hamster S9; multidose data but not SD reported
21000	Sakai et al., 1985	Table 3	Use data for TA97 +S9 for FE, AC, PH, FA, Ch, Pyr, BaP, BeP, Pery, BghiP, CO; dose µg, response as revertants per plate	Point estimate; use 10 µg for AC, PH, FA, BaP, BeP; use 5 µg for FE; use 20 µg for CH, Pyr, BghiP; use 4 µg for Pery; use 100 µg for CO	TA97 with rat Ar S9; multidose data but not SD reported
11860	Sangaiah et al., 1983	Figure 2	Use data for BjAC and BaP; dose as µg/plate, response as revertants/plate	Point estimate; use 10 µg/plate for BjAC; use 6 µg/plate for BaP	TA98 with rat Ar S9; multidose data but not SD was reported
21360	Simmon, 1979a	Table 1	Use data for TA100 for BaA, BaP, BeP; dose as µg, response as revertants/plate after subtracting background	Point estimate	TA100 with rat Ar S9
21640	Teranishi et al., 1975	Table I and Figure 3	Use data for TA1538 for DBaiP and BaP; use data in Figure 3 for TA 1538, PB and DBahA-induced S9 (open circles) for DBaeP	Point estimate	TA1538 with rat PB S9 for DBaiP; TA1538 with PB and DBahA S9 for DBaeP
16180	Utesch et al., 1987	Figures 2 and 3	Use data for homogenized hepatocytes (open circles) for BaA and BaP; dose as µg/plate, response as revertants/plates	Point estimate; use 12.5 µg/plate for BaP; use 25 µg/plate for BaA	TA100 with homo-genized hepatocytes from Ar-treated rats; multidose data but not SD reported
16440	Wood et al., 1980	Chart 3A	Use dose-response curves for BaP and CPcdP; dose as nmol, response as revertants/plate	Point estimate; use 15 nmol for BaP and CPcdP	TA98 with purified microsomal P450; multidose data but not SD reported

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
17030	Andrews et al., 1978	TA100	ArS9	Control	0	µg	150	Revertant colonies						
				BaP	250	µg	1,681	Revertant colonies						
				DBacA	10	µg	2,957	Revertant colonies						
				DBajA	10	µg	843	Revertant colonies						
				DBahA	25	µg	617	Revertant colonies						
				AA	250	µg	1,796	Revertant colonies						
				BghiP	100	µg	793	Revertant colonies						
				BeP	1,000	µg	643	Revertant colonies						
23830	Baker et al., 1980	TA100	Guinea pig-MC	Control	0	µg/plate	134	Revertant colonies				18		
				BaP	2.5	µg/plate	1,278	Revertant colonies	10			97		
				DBaiP	5	µg/plate	737	Revertant colonies	10			73		
				BaA	10	µg/plate	947	Revertant colonies	10			47		
				DBacA	2.5	µg/plate	1,738	Revertant colonies	10			88		
				DBahA	5	µg/plate	1,331	Revertant colonies	10			98		
23660	Bartsch et al., 1980	TA100	Rat MC S9	BaP	0.027	µmol/plate	29,000	Revertants/ plate						Control response subtracted
				BaA	0.067	µmol/plate	6,000	Revertants/ plate						Control response subtracted
17380	Bos et al., 1988	TA100	Rat ArS9	BaP	7.5	µg/plate	824	Revertants/ plate	3	Replic-ates		21	12	
				Control	0	µg/plate	85	Revertants/ plate	3	Replic-ates		12	7	

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				PH	1	µg/plate	108	Revertants/ plate	3	Replic-ates		10	6	
				PH	5	µg/plate	167	Revertants/ plate	3	Replic-ates		5	3	
				PH	25	µg/plate	240	Revertants/ plate	3	Replic-ates		10	6	
				Control	0	µg/plate	86	Revertants/ plate	3	Replic-ates		7	4	
				Pyr	1	µg/plate	93	Revertants/ plate	3	Replic-ates		9	5	
				Pyr	5	µg/plate	164	Revertants/ plate	3	Replic-ates		23	13	
				Pyr	25	µg/plate	279	Revertants/ plate	3	Replic-ates		10	6	
17590	Carver et al., 1986	TA100	Hamster ArS9	Control	0	µg/plate	140	Revertants/ plate						Control curves difficult to digitize; control value estimated from BaP graph and used for all
				BaP	1	µg/plate	141	Revertants/ plate						Continuous data, no SD
				BaP	10	µg/plate	482	Revertants/ plate						
				BaP	50	µg/plate	1,035	Revertants/ plate						
				BaA	15	µg/plate	346	Revertants/ plate						
				BaA	40	µg/plate	892	Revertants/ plate						
				BaA	50	µg/plate	1,263	Revertants/ plate						
				BghiF	10	µg/plate	333	Revertants/ plate						
				BghiF	25	µg/plate	727	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BghiF	50	µg/plate	985	Revertants/ plate						
				Perylene	5	µg/plate	195	Revertants/ plate						
				Perylene	10	µg/plate	993	Revertants/ plate						
				Perylene	15	µg/plate	922	Revertants/ plate						
17630	Cavalieri et al., 1981a	TM677	Ar S9	Control	0	µM	5	Mutants	1×10^5	Survivors	0.000050			Control value estimated
				BaP	10	µM	15	Mutants	1×10^5	Survivors	0.000150			
				BaP	20	µM	26	Mutants	1×10^5	Survivors	0.000256			
				BaP	40	µM	84	Mutants	1×10^5	Survivors	0.000839			
				BaP	60	µM	131	Mutants	1×10^5	Survivors	0.001308			
				CPcdP	20	µM	34	Mutants	1×10^5	Survivors	0.000337			
				CPcdP	40	µM	133	Mutants	1×10^5	Survivors	0.001330			
				ACEP	10	µM	11	Mutants	1×10^5	Survivors	0.000110			
				ACEP	40	µM	25	Mutants	1×10^5	Survivors	0.000248			
				ACEP	120	µM	55	Mutants	1×10^5	Survivors	0.000551			
9620	Chang et al., 2002	TA100	Rat ArS9	Control	0	µg/plate	326	Revertants/ plate						SD not consistently plotted; extracted only point estimate data
				BaP	5	µg/plate	2,543	Revertants/ plate						
				BghiF	5	µg/plate	1,630	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BcPH	10	µg/plate	1,043	Revertants/plate						
24030	De Flora et al., 1984	Rat AR S9		BaP			185	Revertants/nmol (potency)						
				BaA			12	Revertants/nmol (potency)						
				Pery			21	Revertants/nmol (potency)						
				BeP			1.6	Revertants/nmol (potency)						
18050	Eisenstadt and Gold, 1978	TA100	Rat ArS9	BaP	2	µg	1,705	Revertants/plate						Background subtracted from data reported
				CPcdP	1	µg	134	Revertants/plate						
18180	Florin et al., 1980	TA100	Rat MC S9	BaP	0.0030	µmol/plate	255	Revertants/plate						Background subtracted from data reported
		TA100		BaA	0.10	µmol/plate	326	Revertants/plate						Only peak response reported
		TA100		CH	0.0050	µmol/plate	196	Revertants/plate						
		TA98		BaP	0.0030	µmol/plate	235	Revertants/plate						
		TA98		Pery	0.025	µmol/plate	91	Revertants/plate						
		TA98		CO	0.070	µmol/plate	82	Revertants/plate						
24080	Gibson et al., 1978	TA98	[^{60}Co] gamma radiation, for 7 d (2.5×10^7 rad)	Control	0	µg/plate	0	Increase in revertants						Continuous data, no SD

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BaP	10	µg/plate	1.5	Increase in revertants						
				BaP	20	µg/plate	3	Increase in revertants						
				BaP	50	µg/plate	10	Increase in revertants						
				BaP	100	µg/plate	15	Increase in revertants						
				BaP	200	µg/plate	21	Increase in revertants						
				BaP	300	µg/plate	35	Increase in revertants						
				BaA	150	µg/plate	1.8	Increase in revertants						
				BaA	250	µg/plate	6.4	Increase in revertants						
				BghiP	400	µg/plate	4.2	Increase in revertants						
				CH	500	µg/plate	6.1	Increase in revertants						
				CH	1,000	µg/plate	6.7	Increase in revertants						
				FE	200	µg/plate	1.1	Increase in revertants						
				FE	360	µg/plate	2.2	Increase in revertants						
				Pyr	160	µg/plate	28	Increase in revertants						
14080	Gold and Eisenstadt, 1980	TA100	50 µL rat MC S9	BaP	4	nmol	1,103	Revertants/ plate						Background subtracted from data reported
				CPcdP	4	nmol	281	Revertants/ plate						
18650	Hermann, 1981	TA98	Rat Ar S9	BaP			100	Revertants/ nmol (potency)						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BbA			8	Revertants/ nmol (potency)						
				BaA			4	Revertants/ nmol (potency)						
				CH			2	Revertants/ nmol (potency)						
				FA			3	Revertants/ nmol (potency)						
				Tphen			13	Revertants/ nmol (potency)						
				BeP			15	Revertants/ nmol (potency)						
				DBacA			42	Revertants/ nmol (potency)						
				DBahA			8	Revertants/ nmol (potency)						
				BbF			15	Revertants/ nmol (potency)						
				Pery			31	Revertants/ nmol (potency)						
				DBalP			21	Revertants/ nmol (potency)						
				DBaiP			38	Revertants/ nmol (potency)						
				AA			62	Revertants/ nmol (potency)						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Resp-onse	SD	SE	Comments
				CO			60	Revertants/ nmol (potency)						
10670	Johnsen et al., 1997	TA98	PCB micro-somes	Control	0	µg/plate	113	Revertants/ plate	3			8.54		Control response added back to each response for modeling
				BaP	10	µg/plate	128	Revertants/ plate	3			3.66		
				BaP	20	µg/plate	123	Revertants/ plate	3			13.41		
				BjAC	10	µg/plate	192	Revertants/ plate	3			10.98		
				BjAC	20	µg/plate	213	Revertants/ plate	3			9.76		
				BIAC	10	µg/plate	204	Revertants/ plate	3			13.41		
				BIAC	20	µg/plate	207	Revertants/ plate	3			43.90		
19000	Kaden et al., 1979	TM677	ArS9 and PB S9	BaP			1	RPF						Mutagenic activity relative to that of the 80 µmol BaP-positive control performed simultaneously with test compound
				AN	NA		0.010	RPF						
				ANL	NA		0.070	RPF						
				Pyr	NA		0.070	RPF						
				BbFE	NA		0.080	RPF						
				CPcdP	NA		1.5	RPF						
				BaA	NA		0.14	RPF						
				CH	NA		0.20	RPF						
				Tphen	NA		0.070	RPF						
				FA	NA		1.0	RPF						
				BeP	NA		0.11	RPF						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				Pery	NA		6	RPF						
				BghiP	NA		0.080	RPF						
				AA	NA		0.080	RPF						
				DBacA	NA		0.77	RPF						
				DBahA	NA		0.080	RPF						
				DBbeF	NA		0.88	RPF						
24680	Lafleur et al., 1993	TM677	Rat AR S9	BaP	0	µg/mL	7	Mutants	100,000	Survivors	0.000070			
				BaP	0.5	µg/mL	8	Mutants	100,000	Survivors	0.000080			
				BaP	1	µg/mL	10	Mutants	100,000	Survivors	0.000101			
				BaP	2	µg/mL	18	Mutants	100,000	Survivors	0.000175			
				BaP	4	µg/mL	22	Mutants	100,000	Survivors	0.000220			
				BaP	8	µg/mL	33	Mutants	100,000	Survivors	0.000327			
				BghiF	0	µg/mL	11	Mutants	100,000	Survivors	0.00011			
				BghiF	1	µg/mL	10	Mutants	100,000	Survivors	0.00010			
				BghiF	3	µg/mL	14	Mutants	100,000	Survivors	0.00014			
				BghiF	10	µg/mL	55	Mutants	100,000	Survivors	0.00055			
				CPcdP	0	µg/mL	12	Mutants	100,000	Survivors	0.000120			
				CPcdP	0.5	µg/mL	15	Mutants	100,000	Survivors	0.000146			
				CPcdP	1	µg/mL	13	Mutants	100,000	Survivors	0.000130			
				CPcdP	2	µg/mL	17	Mutants	100,000	Survivors	0.000172			
				CPcdP	4	µg/mL	27	Mutants	100,000	Survivors	0.000274			

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				CPcdP	8	µg/mL	60	Mutants	100,000	Survivors	0.000597			
				CPhiACEA	0	µg/mL	8	Mutants	100,000	Survivors	0.000084			
				CPhiACEA	0.5	µg/mL	10	Mutants	100,000	Survivors	0.000103			
				CPhiACEA	1	µg/mL	16	Mutants	100,000	Survivors	0.000157			
				CPhiACEA	2	µg/mL	29	Mutants	100,000	Survivors	0.000286			
				CPhiACEA	4	µg/mL	67	Mutants	100,000	Survivors	0.000670			
				CPhiAPA	0	µg/mL	9	Mutants	100,000	Survivors	0.000090			
				CPhiAPA	10	µg/mL	12	Mutants	100,000	Survivors	0.000117			
				CPhiAPA	30	µg/mL	21	Mutants	100,000	Survivors	0.000210			
				CPhiAPA	100	µg/mL	26	Mutants	100,000	Survivors	0.000263			
				ACEA	0	µg/mL	9	Mutants	100,000	Survivors	0.000092			
				ACEA	10	µg/mL	21	Mutants	100,000	Survivors	0.000214			
				ACEA	35	µg/mL	69	Mutants	100,000	Survivors	0.000686			
				APA	0	µg/mL	16	Mutants	100,000	Survivors	0.000160			
				APA	10	µg/mL	37	Mutants	100,000	Survivors	0.000375			
				APA	30	µg/mL	42	Mutants	100,000	Survivors	0.000416			
				APA	100	µg/mL	22	Mutants	100,000	Survivors	0.000220			
19320	LaVoie et al., 1979	TA98	Rat Ar S9	BaP	10	µg	450	Revertants/plate						Background subtracted from data reported

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BaP	20	µg	480	Revertants/plate						
				BeP	10	µg	20	Revertants/plate						
				BeP	20	µg	20	Revertants/plate						
				Pery	20	µg	70	Revertants/plate						
23650	McCann et al., 1975	Multiple strains	Rat Ar S9	BaP	NA		121	Revertants/nmol (potency)						Paper states that comparison of potency estimates should be done with caution (non-linear dose-response), see table footnotes
				DBaiP	NA		20	Revertants/nmol (potency)						
				BeP	NA		0.6	Revertants/nmol (potency)						
				DBacA	NA		175	Revertants/nmol (potency)						
				DBahA	NA		11	Revertants/nmol (potency)						
				CH	NA		38	Revertants/nmol (potency)						
				BaA	NA		11	Revertants/nmol (potency)						
20220	Pahlman and Pelkonen, 1987	TA100	Rat MC S9	BaP	NA		272	Revertants/nmol (potency)						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BaA	NA		10.4	Revertants/ nmol (potency)						
				CH	NA		9.7	Revertants/ nmol (potency)						
				Tphen	NA		4	Revertants/ nmol (potency)						
				DBacA	NA		35	Revertants/ nmol (potency)						
				DBahA	NA		4.4	Revertants/ nmol (potency)						
20450	Phillipson and Ioannides, 1989	TA100	Hamster S9	BaP	0	µg/plate	0.000	Revertants/ plate						
				BaP	5	µg/plate	68.833	Revertants/ plate						
				BaP	10	µg/plate	118.948	Revertants/ plate						
				BaP	15	µg/plate	99.744	Revertants/ plate						
				BaP	20	µg/plate	96.101	Revertants/ plate						
				BaA	0	µg/plate	0.000	Revertants/ plate						
				BaA	20	µg/plate	109.877	Revertants/ plate						
				BaA	40	µg/plate	115.248	Revertants/ plate						
				BaA	60	µg/plate	114.430	Revertants/ plate						
				BaA	100	µg/plate	98.846	Revertants/ plate						
				DBaiP	0	µg/plate	0.000	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				DBaiP	20	µg/plate	64.638	Revertants/ plate						
				DBaiP	40	µg/plate	75.747	Revertants/ plate						
				DBaiP	60	µg/plate	80.394	Revertants/ plate						
				DBaiP	100	µg/plate	63.880	Revertants/ plate						
				DBahA	0	µg/plate	0.000	Revertants/ plate						
				DBahA	10	µg/plate	50.899	Revertants/ plate						
				DBahA	20	µg/plate	56.886	Revertants/ plate						
				DBahA	30	µg/plate	52.419	Revertants/ plate						
				DBahA	50	µg/plate	34.980	Revertants/ plate						
21000	Sakai et al., 1985	TA97	Rat Ar S9	Control	0	µg	177	Revertants/ plate						
				BaP	1	µg	1,208	Revertants/ plate						
				BaP	5	µg	1,432	Revertants/ plate						
				BaP	10	µg	1,742	Revertants/ plate						
				Control	0	µg	189	Revertants/ plate						
				FE	5	µg	254	Revertants/ plate						
				FE	10	µg	240	Revertants/ plate						
				FE	50	µg	240	Revertants/ plate						
				FE	250	µg	232	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				Control	0	µg	189	Revertants/ plate						
				AC	5	µg	360	Revertants/ plate						
				AC	10	µg	509	Revertants/ plate						
				AC	50	µg	293	Revertants/ plate						
				AC	250	µg	279	Revertants/ plate						
				Control	0	µg	189	Revertants/ plate						
				PH	5	µg	454	Revertants/ plate						
				PH	10	µg	534	Revertants/ plate						
				PH	50	µg	321	Revertants/ plate						
				PH	250	µg	T	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				FA	5	µg	652	Revertants/ plate						
				FA	10	µg	1,012	Revertants/ plate						
				FA	50	µg	1,042	Revertants/ plate						
				FA	250	µg	518	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				CH	5	µg	640	Revertants/ plate						
				CH	10	µg	815	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				CH	20	µg	888	Revertants/ plate						
				CH	50	µg	723	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				Pyr	2	µg	929	Revertants/ plate						
				Pyr	4	µg	1,582	Revertants/ plate						
				Pyr	6	µg	2,057	Revertants/ plate						
				Pyr	10	µg	2,577	Revertants/ plate						
				Pyr	20	µg	2,832	Revertants/ plate						
				Pyr	50	µg	2,296	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				BeP	5	µg	944	Revertants/ plate						
				BeP	10	µg	1,100	Revertants/ plate						
				BeP	50	µg	606	Revertants/ plate						
				BeP	250	µg	640	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				Pery	1	µg	1,516	Revertants/ plate						
				Pery	2	µg	2,236	Revertants/ plate						
				Pery	4	µg	2,784	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				Pery	10	µg	2,550	Revertants/ plate						
				Pery	50	µg	1,808	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				BghiP	10	µg	896	Revertants/ plate						
				BghiP	20	µg	991	Revertants/ plate						
				BghiP	50	µg	896	Revertants/ plate						
				BghiP	250	µg	612	Revertants/ plate						
				Control	0	µg	177	Revertants/ plate						
				CO	5	µg	362	Revertants/ plate						
				CO	10	µg	400	Revertants/ plate						
				CO	50	µg	405	Revertants/ plate						
				CO	100	µg	490	Revertants/ plate						
				CO	200	µg	479	Revertants/ plate						
11860	Sangaiah et al., 1983	TA98	Rat Ar S9	Control	0	µg/plate	35.43	Revertants/ plate						
				BaP	2	µg/plate	177.37	Revertants/ plate						
				BaP	3	µg/plate	266.02	Revertants/ plate						
				BaP	6	µg/plate	419.68	Revertants/ plate						
				BaP	10	µg/plate	312.76	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BaP	30	µg/plate	358.41	Revertants/ plate						
				BaP	50	µg/plate	350.92	Revertants/ plate						
				BaP	100	µg/plate	323.12	Revertants/ plate						
				Control	0	µg/plate	53.15	Revertants/ plate						
				BjAC	2	µg/plate	124.15	Revertants/ plate						
				BjAC	3	µg/plate	331.10	Revertants/ plate						
				BjAC	6	µg/plate	674.11	Revertants/ plate						
				BjAC	10	µg/plate	993.21	Revertants/ plate						
				BjAC	30	µg/plate	1,027.06	Revertants/ plate						
				BjAC	50	µg/plate	883.45	Revertants/ plate						
				BjAC	100	µg/plate	1,021.36	Revertants/ plate						
21360	Simmon, 1979a	TA100	Rat Ar S9	BaP	5	µg	1,141	Revertants/ plate						Background subtracted from data reported
				BaA	50	µg	280	Revertants/ plate						
				BeP	50	µg	57	Revertants/ plate						
21640	Teranishi et al., 1975	TA1538	Rat PB S9	Control	0	µg/plate	38	Revertant colonies/ plate						
				BaP	50	µg/plate	77	Revertant colonies/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				DBaiP	50	µg/plate	102	Revertant colonies/ plate						
		TA1538	Rat PB and DBahA S9	Control	0	µg/plate	25	Revertant colonies/ plate						
				BaP	50	µg/plate	279	Revertant colonies/ plate						
				DBaeP	50	µg/plate	88	Revertant colonies/ plate						
16180	Utesch et al., 1987	TA100	With homogenized hepatocytes from Ar-treated rats	Control	0	µg/plate	159	Revertants/ plates						
				BaP	6.3	µg/plate	998	Revertants/ plate						
				BaP	12.5	µg/plate	1,079	Revertants/ plate						
				BaP	25	µg/plate	1,178	Revertants/ plate						
				BaP	50	µg/plate	1,141	Revertants/ plate						
				BaP	100	µg/plate	1,114	Revertants/ plate						
				Control	0	µg/plate	199	Revertants/ plate						
				BaA	6.3	µg/plate	861	Revertants/ plate						
				BaA	12.5	µg/plate	2,583	Revertants/ plate						
				BaA	25	µg/plate	3,546	Revertants/ plate						
				BaA	50	µg/plate	3,786	Revertants/ plate						

Table C-9. In vitro bacterial mutagenicity: dose-response data

Record number	Reference	Cell type	Activation system	PAH	Dose	Dose units	Response	Response units	n	Units	% Response	SD	SE	Comments
				BaA	100	µg/plate	3,406	Revertants/ plate						
16440	Wood et al., 1980	TA98	Purified microsomal P450	Control	0	nmol	0	Revertants/ plate						Background subtracted from data reported
				BaP	3.75	nmol	45	Revertants/ plate						
				BaP	7.5	nmol	63	Revertants/ plate						
				BaP	15	nmol	99	Revertants/ plate						
				BaP	30	nmol	103	Revertants/ plate						
				Control	0	nmol	0	Revertants/ plate						
				CPcdP	3.75	nmol	303	Revertants/ plate						
				CPcdP	7.5	nmol	491	Revertants/ plate						
				CPcdP	15	nmol	685	Revertants/ plate						
				CPcdP	30	nmol	776	Revertants/ plate						

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Table C-10. In vitro mammalian mutagenicity: data use

Record number	Reference	Data source	Data points	Basis for RPF approach	Comments
16920	Amacher and Paillet, 1982	Figure 1	Use lines for BaP (open circles) and BaA (closed triangles; dose is µg/mL and response is mutation frequency (MF)/10^6 survivors	Model; quantal data	Thymidine kinase assay (resistance to trifluorothymidine) in mouse lymphoma cells (L5178Y) with Syrian golden hamster S9 mix or cocultivated hamster hepatocytes
16940	Amacher and Turner, 1980	Figure 3	Use bars for SM2 S9 activation for BaP and BaA; dose is 1.25×10^{-5} M for BaP and 3.22×10^{-5} M for BaP; response is IMF/10^4 survivors	Point estimate	Thymidine kinase assay (resistance to trifluorothymidine) in mouse lymphoma cells (L5178Y) with mouse S9 mix
16910	Amacher et al., 1980	Table 3	Use dose-response data for BaA and BaP; dose as concentration (M), response as mutants per 10^4 survivors	Model; quantal data	Thymidine kinase assay (resistance to trifluorothymidine) in mouse lymphoma cells (L5178Y) with mouse S9 mix
17140	Barfknecht et al., 1982	Figure 2 (BaP, FA); Figure 4 (BaA, CH, Tphen); Figure 6 (CPcdP)	Dose is µM and mutant fraction $\times 10^6$	Model; quantal data	Thymidine kinase assay (resistance to trifluorothymidine) in human lymphoblast cells with rat Ar S9 mix
14250	Hass et al., 1982	Table 1	Dose-response data for DBaiP, DBahP, and BaP; dose is µg/mL; use response data for TG mutants only (mutants/10^6 cells); control value is 4 ± 1 mutants/ 10^6 cells	Model; quantal data	Hypoxanthine-guanine phosphoribosyl transferase assay (resistance to 6-thioguanine) in V79 Chinese hamster cells with rat MC S9
18740	Huberman and Sachs, 1976	Table 2	Use data for BaP, DBacA, DBahA; 8-azaguanine resistance only; use 1 µg/mL dose for all (*), response as mutants per 10^5 survivors	Point estimate	Hypoxanthine-guanine phosphoribosyl transferase assay (resistance to 8-azaguanine) in V79 Chinese hamster cells with hamster embryo cells
18990	Jotz and Mitchell, 1981	Table 2	Use data for BaP and Pyr with metabolic activation; subtract negative control, dose as µg/mL, response as MF $\times 10^{-6}$	Point estimate	Thymidine kinase assay (resistance to trifluorothymidine) in mouse lymphoma cells (L5178Y) with rat Ar S9
24720	Kligerman et al., 1986	Figure 1	Use dose-response data for BaP and BlAC; dose as µg/mL, response as mutant frequency/10^6 survivors; average data from two experiments	Model; quantal data	Thymidine kinase assay (resistance to trifluorothymidine) in mouse lymphoma cells (L5178Y) with rat Ar S9

Table C-10. In vitro mammalian mutagenicity: data use

Record number	Reference	Data source	Data points	Basis for RPF approach	Comments
19180	Krahn and Heidelberger, 1977	Table II	Use data for BaP, DBahA, DBacA, and BaA; cell survival at 40% control (column 3), controls are 100% survival group (column 1); use 3-MC S9 data only; dose as nmol/mL, response as 6-TG/10^5 cells	Point estimate	Hypoxanthine-guanine phosphoribosyl transferase assay (resistance to 6-thio-guanine) in V79 Chinese hamster cells with hamster embryo cells
24680	Lafleur et al., 1993	Figures 5 and 6	Use dose-response curves for BaP, CPcdP (CPP), CPhiACEA (CPAA), ACEA (AA); dose as µg/mL, response as mutant fraction (ppm)	Model as quantal data (mutant fraction reported)	Thymidine kinase assay (resistance to trifluorothymi-dine) in MCL-3 cells (human B-lymphoblastoid cells)
7550	Li and Lin, 1996	Text	Mutant frequency of controls 2×10^{-5}; 10 ng/mL BaP = 5×10^{-5}; BaA = 5.6×10^{-5}	Point estimate	Hypoxanthine-guanine phos-phoribosyl transferase assay (resistance to 6-thioguanine) in HS1 HeLa cells (human epithelial cells)
11450	Nesnow et al., 1984	Chart 9	Use data for BaP, BlAC, BeAC, and BjAC; dose as µg/mL, response as 6TG-resistant mutants/ 10^6 survivors	Model; quantal data	Hypoxanthine-guanine phos-phoribosyl transferase assay (resistance to 6-thioguanine) in V79 Chinese hamster cells with rat AR S9
15630	Raveh and Huberman, 1983	Table 1	Use data for CPcdP and BaP, with PMA only; dose in µg/mL, response in mutants/10^5 cells	Model; quantal data	Hypoxanthine-guanine phosphoribosyl transferase assay (resistance to 6-thio-guanine) in V79 Chinese hamster cells with hamster embryo cells
15640	Raveh et al., 1982	Figure 4	Use dose-response data for CPcdP and BaP (ouabain resistance only); dose in µg/mL, response in mutants/10^6 cells	Model; quantal data	Hypoxanthine-guanine phos-phoribosyl transferase assay (resistance to ouabain) in V79 Chinese hamster cells with hamster embryo cells
21410	Slaga et al., 1978	Table 3	Use dose-response data for BaA and BaP; dose as µM, response as ouabain resistant mutants/10^4 survivors	Model; quantal data	Hypoxanthine-guanine phos-phoribosyl transferase assay (resistance to ouabain) in V79 Chinese hamster cells with hamster embryo cells
16190	Vaca et al., 1992	Figure 5	Dose-response data for FA and BaP; dose as µM, response as 6-Tg resistant cells/100,000	Model; quantal data	Hypoxanthine-guanine phosphoribosyl transferase assay (resistance to 6-thio-guanine) in UV-sensitive CHO cells with rat Ar S9
21900	Wangenheim and Bolcsfoldi, 1988	Table 1	Use +S9 dose-response data for Pyr, BaP, and FE; dose as mol/L, response as mutation frequency	Model; quantal data	Thymidine kinase assay (resistance to trifluoro-thymidine) in mouse lymph-oma cells (L5178Y) with rat Ar S9

Table C-10. In vitro mammalian mutagenicity: data use

Record number	Reference	Data source	Data points	Basis for RPF approach	Comments
24670	Durant et al., 1999	Table 1	Use dose-response data for BaPery, BbPery, DBaeF, DBafF, DBahP, DBaiP, DBelP, N23aP, N23eP; positive control is reported as 1,000 ng/mL BaP (reported separately for each PAH)	Model; quantal data	Thymidine kinase assay (resistance to trifluoro-thymidine) in human h1Alv2 cells

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
16920	Amacher and Paillet, 1982	Control	0	µg/mL	39	1×10^{6}	Survivors	0.000039	
		BaP	2.5	µg/mL	119	1×10^{6}	Survivors	0.00012	
		BaP	5	µg/mL	170	1×10^{6}	Survivors	0.00017	
		BaP	7.5	µg/mL	196	1×10^{6}	Survivors	0.00020	
		BaP	10	µg/mL	267	1×10^{6}	Survivors	0.00027	
		Control	0	µg/mL	20	1×10^{6}	Survivors	0.000020	
		BaA	2.5	µg/mL	65	1×10^{6}	Survivors	0.000065	
		BaA	5	µg/mL	62	1×10^{6}	Survivors	0.000062	
		BaA	10	µg/mL	88	1×10^{6}	Survivors	0.000088	
		BaA	15	µg/mL	89	1×10^{6}	Survivors	0.000089	
16940	Amacher and Turner, 1980	Control	0	M	0.4	1×10^{4}	Survivors	0.000040	Control without S9 treatment
		BaP	1.25×10^{-5}	M	2.85	1×10^{4}	Survivors	0.000285	
		BaA	3.22×10^{-5}	M	3.12	1×10^{4}	Survivors	0.000312	
16910	Amacher et al., 1980	Control	0	M	0.680	1×10^{4}	Survivors	0.000068	
		BaP	5.30×10^{-6}	M	1.360	1×10^{4}	Survivors	0.000136	
		BaP	7.00×10^{-6}	M	1.790	1×10^{4}	Survivors	0.000179	
		BaP	9.40×10^{-6}	M	1.470	1×10^{4}	Survivors	0.000147	
		BaP	1.25×10^{-5}	M	1.870	1×10^{4}	Survivors	0.000187	
		BaP	1.67×10^{-5}	M	2.600	1×10^{4}	Survivors	0.000260	
		BaP	2.23×10^{-5}	M	2.490	1×10^{4}	Survivors	0.000249	
		BaP	2.97×10^{-5}	M	2.650	1×10^{4}	Survivors	0.000265	
		BaP	3.96×10^{-5}	M	3.970	1×10^{4}	Survivors	0.000397	
		Control	0	M	0.770	1×10^{4}	Survivors	0.000077	
		BaA	1.36×10^{-5}	M	0.810	1×10^{4}	Survivors	0.000081	
		BaA	1.81×10^{-5}	M	0.840	1×10^{4}	Survivors	0.000084	
		BaA	2.42×10^{-5}	M	1.000	1×10^{4}	Survivors	0.000100	
		BaA	3.22×10^{-5}	M	1.230	1×10^{4}	Survivors	0.000123	
		BaA	4.30×10^{-5}	M	1.470	1×10^{4}	Survivors	0.000147	
		BaA	5.47×10^{-5}	M	NS	1×10^{4}	Survivors		NS = no survivors
		BaA	7.65×10^{-5}	M	NS	1×10^{4}	Survivors		

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
		BaA	1.02×10^{-4}	M	NS	1×10^{4}	Survivors		
17140	Barfknecht et al., 1982	Control	0	µM	0	1×10^{6}	Survivors	0.000000	
		BaP	10	µM	51	1×10^{6}	Survivors	0.000051	
		BaP	20	µM	120	1×10^{6}	Survivors	0.000120	
		BaP	30	µM	155	1×10^{6}	Survivors	0.000155	
		Control	0	µM	0	1×10^{6}	Survivors	0.000000	
		FA	10	µM	27	1×10^{6}	Survivors	0.000027	
		FA	20	µM	50	1×10^{6}	Survivors	0.000050	
		FA	40	µM	62	1×10^{6}	Survivors	0.000062	
		Control	0	µM	0	1×10^{6}	Survivors	0.000000	
		BaA	20	µM	12	1×10^{6}	Survivors	0.000012	
		BaA	50	µM	29	1×10^{6}	Survivors	0.000029	
		BaA	100	µM	34	1×10^{6}	Survivors	0.000034	
		BaA	150	µM	64	1×10^{6}	Survivors	0.000064	
		Control	0	µM	0	1×10^{6}	Survivors	0.000000	
		CH	20	µM	17	1×10^{6}	Survivors	0.000017	
		CH	50	µM	26	1×10^{6}	Survivors	0.000026	
		CH	100	µM	30	1×10^{6}	Survivors	0.000030	
		Control	0	µM	0	1×10^{6}	Survivors	0.000000	
		Tphen	50	µM	10	1×10^{6}	Survivors	0.000010	
		Tphen	100	µM	20	1×10^{6}	Survivors	0.000020	
		Tphen	200	µM	35	1×10^{6}	Survivors	0.000035	
		Control	0	µM	3	1×10^{6}	Survivors	0.000003	
		CPcdP	23	µM	11	1×10^{6}	Survivors	0.000011	
		CPcdP	47	µM	24	1×10^{6}	Survivors	0.000024	
		CPcdP	88	µM	27	1×10^{6}	Survivors	0.000027	
24670	Durant et al., 1999	BaP	1,000	ng/mL	170	1×10^{6}	Survivors	0.00017	
		BaP	1,000	ng/mL	170	1×10^{6}	Survivors	0.00017	
		BaP	1,000	ng/mL	200	1×10^{6}	Survivors	0.00020	
		BaP	1,000	ng/mL	200	1×10^{6}	Survivors	0.00020	
		BaP	1,000	ng/mL	160	1×10^{6}	Survivors	0.00016	

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
		BaP	1,000	ng/mL	170	1×10^6	Survivors	0.00017	
		BaP	1,000	ng/mL	190	1×10^6	Survivors	0.00019	
		BaP	1,000	ng/mL	200	1×10^6	Survivors	0.00020	
		BaP	1,000	ng/mL	210	1×10^6	Survivors	0.00021	
		Averaged BaP	1,000	ng/mL	186	1×10^6	Survivors	0.00019	
		Averaged controls	0	ng/mL	20	1×10^6	Survivors	0.00002	
		Control	0	ng/mL	18	1×10^6	Survivors	0.000018	
		BaPery	0.1	ng/mL	21	1×10^6	Survivors	0.000021	
		BaPery	0.3	ng/mL	23	1×10^6	Survivors	0.000023	
		BaPery	1	ng/mL	28	1×10^6	Survivors	0.000028	
		BaPery	3	ng/mL	50	1×10^6	Survivors	0.000050	
		BaPery	10	ng/mL	82	1×10^6	Survivors	0.000082	
		BaPery	100	ng/mL	200	1×10^6	Survivors	0.00020	
		Control	0	ng/mL	18	1×10^6	Survivors	0.000018	
		BbPery	1	ng/mL	19	1×10^6	Survivors	0.000019	
		BbPery	3	ng/mL	22	1×10^6	Survivors	0.000022	
		BbPery	10	ng/mL	32	1×10^6	Survivors	0.000032	
		BbPery	100	ng/mL	54	1×10^6	Survivors	0.000054	
		Control	0	ng/mL	21	1×10^6	Survivors	0.000021	
		DBaeF	1	ng/mL	29	1×10^6	Survivors	0.000029	
		DBaeF	10	ng/mL	72	1×10^6	Survivors	0.000072	
		DBaeF	100	ng/mL	190	1×10^6	Survivors	0.00019	
		DBaeF	1,000	ng/mL	np	1×10^6	Survivors		Not plated due to excessive toxicity
		Control	0	ng/mL	21	1×10^6	Survivors	0.000021	
		DBafF	1	ng/mL	21	1×10^6	Survivors	0.000021	
		DBafF	10	ng/mL	37	1×10^6	Survivors	0.000037	
		DBafF	100	ng/mL	81	1×10^6	Survivors	0.000081	
		DBafF	1,000	ng/mL	190	1×10^6	Survivors	0.00019	
		Control	0	ng/mL	19	1×10^6	Survivors	0.000019	
		DBahP	0.1	ng/mL	24	1×10^6	Survivors	0.000024	

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
		DBahP	1	ng/mL	24	1×10^6	Survivors	0.000024	
		DBahP	10	ng/mL	46	1×10^6	Survivors	0.000046	
		DBahP	100	ng/mL	80	1×10^6	Survivors	0.000080	
		Control	0	ng/mL	20	1×10^6	Survivors	0.000020	
		DBaiP	0.3	ng/mL	20	1×10^6	Survivors	0.000020	
		DBaiP	1	ng/mL	35	1×10^6	Survivors	0.000035	
		DBaiP	10	ng/mL	88	1×10^6	Survivors	0.000088	
		DBaiP	100	ng/mL	150	1×10^6	Survivors	0.00015	
		Control	0	ng/mL	21	1×10^6	Survivors	0.000021	
		DBelP	10	ng/mL	28	1×10^6	Survivors	0.000028	
		DBelP	100	ng/mL	34	1×10^6	Survivors	0.000034	
		DBelP	1,000	ng/mL	55	1×10^6	Survivors	0.000055	
		Control	0	ng/mL	21	1×10^6	Survivors	0.000021	
		N23aP	0.1	ng/mL	23	1×10^6	Survivors	0.000023	
		N23aP	1	ng/mL	44	1×10^6	Survivors	0.000044	
		N23aP	10	ng/mL	84	1×10^6	Survivors	0.000084	
		N23aP	100	ng/mL	94	1×10^6	Survivors	0.000094	
		N23aP	1,000	ng/mL	73	1×10^6	Survivors	0.000073	
		Control	0	ng/mL	19	1×10^6	Survivors	0.000019	
		N23eP	1	ng/mL	20	1×10^6	Survivors	0.000020	
		N23eP	10	ng/mL	41	1×10^6	Survivors	0.000041	
		N23eP	100	ng/mL	74	1×10^6	Survivors	0.000074	
		N23eP	1,000	ng/mL	98	1×10^6	Survivors	0.00010	
14250	Hass et al., 1982	Control	0	µg/mL	4	1×10^6	CFC	0.0000040	
		BaP	0.30	µg/mL	267	1×10^6	CFC	0.00027	
		BaP	1.00	µg/mL	293	1×10^6	CFC	0.00029	
		DBaiP	0.03	µg/mL	124	1×10^6	CFC	0.00012	
		DBaiP	0.10	µg/mL	289	1×10^6	CFC	0.00029	
		DBaiP	0.30	µg/mL	1211	1×10^6	CFC	0.00121	
		DBahP	0.03	µg/mL	110	1×10^6	CFC	0.00011	
		DBahP	0.10	µg/mL	264	1×10^6	CFC	0.00026	
		DBahP	0.30	µg/mL	668	1×10^6	CFC	0.00067	

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
18740	Huberman and Sachs, 1976	Control	0	µg/mL	6	1×10^5	Survivors	0.000060	
		BaP	1	µg/mL	425	1×10^5	Survivors	0.00425	
		DBacA	1	µg/mL	22	1×10^5	Survivors	0.00022	
		DBahA	1	µg/mL	17	1×10^5	Survivors	0.00017	
18990	Jotz and Mitchell, 1981	Control	0	µg/mL	80	1×10^6	Survivors	0.000080	
		BaP	4.5	µg/mL	224	1×10^6	Survivors	0.00022	With metabolic activation
		Control	0	µg/mL	116	1×10^6	Survivors	0.00012	
		Pyr	10.6	µg/mL	150	1×10^6	Survivors	0.00015	With metabolic activation
24720	Kligerman et al., 1986	Control	0	nmol/mL	92	1×10^6	Survivors	0.00009	Average of two experiments
		BaP	2.0	nmol/mL	258	1×10^6	Survivors	0.00026	
		BaP	3.0	nmol/mL	417	1×10^6	Survivors	0.00042	
		BaP	4.0	nmol/mL	557	1×10^6	Survivors	0.00056	
		Control	0	nmol/mL	90	1×10^6	Survivors	0.00009	
		BlAC	0.5	nmol/mL	93	1×10^6	Survivors	0.00009	
		BlAC	2.5	nmol/mL	197	1×10^6	Survivors	0.00020	
		BlAC	5.0	nmol/mL	374	1×10^6	Survivors	0.00037	
19180	Krahn and Heidelberger, 1977	Control	0	nmol/mL	1.7	1×10^5	Survivors	0.000017	
		BaP	15.9	nmol/mL	14	1×10^5	Survivors	0.000136	3-MC S9; 40% survival
		Control	0	nmol/mL	1.5	1×10^5	Survivors	0.000015	
		BaA	46.5	nmol/mL	6.5	1×10^5	Survivors	0.000065	3-MC S9; 40% survival
24680	Lafleur et al., 1993	Control	0	µg/mL	1.2	1×10^6	Survivors	0.0000012	
		BaP	0.02	µg/mL	4.8	1×10^6	Survivors	0.0000048	
		BaP	0.06	µg/mL	24	1×10^6	Survivors	0.000024	
		BaP	0.2	µg/mL	25	1×10^6	Survivors	0.000025	
		BaP	1	µg/mL	39	1×10^6	Survivors	0.000039	
		BaP	5	µg/mL	56	1×10^6	Survivors	0.000056	
		Control	0	µg/mL	1.8	1×10^6	Survivors	0.0000018	
		ACEA	1	µg/mL	6.0	1×10^6	Survivors	0.0000060	

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
		ACEA	3	µg/mL	15	1×10^6	Survivors	0.000015	
		ACEA	8	µg/mL	21	1×10^6	Survivors	0.000021	
		Control	0	µg/mL	2.5	1×10^6	Survivors	0.0000025	
		CPcdP	0.03	µg/mL	4.2	1×10^6	Survivors	0.0000042	
		CPcdP	0.06	µg/mL	4.9	1×10^6	Survivors	0.0000049	
		CPcdP	0.2	µg/mL	5.9	1×10^6	Survivors	0.0000059	
		CPcdP	0.6	µg/mL	10	1×10^6	Survivors	0.000010	
		CPcdP	2	µg/mL	17	1×10^6	Survivors	0.000017	
		Control	0	µg/mL	2.8	1×10^6	Survivors	0.0000028	
		CPhiACEA	0.1	µg/mL	12	1×10^6	Survivors	0.000012	
		CPhiACEA	0.3	µg/mL	25	1×10^6	Survivors	0.000025	
		CPhiACEA	0.8	µg/mL	31	1×10^6	Survivors	0.000031	
7550	Li and Lin, 1996	Control	0	ng/mL	2	1×10^5	Survivors	0.000020	
		BaP	10	ng/mL	5	1×10^5	Survivors	0.000050	
		BaA	10	ng/mL	5.6	1×10^5	Survivors	0.000056	
11450	Nesnow et al., 1984	Control	0	µg/mL	16	1×10^6	Survivors	0.000016	
		BaP	0.5	µg/mL	10	1×10^6	Survivors	0.000010	
		BaP	1.0	µg/mL	46	1×10^6	Survivors	0.000046	
		BaP	2.5	µg/mL	72	1×10^6	Survivors	0.000072	
		BaP	5.0	µg/mL	206	1×10^6	Survivors	0.000206	
		BaP	10.0	µg/mL	215	1×10^6	Survivors	0.000215	
		BaP	20.0	µg/mL	293	1×10^6	Survivors	0.000293	
		BeAC	1.0	µg/mL	17	1×10^6	Survivors	0.000017	
		BeAC	2.5	µg/mL	53	1×10^6	Survivors	0.000053	
		BeAC	5.0	µg/mL	435	1×10^6	Survivors	0.000435	
		BeAC	10.0	µg/mL	235	1×10^6	Survivors	0.000235	
		BeAC	20.0	µg/mL	349	1×10^6	Survivors	0.000349	
		BjAC	1.0	µg/mL	24	1×10^6	Survivors	0.000024	
		BjAC	2.5	µg/mL	94	1×10^6	Survivors	0.000094	
		BjAC	5.0	µg/mL	268	1×10^6	Survivors	0.000268	
		BjAC	10.0	µg/mL	225	1×10^6	Survivors	0.000225	
		BjAC	20.0	µg/mL	215	1×10^6	Survivors	0.000215	

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
		BlAC	1.0	µg/mL	31	1×10^6	Survivors	0.000031	
		BlAC	2.5	µg/mL	454	1×10^6	Survivors	0.000454	
		BlAC	5.0	µg/mL	320	1×10^6	Survivors	0.000320	
		BlAC	10.0	µg/mL	704	1×10^6	Survivors	0.000704	
		BlAC	20.0	µg/mL	769	1×10^6	Survivors	0.000769	
15630	Raveh and Huberman, 1983	Control	0	µg/mL	3	1×10^5	Survivors	0.000030	
		BaP	0.3	µg/mL	25	1×10^5	Survivors	0.00025	
		BaP	1	µg/mL	103	1×10^5	Survivors	0.0010	
		CPcdP	0.3	µg/mL	9	1×10^5	Survivors	0.000090	
		CPcdP	1	µg/mL	20	1×10^5	Survivors	0.00020	
15640	Raveh et al., 1982	BaP	0	µg/mL	7	1×10^6	CFC	0.0000070	
		BaP	0.3	µg/mL	20	1×10^6	CFC	0.000020	
		BaP	1	µg/mL	74	1×10^6	CFC	0.000074	
		BaP	3	µg/mL	74	1×10^6	CFC	0.000074	
		CPcdP	0	µg/mL	1	1×10^6	CFC	0.0000010	
		CPcdP	0.3	µg/mL	5	1×10^6	CFC	0.0000047	
		CPcdP	1	µg/mL	10	1×10^6	CFC	0.000010	
		CPcdP	3	µg/mL	28	1×10^6	CFC	0.000028	
21410	Slaga et al., 1978	Control	0	µM	0.7	1×10^4	Survivors	0.000070	
		BaA	4.4	µM	0.9	1×10^4	Survivors	0.000090	
		BaA	44.0	µM	2.1	1×10^4	Survivors	0.00021	
		BaP	0.4	µM	11.0	1×10^4	Survivors	0.0011	
		BaP	1.3	µM	25.0	1×10^4	Survivors	0.0025	
		BaP	4.0	µM	99.0	1×10^4	Survivors	0.0099	
16190	Vaca et al., 1992	BaP	0	µM	3	1×10^5	Survivors	0.000032	
		BaP	2	µM	10	1×10^5	Survivors	0.000102	
		BaP	4	µM	23	1×10^5	Survivors	0.000229	
		BaP	10	µM	31	1×10^5	Survivors	0.000306	
		FA	0	µM	10	1×10^5	Survivors	0.000105	
		FA	5	µM	20	1×10^5	Survivors	0.000203	
		FA	7.5	µM	27	1×10^5	Survivors	0.000274	

Table C-11. In vitro mammalian mutagenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	Mutants	In number	Units	% Response	Comments
			10	µM	32	1×10^5	Survivors	0.000318	
21900	Wangenheim and Bolcsfoldi, 1988	Control	0	mol/L	61	1×10^6	Survivors	0.000061	
		Control	0	mol/L	62	1×10^6	Survivors	0.000062	Used average of controls
		Average	0	mol/L	62	1×10^6	Survivors	0.000062	
		BaP	0.000001	mol/L	65	1×10^6	Survivors	0.000065	
		BaP	0.000005	mol/L	243	1×10^6	Survivors	0.000243	
		BaP	0.000010	mol/L	858	1×10^6	Survivors	0.00086	
		Control	0	mol/L	68	1×10^6	Survivors	0.00007	
		FE	0.0000195	mol/L	92	1×10^6	Survivors	0.00009	
		FE	0.0000389	mol/L	91	1×10^6	Survivors	0.00009	
		FE	0.0000681	mol/L	114	1×10^6	Survivors	0.00011	
		FE	0.000122	mol/L	154	1×10^6	Survivors	0.00015	
		FE	0.000170	mol/L	147	1×10^6	Survivors	0.00015	
		Control	0	mol/L	125	1×10^6	Survivors	0.00013	
		Control	0	mol/L	106	1×10^6	Survivors	0.00011	
		Average	0	mol/L	116	1×10^6	Survivors	0.00012	
		Pyr	0.0000101	mol/L	162	1×10^6	Survivors	0.00016	
		Pyr	0.0000151	mol/L	228	1×10^6	Survivors	0.00023	
		Pyr	0.0000202	mol/L	345	1×10^6	Survivors	0.00035	
		Pyr	0.0000252	mol/L	418	1×10^6	Survivors	0.00042	
		Pyr	0.0000302	mol/L	650	1×10^6	Survivors	0.00065	

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Table C-12. In vitro malignant/morphological cell transformation: data use

Record number	Reference	Page	Table number	Figure number	PAHs	Data to be extracted	Basis for RPF	Comment	Notes
17610	Casto, 1979	54	I and IV		BaP, DBahA	TF in number foci per 10^5 surviving cells and dose (µg/mL)	Ratio of slopes	Data on enhancement of viral transformation not used; no straightforward way to model dose-response	Model as incidence data using multistage
17970	DiPaolo et al., 1969	871	3		BaP, DBahA, BaA, BeP, DBacA	Total transformants, total number of colonies, and dose (µg/mL)	Point estimate		Do not use percent transformants; appears to be error for DBahA
18020	Dunkel et al., 1981					Use data as reported in 23720 Pienta 1977; report under that record			
18080	Emura et al., 1980	153, 154	I and II		BaP, BbF, BaA, IP	T, number of transformed colonies/1,000 survivals in 10 dishes and dose (µg/mL)	Ratio of slopes		Model as incidence data using multistage
14130	Greb et al., 1980	147	1		BaP, CH, BaA, BbF, DBahA, BeP	Relative transformation rate (potency) in percent/mmol	Ratio of slopes		Relative transformation potency at LC_{50}; slope already calculated
14640	Krolewski et al., 1986	1,648	1		BaP, CPcdP	Transformation frequency per viable cell × 10^{-3}; single dose (5 µM)	Point estimate		Use only BaP and CPcdP alone (not with IVA/AIA)
14700	Laaksonen et al., 1983	62	4		BaP, BaA	Transformation frequency (number of foci/10^5 surviving cells) and dose (µM)	Ratio of slopes		Inverse dose-response relationship possible due to cytotoxicity; use peak
14850	Lubet et al., 1983	992	1		BaP, BeP	DwT-III/td (dishes with Type III foci/ total dishes) and dose (µg/mL)	Ratio of slopes		Control data in caption (no transformants); model as incidence data
24710	Mohapatra et al., 1987	327	1		BaP, BeAC, BjAC, BlAC	Number of dishes scored and percent of dishes with Type II or Type III foci and dose (µg/mL)	Ratio of slope to BaP point estimate	Use BaP incidence as BMR	Convert percent into number of dishes and model as incidence data
24700	Nesnow et al., 1990	224	1		BaP, BlAC	Anchorage independent colonies/50,000 cells and dose (µg/mL)	Ratio of slopes		Continuous data, no SD for controls; use peak
7980	Nesnow et al., 1997	1,975	I		BaP, DBalP	Type II and III foci/dish (mean and SD) and dose (µM)	Ratio of slopes		Model as continuous data
7990	Nesnow et al., 1994	2,227	I		BaP, DBahA	Type II and III Foci/dish and dose; use 1 µg/mL dose for DBahA and mean foci/dish (in parentheses); single dose for BaP	Point estimate		

Table C-12. In vitro malignant/morphological cell transformation: data use

Record number	Reference	Page	Table number	Figure number	PAHs	Data to be extracted	Basis for RPF	Comment	Notes
8000	Nesnow et al., 1993a	28	I		DBkmnoAPH	Peak of Type II and III foci/dish; use 5 µg/mL dose for DBkmnoAPH and 3 µg/mL dose for BaP; average number foci/dish across the two experiments	Point estimate		Peak transformation for each compound; DBkmnoAPH reported in paper as CP(3,4)B[a]P
23720	Pienta et al., 1977	648	IV		BaP, BaA, DBahA	Transformed colonies/surviving colonies and dose (µg/mL, in row across)	Ratio of slopes		Model as incidence data using multistage

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Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
17610	Casto, 1979	Control	0	µg/mL	0			Foci	100,000	Surviving cells	0	
		BaP	0.62	µg/mL	8			Foci	100,000	Surviving cells	0.00008	
		BaP	1.25	µg/mL	10			Foci	100,000	Surviving cells	0.0001	
		DBahA	1.2	µg/mL	0.5			Foci	100,000	Surviving cells	0.000005	
		DBahA	2.5	µg/mL	1			Foci	100,000	Surviving cells	0.00001	
17970	DiPaolo et al., 1969	Control	0	µg/mL	0			Transformants	354	Number of surviving	0	
		BaP	10	µg/mL	8			Transformants	138	Number of surviving	0.058	
		DBahA	10	µg/mL	11			Transformants	354	Number of surviving	0.031	
		BaA	10	µg/mL	2			Transformants	190	Number of surviving	0.011	
		BeP	10	µg/mL	1			Transformants	172	Number of surviving	0.0058	
		DBacA	10	µg/mL	2			Transformants	181	Number of surviving	0.011	
18080	Emura et al., 1980	Control	0	µg/mL	0			Transformed colonies	1,000	Survivals	0	
	Expt 1	BaP	0.01	µg/mL	0			Transformed colonies	1,000	Survivals	0	
		BaP	0.05	µg/mL	1.1			Transformed colonies	1,000	Survivals	0.0011	
		BaP	0.1	µg/mL	2.9			Transformed colonies	1,000	Survivals	0.0029	
		BaP	0.25	µg/mL	5.3			Transformed colonies	1,000	Survivals	0.0053	
		BaP	0.5	µg/mL	6.8			Transformed colonies	1,000	Survivals	0.0068	
		BbF	0.025	µg/mL	0			Transformed colonies	1,000	Survivals	0	
		BbF	0.1	µg/mL	0.4			Transformed colonies	1,000	Survivals	0.00040	
		BbF	0.25	µg/mL	0.3			Transformed colonies	1,000	Survivals	0.00030	

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
		BbF	0.5	µg/mL	0.6			Transformed colonies	1,000	Survivals	0.00060	
		BbF	1	µg/mL	1.2			Transformed colonies	1,000	Survivals	0.0012	
		BaA	0.025	µg/mL	0			Transformed colonies	1,000	Survivals	0	
		BaA	0.1	µg/mL	0.3			Transformed colonies	1,000	Survivals	0.00030	
		BaA	0.25	µg/mL	0.3			Transformed colonies	1,000	Survivals	0.00030	
		BaA	0.5	µg/mL	0.6			Transformed colonies	1,000	Survivals	0.00060	
		BaA	1	µg/mL	1			Transformed colonies	1,000	Survivals	0.0010	
	Expt 2	Control	0	µg/mL	0			Transformed colonies	1,000	Survivals	0	
		BaP	0.01	µg/mL	0.4			Transformed colonies	1,000	Survivals	0.00040	
		BaP	0.05	µg/mL	1			Transformed colonies	1,000	Survivals	0.0010	
		BaP	0.1	µg/mL	2.9			Transformed colonies	1,000	Survivals	0.0029	
		BaP	0.25	µg/mL	4.6			Transformed colonies	1,000	Survivals	0.0046	
		BaP	0.5	µg/mL	7.8			Transformed colonies	1,000	Survivals	0.0078	
		IP	0.025	µg/mL	0			Transformed colonies	1,000	Survivals	0	
		IP	0.1	µg/mL	0.3			Transformed colonies	1,000	Survivals	0.00030	
		IP	0.25	µg/mL	0.3			Transformed colonies	1,000	Survivals	0.00030	
		IP	0.5	µg/mL	0.7			Transformed colonies	1,000	Survivals	0.00070	
		IP	1	µg/mL	1			Transformed colonies	1,000	Survivals	0.0010	

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
14130	Greb et al., 1980	BaP	NA		277			%/mmol				
		CH	NA		37			%/mmol				
		BaA	NA		13.9			%/mmol				
		BbF	NA		11.5			%/mmol				
		DBahA	NA		0.3			%/mmol				
		BeP	NA		3.1			%/mmol				
14640	Krolewski et al., 1986	Control	0	µM	0			Transformation frequency	1,000	Viable cells	0	
		BaP	5	µM	5.5	0.7		Transformation frequency	1,000	Viable cells	0.0055	
		CPcdP	5	µM	1.7	0.3		Transformation frequency	1,000	Viable cells	0.0017	
14700	Laaksonen et al., 1983	Control	0	µM	0			Foci	1×10^5	Surviving cells	0	
		BaP	5	µM	0.8			Foci	1×10^5	Surviving cells	0.0000080	Inverse dose-response relationship possible due to cytotoxicity; use peak
		BaP	10	µM	0.9			Foci	1×10^5	Surviving cells	0.0000090	
		BaP	20	µM	0.3			Foci	1×10^5	Surviving cells	0.0000030	
		BaP	40	µM	0.4			Foci	1×10^5	Surviving cells	0.0000040	
		Control	0		0			Foci	1×10^5	Surviving cells	0	
		BaA	11	µM	1.8			Foci	1×10^5	Surviving cells	0.000018	Inverse dose-response relationship possible due to cytotoxicity; use peak
		BaA	22	µM	1.5			Foci	1×10^5	Surviving cells	0.000015	
		BaA	44	µM	1.1			Foci	1×10^5	Surviving cells	0.000011	
		BaA	88	µM	0.8			Foci	1×10^5	Surviving cells	0.0000080	
14850	Lubet et al., 1983	Control	0	µg/mL	0			Dishes with Type III foci		Total dishes	0	
		BaP	1	µg/mL	1			Dishes with Type III foci	15	Total dishes	0.067	
		BaP	3	µg/mL	4			Dishes with Type III foci	15	Total dishes	0.267	
		BaP	10	µg/mL	5			Dishes with Type III foci	15	Total dishes	0.333	

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
		BeP	10	µg/mL	0			Dishes with Type III foci	15	Total dishes	0	
		BeP	30	µg/mL	1			Dishes with Type III foci	15	Total dishes	0.067	
		BeP	100	µg/mL	7			Dishes with Type III foci	15	Total dishes	0.467	
24710	Mohapatra et al., 1987	Control	0	µg/mL	0			Dishes with Type II or III foci	48	Dishes scored	0	
		BaP	1	µg/mL	44			Dishes with Type II or III foci	48	Dishes scored	0.92	
		BjAC	0.01	µg/mL	2			Dishes with Type II or III foci	48	Dishes scored	0.04	
		BjAC	0.05	µg/mL	5			Dishes with Type II or III foci	48	Dishes scored	0.1	
		BjAC	0.5	µg/mL	34			Dishes with Type II or III foci	48	Dishes scored	0.71	
		BjAC	1	µg/mL	45			Dishes with Type II or III foci	48	Dishes scored	0.94	
		BjAC	2	µg/mL	48			Dishes with Type II or III foci	48	Dishes scored	1	
		Control	0	µg/mL	0			Dishes with Type II or III foci	60	Dishes scored	0	
		BaP	1	µg/mL	50			Dishes with Type II or III foci	60	Dishes scored	0.83	
		BlAC	0.5	µg/mL	8			Dishes with Type II or III foci	60	Dishes scored	0.13	
		BlAC	1	µg/mL	14			Dishes with Type II or III foci	60	Dishes scored	0.26	
		BlAC	2.5	µg/mL	31			Dishes with Type II or III foci	60	Dishes scored	0.52	
		BlAC	5	µg/mL	42			Dishes with Type II or III foci	60	Dishes scored	0.7	
		BlAC	10	µg/mL	51			Dishes with Type II or III foci	60	Dishes scored	0.85	
		Control	0	µg/mL	0			Dishes with Type II or III foci	36	Dishes scored	0	

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
		BaP	1	µg/mL	31			Dishes with Type II or III foci	36	Dishes scored	0.86	
		BeAC	0.5	µg/mL	4			Dishes with Type II or III foci	36	Dishes scored	0.11	
		BeAC	1	µg/mL	6			Dishes with Type II or III foci	36	Dishes scored	0.17	
		BeAC	2.5	µg/mL	13			Dishes with Type II or III foci	36	Dishes scored	0.36	
		BeAC	5	µg/mL	15			Dishes with Type II or III foci	36	Dishes scored	0.42	
		BeAC	10	µg/mL	21			Dishes with Type II or III foci	36	Dishes scored	0.58	
24700	Nesnow et al., 1990	Acetone	0	µg/mL	25			Anchorage independent colonies/ 50,000 cells				
		BaP	0.1	µg/mL	43	14.7		Anchorage independent colonies/ 50,000 cells				
		BaP	0.5	µg/mL	42	20.7		Anchorage independent colonies/ 50,000 cells				
		BaP	2.5	µg/mL	39	19.5		Anchorage independent colonies/ 50,000 cells				
		BaP	10	µg/mL	72	23.1		Anchorage independent colonies/ 50,000 cells				
		Acetone	0	µg/mL	30			Anchorage independent colonies/ 50,000 cells				

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
		BlAC	0.1	µg/mL	74	5.2		Anchorage independent colonies/ 50,000 cells				
		BlAC	0.5	µg/mL	68	14.4		Anchorage independent colonies/ 50,000 cells				
		BlAC	2.5	µg/mL	123	15.6		Anchorage independent colonies/ 50,000 cells				
		BlAC	10	µg/mL	150	16.8		Anchorage independent colonies/ 50,000 cells				
7980	Nesnow et al., 1997	Control	0	µM	0	0		Type II and III foci/dish				
		BaP	0.4	µM	0.44	0.24		Type II and III foci/dish				
		BaP	1.2	µM	1.25	0.15		Type II and III foci/dish				
		BaP	4	µM	2.54	0.56		Type II and III foci/dish				
		DBalP	0.0033	µM	0.14	0.35		Type II and III foci/dish				
		DBalP	0.1	µM	1	0.24		Type II and III foci/dish				
		DBalP	0.33	µM	1.74	0.78		Type II and III foci/dish				
7990	Nesnow et al., 1994	Control	0	µg/mL	0.06	0.10		Type II and III foci/dish				
		BaP	1	µg/mL	1	0.43		Type II and III foci/dish				
		DBahA	0.25	µg/mL	0.23	0.21		Type II and III foci/dish				
		DBahA	0.5	µg/mL	0.25	0.33		Type II and III foci/dish				

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
		DBahA	1	µg/mL	0.43	0.11		Type II and III foci/dish				
		DBahA	2.5	µg/mL	0.29	0.085		Type II and III foci/dish				
8000	Nesnow et al., 1993a	Control	0	µg/mL	0			Type II and III foci/dish				
		BaP	0.3	µg/mL	0.48			Type II and III foci/dish				
		BaP	1	µg/mL	0.665			Type II and III foci/dish				
		BaP	3	µg/mL	1.4			Type II and III foci/dish				
		Control	0	µg/mL	0			Type II and III foci/dish				
		DBkmnoAPH	0.5	µg/mL	0.23			Type II and III foci/dish				
		DBkmnoAPH	1	µg/mL	0.52			Type II and III foci/dish				
		DBkmnoAPH	2.5	µg/mL	0.605			Type II and III foci/dish				
		DBkmnoAPH	5	µg/mL	1.085			Type II and III foci/dish				
23720	Pienta et al., 1977	Control	0	µg/mL	0			Transformed colonies	504	Surviving colonies	0	BaP and BaA data also reported in Record 18020 Dunkel 1981
		BaP	1	µg/mL	1			Transformed colonies	393	Surviving colonies	0.0025	
		BaP	5	µg/mL	2			Transformed colonies	406	Surviving colonies	0.0049	
		BaP	10	µg/mL	3			Transformed colonies	434	Surviving colonies	0.0069	
		BaP	20	µg/mL	5			Transformed colonies	410	Surviving colonies	0.0122	
		BaP	40	µg/mL	4			Transformed colonies	427	Surviving colonies	0.0094	
		Control	0	µg/mL	0			Transformed colonies	229	Surviving colonies	0	

Table C-13. In vitro malignant/morphological cell transformation: dose-response data

Record number	Reference	PAH	Dose	Dose units	Transformation measure				n	units	% Response	Notes
					Mean	SD	SE	Units				
		BaA	0.1	µg/mL	1			Transformed colonies	225	Surviving colonies	0.0044	
		BaA	0.5	µg/mL	2			Transformed colonies	252	Surviving colonies	0.0079	
		BaA	1	µg/mL	2			Transformed colonies	193	Surviving colonies	0.0104	
		BaA	5	µg/mL	1			Transformed colonies	312	Surviving colonies	0.0032	
		BaA	10	µg/mL	7			Transformed colonies	250	Surviving colonies	0.028	
		Control	0	µg/mL	0			Transformed colonies	229	Surviving colonies	0	
		DBahA	0.1	µg/mL	0			Transformed colonies	219	Surviving colonies	0	
		DBahA	0.5	µg/mL	4			Transformed colonies	233	Surviving colonies	0.0172	
		DBahA	1	µg/mL	4			Transformed colonies	217	Surviving colonies	0.0184	
		DBahA	5	µg/mL	5			Transformed colonies	270	Surviving colonies	0.0185	
		DBahA	10	µg/mL	0			Transformed colonies	232	Surviving colonies	0	

Table C-14. In vitro DNA adducts: data use

Record number	Reference	Page	Table number	Figure number	PAHs	Data to be extracted	Basis for RPF	Comment	Notes
16890	Allen and Coombs, 1980	245	1		BaP, BaA	µmol compound/mol DNA P	Point estimate	Adducts in nuclear and mitochondrial DNA	Calculate separate RPFs for nuclear and mitochondrial DNA
6300	Binkova et al., 2000	62		3	BaP, DBalP	Adducts at each dose level	Ratio of slopes	Slope of adduct versus dose curve	May need to drop high-dose data for adequate fit
9510	Bryla and Weyand, 1992	39	1		BaP, BaA, DBacA	Adducts at each dose level	Ratio of slopes	Slope of adduct versus dose curve under light conditions (maximum response for all compounds)	
22800	Grover and Sims, 1968	160	1		BaP, DBahA, DBacA, BaA, Pyr, PH	Reaction with DNA	Point estimate		
10660	Johnsen et al., 1998	80		2	BjAC, BlAC, BaP	Total adduct levels in human lymphocytes and HL-60 cells	Point estimate	Total adducts formed in human lymphocytes or HL-60 cells	Calculate RPFs separately by cell type
10670	Johnsen et al., 1997	196	II		BjAC, BlAC, BaP	DNA adduct levels in PCB-treated rat lung cells	Point estimate	Adducts in PCB-treated rat lung Clara and Type 2 cells	Calculate RPFs separately by cell type
7870	Melendez-Colon et al., 2000	13		2	BaP, DBalP	Stable DNA adducts at each dose level	Ratio of slopes	Slope of adduct versus dose curve at two doses	
21200	Segerback and Vodicka, 1993	2,465		3	Pyr, BghiP, FA, DBahA, BbF, BaP, BaA, CH	Total adduct levels	Point estimate	Total adduct level in optimized nuclease P1 adduct enrichment procedure	

Table C-15. In vitro DNA adducts: dose-response data

Record number	Reference	PAH	Dose	Dose units	DNA adducts			n	Units	Notes
					Mean	SD	Adduct units			
16890	Allen and Coombs, 1980	BaP	0.235	µg/mL	7.5	1.9	µmol/mol DNA P			Nuclear DNA
		BaA	0.644	µg/mL	0.44	0.11	µmol/mol DNA P			Nuclear DNA
		BaP	0.235	µg/mL	413	164	µmol/mol DNA P			Mitochondrial DNA
		BaA	0.644	µg/mL	104	40.2	µmol/mol DNA P			Mitochondrial DNA
6300	Binkova et al., 2000	BaP	0.010	µM	1.8	1.16	Adducts	1×10^8	Nucleotides	
			0.10	µM	18	7.18	Adducts	1×10^8	Nucleotides	
			0.40	µM	95	39.4	Adducts	1×10^8	Nucleotides	
			1.0	µM	258	115	Adducts	1×10^8	Nucleotides	
			4.0	µM	205	81.9	Adducts	1×10^8	Nucleotides	
			10	µM	69	21.9	Adducts	1×10^8	Nucleotides	
			40	µM	37	10.8	Adducts	1×10^8	Nucleotides	
		DBalP	0.010	µM	179	55.3	Adducts	1×10^8	Nucleotides	
			0.020	µM	534	52.6	Adducts	1×10^8	Nucleotides	
			0.040	µM	1,304	375	Adducts	1×10^8	Nucleotides	
			0.080	µM	1,696	644	Adducts	1×10^8	Nucleotides	
			0.10	µM	2,317	774	Adducts	1×10^8	Nucleotides	
			0.40	µM	1,971	729	Adducts	1×10^8	Nucleotides	
			1.0	µM	632	170	Adducts	1×10^8	Nucleotides	
9510	Bryla and Weyand, 1992	BaP	0.12	nmol	0.17		Adducts	1×10^7	Nucleotides	Light conditions; max for BaP and others
		BaP	12	nmol	1.37		Adducts	1×10^7	Nucleotides	
		BaP	120	nmol	2.21		Adducts	1×10^7	Nucleotides	
		BaP	600	nmol	5.45		Adducts	1×10^7	Nucleotides	
		BaA	0.12	nmol	0.15		Adducts	1×10^7	Nucleotides	
		BaA	12	nmol	0.09		Adducts	1×10^7	Nucleotides	
		BaA	120	nmol	0.8		Adducts	1×10^7	Nucleotides	
		BaA	600	nmol	0.95		Adducts	1×10^7	Nucleotides	

Table C-15. In vitro DNA adducts: dose-response data

Record number	Reference	PAH	Dose	Dose units	DNA adducts			n	Units	Notes
					Mean	SD	Adduct units			
		DBacA	0.12	nmol	0		Adducts	1×10^7	Nucleotides	
		DBacA	12	nmol	0.06		Adducts	1×10^7	Nucleotides	
		DBacA	120	nmol	0.57		Adducts	1×10^7	Nucleotides	
		DBacA	600	nmol	1.76		Adducts	1×10^7	Nucleotides	
22800	Grover and Sims, 1968	BaP	5	µg	1.41		µmol/g-atom of DNA P			
		DBahA	5	µg	0.44		µmol/g-atom of DNA P			
		DBacA	5	µg	0.56		µmol/g-atom of DNA P			
		BaA	5	µg	0.7		µmol/g-atom of DNA P			
		Pyr	5	µg	0.31		µmol/g-atom of DNA P			
		PH	5	µg	0.05		µmol/g-atom of DNA P			
10670	Johnsen et al., 1997	BaP	30	µg/mL	0.05		fmol adducts/µg DNA			Clara cells
		BjAC	30	µg/mL	0.15		fmol adducts/µg DNA			Clara cells
		BlAC	30	µg/mL	0.24		fmol adducts/µg DNA			Clara cells
		BaP	30	µg/mL	0.02		fmol adducts/µg DNA			Type 2 cells
		BjAC	30	µg/mL	0.06		fmol adducts/µg DNA			Type 2 cells
		BlAC	30	µg/mL	0.03		fmol adducts/µg DNA			Type 2 cells
10660	Johnsen et al., 1998	BaP	30	µg/mL	0.333	0.093	fmol adducts/µg DNA	3		Human lymphocytes
		BjAC	30	µg/mL	0.110	0.026	fmol adducts/µg DNA	3		Human lymphocytes
		BlAC	30	µg/mL	1.089	0.595	fmol adducts/µg DNA	3		Human lymphocytes
		BaP	30	µg/mL	0.239	0.172	fmol adducts/µg DNA	3		HL-60 cells

Table C-15. In vitro DNA adducts: dose-response data

Record number	Reference	PAH	Dose	Dose units	DNA adducts			n	Units	Notes
					Mean	SD	Adduct units			
		BjAC	30	µg/mL	0.149	0.146	fmol adducts/µg DNA	3		HL-60 cells
		BlAC	30	µg/mL	0.942	0.344	fmol adducts/µg DNA	3		HL-60 cells
7870	Melendez-Colon et al., 2000	BaP	1	µm	18	8.07	Stable adducts	1×10^6	Nucleotides	
		BaP	2	µm	34	6.46	Stable adducts	1×10^6	Nucleotides	
		DBalP	1	µm	254	4.30	Stable adducts	1×10^6	Nucleotides	
		DBalP	2	µm	348	17.20	Stable adducts	1×10^6	Nucleotides	
21200	Segerback and Vodicka, 1993	BaP	100	mM	15		µmol adducts per mol dNp			
		Pyr	100	mM	0.14		µmol adducts per mol dNp			
		BghiP	100	mM	0.50		µmol adducts per mol dNp			
		FA	100	mM	1.5		µmol adducts per mol dNp			
		DBahA	100	mM	2.8		µmol adducts per mol dNp			
		BbF	100	mM	3.7		µmol adducts per mol dNp			
		BaA	100	mM	30		µmol adducts per mol dNp			
		CH	100	mM	50		µmol adducts per mol dNp			

Table C-16. In vitro DNA damage: data use

Record number	Reference	Page	Table number	Figure number	PAHs	Data to be extracted	Basis for RPF	Comment	Notes
16840	Agrelo and Amos, 1981	531	2		BaP, Pyr	Hydroxyurea inhibited [^{3}H]-thymidine incorporation into cells (dpm) and dose (µg/mL); use 10 µg/mL dose for BaP and 100 µg/mL dose for pyrene	Point estimate		
23790	Ichinotsubo et al., 1977	56	Table II		BaP, DBaiP, DBahA	Use column designated JC5519 +S9 for BaP, DBaiP, and DBahA; dose as µg/well and response as diameter of zone of inhibition (mm); the control is wild type strain AB1157	Point estimate	*E. coli* Rec BC, S9 identification unknown	
10660	Johnsen et al., 1998	82		4	BaP, BjAC, BlAC	DNA damage (NAAC, $10^{-3}h^{-1}$), SD and dose (µg/mL) for both human lymphocytes and HL-60 cells; use 24 h + 1 h AraC/HU data (crosshatched bars)	Ratio of slopes (human lympho-cytes); point esti-mates (HL-60 cells)		Model as continuous data
19740	Martin et al., 1978	2,624	1		BaP, BeP, BaA, DBacA, DBahA	Maximum dpm/µg DNA above background and dose (M); dose is in column marked "M"	Point estimate	Background already subtracted	
19830	Mersch-Sundermann et al., 1992	3–6	2		BaP, AA, BaA, BbF, BghiF, BjF, BbFE, BghiP, BeP, CH, DBacA, DBahA, DBalP, DBahP, DBaiP, FA, IP, PH, Tphen	SOS induction potential for assay (+S9) for each compound (already incorporates dose)	Ratio of SOS induction potentials	SOSIP reported in text as slope of steepest portion of the induction factor dose-response curve	No modeling necessary; slopes reported in text
20810	Robinson and Mitchell, 1981	520	1		BaP, Pyr	Maximum [^{3}H]-TDR incorporation and dose (test concentration in µg/mL in parentheses after maximum) for rows with metabolic activation (+); use compound-specific background [^{3}H]-TDR incorporation in same row	Point estimate		
20940	Rossman et al., 1991	354	2		BaP, AC, DBacA, DBahA, PH	Max enhancement of prophage induction over background and dose (amount at max, in µg/well) for those rows with S9 (+ rows).	Point estimate	Background already addressed	
21730	Tong et al., 1981b	480	I		BaP, BaA	DNA repair grains/nucleus, SD, and dose (M); four doses BaA, three doses BaP and DMSO control	Ratio of slopes		Model as continuous data

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Table C-17. In vitro DNA damage: dose-response data

Record number	Reference	PAH	Dose	Dose units	Endpoint	DNA damage			n	Notes
						Mean	SD	Units		
16840	Agrelo and Amos, 1981	Control	0	µg/mL	Unscheduled DNA synthesis	177		dpm		HU inhibited
		BaP	0.001	µg/mL	Unscheduled DNA synthesis	195		dpm		HU inhibited
		BaP	0.01	µg/mL	Unscheduled DNA synthesis	126		dpm		HU inhibited
		BaP	0.1	µg/mL	Unscheduled DNA synthesis	262		dpm		HU inhibited
		BaP	1	µg/mL	Unscheduled DNA synthesis	818		dpm		HU inhibited
		BaP	10	µg/mL	Unscheduled DNA synthesis	2,270		dpm		HU inhibited
		BaP	100	µg/mL	Unscheduled DNA synthesis	819		dpm		HU inhibited
		BaP	1,000	µg/mL	Unscheduled DNA synthesis	373		dpm		HU inhibited
		Control	0	µg/mL	Unscheduled DNA synthesis	1,168		dpm		HU inhibited
		Pyr	0.032	µg/mL	Unscheduled DNA synthesis	1,293		dpm		HU inhibited
		Pyr	0.16	µg/mL	Unscheduled DNA synthesis	1,192		dpm		HU inhibited
		Pyr	0.8	µg/mL	Unscheduled DNA synthesis	1,367		dpm		HU inhibited
		Pyr	4	µg/mL	Unscheduled DNA synthesis	1,510		dpm		HU inhibited
		Pyr	20	µg/mL	Unscheduled DNA synthesis	1,694		dpm		HU inhibited
		Pyr	100	µg/mL	Unscheduled DNA synthesis	1,716		dpm		HU inhibited
23790	Ichinotsubo et al., 1977	Control	0		DNA damage	0		Diameter of zone of inhibition mm		
		BaP	70	µg/well	DNA damage	6		Diameter of zone of inhibition mm		
		Control	0		DNA damage	0		Diameter of zone of inhibition mm		
		DBaiP	600	µg/well	DNA damage	10		Diameter of zone of inhibition mm		
		Control	0		DNA damage	0		Diameter of zone of inhibition mm		

Table C-17. In vitro DNA damage: dose-response data

Record number	Reference	PAH	Dose	Dose units	Endpoint	DNA damage			n	Notes
						Mean	SD	Units		
		DBahA	25	µg/well	DNA damage	10		Diameter of zone of inhibition mm		
10660	Johnsen et al., 1998	DMSO	0	µg/mL	DNA damage	4.4	1.3	NAAC, 10^{-3} h^{-1}	3	Human lymphocytes with AraC/HU
		BaP	3	µg/mL	DNA damage	12	3.2	NAAC, 10^{-3} h^{-6}	3	Human lymphocytes with AraC/HU; no continuous linear model fit
			30	µg/mL	DNA damage	15	2.7	NAAC, 10^{-3} h^{-7}	3	Human lymphocytes with AraC/HU
		BjAC	3	µg/mL	DNA damage	6.0	2.1	NAAC, 10^{-3} h^{-2}	3	Human lymphocytes with AraC/HU
			30	µg/mL	DNA damage	9.4	3.4	NAAC, 10^{-3} h^{-3}	3	Human lymphocytes with AraC/HU
		BIAC	3	µg/mL	DNA damage	8.2	3.2	NAAC, 10^{-3} h^{-4}	3	Human lymphocytes with AraC/HU; no continuous linear model fit
			30	µg/mL	DNA damage	9.3	2.1	NAAC, 10^{-3} h^{-5}	3	Human lymphocytes with AraC/HU
		DMSO	0	µg/mL	DNA damage	7.8	3.1	NAAC, 10^{-3} h^{-5}	3	HL-60 cells with AraC/HU
		BaP	30	µg/mL	DNA damage	13.2	9.5	NAAC, 10^{-3} h^{-5}	3	HL-60 cells with AraC/HU
		BjAC	30	µg/mL	DNA damage	9.6	3.0	NAAC, 10^{-3} h^{-5}	3	HL-60 cells with AraC/HU
		BIAC	30	µg/mL	DNA damage	11.6	5.5	NAAC, 10^{-3} h^{-5}	3	HL-60 cells with AraC/HU
19740	Martin et al., 1978	BaP	1×10^{-5}	M	Unscheduled DNA synthesis	210		Maximum dpm/µg DNA		Increase above background
		BeP	1×10^{-6}	M	Unscheduled DNA synthesis	256		Maximum dpm/µg DNA		Increase above background
		BaA	1×10^{-7}	M	Unscheduled DNA synthesis	59		Maximum dpm/µg DNA		Increase above background
		DBacA	1×10^{-5}	M	Unscheduled DNA synthesis	97		Maximum dpm/µg DNA		Increase above background
		DBahA	1×10^{-5}	M	Unscheduled DNA synthesis	96		Maximum dpm/µg DNA		Increase above background

Table C-17. In vitro DNA damage: dose-response data

Record number	Reference	PAH	Dose	Dose units	Endpoint	DNA damage			n	Notes
						Mean	SD	Units		
19830	Mersch-Sundermann et al., 1992	BaP	NA		SOS induction potential	0.605	NA			Steepest slope of induction factor dose-response curve; + S9
		AA	NA		SOS induction potential	0.142	NA			Steepest slope of induction factor dose-response curve; + S9
		BaA	NA		SOS induction potential	0.1	NA			Steepest slope of induction factor dose-response curve; + S9
		BbF	NA		SOS induction potential	0.045	NA			Steepest slope of induction factor dose-response curve; + S9
		BghiF	NA		SOS induction potential	0.34	NA			Steepest slope of induction factor dose-response curve; + S9
		BjF	NA		SOS induction potential	0.254	NA			Steepest slope of induction factor dose-response curve; + S9
		BbFE	NA		SOS induction potential	0.024	NA			Steepest slope of induction factor dose-response curve; + S9
		BghiP	NA		SOS induction potential	0.033	NA			Steepest slope of induction factor dose-response curve; + S9
		BeP	NA		SOS induction potential	0.032	NA			Steepest slope of induction factor dose-response curve; + S9
		CH	NA		SOS induction potential	0.221	NA			Steepest slope of induction factor dose-response curve; + S9
		DBacA	NA		SOS induction potential	0.104	NA			Steepest slope of induction factor dose-response curve; + S9
		DBahA	NA		SOS induction potential	0.039	NA			Steepest slope of induction factor dose-response curve; + S9
		DBalP	NA		SOS induction potential	2.1	NA			Steepest slope of induction factor dose-response curve; + S9
		DBahP	NA		SOS induction potential	0.117	NA			Steepest slope of induction factor dose-response curve; + S9
		DBaiP	NA		SOS induction potential	0.174	NA			Steepest slope of induction factor dose-response curve; + S9
		FA	NA		SOS induction potential	0.412	NA			Steepest slope of induction factor dose-response curve; + S9

Table C-17. In vitro DNA damage: dose-response data

Record number	Reference	PAH	Dose	Dose units	Endpoint	DNA damage			n	Notes
						Mean	SD	Units		
		IP	NA		SOS induction potential	0.036	NA			Steepest slope of induction factor dose-response curve; + S9
		PH	NA		SOS induction potential	0.053	NA			Steepest slope of induction factor dose-response curve; + S9
		Tphen	NA		SOS induction potential	0.26	NA			Steepest slope of induction factor dose-response curve; + S9
20810	Robinson and Mitchell, 1981	Control	0	µg/mL	Unscheduled DNA synthesis	53	4	[^{3}H]-TdR incorporation		Maximum [^{3}H]-TdR incorporation
		BaP	10	µg/mL	Unscheduled DNA synthesis	142	7	[^{3}H]-TdR incorporation		Maximum [^{3}H]-TdR incorporation
		Control	0	µg/mL	Unscheduled DNA synthesis	52	2	[^{3}H]-TdR incorporation		Maximum [^{3}H]-TdR incorporation
		Pyr	7.2	µg/mL	Unscheduled DNA synthesis	115	9	[^{3}H]-TdR incorporation		Maximum [^{3}H]-TdR incorporation
20940	Rossman et al., 1991	BaP	12.5	µg/mL	DNA damage	10.4		Lambda pro-phage induction		Maximum enhancement over background
		AC	12.5	µg/mL	DNA damage	4.8		Lambda pro-phage induction		Maximum enhancement over background
		DBacA	1.44	µg/mL	DNA damage	8		Lambda pro-phage induction		Maximum enhancement over background
		DBahA	2	µg/mL	DNA damage	4		Lambda pro-phage induction		Maximum enhancement over background
		PH	25	µg/mL	DNA damage	4.5		Lambda pro-phage induction		Maximum enhancement over background

Table C-17. In vitro DNA damage: dose-response data

Record number	Reference	PAH	Dose	Dose units	Endpoint	DNA damage			n	Notes
						Mean	SD	Units		
21730	Tong et al., 1981b	Control	0	M	Unscheduled DNA synthesis	0.1	0.1	Grains/nucleus		
		BaP	1×10^{-4}	M	Unscheduled DNA synthesis	45.1	3.7	Grains/nucleus		
		BaP	5×10^{-4}	M	Unscheduled DNA synthesis	47.7	3.7	Grains/nucleus		
		BaP	1×10^{-3}	M	Unscheduled DNA synthesis	65.6	17.8	Grains/nucleus		
		BaA	5×10^{-5}	M	Unscheduled DNA synthesis	0.6		Grains/nucleus		
		BaA	1×10^{-4}	M	Unscheduled DNA synthesis	14.8	2.6	Grains/nucleus		
		BaA	5×10^{-4}	M	Unscheduled DNA synthesis	17.2	6	Grains/nucleus		
		BaA	1×10^{-3}	M	Unscheduled DNA synthesis	Toxic		Grains/nucleus		

1

Table C-18. In vitro clastogenicity: data use

Record number	Reference	Page	Table number	PAHs	Data to be used	Basis for RPF	Comment
14620	Kochhar, 1982	846	Not numbered	BaP, BaA	Percentage of cells with aberrations and dose (µg/mL)	Ratio of slopes	Model as incidence data
14640	Krolewski et al., 1986	1,648	II	BaP, CPcdP	Mean number sister chromatid exchange/ chromosome, SD, and dose (µM)	Ratio of slopes	Use first column of data; not data with AIA or IVA; model as continuous data
19690	Mane et al., 1990	81	III	BaP, BaA	Sister chromatid exchange frequencies/ for V79 cell + rat MEC and dose	Point estimates	Use sister chromatid exchange data for V79 + rat MEC only
21710	Tong et al., 1981a	469	1	BaP, BaA	Sister chromatid exchange/cell, SD, and dose	Point estimates	Continuous data, no n provided in study

1

Table C-19. In vitro clastogenicity: dose-response data

Record number	Reference	PAH	Dose	Dose units	n	Clastogenicity			Notes
						Mean	SD	Units	
14620	Kochhar, 1982	Control	0	µg/mL	100	0.06		Fraction cells with aberrations	
		BaP	0.6	µg/mL	100	0.23		Fraction cells with aberrations	
		BaP	1.25	µg/mL	100	0.32		Fraction cells with aberrations	
		BaP	2.5	µg/mL	100	0.45		Fraction cells with aberrations	
		BaP	5	µg/mL	100	0.56		Fraction cells with aberrations	
		BaA	0.6	µg/mL	100	0.17		Fraction cells with aberrations	
		BaA	1.25	µg/mL	100	0.23		Fraction cells with aberrations	
		BaA	2.5	µg/mL	100	0.3		Fraction cells with aberrations	
		BaA	5	µg/mL	100	0.38		Fraction cells with aberrations	
14640	Krolewski et al., 1986	Control	0	µM	30	0.147	0.059	Sister chromatid exchange	
		BaP	1	µM	30	0.874	0.275	Sister chromatid exchange	
		BaP	5	µM	30	0.932	0.266	Sister chromatid exchange	
		CPcdP	1	µM	30	0.348	0.119	Sister chromatid exchange	
		CPcdP	5	µM	30	0.432	0.15	Sister chromatid exchange	
19690	Mane et al., 1990	Control	0	µg/mL		0.3	1	Sister chromatid exchange frequency	For V79 cell + rat MEC
		BaP	1	µg/mL		3	1	Sister chromatid exchange frequency	For V79 cell + rat MEC
		BaA	1	µg/mL		0.7	0.5	Sister chromatid exchange frequency	For V79 cell + rat MEC
21710	Tong et al., 1981a	Control	0	M		11.15	3.81	Sister chromatid exchange/cell	
		BaP	1×10^{-6}	M		16.15	3.83	Sister chromatid exchange/cell	
		BaP	1×10^{-5}	M		59.75	16.96	Sister chromatid exchange/cell	
		BaP	1×10^{-4}	M		103.3	22.75	Sister chromatid exchange/cell	
		Control	0	M		15.75	5.18	Sister chromatid exchange/cell	
		BaA	1×10^{-5}	M		21.2	9.59	Sister chromatid exchange/cell	
		BaA	1×10^{-4}	M		29.15	9.93	Sister chromatid exchange/cell	
		BaA	1×10^{-3}	M		26.2	6.96	Sister chromatid exchange/cell	

Table C-20. In vivo DNA adducts: data use

Record number	Reference	Page	Table number	Figure number	PAHs	Data to be extracted	Basis for RPF	Comment	Notes
6210	Arif et al., 1997	36		4	DBalP and BaP	Mean adduct levels for heart, pancreas, bladder, liver	Point estimate	Mean adduct levels summed across mammary epithelial, lung, heart, pancreas, bladder, liver	
17630	Cavalieri et al., 1981a	491	3		CPcdP, ACEP (reported in paper as CPAP), BaP	Done	Point estimate	DNA-bound PAH in mouse skin after 4-hr or 24-hr treatment	Calculate separate RPFs for 4-hr and 24-hr treatment
18810	Hughes and Phillips, 1990	1,614		3	DBalP, DBaeP, DBahP, DBaiP, BaP	AUC for skin and lung through 84 d	Point estimate	Sum of AUCs for skin and lung 0–84 d	
11190	Mass et al., 1993	188	1		BjAC, BaP	Done	Ratio of Slopes	AUC (adduct-time curve) versus dose for lung adducts 24–72 hr	
8010	Nesnow et al., 1993b	39		1 and 2	BbF, BaP	AUC for lung, liver, and PBL through 56 d	Point estimate	Sum of AUCs for lung, liver, and lymphocytes 0–56 d	
24590/ 20920	Nesnow et al., 1998b; Ross et al., 1995	402	2		BaP, BbF, DBahA, CPcdP, DBalP	Done	Ratio of Slopes	Slope of TIDAL/dose (slope reported in Record 24590 based on data from Record 20920); DBalP data reported in separate study without BaP concurrent	
22810	Phillips et al., 1979	205	I		DBahA, DBacA, BaP	Done	Point estimate	Peak binding in mouse skin; BaA dropped; not clear if reported level is peak	
24790	Kligerman et al., 2002	846	1		BaA, BaP, BbF, CH	Done	Point estimate	Adducts in mouse or rat PBLs at single time point after either intraperitoneal or gavage administration	Calculate separate RPFs for intraperitoneal and gavage, rat and mouse
24801	Weyand et al., 2004	12, 14		4 and 6	BcFE, BaP	Mean adduct levels for lung and forestomach	Point estimate	Adducts in mouse lung and forestomach at single time point after either intraperitoneal or dietary administration	Calculate separate RPFs for lung and forestomach after oral exposure and for lung after intraperitoneal exposure

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
6210	Arif et al., 1997	Control	Rat	0	µmol/mammary gland	Liver		0			Adducts/10^9 nucleotides		
		BaP	Rat	0.25	µmol/mammary gland	Mammary gland		300	45		Adducts/10^9 nucleotides		
		BaP	Rat	0.25	µmol/mammary gland	Lung		11	1.3		Adducts/10^9 nucleotides		
		BaP	Rat	0.25	µmol/mammary gland	Heart		9.5			Adducts/10^9 nucleotides		
		BaP	Rat	0.25	µmol/mammary gland	Pancreas		0			Adducts/10^9 nucleotides		
		BaP	Rat	0.25	µmol/mammary gland	Bladder		0			Adducts/10^9 nucleotides		
		BaP	Rat	0.25	µmol/mammary gland	Liver		4.5			Adducts/10^9 nucleotides		
						Sum		324.74					
		DBalP	Rat	0.25	µmol/mammary gland	Mammary gland		1,878	378		Adducts/10^9 nucleotides		
		DBalP	Rat	0.25	µmol/mammary gland	Lung		85	24		Adducts/10^9 nucleotides		
		DBalP	Rat	0.25	µmol/mammary gland	Heart		64			Adducts/10^9 nucleotides		
		DBalP	Rat	0.25	µmol/mammary gland	Pancreas		32			Adducts/10^9 nucleotides		
		DBalP	Rat	0.25	µmol/mammary gland	Bladder		69			Adducts/10^9 nucleotides		
		DBalP	Rat	0.25	µmol/mammary gland	Liver		116			Adducts/10^9 nucleotides		
						Sum		2,244.63					
17630	Cavalieri et al., 1981a	BaP		0.2	µmol/mouse	Skin	4 hr	16.3		1	µmol adduct/mol DNA		
		CPcdP		0.2	µmol/mouse	Skin	4 hr	2.3		0.2	µmol adduct/mol DNA		
		ACEP		0.2	µmol/mouse	Skin	4 hr	2.2		0.1	µmol adduct/mol DNA		
		BaP		0.2	µmol/mouse	Skin	24 hr	6.7		1.6	µmol adduct/mol DNA		

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
		CPcdP		0.2	µmol/mouse	Skin	24 hr	8.8		1	µmol adduct/mol DNA		
		ACEP		0.2	µmol/mouse	Skin	24 hr	0.30		0.1	µmol adduct/mol DNA		
18810	Hughes and Phillips, 1990	BaP		1	µmol	Skin	1 d	7.8			fmol adducts/µg DNA		Only peak extracted; interrupted scale precluded digitizing
		BaP		1	µmol	Lung	2 d	1.2			fmol adducts/µg DNA		
		BaP		1	µmol	Sum skin and lung		9.0			fmol adducts/µg DNA		
		DBaeP		1	µmol	Skin	2 d	0.50			fmol adducts/µg DNA		
		DBaeP		1	µmol	Lung	7 d	Cannot determine			fmol adducts/µg DNA		
		DBaeP		1	µmol	Sum skin and lung		Cannot determine			fmol adducts/µg DNA		
		DBahP		1	µmol	Skin	2 d	3.1			fmol adducts/µg DNA		
		DBahP		1	µmol	Lung	2 d	0.14			fmol adducts/µg DNA		
		DBahP		1	µmol	Sum skin and lung		3.2			fmol adducts/µg DNA		
		DBaiP		1	µmol	Skin	2 d	0.75			fmol adducts/µg DNA		
		DBaiP		1	µmol	Lung	2 d	0.10			fmol adducts/µg DNA		
		DBaiP		1	µmol	Sum skin and lung		0.85			fmol adducts/µg DNA		
		DBalP		1	µmol	Skin	1 d	62			fmol adducts/µg DNA		
		DBalP		1	µmol	Lung	2 d	2.3			fmol adducts/µg DNA		
		DBalP		1	µmol	Sum skin and lung		65			fmol adducts/µg DNA		

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
11190	Mass et al., 1993	BaP		20	mg/kg bw	Lung	24 hr	116	53		amol adducts/µg DNA		AUC calculated using trapezoid rule
		BaP		20	mg/kg bw	Lung	48 hr	122	25		amol adducts/µg DNA		
		BaP		20	mg/kg bw	Lung	72 hr	181	101		amol adducts/µg DNA		
		BaP		50	mg/kg bw	Lung	24 hr	120	20		amol adducts/µg DNA		
		BaP		50	mg/kg bw	Lung	48 hr	201	170		amol adducts/µg DNA		
		BaP		50	mg/kg bw	Lung	72 hr	432	274		amol adducts/µg DNA		
		BaP		100	mg/kg bw	Lung	24 hr	427	140		amol adducts/µg DNA		
		BaP		100	mg/kg bw	Lung	48 hr	407	197		amol adducts/µg DNA		
		BaP		100	mg/kg bw	Lung	72 hr	2,004	314		amol adducts/µg DNA		
		BaP		20	mg/kg bw	Lung	AUC	7,884				469.73	
		BaP		50	mg/kg bw	Lung	AUC	12,888					
		BaP		100	mg/kg bw	Lung	AUC	44,064					
		BjAC		20	mg/kg bw	Lung	24 hr	63	34		amol adducts/µg DNA		AUC calculated using trapezoid rule
		BjAC		20	mg/kg bw	Lung	48 hr	97	101		amol adducts/µg DNA		
		BjAC		20	mg/kg bw	Lung	72 hr	255	392		amol adducts/µg DNA		
		BjAC		50	mg/kg bw	Lung	24 hr	116	121		amol adducts/µg DNA		
		BjAC		50	mg/kg bw	Lung	48 hr	402	237		amol adducts/µg DNA		
		BjAC		50	mg/kg bw	Lung	72 hr	1,954	1,921		amol adducts/µg DNA		
		BjAC		100	mg/kg bw	Lung	24 hr	180	133		amol adducts/µg DNA		

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
		BjAC		100	mg/kg bw	Lung	48 hr	532	559		amol adducts/µg DNA		
		BjAC		100	mg/kg bw	Lung	72 hr	2,439	2,242		amol adducts/µg DNA		
		BjAC		20	mg/kg bw	Lung	AUC	6,900				464.25	
		BjAC		50	mg/kg bw	Lung	AUC	35,880					
		BjAC		100	mg/kg bw	Lung	AUC	46,356					
8010	Nesnow et al., 1993b	BaP		100	mg/kg	Lung	d 1	453					AUC calculated using trapezoid rule
		BaP		100	mg/kg	Lung	d 3	1,001					
		BaP		100	mg/kg	Lung	d 7	574					
		BaP		100	mg/kg	Lung	d 14	386					
		BaP		100	mg/kg	Lung	d 28	381					
		BaP		100	mg/kg	Lung	d 56	143					
		BaP		100	mg/kg	Lung	AUC	20,892					
		BaP		100	mg/kg	Liver	d 1	398					
		BaP		100	mg/kg	Liver	d 3	1,317					
		BaP		100	mg/kg	Liver	d 7	931					
		BaP		100	mg/kg	Liver	d 14	537					
		BaP		100	mg/kg	Liver	d 28	394					
		BaP		100	mg/kg	Liver	d 56	116					
		BaP		100	mg/kg	Liver	AUC	25,207					
		BaP		100	mg/kg	PBL	d 1	158					
		BaP		100	mg/kg	PBL	d 3	273					
		BaP		100	mg/kg	PBL	d 7	162					
		BaP		100	mg/kg	PBL	d 14	187					
		BaP		100	mg/kg	PBL	d 28	72					
		BaP		100	mg/kg	PBL	d 56	41					
		BaP		100	mg/kg	PBL	AUC	5,985					
		BaP		100	mg/kg	Sum of AUCs		52,084					
		BbF		100	mg/kg	Lung	d 1	21					AUC calculated using trapezoid rule

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
		BbF		100	mg/kg	Lung	d 3	184					
		BbF		100	mg/kg	Lung	d 5	233					
		BbF		100	mg/kg	Lung	d 7	211					
		BbF		100	mg/kg	Lung	d 14	229					
		BbF		100	mg/kg	Lung	d 28	145					
		BbF		100	mg/kg	Lung	d 56	106					
		BbF		100	mg/kg	Lung	AUC	8,763					
		BbF		100	mg/kg	Liver	d 1	12					
		BbF		100	mg/kg	Liver	d 3	35					
		BbF		100	mg/kg	Liver	d 5	51					
		BbF		100	mg/kg	Liver	d 7	61					
		BbF		100	mg/kg	Liver	d 14	21					
		BbF		100	mg/kg	Liver	d 28	15					
		BbF		100	mg/kg	Liver	d 56	12					
		BbF		100	mg/kg	Liver	AUC	1,173					
		BbF		100	mg/kg	PBL	d 1	12					
		BbF		100	mg/kg	PBL	d 3	29					
		BbF		100	mg/kg	PBL	d 5	59					
		BbF		100	mg/kg	PBL	d 7	57					
		BbF		100	mg/kg	PBL	d 14	40					
		BbF		100	mg/kg	PBL	d 28	15					
		BbF		100	mg/kg	PBL	d 56	13					
		BbF		100	mg/kg	PBL	AUC	1,378					
		BbF		100	mg/kg	Sum of AUCs		11,314					
24590/ 20920	Nesnow et al., 1998b; Ross, 1995	BaP		NA		Lung	>21 d			3.9		113	Slope of dose versus TIDAL value (in fmol-d/µg DNA)
		BbF		NA		Lung	>21 d			5		37.5	Slope of dose versus TIDAL value (in fmol-d/µg DNA)

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
		CPcdP		NA		Lung	>21 d			3.69		148	Slope of dose versus TIDAL value (in fmol-d/µg DNA)
		DBahA		NA		Lung	>21 d			19.1		219	Slope of dose versus TIDAL value (in fmol-d/µg DNA)
		DBalP		NA		Lung	>21 d			267		1,390	Slope of dose versus TIDAL value (in fmol-d/µg DNA)
22810	Phillips et al., 1979	BaP		1	µmol/mouse	Skin	19 hr	27			pmol adducts/mg DNA		peak
		DBacA		1	µmol/mouse	Skin	24 hr	10			pmol adducts/mg DNA		peak
		DBahA		1	µmol/mouse	Skin	72 hr	15			pmol adducts/mg DNA		peak
24790	Kligerman et al., 2002	BaP	Mice	100	mg/kg	PBL	d 7	4,186	273		amol adducts/µg DNA		Intraperitoneal
		BaA	Mice	100	mg/kg	PBL	d 7	93	8		amol adducts/µg DNA		Intraperitoneal
		BbF	Mice	100	mg/kg	PBL	d 7	516	7		amol adducts/µg DNA		Intraperitoneal
		CH	Mice	100	mg/kg	PBL	d 7	81	11		amol adducts/µg DNA		Intraperitoneal
		Control	Mice	0	mg/kg	PBL	d 7	0			amol adducts/µg DNA		Intraperitoneal
		BaP	Mice	100	mg/kg	PBL	d 7	143	17		amol adducts/µg DNA		Gavage
		BaA	Mice	100	mg/kg	PBL	d 7	32	2		amol adducts/µg DNA		Gavage
		BbF	Mice	100	mg/kg	PBL	d 7	39	4		amol adducts/µg DNA		Gavage
		CH	Mice	100	mg/kg	PBL	d 7	37	1		amol adducts/µg DNA		Gavage
		Control	Mice	0	mg/kg	PBL	d 7	0			amol adducts/µg DNA		Gavage

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
		BaP	Rat	100	mg/kg	PBL	d 7	755	56		amol adducts/µg DNA		Intraperitoneal
		BaA	Rat	100	mg/kg	PBL	d 7	38	3		amol adducts/µg DNA		Intraperitoneal
		BbF	Rat	100	mg/kg	PBL	d 7	63	1		amol adducts/µg DNA		Intraperitoneal
		CH	Rat	100	mg/kg	PBL	d 7	24	2		amol adducts/µg DNA		Intraperitoneal
		Control	Rat	0	mg/kg	PBL	d 7	0			amol adducts/µg DNA		Intraperitoneal
		BaP	Rat	100	mg/kg	PBL	d 7	177	30		amol adducts/µg DNA		Gavage
		BaA	Rat	100	mg/kg	PBL	d 7	20	2		amol adducts/µg DNA		Gavage
		BbF	Rat	100	mg/kg	PBL	d 7	17	1		amol adducts/µg DNA		Gavage
		CH	Rat	100	mg/kg	PBL	d 7	10	4		amol adducts/µg DNA		Gavage
		Control	Rat	0	mg/kg	PBL	d 7	0			amol adducts/µg DNA		Gavage
24801	Weyand et al., 2004	BaP	Mice	230	mg/kg food	Lung	d 14	0.084		0.009	pmol adducts/mg DNA		Diet
		BcFE	Mice	13.6	mg/kg food	Lung	d 14	0.014		0.002	pmol adducts/mg DNA		Diet
		BcFE	Mice	197	mg/kg food	Lung	d 14	0.18		0.023	pmol adducts/mg DNA		Diet
		BaP	Mice	230	mg/kg food	Forestomach	d 14	0.033		0.005	pmol adducts/mg DNA		Diet
		BcFE	Mice	197	mg/kg food	Forestomach	d 14	0.0092		0.001	pmol adducts/mg DNA		Diet
		BaP	Mice	230	mg/kg food	Sum of lung and forestomach	d 14	0.117			pmol adducts/mg DNA		Diet
		BcFE	Mice	13.6	mg/kg food	Sum of lung and forestomach	d 14	0.014			pmol adducts/mg DNA		Diet

Table C-21. In vivo DNA adducts: dose-response data

Record number	Reference	PAH	Species	Dose	Dose units	Organ	Time	DNA adducts				Slope of AUC versus dose	Comments
								Mean	SD	SE	Adduct units		
		BcFE	Mice	197	mg/kg food	Sum of lung and forestomach	d 14	0.19			pmol adducts/mg DNA		Diet
		BaP	Mice	100	mg/kg bw	Lung	24 h	0.78		0.13	pmol adducts/mg DNA		Intraperitoneal
		BcFE	Mice	100	mg/kg bw	Lung	24 h	0.33		0.030	pmol adducts/mg DNA		Intraperitoneal

Table C-22. In vivo clastogenicity: data use

Record number	Reference	Page	Table number	Figure number	PAHs	Data to be extracted	Basis for RPF	Comment
24740	Allen et al., 1999		I and III		BaP, DBalP	Total micronuleated poly-chromatic erythrocytes (MN-PCEs) and dose (mg/kg); extract data for bone marrow and peripheral blood for both A/J mice (Table 1) and p53+/+ (wild type) mice (Table III)	Point estimate	Incidence data; single dose BaP
14270	He and Baker, 1991	166	1		BaP, CH	MN cells/1,000 binucleated and dose (µg/mouse)	Ratio of slopes	Incidence data
17190	Bayer, 1978	426	3		BaP, PH	Sister chromatid exchange/cells and dose (mg/kg)	Point estimate	Continuous data; only one dose PH significant; BaP given as 3,4-BaP
20950	Roszinsky-Kocher et al., 1979	66	1		BaP, DBahA, CH, PH, BeP, BbF, BaA	Sister chromatid exchanges/ metaphase and dose (mg/kg)	Point estimate	
24720	Kligerman et al., 1986	129	3		BaP, BlAC	Sister chromatid exchanges/ metaphase and dose (mg/kg)	Point estimate	Continuous data, no SD for control; use lowest dose approaching peak
24790	Kligerman et al., 2002	846	1		BaP, BaA, BbF, CH	Sister chromatid exchanges/ metaphase, intraperitoneal, for BaP, BaA, BbF, and CH; sister chromatid exchanges, gavage, for BaP and BaA (use 17.91 value for BaP); also use MN bn/1,000 bn, gavage, for BaP and BbF; dose in mg/kg	Point estimates	Separate RPFs for sister chromatid exchanges and micronuclei, oral and intraperitoneal

Table C-23. In vivo clastogenicity: dose-response data

Record number	Reference	PAH	Route of administration	Clastogenicity								$p <$ 0.05	Notes
				Dose	Dose units	Mean	SD	Units	n	% Response	Units		
24740	Allen et al., 1999	Tri-caprylin	Intra-peritoneal	0	mg/kg	2.6		MN-PCEs	1,000	0.0026	PCEs		A/J mice, bone marrow
		BaP	Intra-peritoneal	200	mg/kg	11.2		MN-PCEs	1,000	0.0112	PCEs	x	
		DBalP	Intra-peritoneal	0.3	mg/kg	2		MN-PCEs	1,000	0.0020	PCEs		
		DBalP	Intra-peritoneal	1.5	mg/kg	3.9		MN-PCEs	1,000	0.0039	PCEs	x	
		DBalP	Intra-peritoneal	3	mg/kg	3.4		MN-PCEs	1,000	0.0034	PCEs		
		DBalP	Intra-peritoneal	6	mg/kg	3.8		MN-PCEs	1,000	0.0038	PCEs		
		Tri-caprylin	Intra-peritoneal	0	mg/kg	2.8		MN-PCEs	1,000	0.0028	PCEs		A/J mice, peripheral blood
		BaP	Intra-peritoneal	200	mg/kg	9.5		MN-PCEs	1,000	0.0095	PCEs	x	
		DBalP	Intra-peritoneal	0.3	mg/kg	2.8		MN-PCEs	1,000	0.0028	PCEs		
		DBalP	Intra-peritoneal	1.5	mg/kg	2.9		MN-PCEs	1,000	0.0029	PCEs		
		DBalP	Intra-peritoneal	3	mg/kg	4		MN-PCEs	1,000	0.0040	PCEs		
		DBalP	Intra-peritoneal	6	mg/kg	4.3		MN-PCEs	1,000	0.0043	PCEs	x	
		Tri-caprylin	Intra-peritoneal	0	mg/kg	3.2		MN-PCEs	1,000	0.0032	PCEs		p53 +/+ wt mice, bone marrow
		BaP	Intra-peritoneal	200	mg/kg	5.1		MN-PCEs	1,000	0.0051	PCEs	x	
		DBalP	Intra-peritoneal	9	mg/kg	4.3		MN-PCEs	1,000	0.0043	PCEs		
		DBalP	Intra-peritoneal	12	mg/kg	7.4		MN-PCEs	1,000	0.0074	PCEs	x	
		DBalP	Intra-peritoneal	18	mg/kg	6.1		MN-PCEs	1,000	0.0061	PCEs	x	
		Tri-caprylin	Intra-peritoneal	0	mg/kg	3.5		MN-PCEs	1,000	0.0035	PCEs		p53 +/+ wt mice, peripheral blood

Table C-23. In vivo clastogenicity: dose-response data

Record number	Reference	PAH	Route of administration	Clastogenicity								$p < 0.05$	Notes
				Dose	Dose units	Mean	SD	Units	n	% Response	Units		
		BaP	Intra-peritoneal	200	mg/kg	5.7		MN-PCEs	1,000	0.0057	PCEs	x	
		DBalP	Intra-peritoneal	9	mg/kg	3.1		MN-PCEs	1,000	0.0031	PCEs		
		DBalP	Intra-peritoneal	12	mg/kg	3.1		MN-PCEs	1,000	0.0031	PCEs		
		DBalP	Intra-peritoneal	18	mg/kg	4.6		MN-PCEs	1,000	0.0046	PCEs		
14270	He and Baker, 1991	Control	Dermal	0	µg/mouse	13.3	2.8	MN cells	1,000	0.013	Binucleated		
		BaP	Dermal	0.5	µg/mouse	50.5	11.5	MN cells	1,000	0.051	Binucleated	x	
		BaP	Dermal	5	µg/mouse	66.8	4.1	MN cells	1,000	0.067	Binucleated	x	
		BaP	Dermal	50	µg/mouse	76	2.8	MN cells	1,000	0.076	Binucleated	x	
		BaP	Dermal	100	µg/mouse	64.3	5.4	MN cells	1,000	0.064	Binucleated	x	
		BaP	Dermal	500	µg/mouse	55.8	13	MN cells	1,000	0.056	Binucleated	x	
		Control	Dermal	0	µg/mouse	12.8	2.2	MN cells	1,000	0.013	Binucleated		
		CH	Dermal	50	µg/mouse	43.3	2.2	MN cells	1,000	0.043	Binucleated	x	
		CH	Dermal	100	µg/mouse	56	4.9	MN cells	1,000	0.056	Binucleated	x	
		CH	Dermal	500	µg/mouse	62	8.6	MN cells	1,000	0.062	Binucleated	x	
		CH	Dermal	1,000	µg/mouse	47.3	3.8	MN cells	1,000	0.047	Binucleated	x	
17190	Bayer, 1978	Pooled controls	Intra-peritoneal	0	mg/kg	3.2	0.07	Sister chromatid exchange/ cells					
		BaP	Intra-peritoneal	2.5	mg/kg	3.4	0.8	Sister chromatid exchange/ cells					
		BaP	Intra-peritoneal	25	mg/kg	3.5	0.2	Sister chromatid exchange/ cells					
		BaP	Intra-peritoneal	40	mg/kg	3.9	0.2	Sister chromatid exchange/ cells				x	

Table C-23. In vivo clastogenicity: dose-response data

Record number	Reference	PAH	Route of admini-stration	Clastogenicity								$p <$ 0.05	Notes
				Dose	Dose units	Mean	SD	Units	n	% Response	Units		
		BaP	Intra-peritoneal	50	mg/kg	6.4	0.2	Sister chromatid exchange/ cells				x	
		BaP	Intra-peritoneal	75	mg/kg	6.4	0.3	Sister chromatid exchange/ cells				x	
		BaP	Intra-peritoneal	100	mg/kg	7.4	0.2	Sister chromatid exchange/ cells				x	
		PH	Intra-peritoneal	25	mg/kg	3.5	0.2	Sister chromatid exchange/ cells					Only one dose significant
		PH	Intra-peritoneal	50	mg/kg	3.4	0.2	Sister chromatid exchange/ cells					
		PH	Intra-peritoneal	75	mg/kg	3.5	0.2	Sister chromatid exchange/ cells					
		PH	Intra-peritoneal	100	mg/kg	4.1	0.2	Sister chromatid exchange/ cells				x	
20950	Roszinsky-Kocher et al., 1979	Control	Intra-peritoneal	0	mg/kg	3.9	0.9	Sister chromatid exchanges/ meta-phase					
		BaP	Intra-peritoneal	900	mg/kg	10.6	1.6	Sister chromatid exchanges/ meta-phase				x	

Table C-23. In vivo clastogenicity: dose-response data

Record number	Reference	PAH	Route of admini-stration	Clastogenicity								$p <$ 0.05	Notes
				Dose	Dose units	Mean	SD	Units	n	% Response	Units		
		DBahA	Intra-peritoneal	900	mg/kg	4.9	0.7	Sister chromatid exchanges				x	
		CH	Intra-peritoneal	900	mg/kg	5.1	1	Sister chromatid exchanges				x	
		PH	Intra-peritoneal	900	mg/kg	5.5	0.7	Sister chromatid exchanges				x	
		BeP	Intra-peritoneal	900	mg/kg	5.5	0.7	Sister chromatid exchanges				x	
		BbF	Intra-peritoneal	900	mg/kg	5.6	0.5	Sister chromatid exchanges				x	
		BaA	Intra-peritoneal	900	mg/kg	6.1	0.4	Sister chromatid exchanges				x	
24720	Kligerman et al., 1986	Control	Gavage	0	mg/kg	11.9		Sister chromatid exchanges/ meta-phase					
		BaP	Gavage	63	mg/kg	19.4	0.0	Sister chromatid exchanges/ meta-phase					
		BaP	Gavage	252	mg/kg	21.5	1.4	Sister chromatid exchanges/ meta-phase					
		BaP	Gavage	504	mg/kg	21.7	1.4	Sister chromatid exchanges/ meta-phase					
		Control	Gavage	0	mg/kg	11.0		Sister chromatid exchanges/ meta-phase					

Table C-23. In vivo clastogenicity: dose-response data

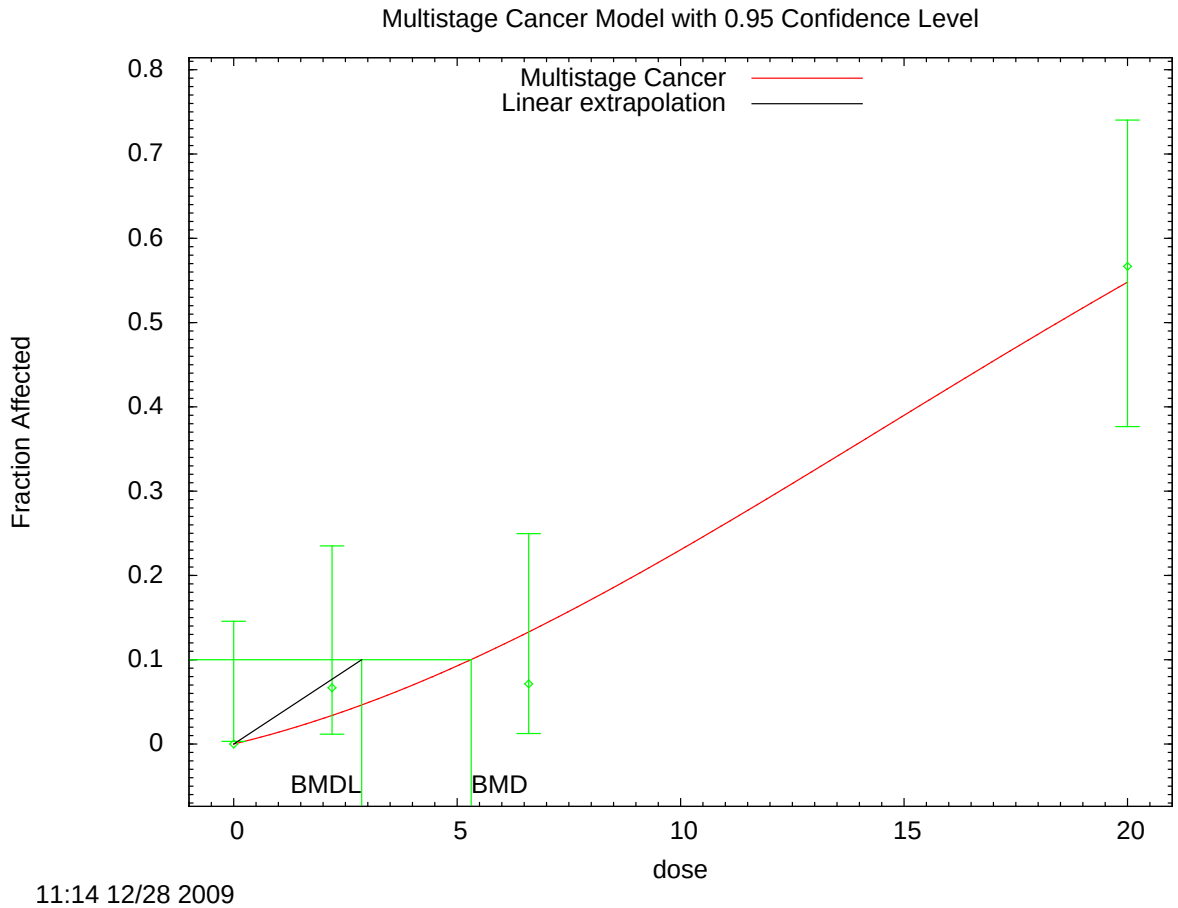
Record number	Reference	PAH	Route of administration	Clastogenicity								$p <$ 0.05	Notes
				Dose	Dose units	Mean	SD	Units	n	% Response	Units		
		BlAC	Gavage	32	mg/kg	16.5	3.6	Sister chromatid exchanges/ meta-phase					
		BlAC	Gavage	63	mg/kg	20.5	1.6	Sister chromatid exchanges/ meta-phase					
		BlAC	Gavage	126	mg/kg	27.8	2.6	Sister chromatid exchanges/ meta-phase					
24790	Kligerman et al., 2002	Control	Intra-peritoneal	0	mg/kg	8.79	1.26	Sister chromatid exchanges					
		BaP	Intra-peritoneal	100	mg/kg	21.21	2.93	Sister chromatid exchanges				x	
		BaA	Intra-peritoneal	100	mg/kg	14.8	3.16	Sister chromatid exchanges				x	
		BbF	Intra-peritoneal	100	mg/kg	22.25	1.45	Sister chromatid exchanges				x	
		CH	Intra-peritoneal	100	mg/kg	11.96	1.8	Sister chromatid exchanges				x	
		Control	Gavage	0	mg/kg	11.12	1.5	Sister chromatid exchanges					
		BaP	Gavage	100	mg/kg	17.91	1.49	Sister chromatid exchanges				x	
		BaA	Gavage	100	mg/kg	13.38	1.53	Sister chromatid exchanges				x	
		Control	Gavage	0	mg/kg	6.6	0.9	MN bn	1,000	0.007	Binucleated		

Table C-23. In vivo clastogenicity: dose-response data

Record number	Reference	PAH	Route of admini-stration	Clastogenicity								$p <$ 0.05	Notes
				Dose	Dose units	Mean	SD	Units	n	% Response	Units		
		BaP	Gavage	100	mg/kg	9.1	1.8	MN bn	1,000	0.009	Binucleated	x	
		BbF	Gavage	100	mg/kg	8.3	0.9	MN bn	1,000	0.008	Binucleated	x	

APPENDIX D. BENCHMARK DOSE MODELING OUTPUTS

D.1. DERMAL BIOASSAYS




```
Cav 1983 bap dermal.out.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\Cavalieri1983\BaP\msc_CavalieriBaP_MS_2.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\Cavalieri1983\BaP\msc_CavalieriBaP_MS_2.plt
                                          Tue Dec 22 14:50:32 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]
```

```
   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                 Default Initial Parameter Values
                    Background =    0.0155298
                       Beta(1) =            0
                       Beta(2) =   0.00204447


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.96

   Beta(2)        -0.96            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *                *
*
        Beta(1)        0.0126577            *                *
*
        Beta(2)       0.00134916            *                *
*

* - Indicates that this value is not calculated.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.0798	4			
Fitted model	-36.0272	2	1.89478	2	0.3878
Reduced model	-55.062	1	39.9644	3	<.0001

AIC: 76.0543

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	29	0.000
2.2000	0.0338	1.014	2.000	30	0.996
6.6000	0.1326	3.714	2.000	28	-0.955
20.0000	0.5474	16.423	17.000	30	0.212

Chi^2 = 1.95 d.f. = 2 P-value = 0.3772

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

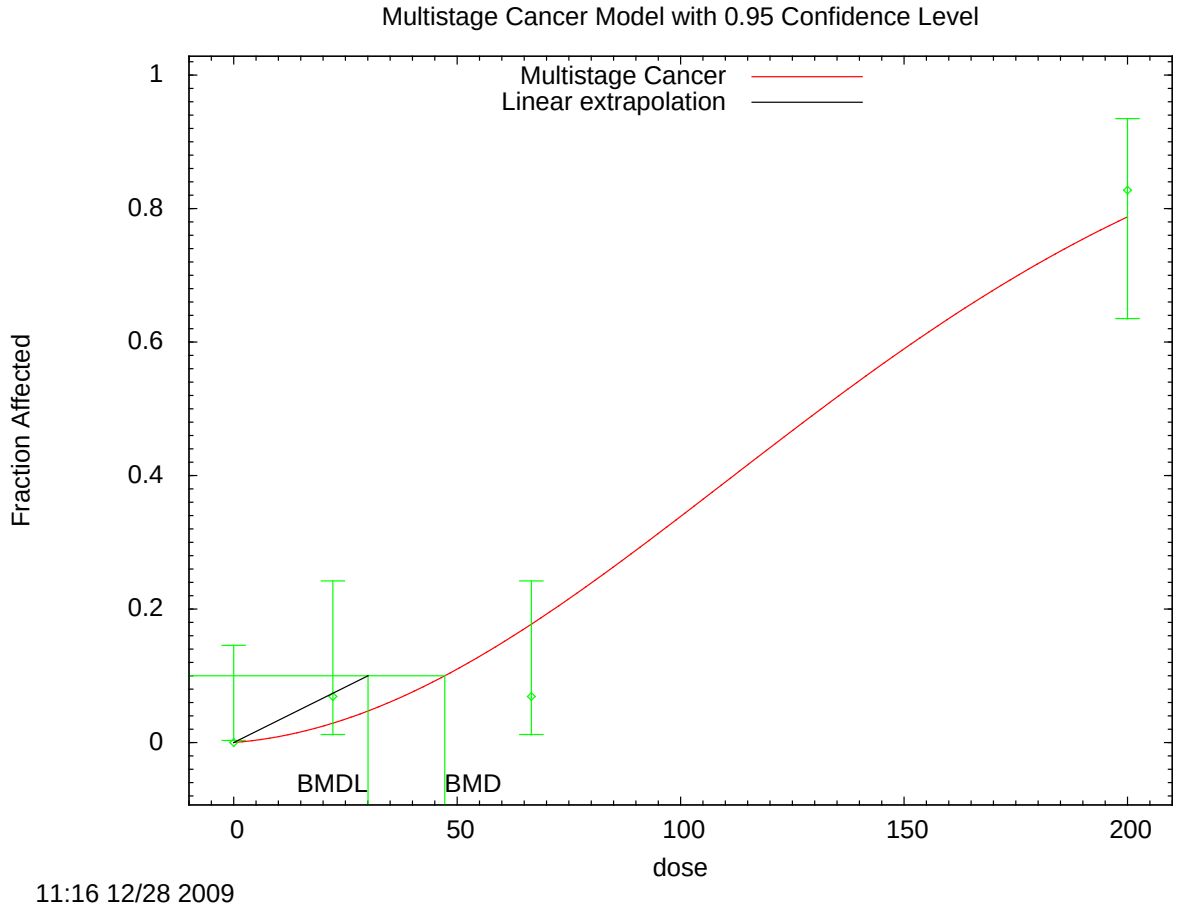
BMD = 5.31398

BMDL = 2.86439

BMDU = 8.84432

Taken together, (2.86439, 8.84432) is a 90 % two-sided confidence interval for the BMD

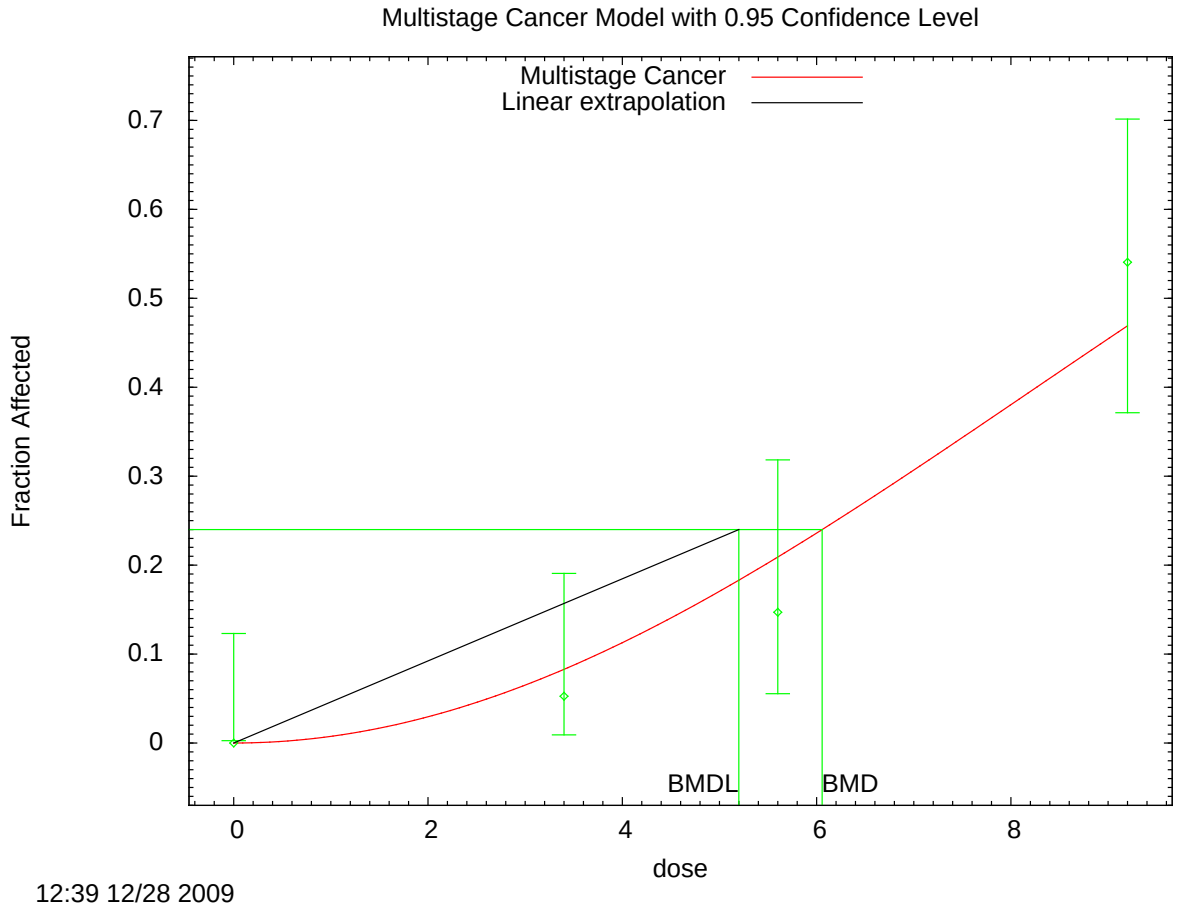
Multistage Cancer Slope Factor = 0.0349115




```
CAVALIERI1983CPcdP.OUT.txt

 ========================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\Cavalieri1983\CPcdP\msc_CavalieriCPcdP_MS_2
.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\Cavalieri1983\CPcdP\msc_CavalieriCPcdP_MS_2
.plt
                                          Tue Dec 22 14:50:32 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

    The form of the probability function is:

    P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2)]

    The parameter betas are restricted to be positive


    Dependent variable = incidence
    Independent variable = dose
```

```
 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) = 4.42193e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.93

   Beta(2)        -0.93            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)      0.000525847           *               *
*
        Beta(2)     3.60995e-005           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
      Full model        -27.8865         4
   Fitted model        -30.0799         2       4.38685      2
0.1115
  Reduced model        -64.1091         1       72.4452      3         <.0001

            AIC:         64.1598


                                  Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          29        0.000
    22.2000     0.0290         0.842     2.000          29        1.281
    66.6000     0.1773         5.141     2.000          29       -1.527
   200.0000     0.7876        22.840    24.000          29        0.527

 Chi^2 = 4.25      d.f. = 2        P-value = 0.1194


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        47.2296

            BMDL =        30.0553

            BMDU =         62.746

Taken together, (30.0553, 62.746 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00332721
```




```
HABS1980BBF.OUT.txt

 ========================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\Habs1980\BbF\msc_HabsBbF_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\Habs1980\BbF\msc_HabsBbF_MS_2_10.plt
                                          Thu Dec 24 10:03:13 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =   0.00945627


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)           1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)                0           *               *
*
        Beta(2)       0.00748156           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -47.5575         4
   Fitted model        -48.6255         1       2.13602      3
0.5447
  Reduced model        -69.4912         1       43.8674      3         <.0001
```

AIC: 99.251

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	35	0.000
3.4000	0.0829	3.148	2.000	38	-0.676
5.6000	0.2091	7.110	5.000	34	-0.890
9.2000	0.4691	17.358	20.000	37	0.870

Chi^2 = 2.01 d.f. = 3 P-value = 0.5711

Benchmark Dose Computation

Specified effect = 0.24

Risk Type = Extra risk

Confidence level = 0.95

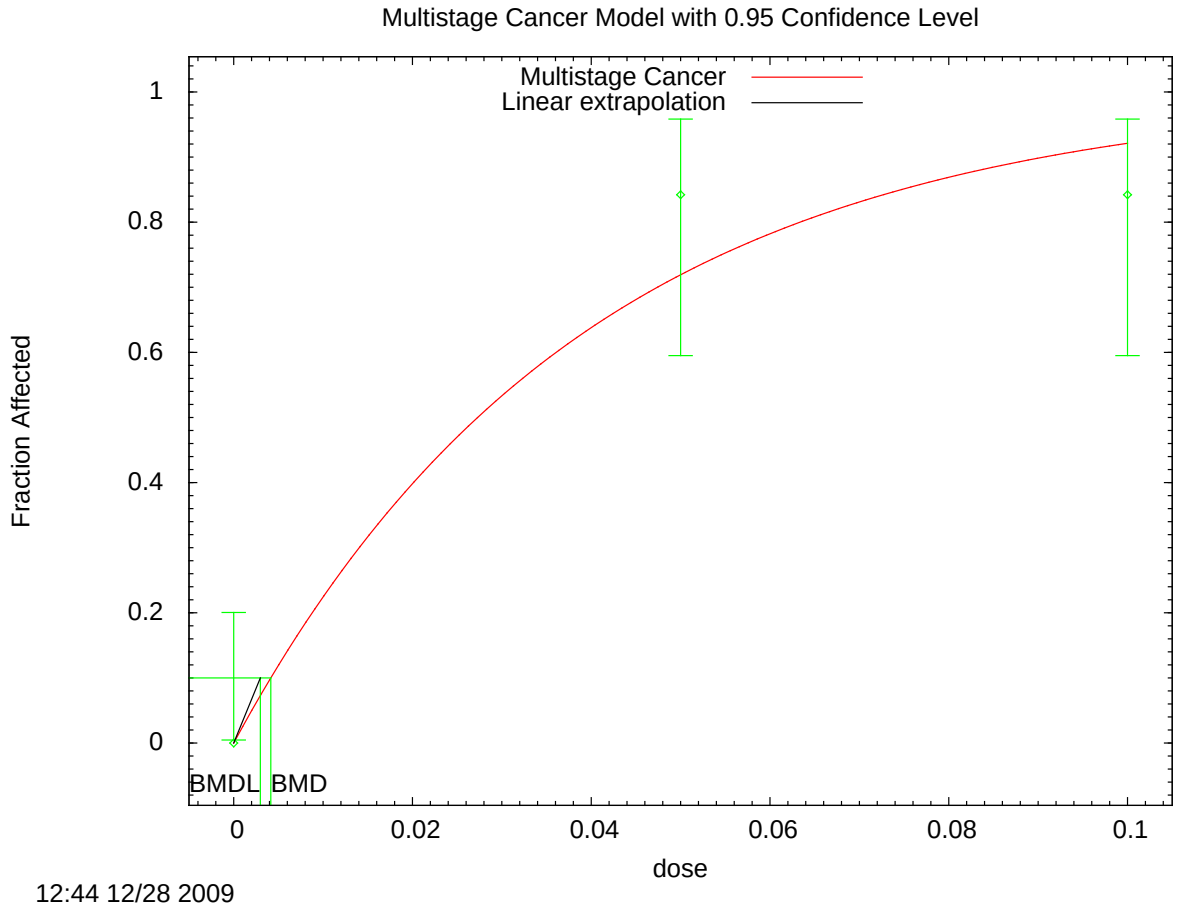
BMD = 6.05655

BMDL = 5.19938

BMDU = 7.17099

Taken together, (5.19938, 7.17099) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0461594



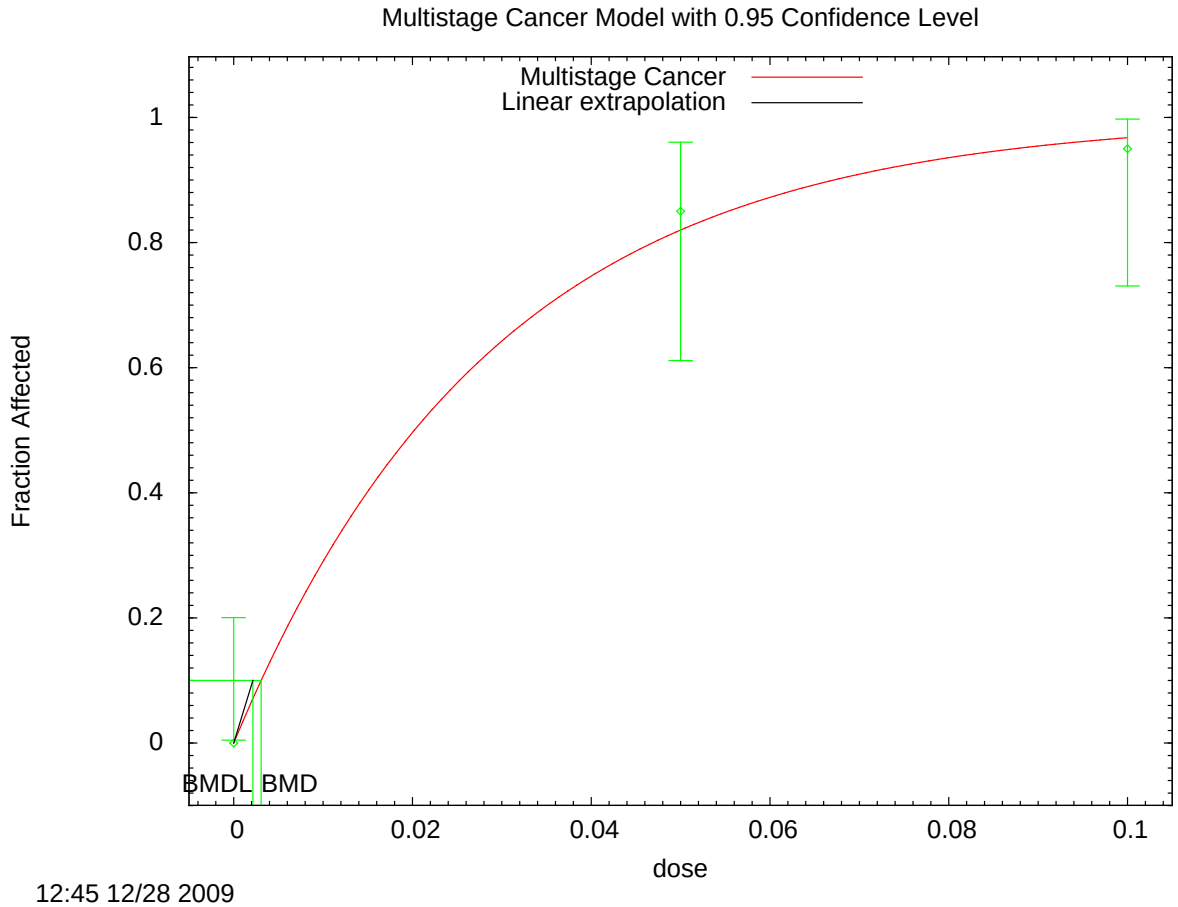
12:44 12/28 2009

HOFFMANWYNDER966DBAIP.OUT.txt

```
 ************************************************************************
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\DBaiP\msc_HoffWynDBaiP_MS_1.(d
)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\DBaiP\msc_HoffWynDBaiP_MS_1.pl
t
                                          Tue Dec 22 14:50:33 2009
 ************************************************************************

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =     0.264818
                        Beta(1) =      18.4583


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)          25.3832           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -16.5742         3
   Fitted model         -18.019         1       2.88957      2
0.2358
  Reduced model        -39.8916         1       46.6349      2         <.0001

           AIC:         38.0379
```

```
                                Goodness  of  Fit
                                                                      Scaled
      Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          20         0.000
     0.0500     0.7189        13.660    16.000          19         1.194
     0.1000     0.9210        17.499    16.000          19        -1.275

  Chi^2 = 3.05      d.f. = 2        P-value = 0.2174


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =     0.00415079

             BMDL =     0.00298234

             BMDU =     0.00587793

Taken together, (0.00298234, 0.00587793) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       33.5308
```



12:45 12/28 2009

HOFFMANWYNDER1966BAP.OUT.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\BaP\msc_HoffWynBaP_MS_1.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\BaP\msc_HoffWynBaP_MS_1.plt
                                          Tue Dec 22 14:50:32 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

  Total number of observations = 3
  Total number of records with missing values = 0
  Total number of parameters in model = 2
```

```
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =     0.124609
                        Beta(1) =      29.9573


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *                *
*
        Beta(1)          34.3074            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -12.4245         3
   Fitted model        -12.5735         1      0.297928      2
0.8616
  Reduced model        -40.3807         1       55.9124      2         <.0001

           AIC:         27.1469


                                Goodness  of  Fit
```

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	20	0.000
0.0500	0.8201	16.402	17.000	20	0.348
0.1000	0.9676	19.353	19.000	20	-0.446

Chi^2 = 0.32 d.f. = 2 P-value = 0.8522

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

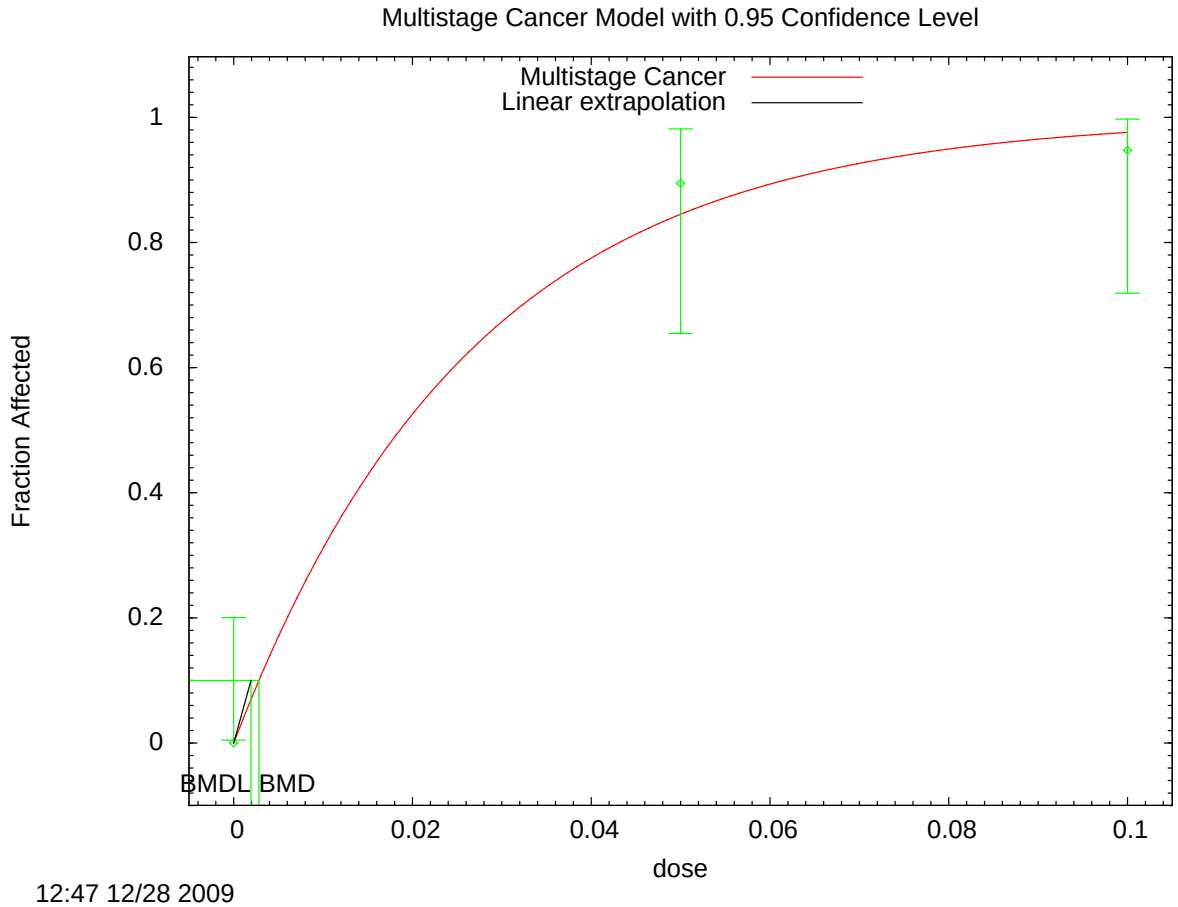
BMD = 0.00307107

BMDL = 0.00215021

BMDU = 0.00440601

Taken together, (0.00215021, 0.00440601) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 46.5071

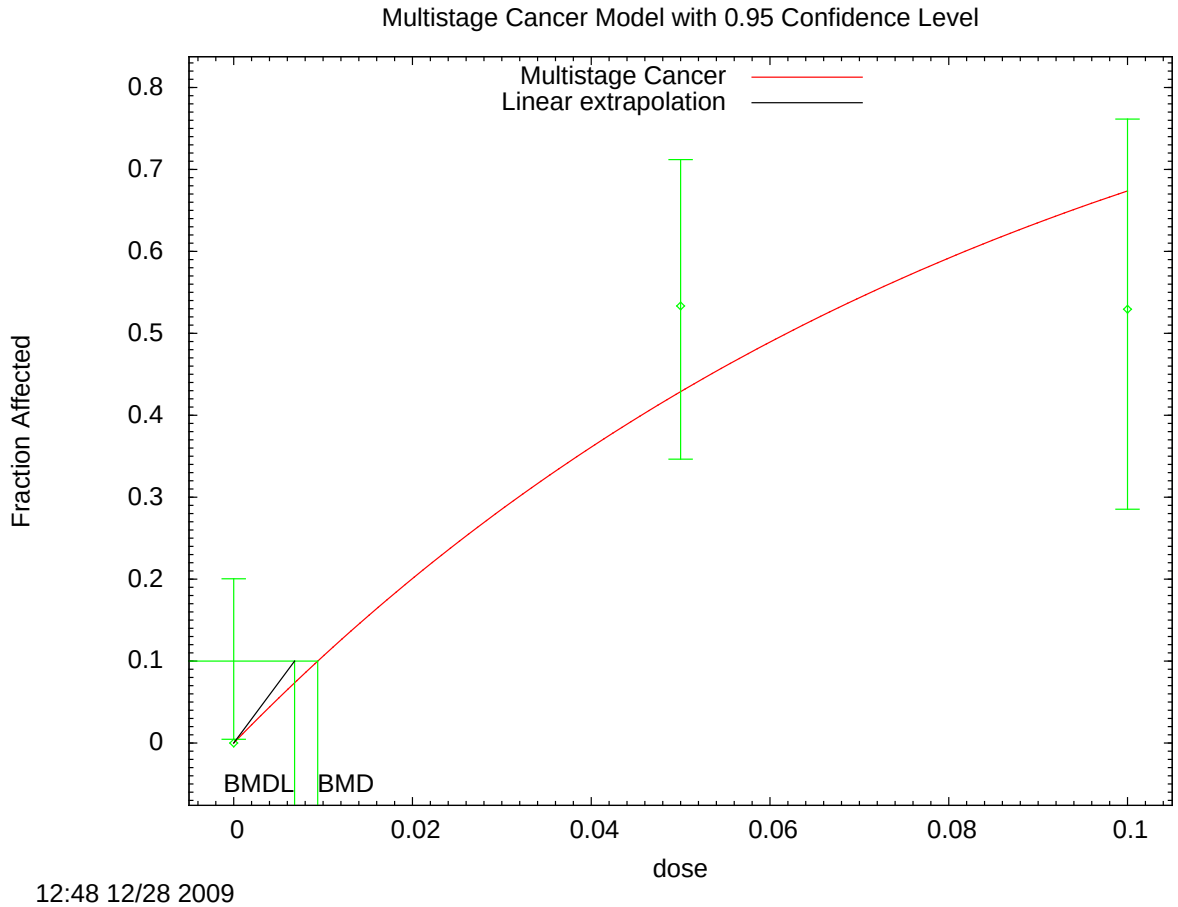


12:47 12/28 2009

```
HOFFMANWYNDER1966DBAEF.OUT.txt

 ************************************************************************
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\DBaeF\msc_HoffWynDBaeF_MS_1.(d
)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\DBaeF\msc_HoffWynDBaeF_MS_1.pl
t
                                          Tue Dec 22 14:50:34 2009
 ************************************************************************

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =      0.22871
                        Beta(1) =      29.4444


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *                *
*
        Beta(1)          37.3037            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -10.3111         3
   Fitted model         -10.7582         1      0.894194      2
0.6395
  Reduced model         -38.9521         1       57.2822      2         <.0001

           AIC:          23.5163
```

```
                                 Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          20        0.000
    0.0500     0.8451        16.058    17.000          19        0.598
    0.1000     0.9760        18.544    18.000          19       -0.816

 Chi^2 = 1.02      d.f. = 2        P-value = 0.5995


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0028244

            BMDL =     0.00193834

            BMDU =     0.00411821

Taken together, (0.00193834, 0.00411821) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       51.5905
```



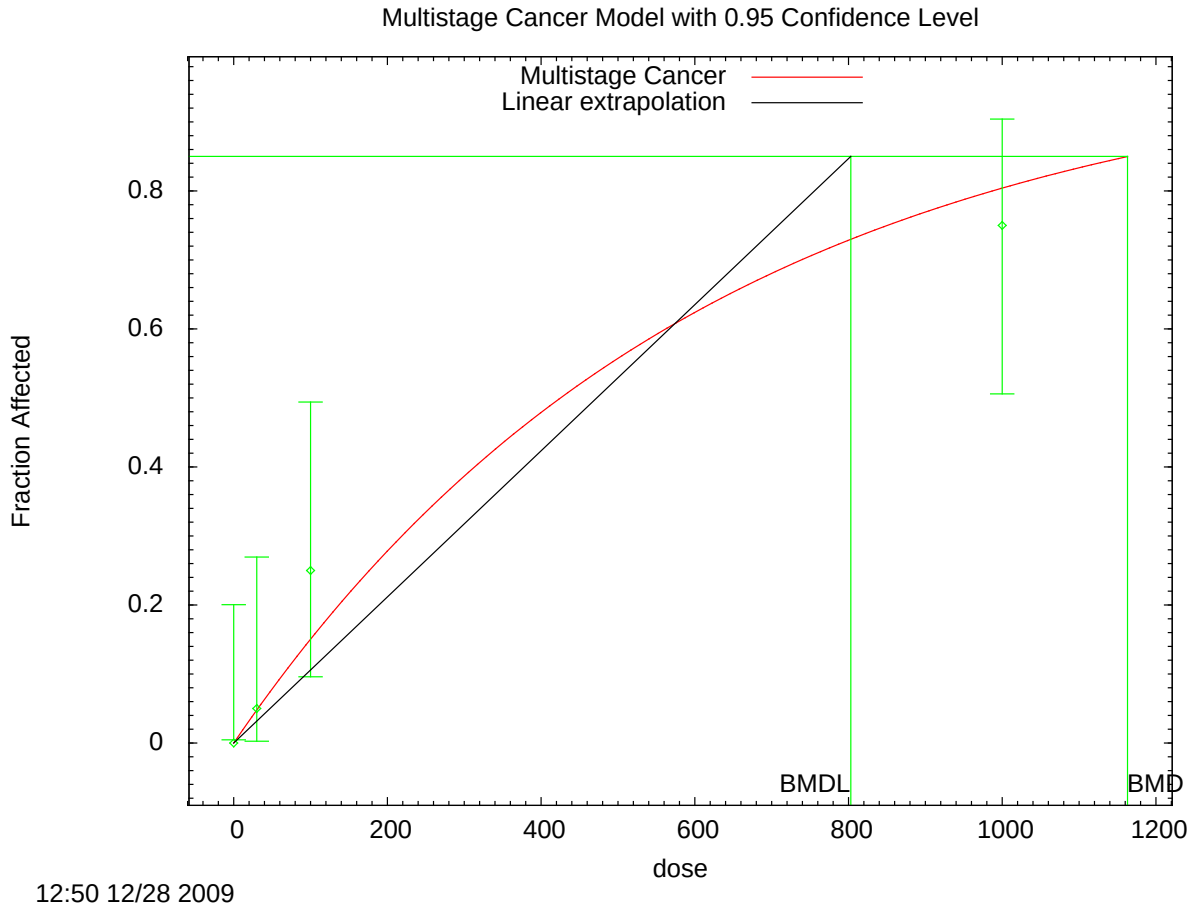
12:48 12/28 2009

HOFFMANWYNDER1996DBAEP.OUT.txt

```
 ************************************************************************
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\DBaeP\msc_HoffWynDBaeP_MS_1.(d
)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\complete\HoffWynd1966\DBaeP\msc_HoffWynDBaeP_MS_1.pl
t
                                          Tue Dec 22 14:50:32 2009
 ************************************************************************

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =     0.120514
                        Beta(1) =      7.53772


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)          11.2084           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -32.4818         3
   Fitted model          -33.903         1       2.84251      2
0.2414
  Reduced model         -44.2604         1       23.5572      2         <.0001

           AIC:          69.8061
```

```
                                  Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          20        0.000
    0.0500     0.4290        12.871    16.000          30        1.154
    0.1000     0.6740        11.458     9.000          17       -1.272

 Chi^2 = 2.95      d.f. = 2        P-value = 0.2288


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =     0.00940018

            BMDL =     0.00681373

            BMDU =      0.0134192

Taken together, (0.00681373, 0.0134192) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       14.6763
```




```
LAVOIE1982BkF.OUT.txt


 ========================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\LaVoie1982\BkF\msc_LaVoieBkF_MS_2_85.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\LaVoie1982\BkF\msc_LaVoieBkF_MS_2_85.plt
                                          Thu Dec 24 10:09:52 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =    0.0504814
                        Beta(1) =   0.00134342
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)       0.00163117           *               *
*
        Beta(2)                0           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -26.4637         4
   Fitted model        -27.3094         1       1.69146      3
0.6388
  Reduced model        -46.0525         1       39.1775      3         <.0001
```

AIC: 56.6189

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	20	0.000
30.0000	0.0478	0.955	1.000	20	0.047
100.0000	0.1505	3.010	5.000	20	1.244
1000.0000	0.8043	16.086	15.000	20	-0.612

Chi^2 = 1.93 d.f. = 3 P-value = 0.5881

Benchmark Dose Computation

Specified effect = 0.85

Risk Type = Extra risk

Confidence level = 0.95

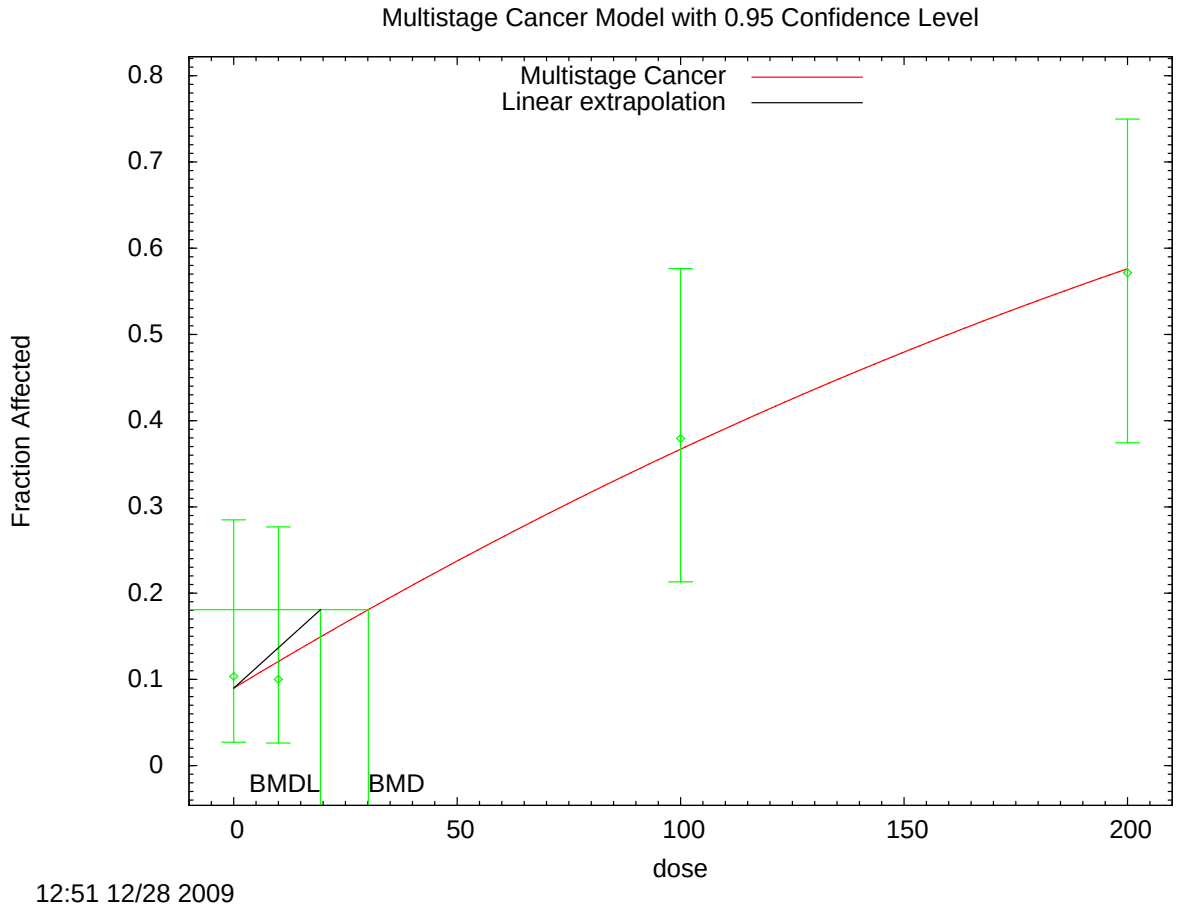
BMD = 1163.04

BMDL = 802.998

BMDU = 1836.46

Taken together, (802.998, 1836.46) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00105853




```
RAVEH1982CPCDP.OUT.txt


 ******************************************************************
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\Raveh1982\CPcdP\msc_RavehCPcdP_MS_2.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\Raveh1982\CPcdP\msc_RavehCPcdP_MS_2.plt
                                          Tue Dec 22 14:50:35 2009
 ******************************************************************

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =     0.086614
                        Beta(1) =   0.00379482
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)      Beta(2)

Background            1        -0.51         0.37

   Beta(1)        -0.51            1        -0.96

   Beta(2)         0.37        -0.96            1



                                Parameter Estimates

                                                                    95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background        0.0898027            *                *
*
        Beta(1)        0.0034393            *                *
*
        Beta(2)     1.91358e-006            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -57.7672         4
   Fitted model         -57.8738         3      0.213129      1
0.6443
  Reduced model         -69.2679         1       23.0015      3         <.0001

            AIC:         121.748
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0898	2.604	3.000	29	0.257
10.0000	0.1207	3.622	3.000	30	-0.349
100.0000	0.3669	10.641	11.000	29	0.138
200.0000	0.5762	16.134	16.000	28	-0.051

Chi^2 = 0.21 d.f. = 1 P-value = 0.6472

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

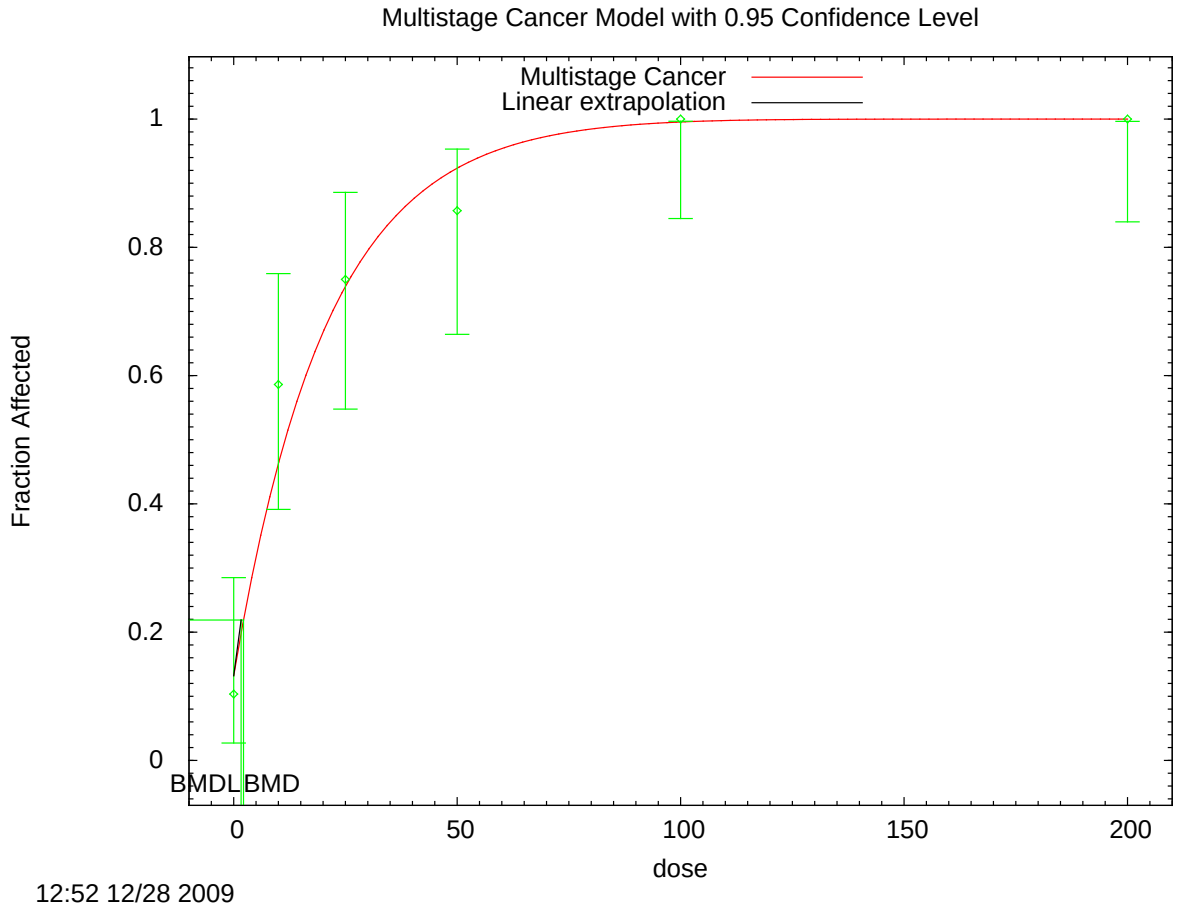
BMD = 30.1292

BMDL = 19.4197

BMDU = 83.2495

Taken together, (19.4197, 83.2495) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00514942




```
RAVEH_1982BaP.OUT.txt

 ************************************************************************
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\Raveh1982\BaP\msc_RavehBaP_MS_4.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\Raveh1982\BaP\msc_RavehBaP_MS_4.plt
                                          Tue Dec 22 14:50:34 2009
 ************************************************************************

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 6
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) = 6.01899e+017
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)    -Beta(3)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)      Beta(4)

Background            1        -0.66         0.27

   Beta(1)        -0.66            1        -0.52

   Beta(4)         0.27        -0.52            1



                                  Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.132052            *               *
*
        Beta(1)        0.0479561            *               *
*
        Beta(2)                0            *               *
*
        Beta(3)                0            *               *
*
        Beta(4)     4.58928e-009            *               *
*

* - Indicates that this value is not calculated.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-56.5419	6			
Fitted model	-58.376	3	3.66814	3	0.2996
Reduced model	-101.065	1	89.0461	5	<.0001

AIC: 122.752

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1321	3.829	3.000	29	-0.455
10.0000	0.4627	13.419	17.000	29	1.334
25.0000	0.7388	20.685	21.000	28	0.135
50.0000	0.9233	25.853	24.000	28	-1.316
100.0000	0.9955	26.878	27.000	27	0.351
200.0000	1.0000	26.000	26.000	26	0.001

Chi^2 = 3.86 d.f. = 3 P-value = 0.2771

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

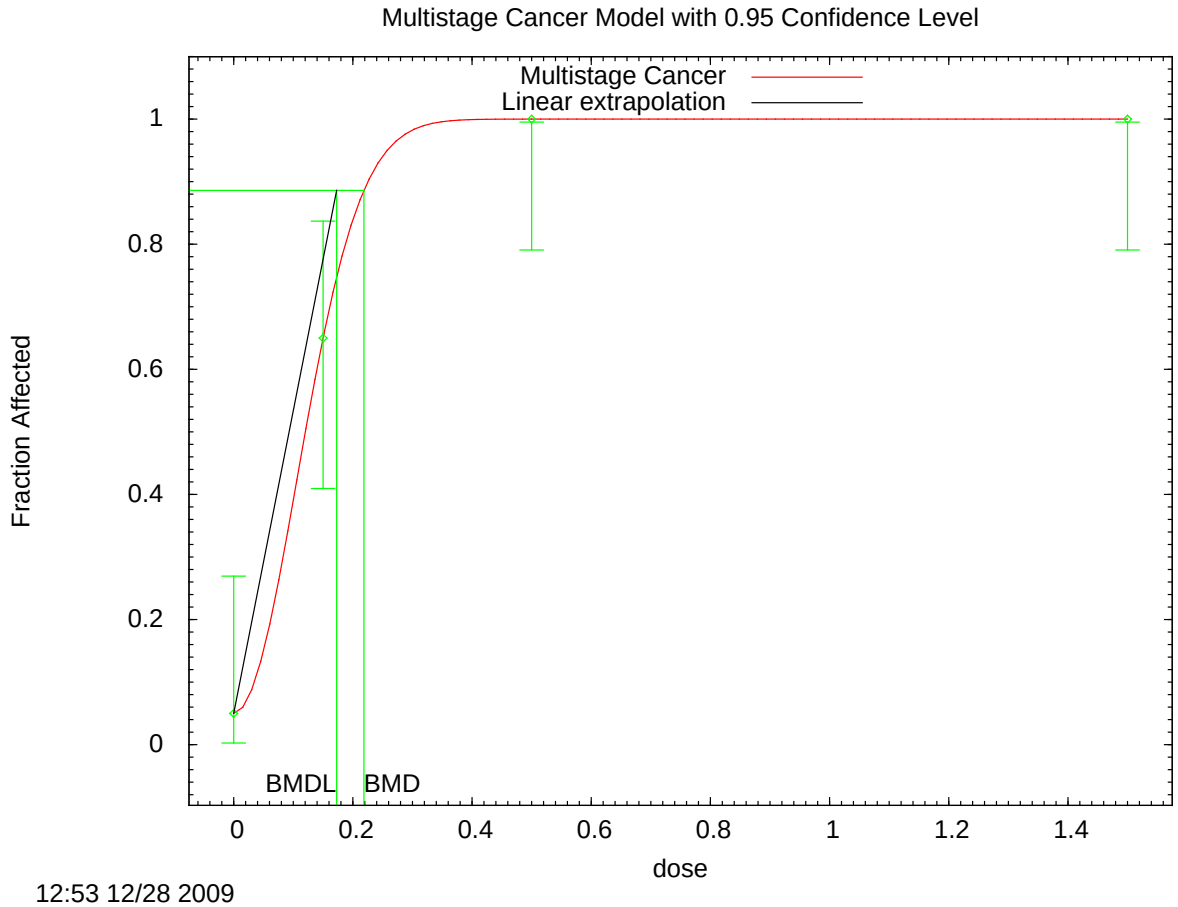
BMD = 2.19702

BMDL = 1.66278

BMDU = 3.30927

Taken together, (1.66278, 3.30927) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0601403



12:53 12/28 2009

```
RICE_CPDEFC.OUT.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\Rice\CPdefC\msc_RiceCPdefC_MS_2_88.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\Rice\CPdefC\msc_RiceCPdefC_MS_2_88.plt
                                          Tue Dec 22 16:05:10 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
```

```
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            1
                        Beta(1) = 6.76726e+019
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.52

   Beta(2)        -0.52            1


                                  Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background        0.0499931            *               *
*
        Beta(1)                0            *               *
*
        Beta(2)          44.3919            *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -16.9192         4
   Fitted model        -16.9195         2   0.000547543      2
0.9997
  Reduced model        -49.6481         1       65.4577      3         <.0001
```

AIC: 37.839

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0500	1.000	1.000	20	0.000
0.1500	0.6501	13.002	13.000	20	-0.001
0.5000	1.0000	19.000	19.000	19	0.017
1.5000	1.0000	19.000	19.000	19	0.000

Chi^2 = 0.00 d.f. = 2 P-value = 0.9999

Benchmark Dose Computation

Specified effect = 0.88

Risk Type = Extra risk

Confidence level = 0.95

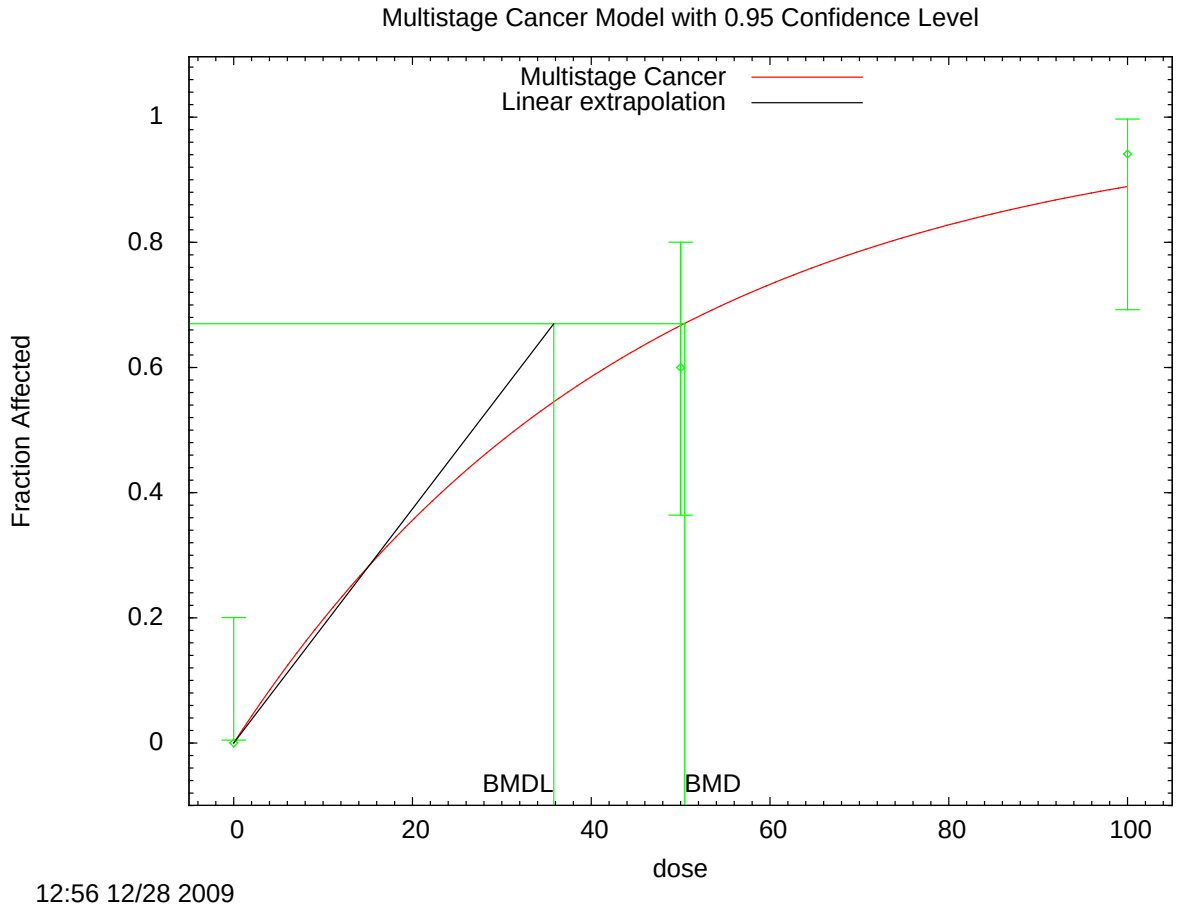
BMD = 0.218546

BMDL = 0.172781

BMDU = 0.384831

Taken together, (0.172781, 0.384831) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 5.09315



12:56 12/28 2009

NESNOW_1984_DERMAL_BLAC_MALE.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\Nesnow1984\BIACmale\msc_NesnowBAICmale3HD
D_MS_1.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\Nesnow1984\BIACmale\msc_NesnowBAICmale3HD
D_MS_1.plt
                                        Tue Dec 22 16:05:10 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

```

```
 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =    0.0283321


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *               *
*
        Beta(1)        0.0219722            *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -17.2634         3
   Fitted model        -17.7362         1      0.945584      2
0.6233
  Reduced model        -39.5006         1       44.4744      2         <.0001

           AIC:         37.4725
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	20	0.000
50.0000	0.6667	13.333	12.000	20	-0.632
100.0000	0.8889	15.111	16.000	17	0.686

Chi^2 = 0.87 d.f. = 2 P-value = 0.6471

Benchmark Dose Computation

Specified effect = 0.67

Risk Type = Extra risk

Confidence level = 0.95

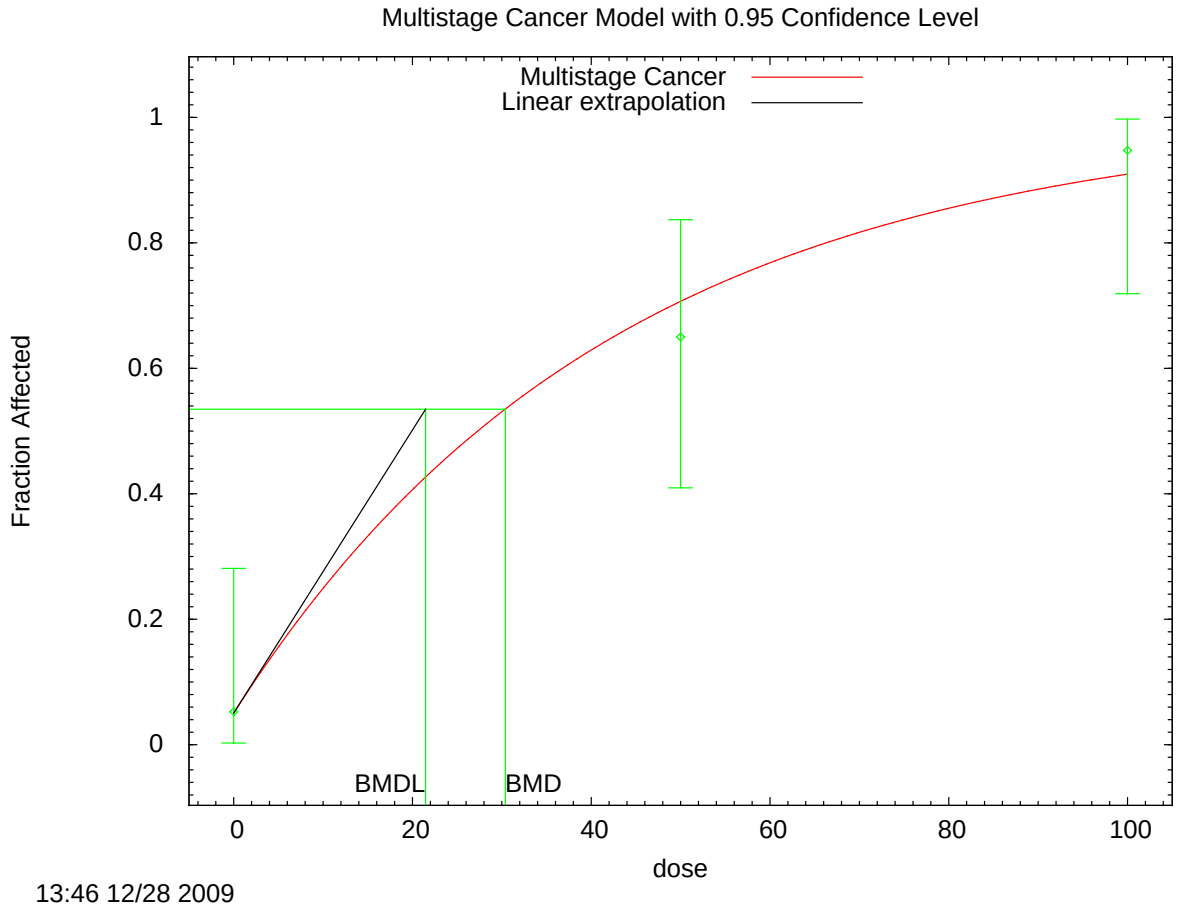
BMD = 50.4574

BMDL = 35.8134

BMDU = 72.6771

Taken together, (35.8134, 72.6771) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0187081



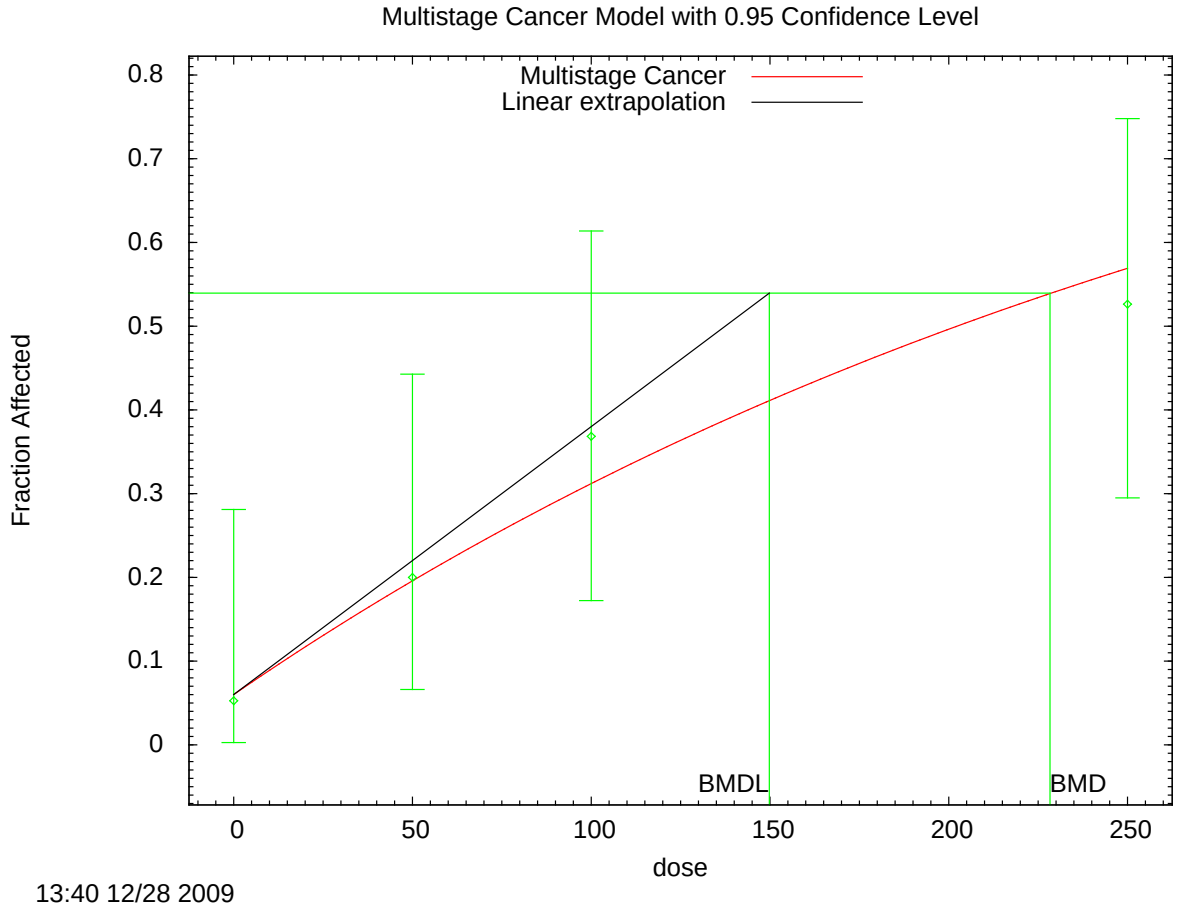
13:46 12/28 2009

NESNOW_1984_DERMAL_BLAC_FEMALE.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\Nesnow1984\BIACfemale\msc_NesnowBlaCfemal
e3HDD_MS_4.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\Nesnow1984\BIACfemale\msc_NesnowBlaCfemal
e3HDD_MS_4.plt
                                          Mon Dec 28 13:46:08 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =    0.0289037


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.49

   Beta(1)        -0.49            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background        0.0505105            *               *
*
        Beta(1)        0.0234713            *               *
*

* - Indicates that this value is not calculated.



                         Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -20.7842         3
   Fitted model        -21.1281         2      0.687832      1
0.4069
  Reduced model        -39.8916         1       38.2148      2         <.0001

           AIC:         46.2563


                                  Goodness  of  Fit
                                                          Scaled
```

```
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0505         0.960     1.000          19        0.042
    50.0000     0.7064        14.127    13.000          20       -0.553
   100.0000     0.9092        17.275    18.000          19        0.579

 Chi^2 = 0.64      d.f. = 1        P-value = 0.4224


   Benchmark Dose Computation

Specified effect =           0.51

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        30.3924

            BMDL =        21.4681

            BMDU =        44.3165

Taken together, (21.4681, 44.3165) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0237562
```

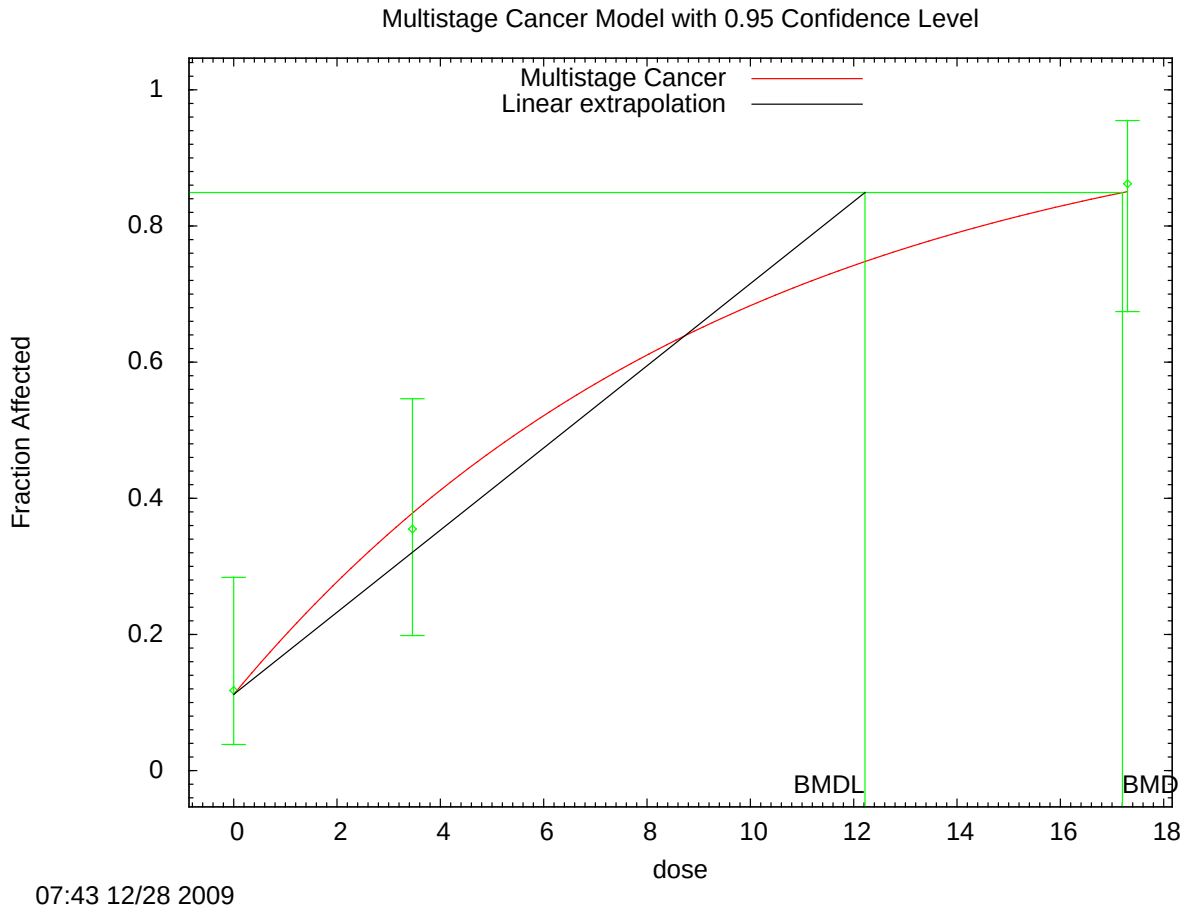



```
NESNOW_1984_DERMAL_BEAC_FEMALE.txt

 ============================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\dermal\initiation\Nesnow1984\BeACfemale\msc_NesnowBeACfemal
e2HDD_MS_2_51.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\dermal\initiation\Nesnow1984\BeACfemale\msc_NesnowBeACfemal
e2HDD_MS_2_51.plt
                                        Tue Dec 22 16:05:10 2009
 ============================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose
```

```
 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =    0.0934237
                        Beta(1) =   0.00272909
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1         -0.7

   Beta(1)         -0.7            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background        0.0601262            *                *
*
        Beta(1)       0.00312448            *                *
*
        Beta(2)                0            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
      Full model        -39.5733         4
   Fitted model        -39.7914         2      0.436272      2
0.804
  Reduced model        -46.0668         1        12.987      3
0.004665

            AIC:         83.5828


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------
     0.0000     0.0601         1.142     1.000          19       -0.137
    50.0000     0.1961         3.921     4.000          20        0.044
   100.0000     0.3123         5.934     7.000          19        0.527
   250.0000     0.5696        10.823    10.000          19       -0.381

 Chi^2 = 0.44      d.f. = 2        P-value = 0.8007


   Benchmark Dose Computation

Specified effect =           0.51

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         228.31

            BMDL =        149.811

            BMDU =        436.477

Taken together, (149.811, 436.477) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00340429
```

D.2. INTRAPERITONEAL BIOASSAYS




```
lavoie 1994 female lung FA.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Lavoie1994\FAfemalelung\msc_LaVoieFAfemalelung_MS_1_83.(
d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Lavoie1994\FAfemalelung\msc_LaVoieFAfemalelung_MS_1_83.p
lt
                                          Wed Dec 23 11:10:40 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive
```

```
  Dependent variable = incidence
  Independent variable = dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =    0.0929049
                        Beta(1) =     0.108473


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.48

   Beta(1)        -0.48            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.112498            *               *
*
        Beta(1)         0.103015            *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -44.1118         3
   Fitted model         -44.1689         2      0.114322      1
0.7353
  Reduced model         -64.1094         1       39.9952      2         <.0001
```

AIC: 92.3379

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1125	3.825	4.000	34	0.095
3.4600	0.3786	11.737	11.000	31	-0.273
17.3000	0.8507	24.669	25.000	29	0.172

Chi^2 = 0.11 d.f. = 1 P-value = 0.7366

Benchmark Dose Computation

Specified effect = 0.83

Risk Type = Extra risk

Confidence level = 0.95

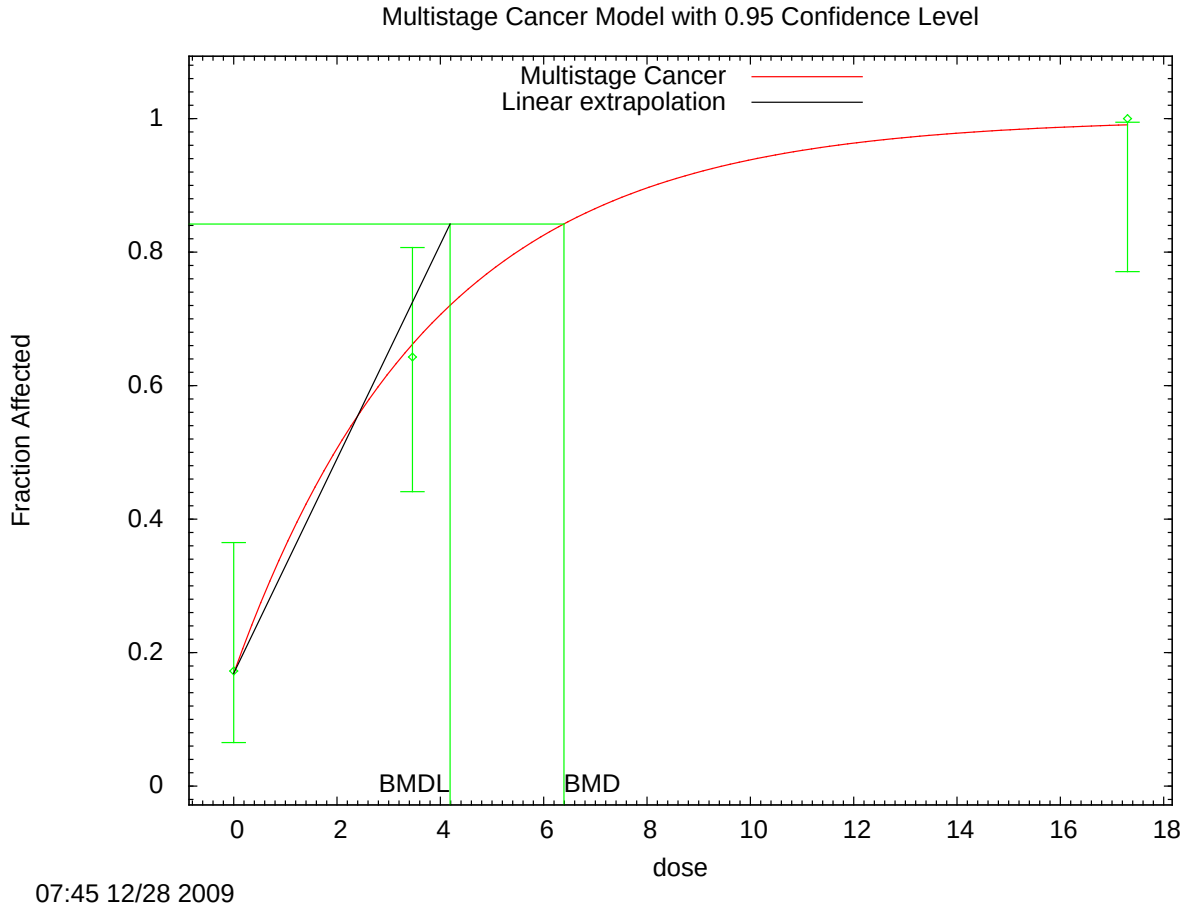
BMD = 17.201

BMDL = 12.2186

BMDU = 25.6067

Taken together, (12.2186, 25.6067) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.067929



07:45 12/28 2009

```
LAVOIEETAL1994LIVERmale.OUT.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Lavoie1994\FAmaleliver\msc_LaVoieFAmaleliver_MS_1_81.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Lavoie1994\FAmaleliver\msc_LaVoieFAmaleliver_MS_1_81.plt
                                          Wed Dec 23 11:10:41 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) = 6.19323e+018


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.47

   Beta(1)        -0.47            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.168707            *                *
*
        Beta(1)         0.259821            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -31.5803         3
   Fitted model        -31.7622         2      0.363803      1
0.5464
  Reduced model        -51.0494         1       38.9382      2         <.0001

           AIC:         67.5244


                                 Goodness  of  Fit
                                                          Scaled
```

Dose	Est._Prob.	Expected	Observed	Size	Residual
0.0000	0.1687	4.893	5.000	29	0.053
3.4600	0.6617	18.527	18.000	28	-0.210
17.3000	0.9907	16.842	17.000	17	0.399

Chi^2 = 0.21 d.f. = 1 P-value = 0.6496

Benchmark Dose Computation

Specified effect = 0.81

Risk Type = Extra risk

Confidence level = 0.95

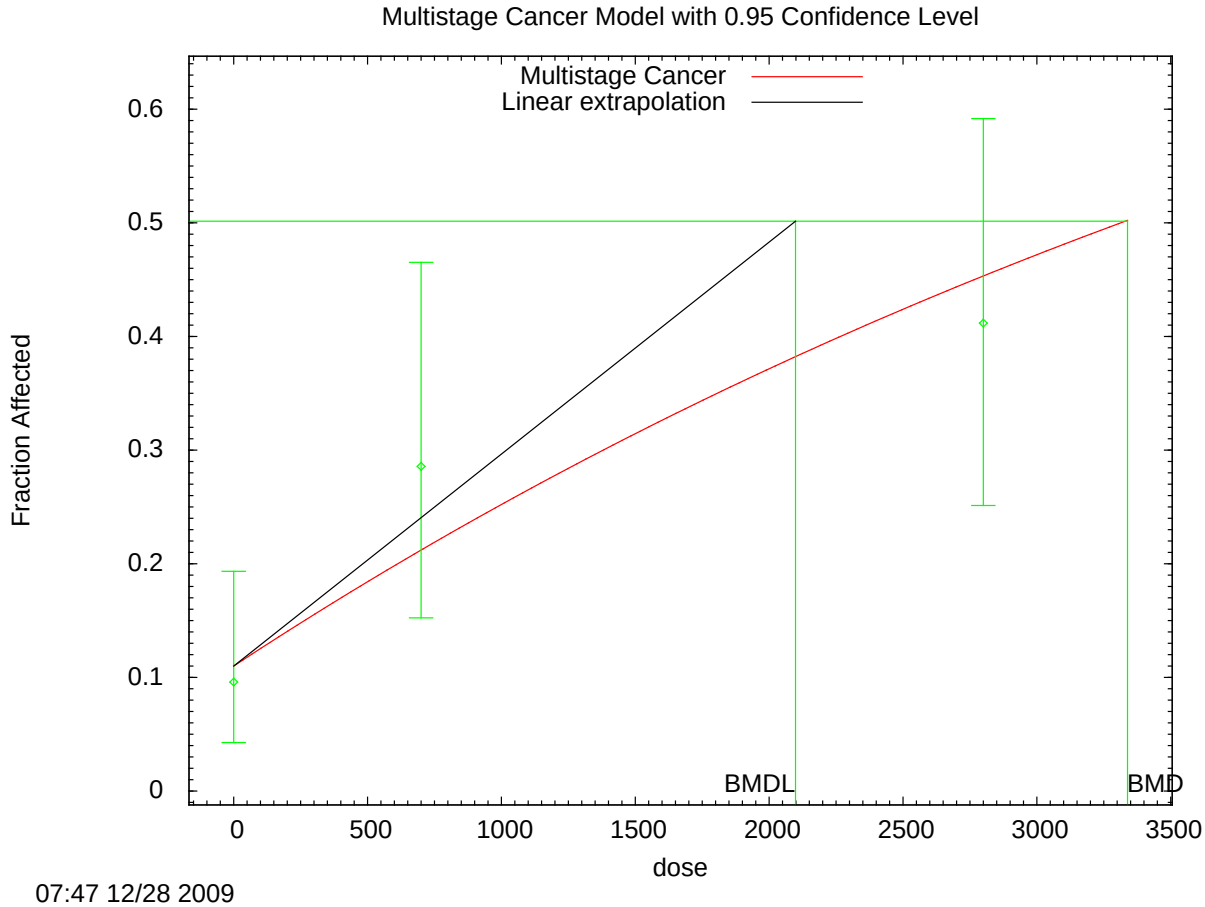
BMD = 6.39184

BMDL = 4.18834

BMDU = 10.3811

Taken together, (4.18834, 10.3811) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.193394

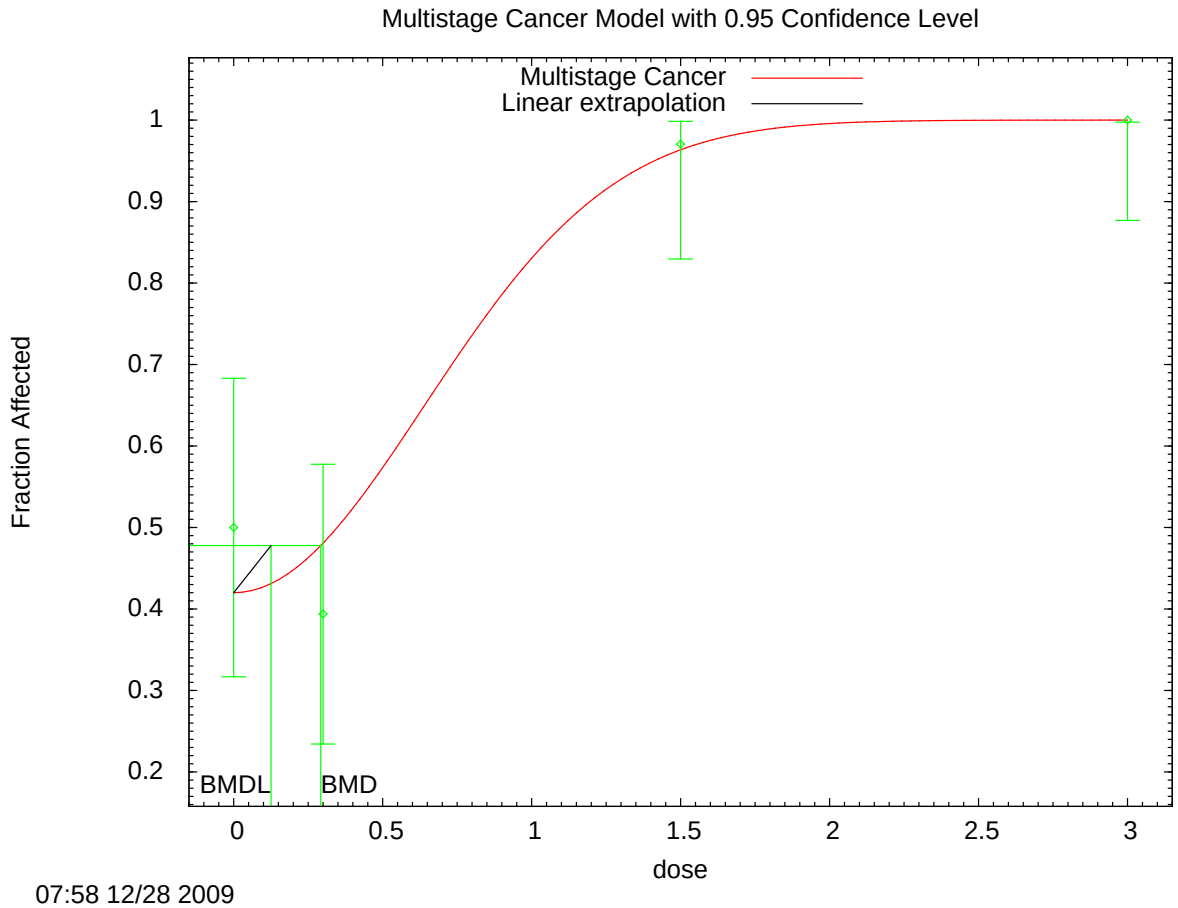


WISLOCKI_CHRYSENE_MALE_LIVER.OUT.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Wislocki1986\CH\msc_WislockiCHliver_MS_1_44.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Wislocki1986\CH\msc_WislockiCHliver_MS_1_44.plt
                                        Wed Dec 23 11:10:41 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose
```

```
 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =     0.147839
                        Beta(1) =  0.000139419


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.57

   Beta(1)        -0.57            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.109703            *               *
*
        Beta(1)       0.00017367            *               *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -67.0392         3
   Fitted model        -67.7628         2       1.44719      1
0.229
  Reduced model         -74.516         1       14.9536      2
0.0005661

           AIC:         139.526
```

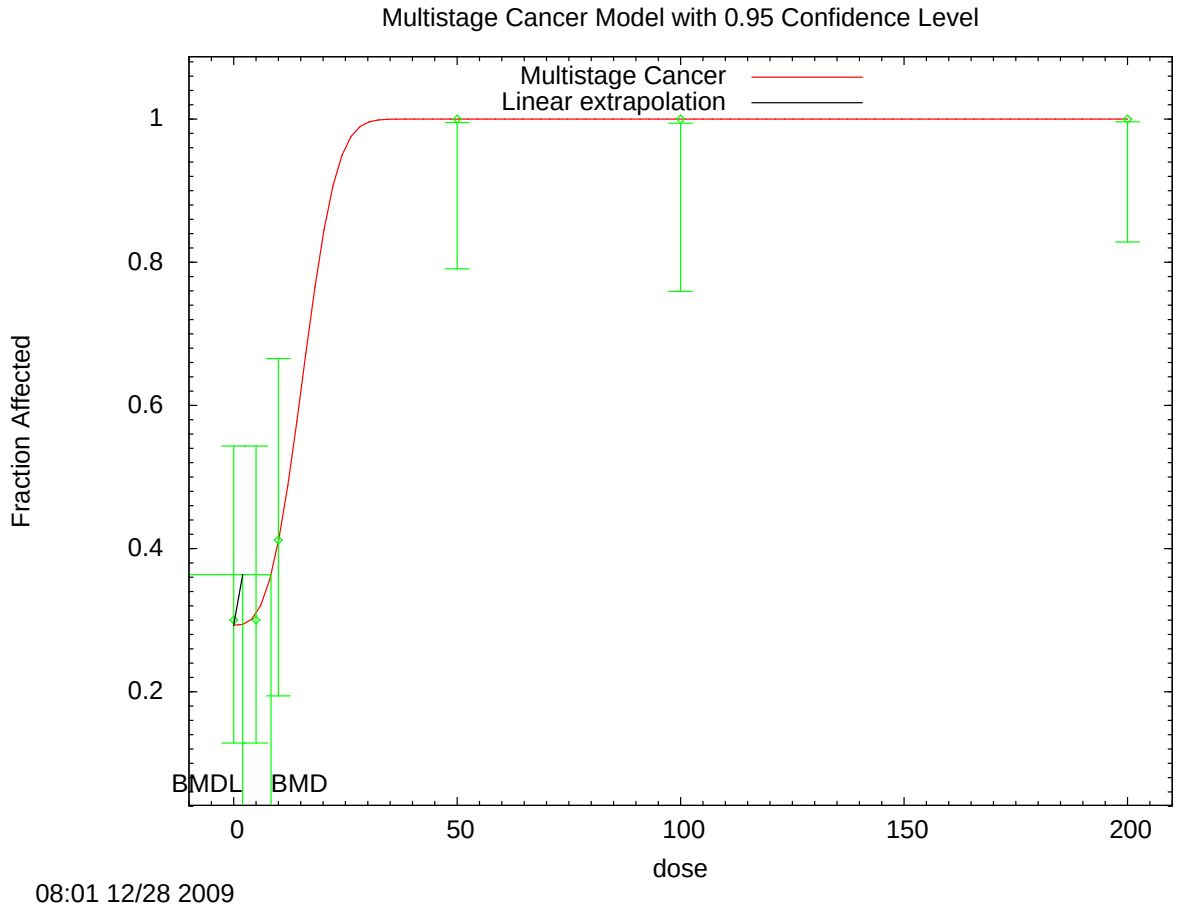
```
                                 Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.1097         8.008     7.000          73       -0.378
  700.0000     0.2116         7.407    10.000          35        1.073
 2800.0000     0.4525        15.387    14.000          34       -0.478

 Chi^2 = 1.52      d.f. = 1        P-value = 0.2172


   Benchmark Dose Computation

Specified effect =           0.44

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3338.63

            BMDL =        2098.51

            BMDU =        6591.77

Taken together, (2098.51, 6591.77) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000209673
```




```
Nesnow et al. 1998b  i.p DBalP male lung High dose dropped



 ======================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\DBalP\msc_NesnowDBalPHDD_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\DBalP\msc_NesnowDBalPHDD_MS_2_10.plt
                                          Wed Dec 23 14:50:54 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
```

```
  Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) = 1.14332e+019


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)

Background            1        -0.27

   Beta(2)        -0.27            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.419864            *               *
*
        Beta(1)                0            *               *
*
        Beta(2)          1.23372            *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

```

```
         Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
       Full model        -47.4317         4
      Fitted model       -48.3498         2       1.83615      2
0.3993
     Reduced model       -77.3457         1       59.8281      3         <.0001

              AIC:           100.7


                                    Goodness  of  Fit
                                                                          Scaled
       Dose     Est._Prob.    Expected    Observed     Size       Residual
    ----------------------------------------------------------------------
      0.0000     0.4199        12.596    15.000          30        0.889
      0.3000     0.4808        15.867    13.000          33       -0.999
      1.5000     0.9639        32.771    33.000          34        0.210
      3.0000     1.0000        35.000    35.000          35        0.017

 Chi^2 = 1.83      d.f. = 2        P-value = 0.3998


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.292233

             BMDL =       0.125394

             BMDU =       0.383954

Taken together, (0.125394, 0.383954) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.797488
```




```
Nesnow et al. 1998b  i.p BaP male lung


 ======================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\BaP\msc_NesnowBaP_MS_4_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\BaP\msc_NesnowBaP_MS_4_10.plt
                                        Wed Dec 23 14:46:42 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose
```

```
 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            1
                        Beta(1) =  5.5061e+017
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(3)      Beta(4)

Background            1        -0.67         0.64

   Beta(3)        -0.67            1           -1

   Beta(4)         0.64           -1            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background          0.29287            *               *
*
        Beta(1)                0            *               *
*
        Beta(2)                0            *               *
*
        Beta(3)      0.000178164            *               *
*
        Beta(4)     3.09556e-007            *               *
*
```

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.952	6			
Fitted model	-35.958	3	0.0120148	3	0.9997
Reduced model	-73.3649	1	74.8258	5	<.0001

AIC: 77.916

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2929	5.857	6.000	20	0.070
5.0000	0.3086	6.172	6.000	20	-0.083
10.0000	0.4101	6.972	7.000	17	0.014
50.0000	1.0000	19.000	19.000	19	0.000
100.0000	1.0000	16.000	16.000	16	0.000
200.0000	1.0000	24.000	24.000	24	0.000

Chi^2 = 0.01 d.f. = 3 P-value = 0.9997

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

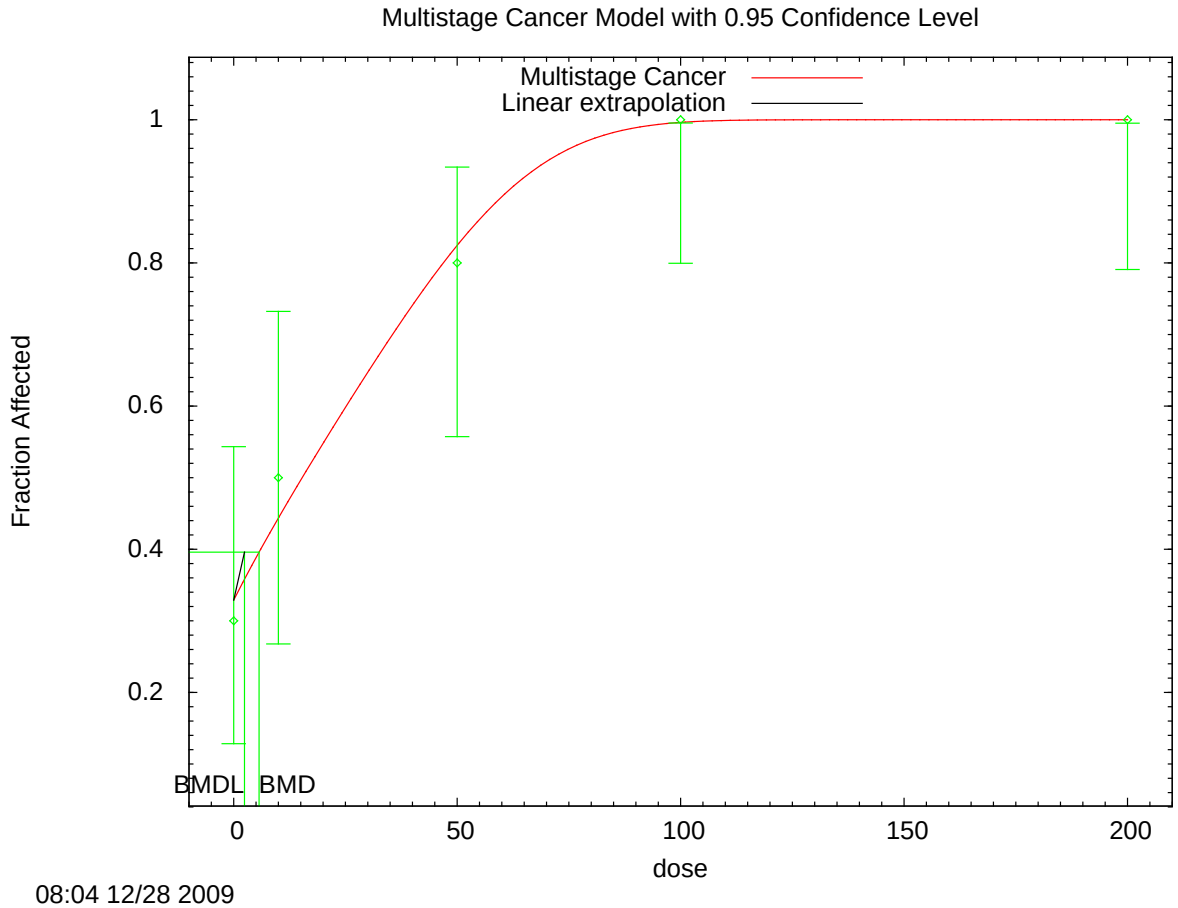
BMD = 8.35346

BMDL = 2.00564

BMDU = 22.6111

Taken together, (2.00564, 22.6111) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0498594

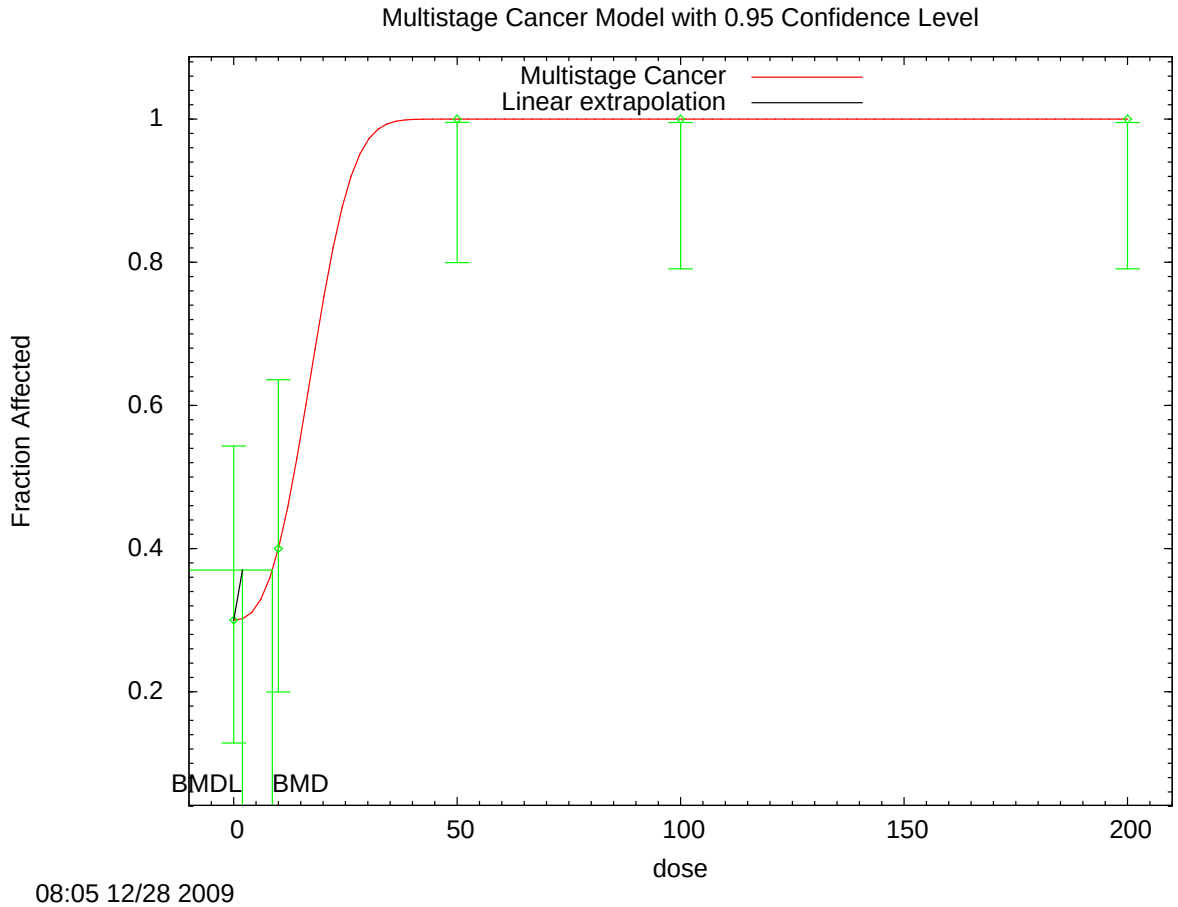


08:04 12/28 2009

```
Nesnow et al. 1998b  i.p BbF male lung



 ======================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\BbF\msc_NesnowBbF_MS_3.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\BbF\msc_NesnowBbF_MS_3.plt
                                          Wed Dec 23 14:46:42 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 5
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) = 5.84708e+017
                        Beta(2) =            0
                        Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)      Beta(3)

Background            1        -0.56         0.31

   Beta(1)        -0.56            1         -0.8

   Beta(3)         0.31         -0.8            1



                                Parameter Estimates

                                                                95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.328834            *               *
*
        Beta(1)        0.0184355            *               *
*
        Beta(2)                0            *               *
*
        Beta(3)     3.37339e-006            *               *
*

* - Indicates that this value is not calculated.
```

```
                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model          -34.702          5
    Fitted model         -34.9693          3       0.53462      2
0.7654
  Reduced model         -57.3647          1       45.3254      4         <.0001

            AIC:          75.9386


                                   Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.3288         6.577     6.000          20       -0.274
    10.0000     0.4437         7.987     9.000          18        0.481
    50.0000     0.8249        16.497    16.000          20       -0.293
   100.0000     0.9964        19.927    20.000          20        0.270
   200.0000     1.0000        19.000    19.000          19        0.000

 Chi^2 = 0.47      d.f. = 2        P-value = 0.7925


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        5.68153

            BMDL =        2.40867

            BMDU =         28.009

Taken together, (2.40867, 28.009 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0415166
```




```
Nesnow et al. 1998b  i.p CPcdP male lung


 ======================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\CPcdP\msc_NesnowCPcdP_MS_3.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\CPcdP\msc_NesnowCPcdP_MS_3.plt
                                          Wed Dec 23 14:46:43 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

```

```
 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            1
                        Beta(1) = 5.02249e+017
                        Beta(2) =            0
                        Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(2)      Beta(3)

Background            1        -0.13        0.025

   Beta(2)        -0.13            1        -0.99

   Beta(3)        0.025        -0.99            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.299994            *               *
*
        Beta(1)                0            *               *
*
        Beta(2)      0.000554719            *               *
*
        Beta(3)     9.86997e-005            *               *
*

* - Indicates that this value is not calculated.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-25.6775	5			
Fitted model	-25.6775	3	3.06836e-005	2	
Reduced model	-56.6963	1	62.0376	4	<.0001

AIC: 57.3551

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3000	6.000	6.000	20	0.000
10.0000	0.4000	8.000	8.000	20	-0.000
50.0000	1.0000	20.000	20.000	20	0.004
100.0000	1.0000	19.000	19.000	19	0.000
200.0000	1.0000	19.000	19.000	19	0.000

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

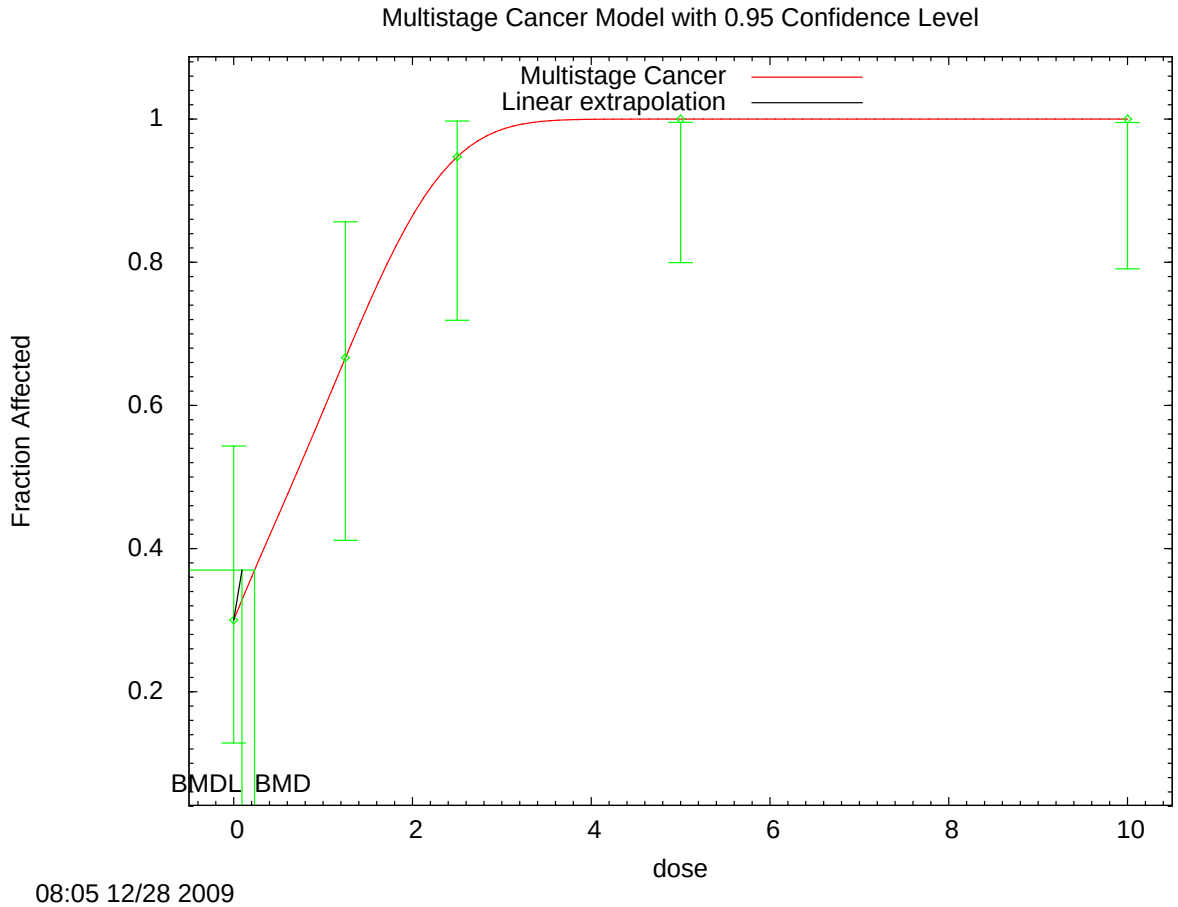
BMD = 8.64922

BMDL = 1.95607

BMDU = 17.5713

Taken together, (1.95607, 17.5713) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0511229




```
Nesnow et al. 1998b  i.p DBahA male lung



 ======================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\DBahA\msc_NesnowDBahA_MS_3.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\IP\Nesnow1998b\DBahA\msc_NesnowDBahA_MS_3.plt
                                          Wed Dec 23 14:46:43 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 5
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =     1.2e+019
                        Beta(2) =            0
                        Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)      Beta(3)

Background            1        -0.48          0.2

   Beta(1)        -0.48            1        -0.81

   Beta(3)          0.2        -0.81            1


                                Parameter Estimates

                                                                  95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.300001            *               *
*
        Beta(1)         0.446326            *               *
*
        Beta(2)                0            *               *
*
        Beta(3)        0.0942115            *               *
*

* - Indicates that this value is not calculated.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-27.5922	5			
Fitted model	-27.5922	3	2.31121e-005	2	
Reduced model	-50.4308	1	45.6773	4	<.0001

AIC: 61.1844

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3000	6.000	6.000	20	-0.000
1.2500	0.6667	12.000	12.000	18	0.000
2.5000	0.9474	18.000	18.000	19	-0.000
5.0000	1.0000	20.000	20.000	20	0.003
10.0000	1.0000	19.000	19.000	19	0.000

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.233378

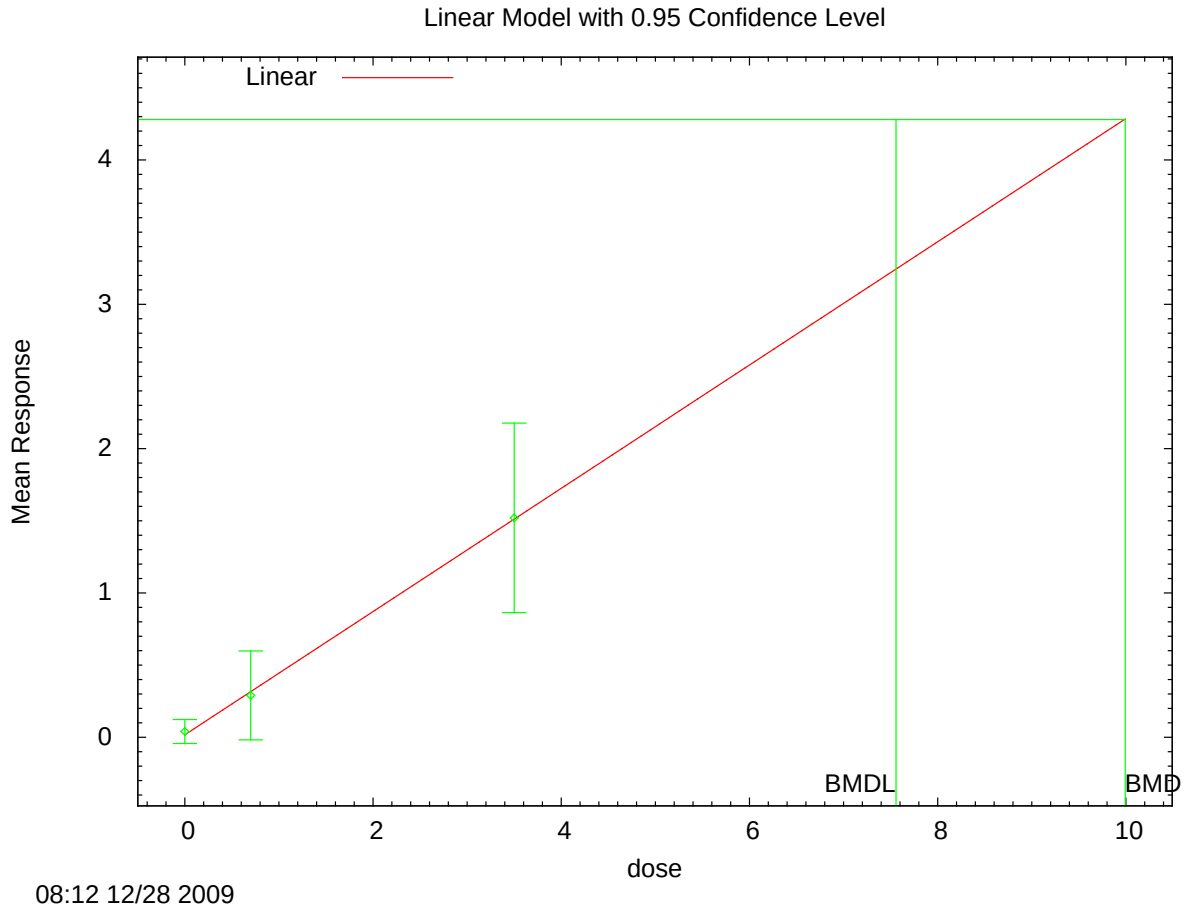
BMDL = 0.0933198

BMDU = 0.955315

Taken together, (0.0933198, 0.955315) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 1.07158

```
Busby 1984 i.p. multiplicity
FA male
Linear
Nonconstant variance
BMR = lowest statistically significant response in BaP treated animals (after
control subtracted)

```



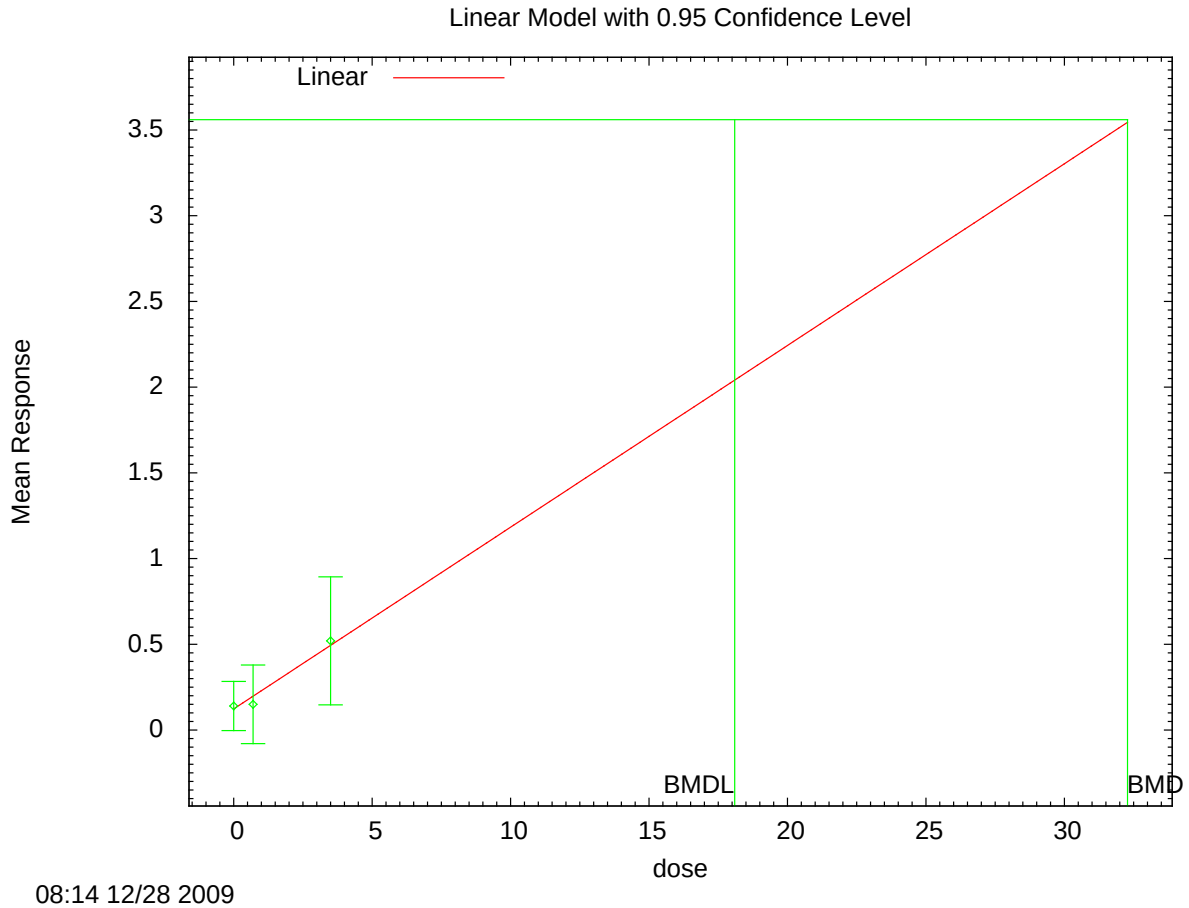

```
08:12 12/28 2009


 ========================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\IPmult\Busby1984\FAmale\lin_BusbyFAM_linear_4_28.(d)
        Gnuplot Plotting File:
C:\IPmult\Busby1984\FAmale\lin_BusbyFAM_linear_4_28.plt
                                          Wed Dec 23 15:26:52 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = mean
```

```
    Independent variable = dose
    The polynomial coefficients are restricted to be positive
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

    Total number of dose groups = 3
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =     0.136152
                            rho =            0
                         beta_0 =    0.0180952
                         beta_1 =     0.427551


           Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

     lalpha            1         0.65        0.015      0.00041

        rho         0.65            1         0.22       -0.061

     beta_0        0.015         0.22            1        -0.24

     beta_1      0.00041       -0.061        -0.24            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         0.634298         0.204652            0.233188
1.03541
            rho         0.923372        0.0876305            0.751619
1.09512
         beta_0        0.0170376        0.0434041          -0.0680328
0.102108
         beta_1         0.426604        0.0861283            0.257796
0.595413


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    27       0.04        0.017         0.21         0.21           0.57
  0.7    31       0.29        0.316         0.84        0.806         -0.177
  3.5    27       1.52         1.51         1.66         1.66         0.0308
```

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -46.759351            4     101.518703
             A2           -7.114400            6      26.228800
             A3           -7.317284            5      24.634569
          fitted          -7.329046            4      22.658093
              R          -59.984569            2     123.969139


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              105.74          4          <.0001
  Test 2             79.2899          2          <.0001
  Test 3            0.405769          1          0.5241
  Test 4           0.0235238          1          0.8781

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
```

```
to adequately describe the data


              Benchmark Dose Computation

Specified effect =          4.28

Risk Type        =     Point risk

Confidence level =          0.95

              BMD =        9.99278


             BMDL =        7.55762
```

Busby 1984 i.p. multiplicity
FA female
Linear
Nonconstant variance
BMR = lowest statistically significant response in BaP treated animals (after control subtracted)



08:14 12/28 2009

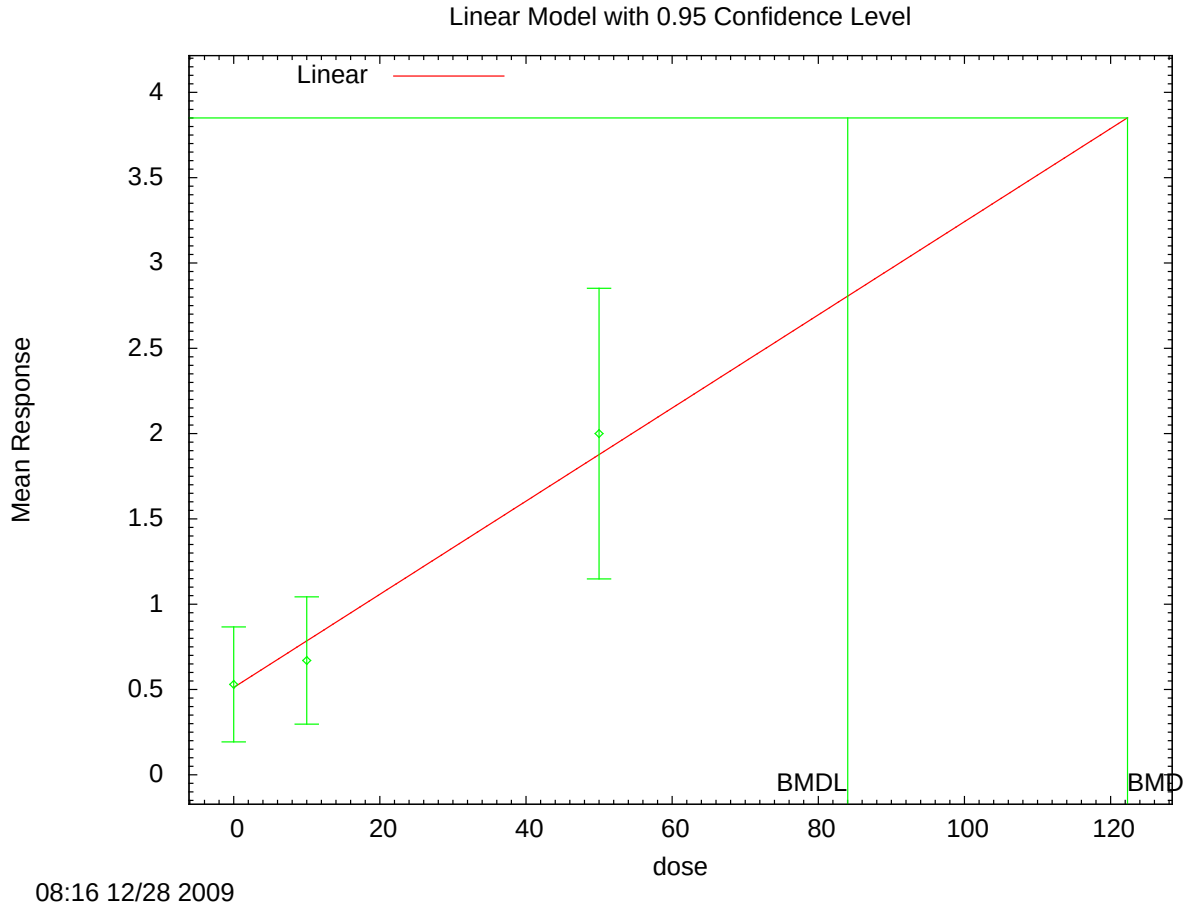
```
 ================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\IPmult\Busby1984\FAfemale\lin_BusbyFAF_linear_3_56.(d)
        Gnuplot Plotting File:
C:\IPmult\Busby1984\FAfemale\lin_BusbyFAF_linear_3_56.plt
                                        Wed Dec 23 15:26:52 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
```

```
    Dependent variable = mean
    Independent variable = dose
    The polynomial coefficients are restricted to be positive
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

    Total number of dose groups = 3
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                         lalpha =     -1.11206
                            rho =            0
                         beta_0 =     0.108571
                         beta_1 =     0.115306


            Asymptotic Correlation Matrix of Parameter Estimates

                   lalpha          rho       beta_0       beta_1

     lalpha             1         0.94        0.036       -0.047

        rho          0.94            1         0.04       -0.052

     beta_0         0.036         0.04            1        -0.46

     beta_1        -0.047       -0.052        -0.46            1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         0.353344         0.480274          -0.587974
1.29466
            rho           1.1315         0.292904           0.557421
1.70558
         beta_0         0.123135        0.0618608          0.00189039
0.24438
         beta_1         0.106469        0.0535364          0.00153987
0.211399


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

     0    28       0.14        0.123         0.37        0.365          0.245
   0.7    20       0.15        0.198         0.49        0.477         -0.447
```

```
 3.5    21       0.52        0.496         0.82        0.802          0.138


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
             Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1            5.399546           4      -2.799091
              A2           13.307908           6     -14.615816
              A3           13.189903           5     -16.379806
          fitted           13.167852           4     -18.335705
               R            2.264796           2      -0.529591


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              22.0862          4       0.0001927
   Test 2              15.8167          2       0.0003677
   Test 3              0.23601          1          0.6271
   Test 4            0.0441012          1          0.8337

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here
```

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =          3.56

Risk Type        =     Point risk

Confidence level =          0.95

             BMD =        32.2804


            BMDL =         18.094
```

Nesnow 1998b i.p. multiplicity
BbF
Drop 2 high doses
Linear
Nonconstant variance
BMR = lowest statistically significant response in BaP treated animals (after control subtracted)



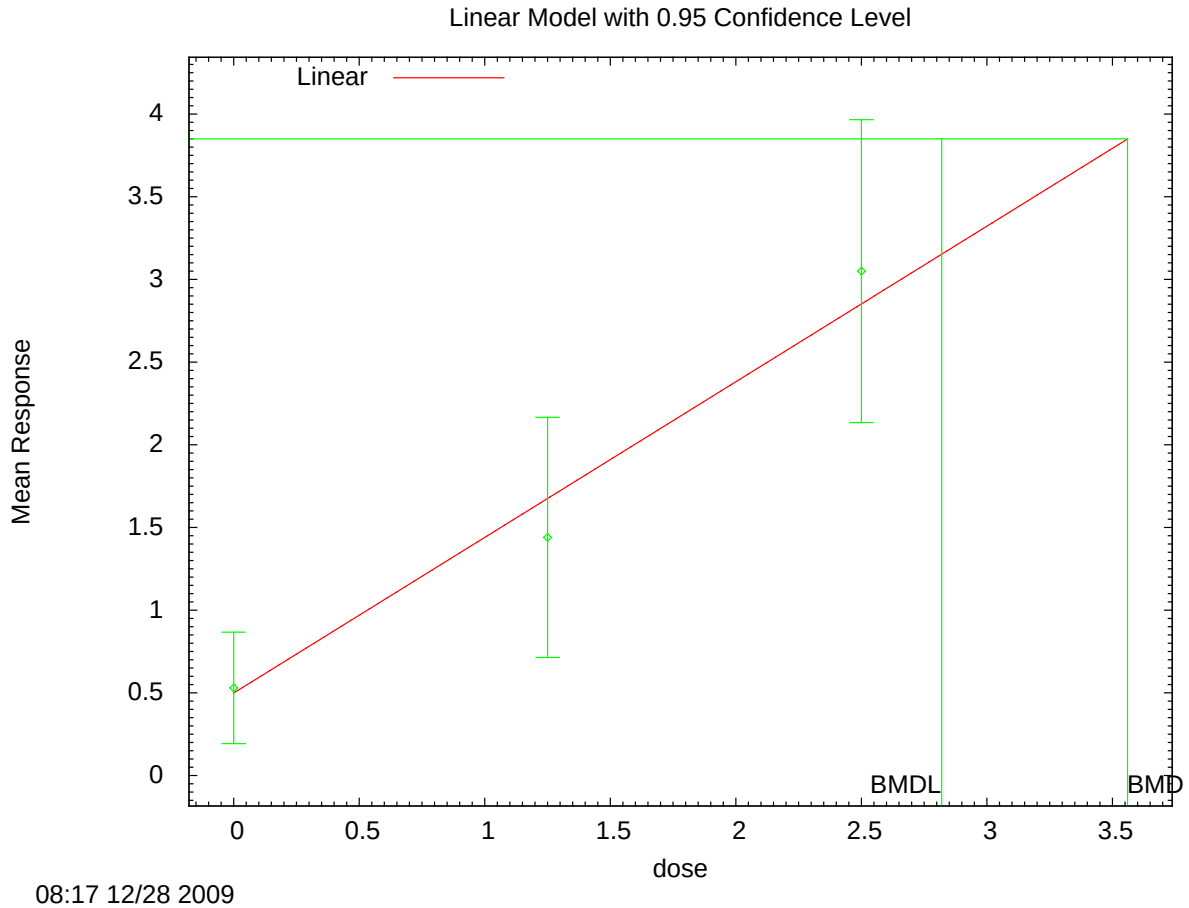

```
 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\IPmult\Nesnow1998b\BbF\lin_NesnowBbF_linear_3_85.(d)
        Gnuplot Plotting File:
C:\IPmult\Nesnow1998b\BbF\lin_NesnowBbF_linear_3_85.plt
                                          Wed Dec 23 15:26:52 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...
```

```
    Dependent variable = mean
    Independent variable = dose
    The polynomial coefficients are restricted to be positive
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

    Total number of dose groups = 3
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008



                   Default Initial Parameter Values
                          lalpha =     0.403617
                             rho =            0
                          beta_0 =     0.456667
                          beta_1 =       0.0305


            Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

     lalpha            1         0.15        0.059        -0.07

        rho         0.15            1       -0.059        0.006

     beta_0        0.059       -0.059            1        -0.49

     beta_1        -0.07        0.006        -0.49            1



                                 Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha         0.123284         0.188418           -0.246009
0.492576
            rho          1.49465         0.320356            0.866761
2.12253
         beta_0         0.511616         0.132543            0.251836
0.771396
         beta_1        0.0272932       0.00827339           0.0110776
0.0435087



      Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    20       0.53        0.512         0.72        0.645          0.128
   10    18       0.67        0.785         0.75        0.887         -0.548
```

```
  50    20          2         1.88         1.82          1.7          0.325


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


                       Likelihoods of Interest

             Model      Log(likelihood)   # Param's      AIC
              A1          -39.164718            4      86.329436
              A2          -27.688080            6      67.376160
              A3          -27.755992            5      65.511983
          fitted          -28.699972            4      65.399945
               R          -47.123187            2      98.246375


                    Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1             38.8702          4          <.0001
   Test 2             22.9533          2          <.0001
   Test 3            0.135824          1          0.7125
   Test 4             1.88796          1          0.1694

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here
```

```
The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


             Benchmark Dose Computation

Specified effect =          3.85

Risk Type        =     Point risk

Confidence level =          0.95

              BMD =        122.316


             BMDL =        84.0259
```

```
Nesnow 1998b i.p. multiplicity
DBahA
Drop 2 high doses
Linear
Nonconstant variance
BMR = lowest statistically significant response in BaP treated animals (after
control subtracted)

```



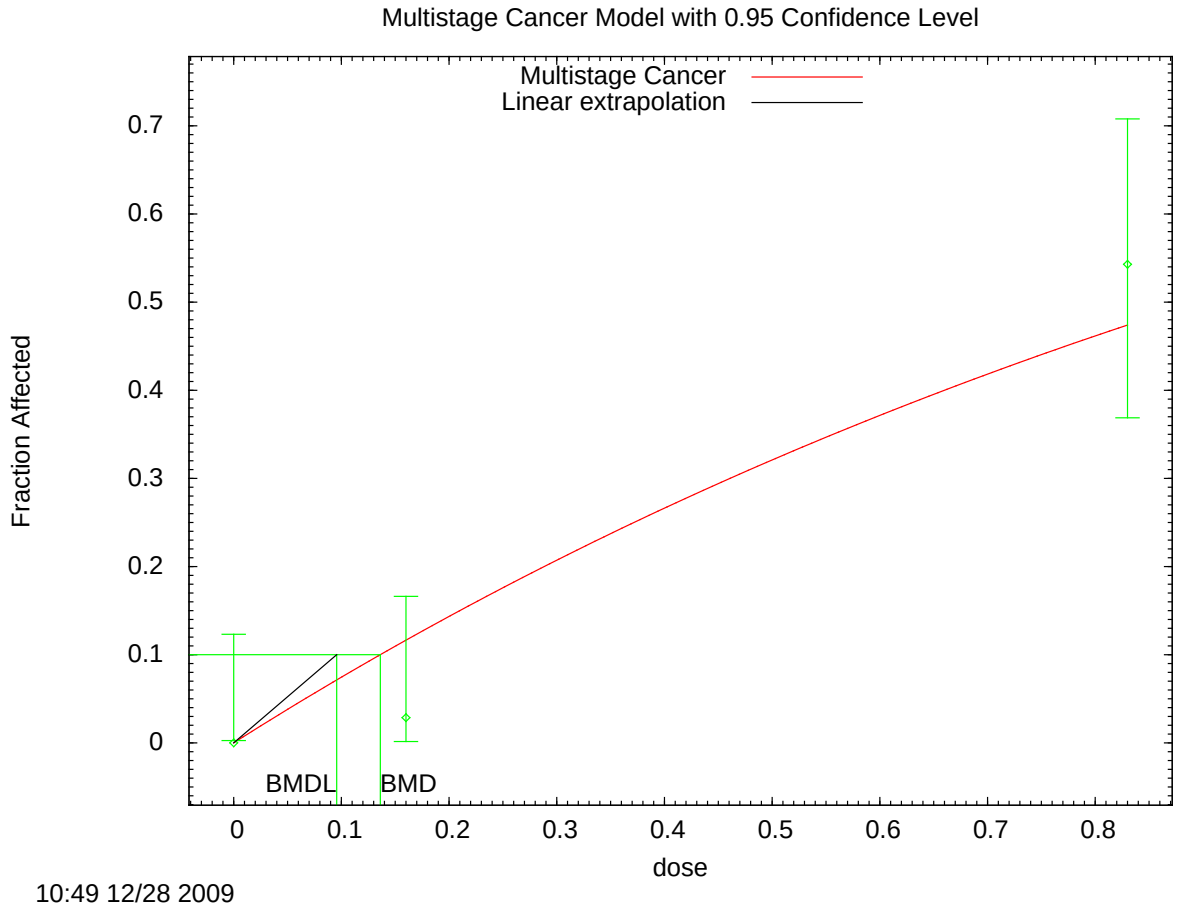

```
  08:17 12/28 2009


 ======================================================================
        Polynomial Model. (Version: 2.13;  Date: 04/08/2008)
        Input Data File:
C:\IPmult\Nesnow1998b\DBahA\lin_NesnowDBahA_linear_3_85.(d)
        Gnuplot Plotting File:
C:\IPmult\Nesnow1998b\DBahA\lin_NesnowDBahA_linear_3_85.plt
                                        Wed Dec 23 15:26:52 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = mean
```

```
    Independent variable = dose
    The polynomial coefficients are restricted to be positive
    The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

    Total number of dose groups = 3
    Total number of records with missing values = 0
    Maximum number of iterations = 250
    Relative Function Convergence has been set to: 1e-008
    Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                        lalpha =     0.721148
                           rho =            0
                        beta_0 =     0.413333
                        beta_1 =        1.008


           Asymptotic Correlation Matrix of Parameter Estimates

                  lalpha          rho       beta_0       beta_1

     lalpha            1        -0.35       -0.035        0.037

        rho        -0.35            1        0.073       -0.083

     beta_0       -0.035        0.073            1        -0.49

     beta_1        0.037       -0.083        -0.49            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
         lalpha        0.0932028         0.199643            -0.29809
0.484496
            rho          1.12871         0.256611            0.625764
1.63166
         beta_0         0.498826         0.155419             0.19421
0.803442
         beta_1         0.941334         0.166649            0.614709
1.26796


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled
Res.
------     ---   --------     --------   -----------  -----------   ---------
-

    0    20       0.53        0.499         0.72        0.708          0.197
 1.25    18       1.44         1.68         1.46          1.4         -0.713
  2.5    19       3.05         2.85          1.9         1.89          0.456
```

```
Model Descriptions for likelihoods calculated


Model A1:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2

Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
    Model A3 uses any fixed variance parameters that
    were specified by the user

Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                      Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -47.511796            4     103.023592
             A2          -39.396001            6      90.792002
             A3          -39.581359            5      89.162719
         fitted          -39.787219            4      87.574439
              R          -60.336483            2     124.672966


                   Explanation of Tests

Test 1:  Do responses and/or variances differ among Dose levels?
         (A2 vs. R)
Test 2:  Are Variances Homogeneous? (A1 vs A2)
Test 3:  Are variances adequately modeled? (A2 vs. A3)
Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
(Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

  Test    -2*log(Likelihood Ratio)  Test df        p-value

  Test 1              41.881          4          <.0001
  Test 2             16.2316          2       0.0002988
  Test 3            0.370717          1          0.5426
  Test 4             0.41172          1          0.5211

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1.  A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
```

```
to adequately describe the data


              Benchmark Dose Computation

Specified effect =          3.85

Risk Type        =     Point risk

Confidence level =          0.95

             BMD =       3.56003


            BMDL =       2.81986
```

D.3. LUNG IMPLANTATION BIOASSAYS

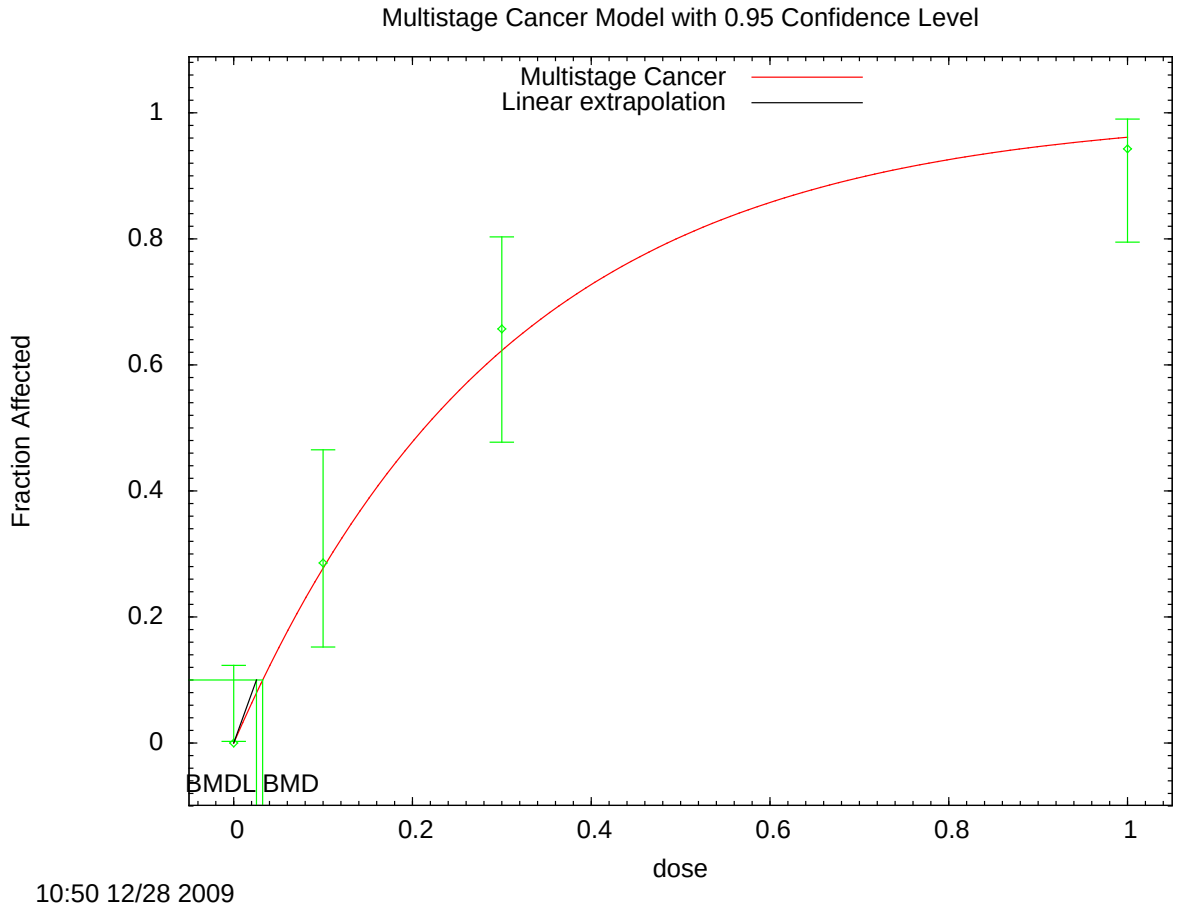


DEUTSCH-WENZEL1983AA.OUT.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
```

```
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\AA\msc_DeutschAA_MS_1_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\AA\msc_DeutschAA_MS_1_10.plt
                                          Wed Dec 23 11:48:09 2009
 ===============================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =     0.996523


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                                Parameter Estimates

```

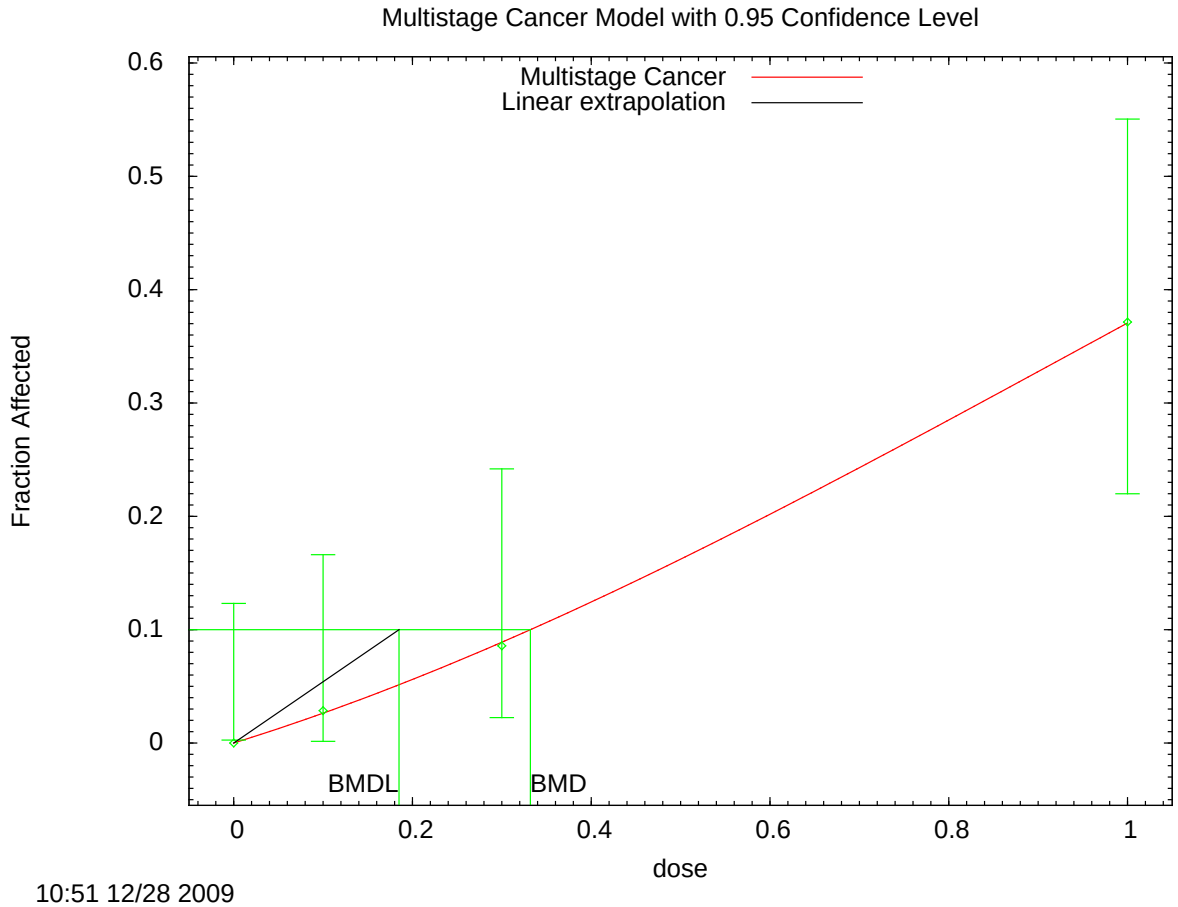
```
                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *                *
*
        Beta(1)         0.773841            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -28.6723         3
   Fitted model         -30.8245         1       4.30422      2
0.1162
  Reduced model         -51.1258         1        44.907      2         <.0001

           AIC:          63.6489


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          35         0.000
    0.1600     0.1165         4.076     1.000          35        -1.621
    0.8300     0.4739        16.587    19.000          35         0.817

 Chi^2 = 3.29      d.f. = 2        P-value = 0.1926


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.136153

            BMDL =      0.0956191

            BMDU =       0.202527

Taken together, (0.0956191, 0.202527) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       1.04582
```




```
DEUTSCH-WENZEL1983BaP.OUT.txt

 ========================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BaP\msc_DeutschBaP_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BaP\msc_DeutschBaP_MS_2_10.plt
                                          Wed Dec 23 11:48:08 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
```

```
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =    0.0757681
                        Beta(1) =      2.82425
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)          3.25323           *               *
*
        Beta(2)                0           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -51.1075         4
   Fitted model         -51.3412         1      0.467435      3
0.926
  Reduced model         -96.8119         1       91.4088      3         <.0001
```

```
            AIC:         104.682


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          35         0.000
     0.1000     0.2777         9.720    10.000          35         0.106
     0.3000     0.6232        21.811    23.000          35         0.415
     1.0000     0.9614        33.647    33.000          35        -0.568

  Chi^2 = 0.51      d.f. = 3        P-value = 0.9177


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0323864

            BMDL =      0.0255063

            BMDU =      0.0445507

Taken together, (0.0255063, 0.0445507) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =        3.9206
```



10:51 12/28 2009

DEUTSCH-WENZEL1983BbF.OUT.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BbF\msc_DeutschBbF_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BbF\msc_DeutschBbF_MS_2_10.plt
                                          Wed Dec 23 11:48:08 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

  Total number of observations = 4
  Total number of records with missing values = 0
  Total number of parameters in model = 3
```

```
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =   0.00149382
                        Beta(1) =     0.226374
                        Beta(2) =     0.236366


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.97

   Beta(2)        -0.97            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)          0.24518           *               *
*
        Beta(2)         0.217701           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -37.8686         4
    Fitted model        -37.8743         2     0.0112712      2
0.9944
   Reduced model        -51.7666         1        27.796      3         <.0001
```

AIC: 79.7485

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	35	0.000
0.1000	0.0263	0.922	1.000	35	0.082
0.3000	0.0889	3.113	3.000	35	-0.067
1.0000	0.3705	12.969	13.000	35	0.011

Chi^2 = 0.01 d.f. = 2 P-value = 0.9943

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

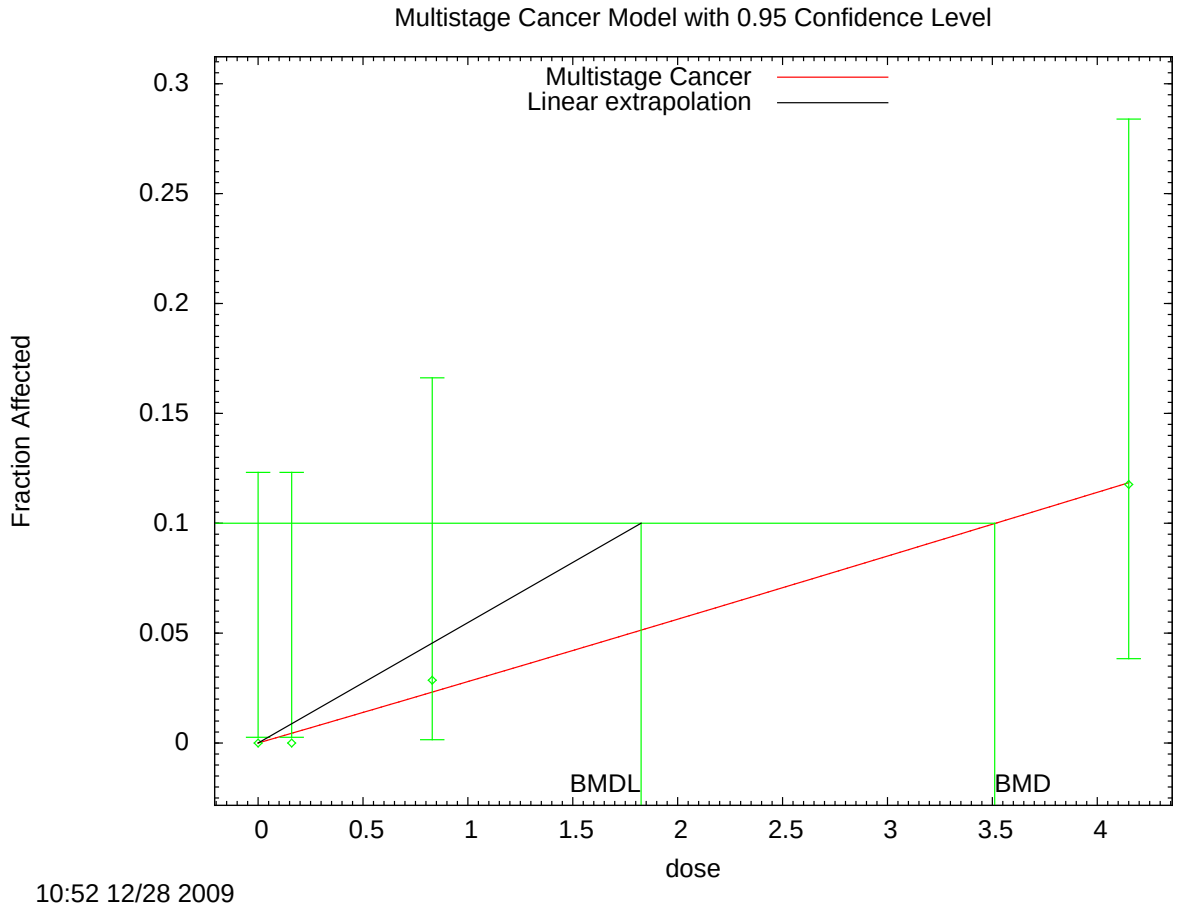
BMD = 0.33191

BMDL = 0.184961

BMDU = 0.544229

Taken together, (0.184961, 0.544229) is a 90 % two-sided confidence interval for the BMD

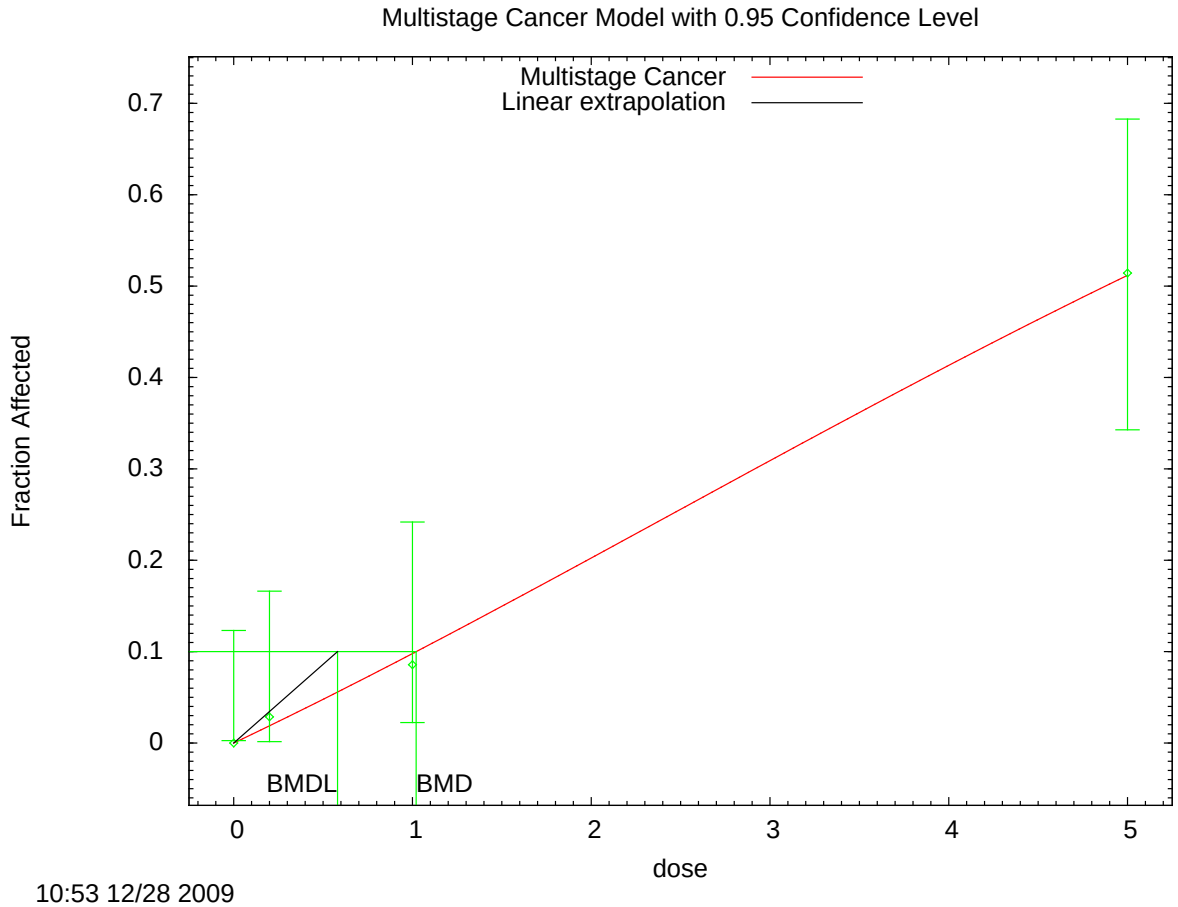
Multistage Cancer Slope Factor = 0.540655




```
DEUTSCH-WENZEL1983BghiP.OUT.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BghiP\msc_DeutschBghiP_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BghiP\msc_DeutschBghiP_MS_2_10.plt
                                          Wed Dec 23 11:48:09 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =    0.0304801
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.98

   Beta(2)        -0.98            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)        0.0277423           *               *
*
        Beta(2)      0.000645059           *               *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -16.8561         4
   Fitted model         -17.033         2      0.353756      2
0.8379
```

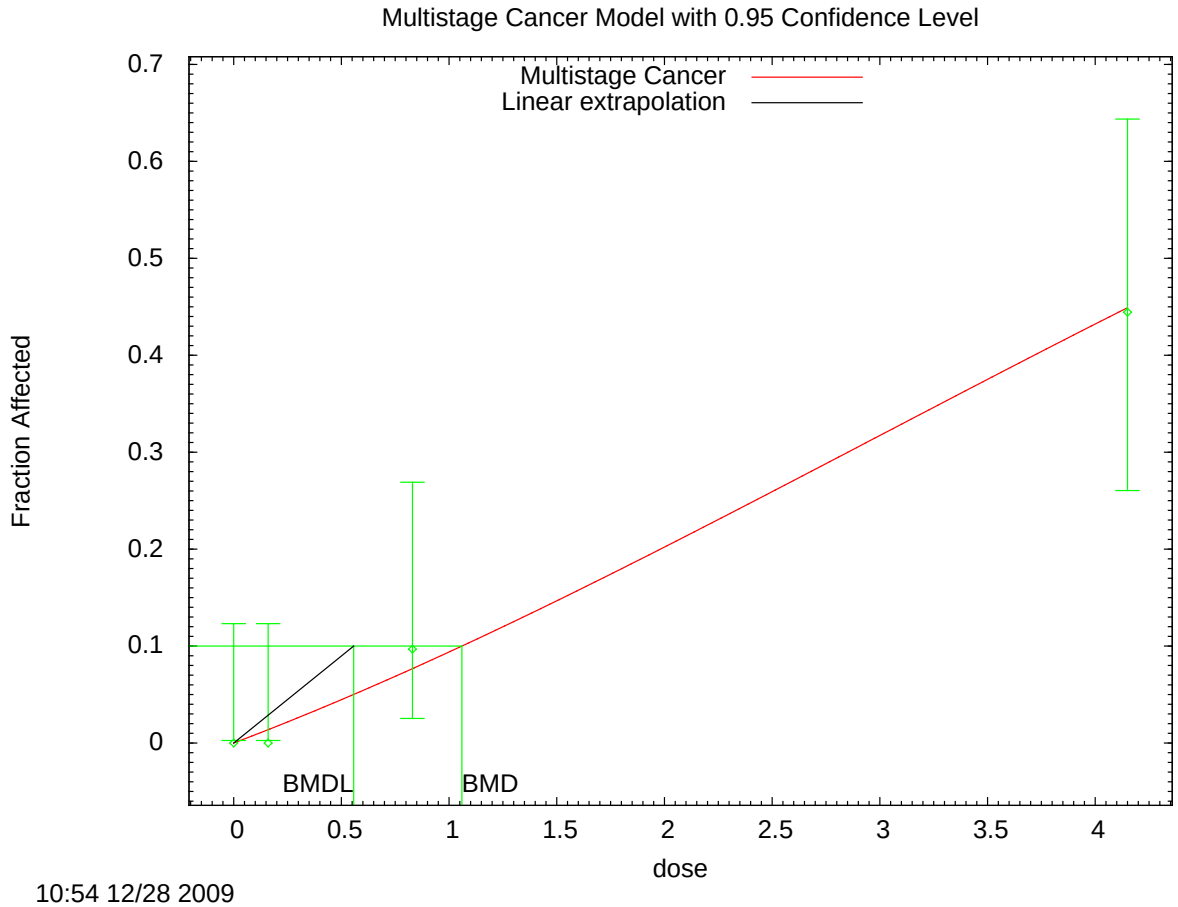
```
  Reduced model        -21.5342         1       9.35614      3
0.02491

            AIC:         38.0659


                                  Goodness  of  Fit
                                                                          Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          35        0.000
     0.1600     0.0044         0.156     0.000          35       -0.395
     0.8300     0.0232         0.812     1.000          35        0.211
     4.1500     0.1186         4.032     4.000          34       -0.017

 Chi^2 = 0.20      d.f. = 2        P-value = 0.9043


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        3.51117

             BMDL =        1.82558

             BMDU =        8.33008

Taken together, (1.82558, 8.33008) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0547771
```




```
DEUTSCH-WENZEL1983BjF.OUT.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BjF\msc_DeutschBjF_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BjF\msc_DeutschBjF_MS_2_10.plt
                                          Wed Dec 23 11:48:08 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =   0.00616121
                        Beta(1) =    0.0709095
                        Beta(2) =    0.0144537


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.98

   Beta(2)        -0.98            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)        0.0929144           *               *
*
        Beta(2)        0.0101278           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -39.0246         4
   Fitted model        -39.1336         2      0.218103      2
0.8967
```

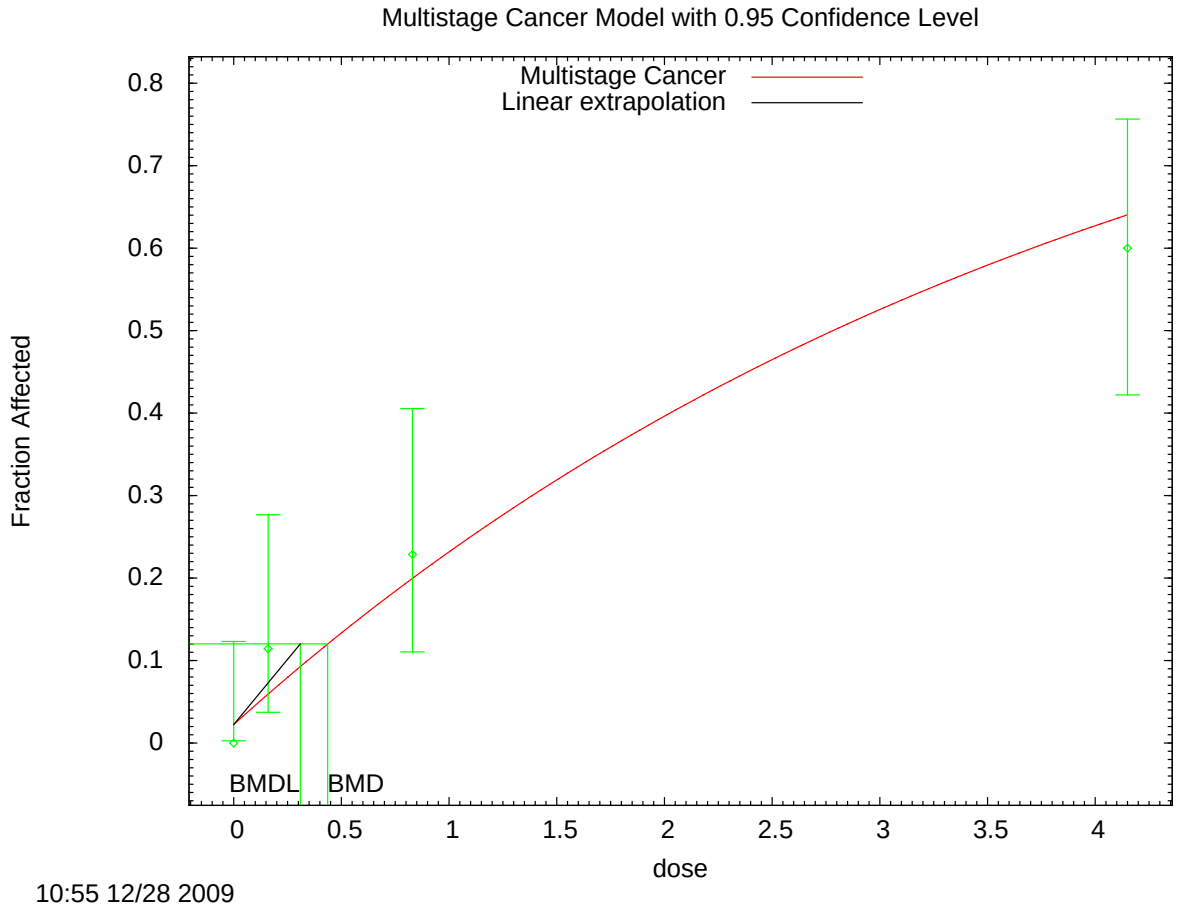
```
  Reduced model        -60.8862         1       43.7233      3         <.0001

            AIC:         82.2673


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          35         0.000
     0.2000     0.0188         0.658     1.000          35         0.425
     1.0000     0.0979         3.427     3.000          35        -0.243
     5.0000     0.5122        17.926    18.000          35         0.025

 Chi^2 = 0.24      d.f. = 2        P-value = 0.8868


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.02045

            BMDL =       0.580958

            BMDU =        2.07945

Taken together, (0.580958, 2.07945) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.172129
```




```
DEUTSCH-WENZEL1983BkF.OUT.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BkF\msc_DeutschBkF_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\BkF\msc_DeutschBkF_MS_2_10.plt
                                          Wed Dec 23 11:48:09 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

  Total number of observations = 4
  Total number of records with missing values = 0
  Total number of parameters in model = 3
```

```
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =     0.126747
                        Beta(2) =   0.00410997


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.97

   Beta(2)        -0.97            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)        0.0842968           *               *
*
        Beta(2)        0.0142917           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model          -28.404         4
   Fitted model         -28.9719         2        1.1357      2
0.5667
  Reduced model         -46.2443         1       35.6806      3         <.0001
```

```
            AIC:         61.9437


                                  Goodness  of  Fit
                                                                  Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000          35        0.000
    0.1600     0.0138         0.482     0.000          35       -0.699
    0.8300     0.0767         2.378     3.000          31        0.420
    4.1500     0.4490        12.122    12.000          27       -0.047

 Chi^2 = 0.67      d.f. = 2        P-value = 0.7165


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.05954

            BMDL =       0.557079

            BMDU =        1.79525

Taken together, (0.557079, 1.79525) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.179508
```



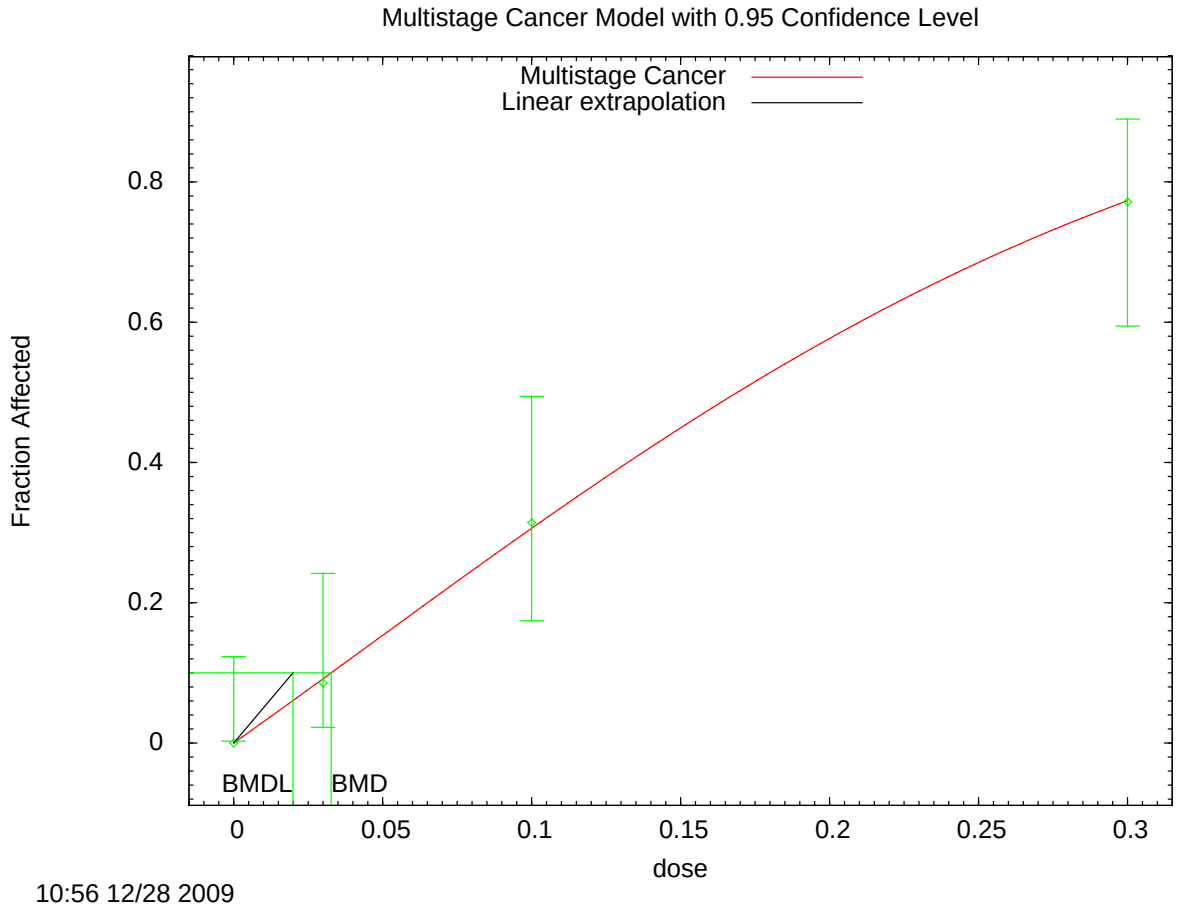
10:55 12/28 2009

DEUTSCH-WENZEL1983IP.OUT.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\IP\msc_DeutschIP_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Deutsch1983\IP\msc_DeutschIP_MS_2_10.plt
                                          Wed Dec 23 11:48:09 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =    0.0539703
                        Beta(1) =      0.20919
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1        -0.55

   Beta(1)        -0.55            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background        0.0224449            *               *
*
        Beta(1)         0.241452            *               *
*
        Beta(2)                0            *               *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -54.8079         4
   Fitted model        -56.5662         2        3.5166      2
0.1723
```

```
  Reduced model        -76.4525         1       43.2893      3         <.0001

           AIC:         117.132


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size        Residual
   ----------------------------------------------------------------------------
     0.0000     0.0224         0.786     0.000          35       -0.896
     0.1600     0.0595         2.082     4.000          35        1.370
     0.8300     0.2000         6.999     8.000          35        0.423
     4.1500     0.6411        22.439    21.000          35       -0.507

 Chi^2 = 3.12      d.f. = 2        P-value = 0.2104


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.436361

            BMDL =       0.309504

            BMDU =       0.819969

Taken together, (0.309504, 0.819969) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =      0.323098
```



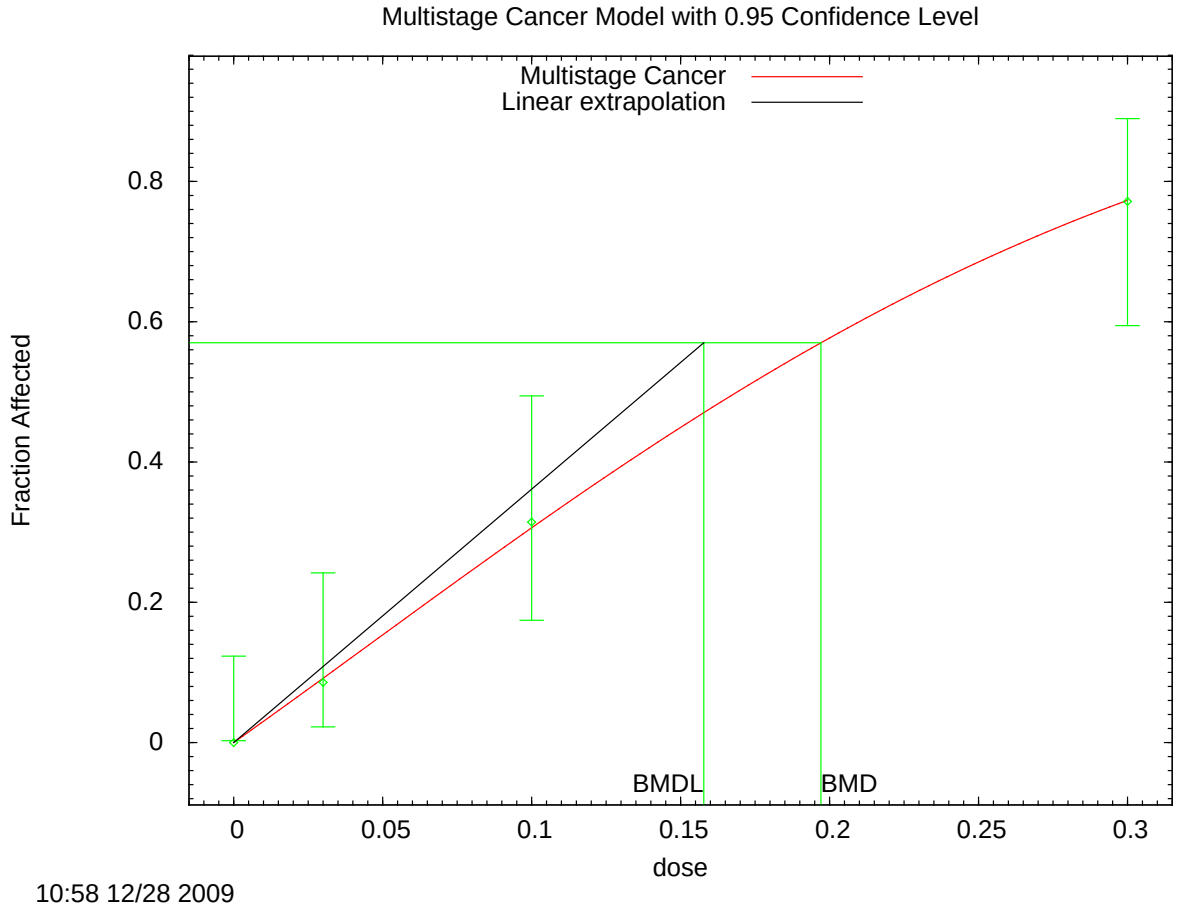
10:56 12/28 2009

WENZEL-HARTUNG1990BaP.OUT.txt

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Wenzel1990\BaP\msc_WenzelBaP_MS_2_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Wenzel1990\BaP\msc_WenzelBaP_MS_2_10.plt
                                          Wed Dec 23 11:48:09 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 4
 Total number of records with missing values = 0
```

```
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =      3.21631
                        Beta(2) =       5.7325


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.93

   Beta(2)        -0.93            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0           *               *
*
        Beta(1)          3.01149           *               *
*
        Beta(2)          6.44644           *               *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model        -50.8389         4
   Fitted model         -50.8521         2     0.0264626      2
0.9869
```

```
  Reduced model        -84.6566         1       67.6355      3         <.0001

           AIC:         105.704


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
   ----------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          35        0.000
     0.0300     0.0917         3.208     3.000          35       -0.122
     0.1000     0.3062        10.718    11.000          35        0.103
     0.3000     0.7732        27.062    27.000          35       -0.025

 Chi^2 = 0.03      d.f. = 2        P-value = 0.9870


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0326976

            BMDL =      0.0198862

            BMDU =      0.0559366

Taken together, (0.0198862, 0.0559366) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =       5.02861
```




```
WENZEL-HARTUNG1990BaP.OUT.txt – alternative BMR = 0.57


 ========================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Wenzel1990\BaPalt\msc_WenzelBaPalt_MS_2_57.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Wenzel1990\BaPalt\msc_WenzelBaPalt_MS_2_57.plt
                                          Wed Dec 23 11:48:11 2009
 ========================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose
```

```
 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =      3.21631
                        Beta(2) =       5.7325


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.93

   Beta(2)        -0.93            1


                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *                *
*
        Beta(1)          3.01149            *                *
*
        Beta(2)          6.44644            *                *
*

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
```

```
      Full model        -50.8389         4
    Fitted model        -50.8521         2     0.0264626      2
0.9869
   Reduced model        -84.6566         1       67.6355      3         <.0001

             AIC:         105.704


                                    Goodness  of  Fit
                                                                          Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
    ---------------------------------------------------------------------------
     0.0000     0.0000         0.000     0.000          35        0.000
     0.0300     0.0917         3.208     3.000          35       -0.122
     0.1000     0.3062        10.718    11.000          35        0.103
     0.3000     0.7732        27.062    27.000          35       -0.025

 Chi^2 = 0.03      d.f. = 2        P-value = 0.9870


    Benchmark Dose Computation

Specified effect =           0.57

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.197095

             BMDL =       0.157781

             BMDU =       0.247357

Taken together, (0.157781, 0.247357) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =        3.6126
```

```
WENZEL-HARTUNG1990BaPforDBahA.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\PAH\BMD ANALYSIS\BIOASSAY\OTHER
ROUTE\SETS\WENZEL-HARTUNG1990.(d)
        Gnuplot Plotting File:  C:\PAH\BMD ANALYSIS\BIOASSAY\OTHER
ROUTE\SETS\WENZEL-HARTUNG1990.plt
                                          Thu Jun 02 09:02:58 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = responseBaP
   Independent variable = doseBaP

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =           0
                        Beta(1) =     3.21631
                        Beta(2) =      5.7325


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.93

   Beta(2)        -0.93            1



                         Parameter Estimates

```

Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	3.01149	2.79594
Beta(2)	6.44644	10.7674

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-50.8389			
Fitted model	-50.8521	0.0264626	2	0.9869
Reduced model	-84.6566	67.6355	3	<.0001

AIC: 105.704

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	35	0.000
i: 2					
0.0300	0.0917	3.208	3	35	-0.072
i: 3					
0.1000	0.3062	10.718	11	35	0.038
i: 4					
0.3000	0.7732	27.062	27	35	-0.010

Chi-square = 0.03 DF = 2 P-value = 0.9870

Benchmark Dose Computation

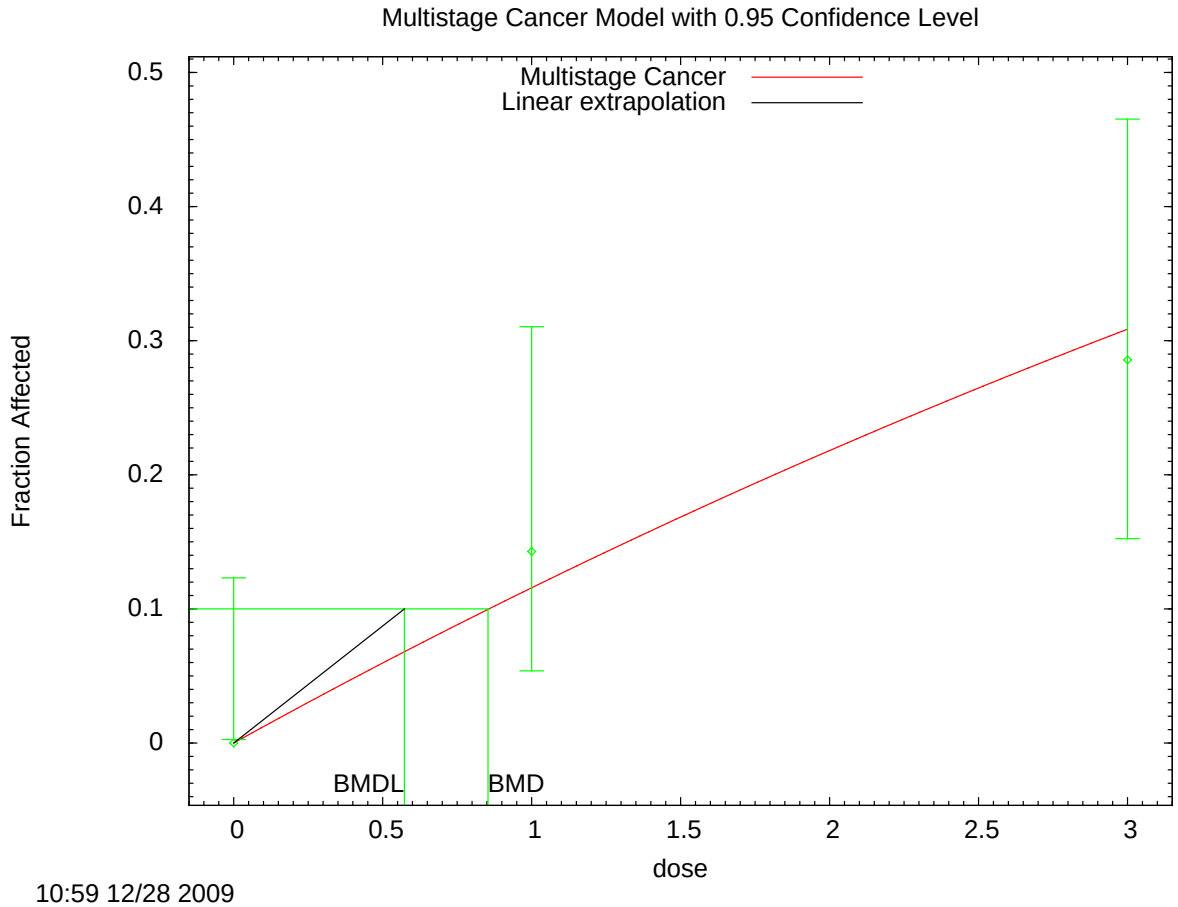
Specified effect = 0.57

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.197095

BMDL = 0.157781




```
WENZEL-HARTUNG1990CH.OUT.txt

 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\lungimplant\Wenzel1990\CH\msc_WenzelCH_MS_1_10.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\lungimplant\Wenzel1990\CH\msc_WenzelCH_MS_1_10.plt
                                          Wed Dec 23 11:48:10 2009
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

  Total number of observations = 3
  Total number of records with missing values = 0
  Total number of parameters in model = 2
```

```
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****



                  Default Initial Parameter Values
                     Background =    0.0178361
                        Beta(1) =     0.109158


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                        95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0            *                *
*
        Beta(1)         0.123432            *                *
*

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -35.2935         3
   Fitted model         -35.455         1      0.323044      2
0.8508
  Reduced model        -43.0622         1       15.5374      2
0.0004228

           AIC:         72.9101
```

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	35	0.000
1.0000	0.1161	4.064	5.000	35	0.494
3.0000	0.3095	10.831	10.000	35	-0.304

Chi^2 = 0.34 d.f. = 2 P-value = 0.8453

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.853595

BMDL = 0.57298

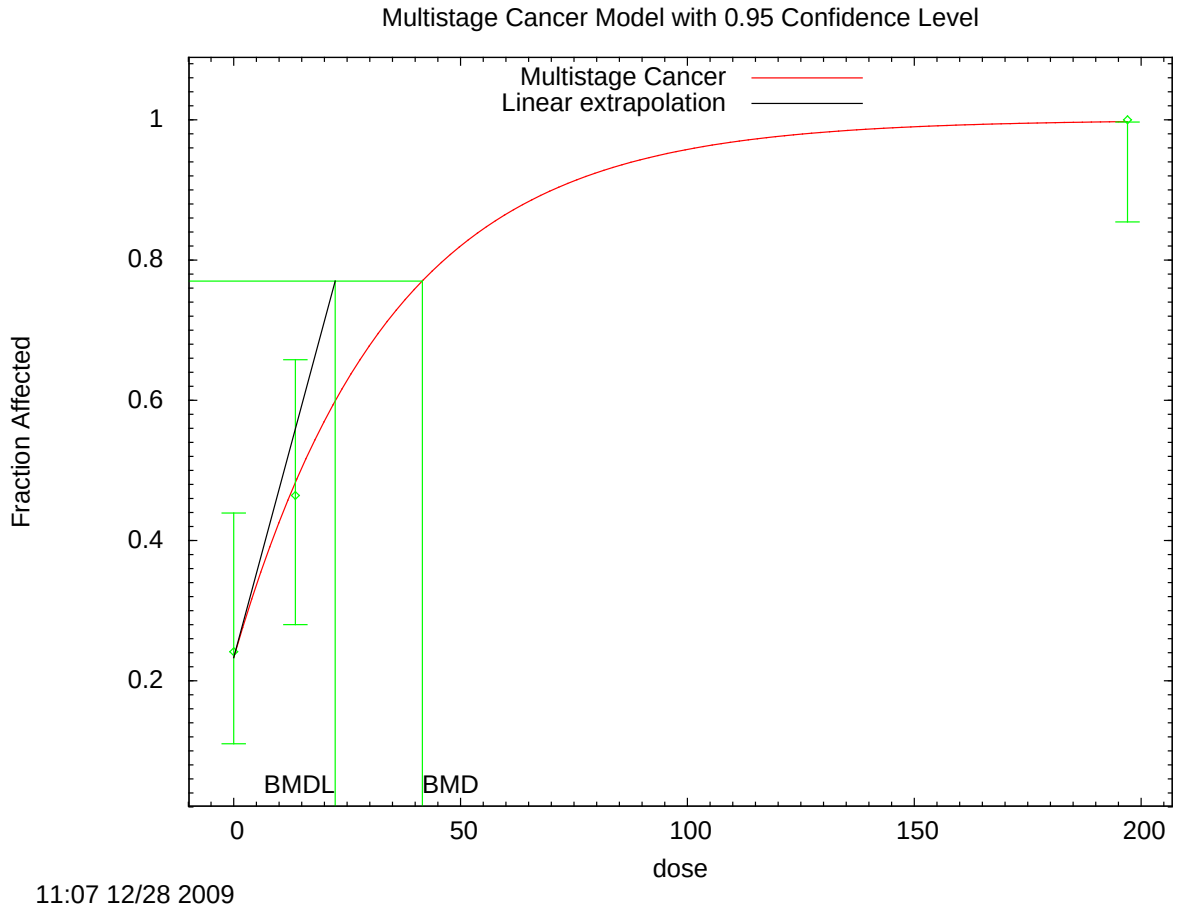
BMDU = 1.36494

Taken together, (0.57298, 1.36494) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.174526

D.4. ORAL BIOASSAYS

Weyand et al. 2004 BcFE lung




```
 ======================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\IRIS\PAH\oral\Weyand2004\BcFE\msc_WeyandBcFE_MS_1_70.(d)
        Gnuplot Plotting File:
C:\USEPA\IRIS\PAH\oral\Weyand2004\BcFE\msc_WeyandBcFE_MS_1_70.plt
                                          Wed Dec 23 14:10:13 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]
```

```
   The parameter betas are restricted to be positive


   Dependent variable = incidence
   Independent variable = dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 2.22045e-016
 Parameter Convergence has been set to: 1.49012e-008

****  We are sorry but Relative Function and Parameter Convergence    ****
****  are currently unavailable in this model.  Please keep checking  ****
****  the web sight for model updates which will eventually           ****
****  incorporate these convergence criterion.  Default values used.  ****


                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) = 5.23754e+017


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.45

   Beta(1)        -0.45            1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background         0.233316            *                *
*
        Beta(1)        0.0289518            *                *
*

* - Indicates that this value is not calculated.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-35.3639	3			
Fitted model	-35.4627	2	0.197606	1	0.6567
Reduced model	-58.7707	1	46.8136	2	<.0001

AIC: 74.9254

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2333	6.766	7.000	29	0.103
13.6000	0.4829	13.520	13.000	28	-0.197
197.0000	0.9974	28.926	29.000	29	0.273

Chi^2 = 0.12 d.f. = 1 P-value = 0.7253

Benchmark Dose Computation

Specified effect = 0.7

Risk Type = Extra risk

Confidence level = 0.95

BMD = 41.5854

BMDL = 22.3673

BMDU = 81.9344

Taken together, (22.3673, 81.9344) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0312958

D.5. BACTERIAL MUTAGENICITY

```
Hass 1981 bact mut bap.out.txt
 ================================================================
        Polynomial Model. Revision: 2.2  Date: 9/12/2002
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                        Wed Jul 06 11:29:07 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = MEAN
   Independent variable = COLUMN1
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =        194.5
                            rho =            0   Specified
                         beta_0 =        121.8
                         beta_1 =      297.029


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha           132.71          54.1784             26.5217
238.897
         beta_0            121.8          5.15188             111.702
131.898
         beta_1          297.029          8.99387             279.401
314.656


            Asymptotic Correlation Matrix of Parameter Estimates

                    alpha       beta_0       beta_1
     alpha              1    -1.4e-009    -1.1e-008
    beta_0    -1.4e-009             1        -0.76
    beta_1    -1.1e-008         -0.76            1
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	3	124	8	122	11.5	0.331
0.25	3	194	16	196	11.5	-0.309
0.5	3	269	13	270	11.5	-0.198
1	3	420	17	419	11.5	0.176

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-35.189802	5	80.379605
A2	-34.317788	8	84.635576
fitted	-35.328976	2	74.657952
R	-62.974684	2	129.949369

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)
Test 2: Are Variances Homogeneous (A1 vs A2)
Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	57.3138	6	<.0001
Test 2	1.74403	3	0.6272
Test 3	0.278348	2	0.8701

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels.
It seems appropriate to model the data

The p-value for Test 2 is greater than .05. A homogeneous variance
model appears to be appropriate here

```
The p-value for Test 3 is greater than .05.  The model
chosen appears
to adequately describe the data


 Benchmark Dose Computation
Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean


Confidence level =          0.95

              BMD =      0.038784


             BMDL =     0.0286028
```

```
HASS_1981_BACT_MUT_BEP.OUT.txt
 ================================================================
        Polynomial Model. Revision: 2.2  Date: 9/12/2002
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\HASS_1981_BACT_MUT_BEP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\HASS_1981_BACT_MUT_BEP.plt
                                          Wed Jul 06 13:42:38 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = MEAN
   Independent variable = COLUMN1
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =        117.5
                            rho =            0   Specified
                         beta_0 =       120.75
                         beta_1 =         77.5


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          98.6458           40.272             19.7142
177.577
         beta_0           120.75          4.19706             112.524
128.976
         beta_1             77.5          7.66275             62.4813
92.5187


            Asymptotic Correlation Matrix of Parameter Estimates

                    alpha       beta_0       beta_1
     alpha              1      -8e-012     1.1e-011
     beta_0      -8e-012            1        -0.73
     beta_1     1.1e-011        -0.73            1
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	3	124	8	121	9.93	0.567
0.2	3	129	6	136	9.93	-1.26
0.4	3	156	9	152	9.93	0.741
1	3	198	17	198	9.93	-0.0436

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-32.165839	5	74.331679
A2	-30.272126	8	76.544252
fitted	-33.549216	2	71.098432
R	-47.594288	2	99.188576

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)
Test 2: Are Variances Homogeneous (A1 vs A2)
Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	34.6443	6	<.0001
Test 2	3.78743	3	0.2854
Test 3	2.76675	2	0.2507

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels.
It seems appropriate to model the data

The p-value for Test 2 is greater than .05. A homogeneous variance
model appears to be appropriate here

```
The p-value for Test 3 is greater than .05.  The model
chosen appears
to adequately describe the data


 Benchmark Dose Computation
Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean


Confidence level =          0.95

              BMD =      0.128156


             BMDL =     0.0923937
```

```
JOHNSEN_1997_BAC_MUT_BAP.OUT.txt
 ================================================================
        Polynomial Model. Revision: 2.2  Date: 9/12/2002
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\JOHNSEN_1997_BAC_MUT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\JOHNSEN_1997_BAC_MUT_BAP.plt
                                        Fri Jul 08 09:02:29 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = MEAN
   Independent variable = COLUMN1
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                          alpha =      70.2768
                            rho =            0   Specified
                         beta_0 =        115.5
                         beta_1 =         0.65


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
       Variable        Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
          alpha          59.3512          27.9784             4.51449
114.188
         beta_0            115.5          4.06035             107.542
123.458
         beta_1             0.65         0.314513           0.0335651
1.26643


            Asymptotic Correlation Matrix of Parameter Estimates

                    alpha       beta_0       beta_1
     alpha              1    -7.9e-010    -3.4e-012
     beta_0    -7.9e-010            1        -0.77
     beta_1    -3.4e-012        -0.77            1
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	3	113	9.68	115	7.7	-0.562
10	3	127	4.84	122	7.7	1.12
20	3	126	9.68	128	7.7	-0.562

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-21.811395	4	51.622790
A2	-21.026523	6	54.053045
fitted	-22.875626	2	49.751251
R	-24.653317	2	53.306634

Test 1: Does response and/or variances differ among dose levels
(A2 vs. R)
Test 2: Are Variances Homogeneous (A1 vs A2)
Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	7.25359	4	0.0266
Test 2	1.56974	2	0.4562
Test 3	2.12846	1	0.1446

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels.
It seems appropriate to model the data

The p-value for Test 2 is greater than .05. A homogeneous variance
model appears to be appropriate here

```
The p-value for Test 3 is greater than .05.  The model
chosen appears
to adequately describe the data


 Benchmark Dose Computation
Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean


Confidence level =          0.95

              BMD =       11.8523


             BMDL =       6.27094
```

D.6. MAMMALIAN MUTAGENICITY

```
BARF_MUT_BAA.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\BARF_MUT_BAA.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\BARF_MUT_BAA.plt
                                          Thu Jun 30 12:46:38 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 3.89426e-006
                        Beta(1) = 3.46216e-007
                        Beta(2) =            0
                        Beta(3) = 1.93939e-012
**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
pont****



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1

```

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	4.34385e-007	5.43792e-006
Beta(2)	0	NA
Beta(3)	0	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-1545.82			
Fitted model	-1548.6	5.57201	4	0.2335
Reduced model	-1597.17	102.713	4	<.0001

AIC: 3099.21

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	1000000	0.000
i: 2					
20.0000	0.0000	8.688	12	1000000	0.381
i: 3					
50.0000	0.0000	21.719	29	1000000	0.335
i: 4					
100.0000	0.0000	43.438	34	1000000	-0.217
i: 5					
150.0000	0.0001	65.156	64	1000000	-0.018

Chi-square = 5.77 DF = 4 P-value = 0.2166

Benchmark Dose Computation

Specified effect = 1e-005

Risk Type = Extra risk

Confidence level = 0.95

BMD = 23.0212

**** WARNING: Completion code = -2. Optimum not found. Trying new starting point****

**** WARNING 0: Completion code = -2 trying new start****

**** WARNING 1: Completion code = -2 trying new start****

```
**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****

**** WARNING 4:  Completion code = -2 trying new start****

**** WARNING 5:  Completion code = -2 trying new start****

**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -2 trying new start****

**** WARNING 8:  Completion code = -2 trying new start****

**** WARNING 9:  Completion code = -2 trying new start****

**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -2 trying new start****

**** WARNING 1:  Completion code = -3 trying new start****

**** WARNING 2:  Completion code = -3 trying new start****

**** WARNING 3:  Completion code = -3 trying new start****

**** WARNING 4:  Completion code = -3 trying new start****

**** WARNING 5:  Completion code = -3 trying new start****

**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -3 trying new start****

**** WARNING 8:  Completion code = -3 trying new start****

**** WARNING 9:  Completion code = -3 trying new start****


Warning:  completion code still negative
BMDL did not converge for BMR = 0.000010

Program execution is stopped
```

```
BARF_MUT_BAP.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\BARF_MUT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\BARF_MUT_BAP.plt
                                          Thu Jun 30 12:40:17 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 1.39884e-006
                        Beta(1) = 5.34042e-006
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
```

```
         Beta(1)        5.43367e-006        2.68102e-005
         Beta(2)                   0                  NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -3273.08
    Fitted model         -3273.96       1.75092      3          0.6257
   Reduced model         -3395.25       244.327      3         <.0001

            AIC:          6549.92


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0     1000000       0.000
i: 2
   10.0000     0.0001        54.335        51     1000000      -0.061
i: 3
   20.0000     0.0001       108.668       120     1000000       0.104
i: 4
   30.0000     0.0002       162.997       155     1000000      -0.049

 Chi-square =       1.78     DF = 3        P-value = 0.6195


   Benchmark Dose Computation

Specified effect =         1e-005

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        1.84039

**** WARNING:  Completion code = -3.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -3 trying new start****

**** WARNING 1:  Completion code = -3 trying new start****

**** WARNING 2:  Completion code = -3 trying new start****

**** WARNING 3:  Completion code = -3 trying new start****

**** WARNING 4:  Completion code = -3 trying new start****

**** WARNING 5:  Completion code = -3 trying new start****
```

```
**** WARNING 6:  Completion code = -3 trying new start****

**** WARNING 7:  Completion code = -3 trying new start****

**** WARNING 8:  Completion code = -3 trying new start****

**** WARNING 9:  Completion code = -3 trying new start****

**** WARNING:  Completion code = -3.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -1 trying new start****

**** WARNING 1:  Completion code = -1 trying new start****

**** WARNING 2:  Completion code = -1 trying new start****

             BMDL =        1.68248

```

```
BARF_MUT_CH.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\BARF_MUT_CH.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\BARF_MUT_CH.plt
                                          Thu Jun 30 12:48:57 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 2.60526e-006
                        Beta(1) = 5.02638e-007


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
         Beta(1)       6.14293e-007        1.93539e-005
```

```
NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -504.191
    Fitted model          -505.38       2.37752      2          0.3046
   Reduced model         -522.575       36.7681      2         <.0001

            AIC:          1012.76


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0     1000000       0.000
i: 2
   20.0000     0.0000        12.286        17     1000000       0.384
i: 3
   50.0000     0.0000        30.714        26     1000000      -0.153

 Chi-square =       2.53     DF = 2        P-value = 0.2819


   Benchmark Dose Computation

Specified effect =         1e-005

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         16.279

**** WARNING:  Completion code = -1.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -1 trying new start****

**** WARNING 1:  Completion code = -1 trying new start****

**** WARNING 2:  Completion code = -1 trying new start****

**** WARNING 3:  Completion code = -1 trying new start****

**** WARNING 4:  Completion code = -1 trying new start****

**** WARNING 5:  Completion code = -1 trying new start****

**** WARNING 6:  Completion code = -1 trying new start****

**** WARNING 7:  Completion code = -1 trying new start****
```

```
**** WARNING 8:  Completion code = -1 trying new start****

**** WARNING 9:  Completion code = -1 trying new start****

**** WARNING:  Completion code = -1.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -3 trying new start****

**** WARNING 1:  Completion code = -3 trying new start****

**** WARNING 2:  Completion code = -3 trying new start****

**** WARNING 3:  Completion code = -3 trying new start****

**** WARNING 4:  Completion code = -3 trying new start****

**** WARNING 5:  Completion code = -3 trying new start****

**** WARNING 6:  Completion code = -3 trying new start****

**** WARNING 7:  Completion code = -3 trying new start****

**** WARNING 8:  Completion code = -3 trying new start****

**** WARNING 9:  Completion code = -3 trying new start****


Warning:  completion code still negative
BMDL did not converge for BMR = 0.000010

Program execution is stopped
```

```
BARF_MUT_FA.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\BARF_MUT_FA.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\BARF_MUT_FA.plt
                                          Thu Jun 30 12:43:11 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =  6.6658e-007
                        Beta(1) = 2.50006e-006


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
         Beta(1)        2.56672e-006        4.49565e-005
```

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-856.204			
Fitted model	-856.255	0.103	2	0.9498
Reduced model	-890.913	69.419	2	<.0001

AIC: 1714.51

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	1000000	0.000
i: 2					
10.0000	0.0000	25.667	27	1000000	0.052
i: 3					
20.0000	0.0001	51.333	50	1000000	-0.026

Chi-square = 0.10 DF = 2 P-value = 0.9494

Benchmark Dose Computation

Specified effect = 1e-005

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.89604

**** WARNING: Completion code = -1. Optimum not found. Trying new starting point****

**** WARNING 0: Completion code = -1 trying new start****

**** WARNING 1: Completion code = -5 trying new start****

BMDL = 0

```
BARF_MUT_TPHEN.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\BARF_MUT_TPHEN.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\BARF_MUT_TPHEN.plt
                                          Thu Jun 30 12:52:56 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 9.99937e-007
                        Beta(1) = 1.74289e-007
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
```

```
         Beta(1)        1.85717e-007        4.42148e-006
         Beta(2)                   0                  NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -755.63
    Fitted model        -755.773        0.2868      3          0.9625
   Reduced model        -781.782       52.3039      3         <.0001

            AIC:         1513.55


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0     1000000       0.000
i: 2
   50.0000     0.0000         9.286        10     1000000       0.077
i: 3
  100.0000     0.0000        18.572        20     1000000       0.077
i: 4
  200.0000     0.0000        37.143        35     1000000      -0.058

 Chi-square =       0.29     DF = 3        P-value = 0.9622


   Benchmark Dose Computation

Specified effect =         1e-005

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        53.8457

**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -2 trying new start****

**** WARNING 1:  Completion code = -2 trying new start****

**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****

**** WARNING 4:  Completion code = -2 trying new start****

**** WARNING 5:  Completion code = -2 trying new start****
```

```
**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -2 trying new start****

**** WARNING 8:  Completion code = -2 trying new start****

**** WARNING 9:  Completion code = -2 trying new start****

**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -2 trying new start****

**** WARNING 1:  Completion code = -5 trying new start****

**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****

**** WARNING 4:  Completion code = -2 trying new start****

**** WARNING 5:  Completion code = -2 trying new start****

**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -5 trying new start****

**** WARNING 8:  Completion code = -2 trying new start****

**** WARNING 9:  Completion code = -5 trying new start****


Warning:  completion code still negative
BMDL did not converge for BMR = 0.000010

Program execution is stopped
```

```
RAVEH_HUB_MUT_BAP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\RAVEH_HUB_MUT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\RAVEH_HUB_MUT_BAP.plt
                                          Wed Jun 29 12:15:41 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =   0.00102082
**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
pont****

**** WARNING 0:  Completion code = -2 trying new start****

**** WARNING 1:  Completion code = -2 trying new start****

**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****

**** WARNING 4:  Completion code = -2 trying new start****

**** WARNING 5:  Completion code = -2 trying new start****

**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -2 trying new start****

**** WARNING 8:  Completion code = -2 trying new start****
```

```
**** WARNING 9:  Completion code = -2 trying new start****

**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -2 trying new start****

**** WARNING 1:  Completion code = -2 trying new start****

**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.71

   Beta(1)        -0.71            1


                         Parameter Estimates

       Variable           Estimate             Std. Err.
     Background         2.6399e-005          0.00257721
        Beta(1)         0.000947187          0.00419869


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model        -1077.99
    Fitted model       -1078.81       1.63811      1          0.2006
   Reduced model       -1144.43        132.88      2         <.0001

           AIC:         2161.62


                    Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         2.640         3      100000       0.136
i: 2
    0.3000     0.0003        31.051        25      100000      -0.195
i: 3
    1.0000     0.0010        97.311       103      100000       0.059

 Chi-square =       1.56     DF = 1        P-value = 0.2115


    Benchmark Dose Computation
```

```
Specified effect =         0.0001

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.105581

             BMDL =      0.0908465
```

```
RAVEH_HUB_MUT_cpcdp.OUT.txt
 ================================================================
        Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\RAVEH_HUB_MUT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\RAVEH_HUB_MUT_BAP.plt
                                          Wed Jun 29 12:09:01 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose)]


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background = 3.49997e-005
                          Slope =  0.000170019
                          Power =            1   Specified


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Power
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background        Slope

Background            1        -0.51

     Slope        -0.51            1



                           Parameter Estimates

       Variable           Estimate             Std. Err.
     Background        3.16959e-005        1.69176e-005
          Slope         0.000173022        4.78826e-005


                        Analysis of Deviance Table

```

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-317.426			
Fitted model	-317.46	0.0679084	1	0.7944
Reduced model	-324.664	14.4766	2	0.0007185

AIC: 638.919

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	3.170	3	100000	-0.09526
0.3000	0.0001	8.360	9	100000	0.2214
1.0000	0.0002	20.470	20	100000	-0.1038

Chi-square = 0.07 DF = 1 P-value = 0.7930

Benchmark Dose Computation

Specified effect = 0.0001

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.577991

BMDL = 0.390507

```
RAVEH_MUT_bap.OUT.txt
 ================================================================
        Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\RAVEH_MUT_CPCDP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\RAVEH_MUT_CPCDP.plt
                                          Wed Jun 29 12:33:35 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose)]


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background = 7.49999e-006
                          Slope = 6.70027e-005
                          Power =            1   Specified


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Power
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

              Background        Slope

Background            1        -0.38

     Slope        -0.38            1


                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background        6.11766e-006        2.23574e-006
           Slope        6.35766e-005        8.04156e-006


                         Analysis of Deviance Table
```

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-1104.33			
Fitted model	-1105.09	1.53413	1	0.2155
Reduced model	-1141.2	73.7415	2	<.0001

AIC: 2214.19

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	6.118	7	1000000	0.3567
0.3000	0.0000	25.190	20	1000000	-1.034
1.0000	0.0001	69.692	74	1000000	0.5161

Chi-square = 1.46 DF = 1 P-value = 0.2264

Benchmark Dose Computation

Specified effect = 1e-005

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.157291

BMDL = 0.12931

```
RAVEH_MUT_CPCDP.OUT.txt
 ================================================================
        Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\RAVEH_MUT_CPCDP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\RAVEH_MUT_CPCDP.plt
                                          Wed Jun 29 12:31:46 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-slope*dose)]


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                  Default Initial (and Specified) Parameter Values
                     Background =     1.5e-006
                          Slope = 9.00013e-006
                          Power =            1   Specified


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Power
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background        Slope

Background            1        -0.43

     Slope        -0.43            1



                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background        1.26496e-006        1.07098e-006
           Slope        9.05599e-006        1.68076e-006


                        Analysis of Deviance Table

```

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-527.507			
Fitted model	-527.666	0.317201	2	0.8533
Reduced model	-546.375	37.7352	3	<.0001

AIC: 1059.33

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	1.265	1	1000000	-0.2356
0.3000	0.0000	3.982	5	1000000	0.5103
1.0000	0.0000	10.321	10	1000000	-0.09989
3.0000	0.0000	28.433	28	1000000	-0.08112

Chi-square = 0.33 DF = 2 P-value = 0.8469

Benchmark Dose Computation

Specified effect = 1e-005

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.10425

BMDL = 0.835597

```
SLAGA_MUT_BAA.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\SLAGA_MUT_BAA.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\SLAGA_MUT_BAA.plt
                                          Thu Jul 07 15:25:30 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 7.29666e-005
                        Beta(1) = 3.12233e-006
**** WARNING:  Completion code = 7.  Optimum not found. Trying new starting
pont****

**** WARNING 0:  Completion code = 7 trying new start****

**** WARNING 1:  Completion code = -2 trying new start****

**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****

**** WARNING 4:  Completion code = 7 trying new start****

**** WARNING 5:  Completion code = -2 trying new start****

**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -2 trying new start****

**** WARNING 8:  Completion code = -2 trying new start****
```

```
**** WARNING 9:  Completion code = 7 trying new start****

**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -2 trying new start****


            Asymptotic Correlation Matrix of Parameter Estimates

              Background      Beta(1)

Background            1        -0.63

   Beta(1)        -0.63            1


                           Parameter Estimates

        Variable           Estimate            Std. Err.
      Background        7.26607e-005          0.0023585
         Beta(1)        3.14129e-006       9.25599e-005


                         Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -365.644
    Fitted model         -365.656     0.0243422      1           0.876
   Reduced model         -370.021       8.75326      2         0.01257

            AIC:          735.312


                      Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0001         7.266         7      100000      -0.037
i: 2
    4.4000     0.0001         8.648         9      100000       0.041
i: 3
   44.0000     0.0002        21.086        21      100000      -0.004

 Chi-square =       0.02     DF = 1        P-value = 0.8758


   Benchmark Dose Computation

Specified effect =         0.0001

Risk Type        =      Extra risk

Confidence level =           0.95
```

```
BMD =        31.8356

BMDL =       19.0163
```

```
SLAGA_MUT_BAP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\SLAGA_MUT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\SLAGA_MUT_BAP.plt
                                          Wed Jun 29 13:01:31 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =  0.000214668
                        Beta(1) =   0.00154564
                        Beta(2) =   0.00022152


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.98

   Beta(2)        -0.98            1



                         Parameter Estimates

```

```
        Variable           Estimate             Std. Err.
      Background                  0                   NA
         Beta(1)          0.00207246            0.0109511
         Beta(2)       9.74689e-005            0.00286413

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.

 Warning: Likelihood for the fitted model larger than the Likelihood for the
full model.
Error in computing chi-square; returning 2


                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -823.498
   Fitted model         -816.691      -13.6145      2               2
  Reduced model         -907.084       167.172      3         <.0001

           AIC:          1637.38


                    Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         1       1000070000000.000
i: 2
    0.4000     0.0008         8.442        11       10000       0.303
i: 3
    1.3000     0.0029        28.548        25       10000      -0.125
i: 4
    4.0000     0.0098        98.010        99       10000       0.010

 Chi-square =       1.23     DF = 2        P-value = 0.5412


   Benchmark Dose Computation

Specified effect =         0.0001

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0481451

            BMDL =      0.0370516
```

D.7. MALIGNANT TRANSFORMATION

```
CASTO_MT_BAP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\CASTO_MT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\CASTO_MT_BAP.plt
                                          Thu Jun 23 13:30:59 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 1.02144e-005
                        Beta(1) = 7.98743e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                           Parameter Estimates

        Variable           Estimate             Std. Err.
```

```
      Background                   0              NA
         Beta(1)       9.62612e-005         0.00234809

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -185.57
    Fitted model        -186.065      0.988828      2          0.6099
   Reduced model         -192.98         14.82      2       0.0006052

           AIC:          374.13


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0      100000       0.000
i: 2
    0.6200     0.0001         5.968         8      100000       0.340
i: 3
    1.2500     0.0001        12.032        10      100000      -0.169

 Chi-square =       1.04     DF = 2        P-value = 0.5960


   Benchmark Dose Computation

Specified effect =         1e-005

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.103885

**** WARNING:  Completion code = -5.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -5 trying new start****

**** WARNING 1:  Completion code = -5 trying new start****

**** WARNING 2:  Completion code = -5 trying new start****

**** WARNING 3:  Completion code = -5 trying new start****

**** WARNING 4:  Completion code = -5 trying new start****

**** WARNING 5:  Completion code = -5 trying new start****

**** WARNING 6:  Completion code = -5 trying new start****
```

```
**** WARNING 7:  Completion code = -5 trying new start****

**** WARNING 8:  Completion code = -5 trying new start****

**** WARNING 9:  Completion code = -5 trying new start****

**** WARNING:  Completion code = -5.  Optimum not found. Trying new starting
point****

            BMDL =      0.0721753

```

```
CASTO_MT_DBAHA.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\CASTO_MT_DBAHA.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\CASTO_MT_DBAHA.plt
                                          Thu Jun 23 13:32:00 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 6.92924e-008
                        Beta(1) = 3.99789e-006
**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
pont****

**** WARNING 0:  Completion code = -2 trying new start****

**** WARNING 1:  Completion code = -2 trying new start****

**** WARNING 2:  Completion code = -2 trying new start****

**** WARNING 3:  Completion code = -2 trying new start****

**** WARNING 4:  Completion code = -2 trying new start****

**** WARNING 5:  Completion code = -2 trying new start****

**** WARNING 6:  Completion code = -2 trying new start****

**** WARNING 7:  Completion code = -2 trying new start****

**** WARNING 8:  Completion code = -2 trying new start****
```

```
**** WARNING 9:  Completion code = -2 trying new start****

**** WARNING:  Completion code = -2.  Optimum not found. Trying new starting
point****



           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1



                         Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
         Beta(1)       4.05407e-006         0.000361631

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -191.16
    Fitted model        -191.162    0.00552866      2          0.9972
   Reduced model        -198.091        13.863      2       0.0009765

           AIC:         384.325


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0     1000000       0.000
i: 2
    1.2000     0.0000         4.865         5     1000000       0.028
i: 3
    2.5000     0.0000        10.135        10     1000000      -0.013

 Chi-square =       0.01     DF = 2        P-value = 0.9972


   Benchmark Dose Computation

Specified effect =         1e-005
```

```
Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        2.46667

**** WARNING:  Completion code = -5.  Optimum not found. Trying new starting
point****

**** WARNING 0:  Completion code = -1 trying new start****

**** WARNING 1:  Completion code = -1 trying new start****

**** WARNING 2:  Completion code = -1 trying new start****

**** WARNING 3:  Completion code = -1 trying new start****

**** WARNING 4:  Completion code = -1 trying new start****

**** WARNING 5:  Completion code = -1 trying new start****

**** WARNING 6:  Completion code = -1 trying new start****

**** WARNING 7:  Completion code = -1 trying new start****

**** WARNING 8:  Completion code = -1 trying new start****

**** WARNING 9:  Completion code = -1 trying new start****

**** WARNING:  Completion code = -1.  Optimum not found. Trying new starting
point****

             BMDL =        1.65901

```

```
EMURA_MT_Baa.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\EMURA_MT_BBF.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\EMURA_MT_BBF.plt
                                          Thu Jun 23 15:46:49 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 6.24839e-005
                        Beta(1) =  0.000973789
                        Beta(2) =           0
                        Beta(3) =           0
                        Beta(4) =           0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
-Beta(4)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                         Parameter Estimates
```

```
        Variable           Estimate            Std. Err.
      Background                  0                  NA
         Beta(1)         0.00117377           0.0091424
         Beta(2)                  0                  NA
         Beta(3)                  0                  NA
         Beta(4)                  0                  NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -184.252
    Fitted model         -185.671       2.83903      5          0.7248
   Reduced model         -196.039        23.575      5        0.000262

            AIC:          373.342


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0       10000       0.000
i: 2
    0.0250     0.0000         0.293         0       10000      -1.000
i: 3
    0.1000     0.0001         1.174         3       10000       1.556
i: 4
    0.2500     0.0003         2.934         3       10000       0.023
i: 5
    0.5000     0.0006         5.867         6       10000       0.023
i: 6
    1.0000     0.0012        11.731        10       10000      -0.148

 Chi-square =       3.40     DF = 5        P-value = 0.6392


    Benchmark Dose Computation

Specified effect =          0.001

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        0.85238
           BMDL =       0.611981
EMURA_MT_BBF.OUT.txt
 ======================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\EMURA_MT_BBF.(d)
```

```
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\EMURA_MT_BBF.plt
                                          Thu Jun 23 15:37:20 2005
 ===============================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 6.48647e-005
                        Beta(1) =   0.00111706
                        Beta(2) =            0
                        Beta(3) = 1.51794e-005
                        Beta(4) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
-Beta(4)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1



                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
         Beta(1)         0.00133391          0.00909075
         Beta(2)                  0                   NA
```

```
         Beta(3)                    0               NA
         Beta(4)                    0               NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -205.838
    Fitted model         -208.019       4.36272      5          0.4985
   Reduced model         -219.575       27.4752      5         <.0001

            AIC:          418.038


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0       10000       0.000
i: 2
    0.0250     0.0000         0.333         0       10000      -1.000
i: 3
    0.1000     0.0001         1.334         4       10000       1.999
i: 4
    0.2500     0.0003         3.334         3       10000      -0.100
i: 5
    0.5000     0.0007         6.667         6       10000      -0.100
i: 6
    1.0000     0.0013        13.330        12       10000      -0.100

 Chi-square =       5.90     DF = 5        P-value = 0.3164


   Benchmark Dose Computation

Specified effect =          0.001

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =       0.750052
             BMDL =        0.54909
```

```
EMURA_MT_I_BAP.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\EMURA_MT_I_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\EMURA_MT_I_BAP.plt
                                          Thu Jun 23 15:28:17 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 6.51885e-005
                        Beta(1) =     0.021934
                        Beta(2) =            0
                        Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                           Parameter Estimates

        Variable           Estimate             Std. Err.
```

```
      Background                  0              NA
         Beta(1)          0.0227293          0.0369378
         Beta(2)                  0              NA
         Beta(3)                  0              NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model        -614.919
     Fitted model       -618.123       6.40862      4          0.1706
    Reduced model       -677.621       125.404      4         <.0001

           AIC:         1238.25


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0       10000       0.000
i: 2
    0.0100     0.0002         2.273         0       10000      -1.000
i: 3
    0.0500     0.0011        11.358        11       10000      -0.032
i: 4
    0.1000     0.0023        22.703        29       10000       0.278
i: 5
    0.2500     0.0057        56.662        53       10000      -0.065

 Chi-square =       4.27     DF = 4        P-value = 0.3703


   Benchmark Dose Computation

Specified effect =          0.001

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =      0.0440182

            BMDL =       0.037291
```

```
EMURA_MT_II_BAP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\EMURA_MT_II_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\EMURA_MT_II_BAP.plt
                                          Thu Jun 23 15:54:16 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0002687
                        Beta(1) =    0.0184676
                        Beta(2) =            0
                        Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1



                           Parameter Estimates

        Variable           Estimate            Std. Err.
```

```
      Background                  0              NA
         Beta(1)           0.021747          0.0381969
         Beta(2)                  0              NA
         Beta(3)                  0              NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model        -606.226
     Fitted model        -608.64       4.82649      4          0.3056
    Reduced model        -652.392      92.3321      4         <.0001

            AIC:         1219.28


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0       10000       0.000
i: 2
    0.0100     0.0002         2.174         4       10000       0.840
i: 3
    0.0500     0.0011        10.868        10       10000      -0.080
i: 4
    0.1000     0.0022        21.723        29       10000       0.336
i: 5
    0.2500     0.0054        54.220        46       10000      -0.152

 Chi-square =       5.30     DF = 4        P-value = 0.2581


   Benchmark Dose Computation

Specified effect =          0.001

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =      0.0460064

             BMDL =      0.0388361
```

```
EMURA_MT_IP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\EMURA_MT_IP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\EMURA_MT_IP.plt
                                          Thu Jun 23 15:50:44 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 7.12074e-005
                        Beta(1) =   0.00099924
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
-Beta(4)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                         Parameter Estimates
```

Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	0.00122714	0.00918598
Beta(2)	0	NA
Beta(3)	0	NA
Beta(4)	0	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-191.591			
Fitted model	-193.089	2.99724	5	0.7004
Reduced model	-203.928	24.6739	5	0.0001611

AIC: 388.178

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	10000	0.000
i: 2					
0.0250	0.0000	0.307	0	10000	-1.000
i: 3					
0.1000	0.0001	1.227	3	10000	1.445
i: 4					
0.2500	0.0003	3.067	3	10000	-0.022
i: 5					
0.5000	0.0006	6.134	7	10000	0.141
i: 6					
1.0000	0.0012	12.264	10	10000	-0.185

Chi-square = 3.41 DF = 5 P-value = 0.6369

Benchmark Dose Computation

Specified effect = 0.001

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.815309
BMDL = 0.589412

```
LUBET_MT_BAP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\LUBET_MT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\LUBET_MT_BAP.plt
                                          Thu Jun 23 16:11:06 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0617408
                        Beta(1) =    0.0378355
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1


                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
```

```
         Beta(1)            0.056828          0.0340172
         Beta(2)                   0                 NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -21.9204
     Fitted model        -22.8416       1.84243      3          0.6057
    Reduced model        -27.0337       10.2266      3         0.01674

            AIC:          47.6832


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          15       0.000
i: 2
    1.0000     0.0552         0.829         1          15       0.219
i: 3
    3.0000     0.1567         2.351         4          15       0.832
i: 4
   10.0000     0.4335         6.503         5          15      -0.408

 Chi-square =       2.02     DF = 3        P-value = 0.5679


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        1.85403

             BMDL =        1.14367
```

```
LUBET_MT_BeP.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\LUBET_MT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\LUBET_MT_BAP.plt
                                          Thu Jun 23 16:14:09 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =  0.000632445
                        Beta(2) = 5.70088e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)           1


                           Parameter Estimates

        Variable           Estimate             Std. Err.
      Background                  0                   NA
```

```
         Beta(1)                    0               NA
         Beta(2)        6.35618e-005        3.53139e-005

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -14.0378
    Fitted model         -14.1501      0.224517      3          0.9735
   Reduced model         -23.5605       19.0453      3       0.0002676

            AIC:          30.3001


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0          15       0.000
i: 2
   10.0000     0.0063         0.095         0          15      -1.006
i: 3
   30.0000     0.0556         0.834         1          15       0.211
i: 4
  100.0000     0.4704         7.056         7          15      -0.015

 Chi-square =       0.13     DF = 3        P-value = 0.9878


    Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        40.7137

             BMDL =        18.2541
```

```
MOHAPATRA_MT_BJAC.txt
================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\_PAH
RPS\MODELING\MOHAPATRA_MT_BJAC.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\_PAH RPS\MODELING\MOHAPATRA_MT_BJAC.plt
                                          Thu Feb 08 10:11:06 2007
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) = 6.31048e+018


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

                Beta(1)      Beta(4)

   Beta(1)            1        -0.73

   Beta(4)        -0.73            1
```

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	2.44509	0.568863
Beta(2)	0	NA
Beta(3)	0	NA
Beta(4)	0.332129	0.778407

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-64.5493			
Fitted model	-64.8387	0.578751	4	0.9654
Reduced model	-198.931	268.764	5	<.0001

AIC: 133.677

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	48	0.000
i: 2					
0.0100	0.0242	1.159	2	48	0.743
i: 3					
0.0500	0.1151	5.524	5	48	-0.107
i: 4					
0.5000	0.7116	34.155	34	48	-0.016
i: 5					
1.0000	0.9378	45.014	45	48	-0.005
i: 6					
2.0000	1.0000	47.998	48	48	1.000

Chi-square = 0.68 DF = 4 P-value = 0.9532

Benchmark Dose Computation

Specified effect = 0.92

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.930952

BMDL = 0.766826

```
MOHAPATRA_MT_BLAC.txt
=====================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\_PAH
RPS\MODELING\MOHAPATRA_MT_BLAC.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\_PAH RPS\MODELING\MOHAPATRA_MT_BLAC.plt
                                          Thu Feb 08 10:13:14 2007
 =====================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0997842
                        Beta(1) =     0.189801
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)    -Beta(3)
-Beta(4)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1


                         Parameter Estimates
```

Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	0.237265	0.0278061
Beta(2)	0	NA
Beta(3)	0	NA
Beta(4)	0	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-159.727			
Fitted model	-161.509	3.56545	5	0.6135
Reduced model	-243.072	166.691	5	<.0001

AIC: 325.019

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0000	0.000	0	60	0.000
i: 2					
0.5000	0.1119	6.712	8	60	0.216
i: 3					
1.0000	0.2112	12.673	14	60	0.133
i: 4					
2.5000	0.4474	26.845	31	60	0.280
i: 5					
5.0000	0.6947	41.679	42	60	0.025
i: 6					
10.0000	0.9068	54.406	51	60	-0.671

Chi-square = 3.91 DF = 5 P-value = 0.5620

Benchmark Dose Computation

Specified effect = 0.83

Risk Type = Extra risk

Confidence level = 0.95

BMD = 7.46828

BMDL = 6.45083

```
MOHAPATRA_MT_BEAC.txt
================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\_PAH
RPS\MODELING\MOHAPATRA_MT_BEAC.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\_PAH RPS\MODELING\MOHAPATRA_MT_BEAC.plt
                                          Fri Feb 09 10:49:12 2007
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0946116
                        Beta(1) =     0.082434
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Beta(2)    -Beta(3)    -Beta(4)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

              Background      Beta(1)

Background            1        -0.68

   Beta(1)        -0.68            1
```

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0246825	0.106613
Beta(1)	0.109348	0.0321778
Beta(2)	0	NA
Beta(3)	0	NA
Beta(4)	0	NA

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-101.226			
Fitted model	-104.24	6.02698	4	0.1971
Reduced model	-126.655	50.8576	5	<.0001

AIC: 212.479

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0247	0.889	0	36	-1.025
i: 2					
0.5000	0.0766	2.757	4	36	0.488
i: 3					
1.0000	0.1257	4.525	6	36	0.373
i: 4					
2.5000	0.2580	9.287	13	36	0.539
i: 5					
5.0000	0.4355	15.676	15	36	-0.076
i: 6					
10.0000	0.6732	24.236	21	36	-0.409

Chi-square = 5.44 DF = 4 P-value = 0.2448

Benchmark Dose Computation

Specified effect = 0.86

Risk Type = Extra risk

Confidence level = 0.95

BMD = 17.9803

BMDL = 12.7064

```
PIENTA_MT_BAA.OUT.txt
 ================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\PIENTA_MT_BAA.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\PIENTA_MT_BAA.plt
                                          Tue Jul 05 13:52:46 2005
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 6
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00472474
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) = 2.31177e-005
                        Beta(4) =            0


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Beta(1)    -Beta(2)    -Beta(3)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

              Background      Beta(4)

Background            1        -0.43

   Beta(4)        -0.43            1
```

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.00480466	0.0290234
Beta(1)	0	NA
Beta(2)	0	NA
Beta(3)	0	NA
Beta(4)	2.25394e-006	6.9765e-006

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-67.8785			
Fitted model	-69.9491	4.14115	4	0.3872
Reduced model	-74.327	12.8971	5	0.02436

AIC: 143.898

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0048	1.100	0	229	-1.005
i: 2					
0.1000	0.0048	1.081	1	225	-0.075
i: 3					
0.5000	0.0048	1.211	2	252	0.655
i: 4					
1.0000	0.0048	0.928	2	193	1.161
i: 5					
5.0000	0.0062	1.936	1	312	-0.487
i: 6					
10.0000	0.0270	6.746	7	250	0.039

Chi-square = 3.34 DF = 4 P-value = 0.5028

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 8.17165

**** WARNING: Completion code = -2. Optimum not found. Trying new starting point****

BMDL = 4.47767

```
PIENTA_MT_BAP.OUT.txt
 ========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\PIENTA_MT_BAP.(d)
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\PIENTA_MT_BAP.plt
                                          Mon Jun 27 16:28:28 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 5
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 0
 Degree of polynomial = 4


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00129459
                        Beta(1) =   0.00056154
                        Beta(2) =            0
                        Beta(3) =            0
                        Beta(4) =            0


            Asymptotic Correlation Matrix of Parameter Estimates

            ( *** The model parameter(s)  -Beta(2)    -Beta(3)    -Beta(4)
                  have been estimated at a boundary point, or have been
specified by the user,
                  and do not appear in the correlation matrix )

              Background      Beta(1)

Background            1        -0.72

   Beta(1)        -0.72            1
```

```
                          Parameter Estimates

        Variable           Estimate            Std. Err.
      Background         0.000529694           0.0310484
         Beta(1)         0.000662444          0.00321227
         Beta(2)                   0                  NA
         Beta(3)                   0                  NA
         Beta(4)                   0                  NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.



                        Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model        -64.5099
     Fitted model       -65.0987       1.17762      3          0.7584
    Reduced model        -68.985       8.95024      4         0.06236

            AIC:         134.197


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
   ----------------------------------------------------------------------
i: 1
    0.0000     0.0005         0.267         0         504      -1.001
i: 2
    1.0000     0.0012         0.468         1         393       1.137
i: 3
    5.0000     0.0038         1.557         2         406       0.286
i: 4
   10.0000     0.0071         3.094         3         434      -0.031
i: 5
   20.0000     0.0137         5.611         5         410      -0.110

 Chi-square =       1.07     DF = 3        P-value = 0.7847


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        15.1716

            BMDL =        8.76437
PIENTA_MT_DBAHA.OUT.txt
 ======================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\PIENTA_MT_DBAHA.(d)
```

```
        Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY
DOCUMENTS\PAH RPS\MODELING\PIENTA_MT_DBAHA.plt
                                          Mon Jun 27 16:35:08 2005
 ===============================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN2
   Independent variable = COLUMN1

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =  0.000660992
                        Beta(1) =     0.020798
                        Beta(2) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)           1



                          Parameter Estimates

        Variable           Estimate            Std. Err.
      Background                  0                 NA
         Beta(1)          0.0227021           0.0618036
         Beta(2)                  0                 NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
```

```
      has no standard error.


                          Analysis of Deviance Table

        Model      Log(likelihood)  Deviance  Test DF     P-value
      Full model         -40.1618
    Fitted model         -41.0551       1.78665      3          0.6178
   Reduced model         -45.7301       11.1367      3         0.01101

            AIC:          84.1102


                     Goodness  of  Fit

      Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ------------------------------------------------------------------------
i: 1
    0.0000     0.0000         0.000         0         229       0.000
i: 2
    0.1000     0.0023         0.497         0         219      -1.002
i: 3
    0.5000     0.0113         2.630         4         233       0.527
i: 4
    1.0000     0.0224         4.871         4         217      -0.183

 Chi-square =       1.38     DF = 3        P-value = 0.7105


   Benchmark Dose Computation

Specified effect =           0.01

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.442705

            BMDL =       0.260515
```

D.8. IN VITRO DNA DAMAGE

```
JOHNSEN_DNA_DAM_BJAC.OUT.txt
 ========================================================================
         Polynomial Model. Revision: 2.2  Date: 9/12/2002
         Input Data File: C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\JOHNSEN_DNA_DAM_BAP.(d)
         Gnuplot Plotting File:  C:\DOCUMENTS AND SETTINGS\HCLYNCH\MY DOCUMENTS\PAH
RPS\MODELING\JOHNSEN_DNA_DAM_BAP.plt
                                                  Mon Jul 04 21:51:27 2005
 ========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = MEAN
   Independent variable = COLUMN1
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                         alpha =      5.88667
                           rho =            0   Specified
                        beta_0 =      4.94396
                        beta_1 =     0.150549


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          4.14606          1.95447           0.315366             7.97675
        beta_0          4.94396         0.875754            3.22751              6.6604
        beta_1         0.150549        0.0503107          0.0519422            0.249157


           Asymptotic Correlation Matrix of Parameter Estimates

                  alpha       beta_0       beta_1
    alpha             1     7.6e-015     1.7e-015
   beta_0     7.6e-015            1        -0.63
   beta_1     1.7e-015        -0.63            1


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean    Obs Std Dev   Est Mean   Est Std Dev   Chi^2
Res.
------     ---   --------    -----------   --------   -----------   ----------

    0     3        4.4          1.3         4.94         2.04         -0.463
    3     3          6          2.1          5.4         2.04          0.514
   30     3        9.4          3.4         9.46         2.04        -0.0514


  Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
```

```
            Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = Sigma(i)^2

 Model  R:         Yi = Mu + e(i)
             Var{e(i)} = Sigma^2


                        Likelihoods of Interest

             Model      Log(likelihood)   DF        AIC
              A1          -10.652512       4      29.305023
              A2           -9.359638       6      30.719276
            fitted        -10.899709       2      25.799418
               R          -14.037484       2      32.074967

 Test 1:  Does response and/or variances differ among dose
levels
           (A2 vs. R)
 Test 2:  Are Variances Homogeneous (A1 vs A2)
 Test 3:  Does the Model for the Mean Fit (A1 vs. fitted)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df     p-value

   Test 1              9.35569          4        0.009299
   Test 2              2.58575          2          0.2745
   Test 3             0.494395          1           0.482

The p-value for Test 1 is less than .05.  There appears
to be a
difference between response and/or variances among the
dose levels.
It seems appropriate to model the data

The p-value for Test 2 is greater than .05.  A
homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .05.  The model
chosen appears
to adequately describe the data



 Benchmark Dose Computation
Specified effect =           7.6

Risk Type        =     Point risk

Confidence level =          0.95

              BMD =       17.6423


              BMDL =       9.58925
```

APPENDIX E. CALCULATION OF RPFs

Table E-1. Dermal bioassays: RPF calculations for incidence data

Record number	Reference	Tumor type(s)	Sex	PAH	Relative potency calculation								
					BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
Complete carcinogenicity studies													
600	Habs et al., 1980	Sum of Papilloma, carcinoma, sarcoma	F	BaP			0.24	1.7	µg/animal			1	No model fit; lowest statistically significant point used
			F	BbF	0.24	6.05			µg/animal			0.28	
13640	Cavalieri et al., 1983	Papilloma, adenoma, carcinoma	F	BaP	0.1	5.3			nmol	0.001	mg	1	
			F	CPcdP	0.1	47			nmol	0.011	mg	0.13	
620	Hoffmann and Wynder, 1966	Papilloma	F	BaP	0.1	0.0031			%			1	
			F	DBaeP	0.1	0.0094			%			0.33	Toxicity resulted in significant mortality unrelated to tumor induction
			F	DBaiP	0.1	0.0042			%			0.74	
			F	DBaeF	0.1	0.0028			%			1.1	
17660	Cavalieri et al., 1977	Papilloma, kerato-acanthoma, carcinoma	F	BaP			0.79	0.396	µmol/ application	0.100	mg/ application	1	
			F	AA			0.47	0.396	µmol/ application	0.109	mg/ application	0.55	
Initiation studies													
630	LaVoie et al., 1982	Primarily squamous cell papilloma	F	BaP			0.85	30	µg/animal			1	
			F	BbF			0.8	100	µg/animal			0.28	No model fit; point estimate using incidence/ dose point closest to BaP incidence
			F	BjF			0.95	1,000	µg/animal			0.03	No model fit; point estimate using incidence/dose point closest to BaP incidence

Table E-1. Dermal bioassays: RPF calculations for incidence data

Record number	Reference	Tumor type(s)	Sex	PAH	Relative potency calculation								
					BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
			F	BkF	0.85	1,163			µg/animal			0.03	
18570	Hecht et al., 1974	Unspecified	F	BaP			0.3	0.05	mg/animal			1	
			F	CH			0.58	1	mg/animal			0.10	
21420	Slaga et al., 1980	Papilloma	F	BaP			0.64	200	nmol	0.050	mg	1	
			F	CH			0.71	2,000	nmol	0.457	mg	0.12	Not clear if BaP administered simultaneously; control groups pooled for analysis
			F	DBahA			0.45	100	nmol	0.028	mg	1.27	
15640	Raveh et al., 1982	Papilloma	F	BaP	0.1	2.2			µg			1	
			F	CPcdP	0.1	30			µg			0.07	
620	Hoffmann and Wynder, 1966	Papilloma	F	BaP			0.79	0.25	mg/animal			1	
			F	DBaeF			0.57	0.25	mg/animal			0.73	
			F	DBaeP			0.33	0.25	mg/animal			0.41	
			F	DBahP			0.7	0.25	mg/animal			0.90	
			F	DBaiP			0.36	0.25	mg/animal			0.45	
			F	N23eP			0.25	0.25	mg/animal			0.32	
13650	Cavalieri et al., 1981b	Papilloma	F	BaP			0.33	0.2	µmol	0.050	mg	1	
			F	CPcdP			0.23	0.6	µmol	0.136	mg	0.26	Mid dose borderline significant, high dose not, trend not; no model fit; RPF uses mid dose for point estimate
15700	Rice et al., 1988	Unspecified	F	BaP			0.88	0.1	µmol	0.025	mg	1	
			F	CH			0.89	0.5	µmol	0.114	mg	0.22	No model fit; point estimate using point closest to BaP incidence
			F	CPdefC	0.88	0.22			µmol	0.053	mg	0.47	
			F	BbcAC			0.89	2	µmol	0.481	mg	0.05	No model fit; point estimate using point closest to BaP incidence

Table E-1. Dermal bioassays: RPF calculations for incidence data

Record number	Reference	Tumor type(s)	Sex	PAH	Relative potency calculation								
					BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
24800	Nesnow et al., 1984	Papilloma	M	BaP			0.67	200	nmol	0.050	mg	1	
			M	BeAC			0.60	250	nmol	0.063	mg	0.71	No model fit; point estimate using point closest to BaP incidence
			M	BlAC	0.67	50			nmol	0.013	mg	4.00	Three high doses dropped due to plateau
			F	BaP			0.51	200	nmol	0.050	mg	1	
			F	BeAC	0.51	228			nmol	0.058	mg	0.88	Two high doses dropped to achieve model fit
			F	BlAC	0.51	30			nmol	0.008	mg	6.67	Three high doses dropped to achieve model fit

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Table E-2. Dermal bioassays: RPF calculations for multiplicity data

Record number	Reference	Tumor type(s)	Sex	PAH	Relative potency calculation						
					Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
Complete carcinogenicity studies											
13640	Cavalieri et al., 1983	Papilloma, adenoma, carcinoma	F	BaP	1.5	20	nmol	0.0050	mg	1	Variance not reported
			F	CPcdP	2.5	200	nmol	0.045	mg	0.18	Variance not reported
13650	Cavalieri et al., 1981b	Primarily squamous cell carcinoma	US	BaP	1.5	0.2	µmol	0.050	mg	1	
			US	CPcdP	0.80	0.2	µmol	0.045	mg	0.59	Variance not reported
Initiation studies											
630	LaVoie et al., 1982	Primarily squamous cell papilloma	F	BaP	4.9	30	µg			1	
			F	BbF	7.1	100	µg			0.43	Variance not reported
			F	BjF	7.2	1,000	µg			0.044	Variance not reported
			F	BkF	2.8	1,000	µg			0.017	Variance not reported
18570	Hecht et al., 1974	Unspecified	F	BaP	0.5	0.05	mg			1	
			F	CH	1.0	1	mg			0.10	
21420	Slaga et al., 1980	Papilloma	F	BaP	2.1	200	nmol	0.050	mg	1	
			F	CH	1.5	2,000	nmol	0.46	mg	0.078	
			F	DBahA	1.3	100	nmol	0.028	mg	1.1	
15640	Raveh et al., 1982	Papilloma	F	BaP	1.1	10	µg			1	Variance not reported
			F	CPcdP	0.7	200	µg			0.032	Variance not reported
13650	Cavalieri et al., 1981	Papilloma	F	BaP	1.1	0.2	µmol	0.050	mg	1	
			F	CPcdP	0.17	0.6	µmol	0.14	mg	0.060	Variance not reported
21410	Slaga et al., 1978	Papilloma	F	BaP	5.2	0.2	µmol	0.050	mg	1	
			F	BaA	1.1	2	µmol	0.46	mg	0.023	
16310	Weyand et al., 1992	Unspecified	US	BaP	4.0	0.01	µmol	0.0025	mg	1	
			US	BjF	4.0	1	µmol	0.252	mg	0.010	Variance not reported
10200	El-Bayoumy et al., 1982	Primarily squamous cell papilloma	F	BaP	7.0	0.05	mg			1	
			F	CH	7.6	1	mg			0.054	
24300	Rice et al., 1985	Unspecified	F	BaP	7.9	0.3	mg			1	
			F	CH	4.9	1	mg			0.18	
			F	CPdefC	5.5	1	mg			0.21	
13660	Cavalieri et al., 1991	Primarily papilloma	F	BaP Expt I	5.2	300	nmol	0.0757	mg	1	16 Wk experiment; variance not reported
			F	DBalP Expt I	6.8	33.3	nmol	0.010	mg	9.7	
13660	Cavalieri et al., 1991	Primarily papilloma	F	BaP Expt II	3.4	100	nmol	0.0252	mg	1	27 Wk experiment; variance not reported
			F	DBalP Expt II	7.0	4	nmol	0.0012	mg	42	
24800	Nesnow et al., 1984	Papilloma	M	BaP	1.4	200	nmol	0.050	mg	1	Variance not reported
			M	BeAC	1.3	250	nmol	0.063	mg	0.74	Variance not reported
			M	BlAC	1.4	50	nmol	0.013	mg	4.0	Variance not reported
			F	BaP	1.5	200	nmol	0.050	mg	1	Variance not reported
			F	BeAC	1.1	250	nmol	0.063	mg	0.58	Variance not reported
			F	BlAC	1.1	50	nmol	0.013	mg	2.9	Variance not reported

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Table E-3. Intraperitoneal bioassays: RPF calculations for incidence data

Record number	Reference	Target organ	Tumor type(s)	Sex	PAH	Relative potency calculation								
						BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
17560	Busby et al., 1989	Lung	Adenoma, adenocarcinoma	F	BaP			0.68	59.5	µg			1	
					FA			0.26	257.6	µg			0.09	
640	LaVoie et al., 1987	Lung	Adenoma	M	BaP			0.82	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					BjF			0.52	1.1	µmol/ mouse	0.28	mg/ mouse	0.64	Do not use: use liver or lung RPF below
				F	BaP			0.64	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					BjF			0.22	1.1	umol/ mouse	0.28	mg/ mouse	0.35	Do not use: use liver or lung RPF below
		Liver	Adenoma, hepatoma	M	BaP			0.75	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					BbF			0.5	0.5	µmol/ mouse	0.13	mg/ mouse	1.50	Do not use: use liver or lung RPF below
					BjF			0.49	1.1	µmol/ mouse	0.28	mg/ mouse	0.66	Do not use: use liver or lung RPF below
		Liver or lung	Adenoma, hepatoma	M	BaP			0.75	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					BbF			0.51	0.5	µmol/ mouse	0.13	mg/ mouse	1.50	
					BjF			0.8	1.1	µmol/ mouse	0.28	mg/ mouse	1.10	
				F	BaP			0.64	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					BjF			0.22	1.1	µmol/ mouse	0.28	mg/ mouse	0.35	
7510	LaVoie et al., 1994	Lung	Total	M	BaP			0.7	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					FA	0.7	22			µmol/ mouse	4.45	mg/ mouse	0.06	Do not use: male liver RPF is higher

Table E-3. Intraperitoneal bioassays: RPF calculations for incidence data

Record number	Reference	Target organ	Tumor type(s)	Sex	PAH	Relative potency calculation								
						BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
				F	BaP			0.83	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					FA	0.83	17			µmol/ mouse	3.44	mg/ mouse	0.08	
		Liver	Foci, adenoma, carcinoma	M	BaP			0.81	1.1	µmol/ mouse	0.28	mg/ mouse	1	
					FA	0.81	6.4			µmol/ mouse	1.29	mg/ mouse	0.21	
24590	Nesnow et al., 1998	Lung	NS	M	BaP	0.1	8.35			mg/kg			1	
					BbF	0.1	5.68			mg/kg			1.47	
					CPcdP	0.1	8.65			mg/kg			0.97	
					DBahA	0.1	0.23			mg/kg			36	
					DBalP	0.1	0.29			mg/kg			29	
24801	Weyand et al., 2004	Lung	Adenoma	F	BaP			0.81	100	mg/kg bw			1	
					BcFE			0.85	100	mg/kg bw			1.05	
22510	Wislocki et al., 1986	Liver	Adenoma, carcinoma	M	BaP			0.44	560	nmol	0.14	mg	1	
					CH	0.44	3,339			nmol	0.76	mg	0.19	Using pooled controls
					BaA			0.77	2,800	nmol	0.64	mg	0.39	
		Lung	Unspecified	M	BaP			0.3	560	nmol	0.14	mg	1	
					CH	0.3	5,601			nmol	1.28	mg	0.11	Do not use: male liver RPF is higher; using pooled controls
				F	BaP			0.46	560	nmol	0.14	mg	1	
					BaA			0.16	2,800	nmol	0.64	mg	0.08	

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Table E-4. Intraperitoneal bioassays: RPF calculations for multiplicity data

Record number	Reference	Target organ(s)	Tumor type(s)	Sex	PAH	RPF Calculation								
						BMR	BMD	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
17560	Busby et al., 1989	Lung	Adenoma, adenocarcinoma	F	BaP			1.11	59.5	µg			1	
					FA			0.33	257.6	µg			0.069	
7510	LaVoie et al., 1994	Lung	Total	M	BaP			4.13	1.1	µmol	0.28	mg	1	
					FA			0.95	17.30	µmol	3.50	mg	0.018	Do not use: male liver RPF is higher
				F	BaP			3.40	1.1	µmol	0.28	mg	1	
					FA			2.30	17.30	µmol	3.50	mg	0.054	
		Liver	Foci, adenoma, carcinoma	M	BaP			4.12	1.1	µmol	0.28	mg	1	
					FA			1.45	3.46	µmol	0.700	mg	0.14	
22510	Wislocki et al., 1986	Liver	Adenoma, carcinoma	M	BaP			1.36	560	nmol	0.141	mg	1	
					CH			0.93	2,800	nmol	0.639	mg	0.15	Using pooled controls
					BaA			2.28	2,800	nmol	0.639	mg	0.37	
13610	Busby et al., 1984	Lung	Adenoma, carcinoma	M	BaP			4.28	0.28	mg			1	No model fit
					FA	4.28	9.99			mg			0.028	
				F	BaP			3.56	0.28	mg			1	No model fit
					FA	3.56	32.28			mg			0.0086	
24590	Nesnow et al., 1998b	Lung	Not specified	M	BaP			3.85	50	mg/kg			1	No model fit
					BbF	3.85	123			mg/kg			0.41	BMR = BaP response
					CPcdP			4.15	50	mg/kg			1.1	No model fit
					DBahA	3.85	3.57			mg/kg			14	BMR = BaP response
					DBalP			3.66	1.5	mg/kg			32	No model fit These data from Record 8180 Prahalad 1987 but use BaP data from Record 24590

Table E-4. Intraperitoneal bioassays: RPF calculations for multiplicity data

Record number	Reference	Target organ(s)	Tumor type(s)	Sex	PAH	RPF Calculation								
						BMR	BMD	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
11190	Mass et al., 1993	Lung	Not specified	M	BaP			5.05	100	mg/kg			1	No model fit
					BjAC			59.45	20	mg/kg			59	No model fit
24801	Weyand et al., 2004	Lung	Adenoma	F	BaP			6.1	100	mg/kg bw			1	
					BcFE			3.4	100	mg/kg bw			0.56	

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Table E-5. Lung implantation bioassays: RPF calculations (incidence data)

Record number	Reference	Target organ(s)	Tumor type(s)	PAH	Relative potency calculation						
					BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	RPF	Comments
17940	Deutsch-Wenzel et al., 1983	Lung	Sum carcinoma + sarcoma	BaP	0.1	0.032			mg	1	
				AA	0.1	0.14			mg	0.24	
				BbF	0.1	0.33			mg	0.10	
				BghiP	0.1	3.5			mg	0.0092	
				BjF	0.1	1.0			mg	0.032	
				BkF	0.1	1.1			mg	0.031	
				IP	0.1	0.44			mg	0.074	
22000	Wenzel-Hartung et al., 1990	Lung	Carcinoma	BaP	0.1	0.033			mg/ animal	1	
				CH	0.1	0.85			mg/ animal	0.038	
				BaP	0.57	0.20			mg/ animal	1	
				DBahA			0.57	0.1	mg/ animal	2.0	Single dose

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Table E-6. Oral bioassays: RPF calculations (incidence and multiplicity data)

Record number	Reference	Target organ	Tumor and data type	PAH	Relative potency calculation						
					BMR	BMD	Point estimate extra risk response	Point estimate dose	Dose units	RPF	Comments
24801	Weyand et al., 2004	Lung	Adenoma incidence	BaP			0.7	230	µg/mouse/day	1	
				BcFE	0.7	42			µg/mouse/day	5.48	
24801	Weyand et al., 2004	Lung	Adenoma multiplicity	BaP			1.09	230	µg/mouse/day	1	
				BcFE			45.69	197	µg/mouse/day	48.9	No model fit

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Table E-7. In vivo DNA adducts: RPF calculations

Record number	Reference	Target organ(s)/route	PAH	Relative potency calculation								
				AUC	AUC versus dose	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
6210	Arif et al., 1997	Sum of adducts in mammary gland, lung, heart, pancreas, bladder, liver	BaP			325	0.25	µmol/ mammary gland	0.063	mg/ mammary gland	1	
			DBalP			2,245	0.25	µmol/ mammary gland	0.076	mg/mammary gland	5.8	
17630	Cavalieri et al., 1981a	Skin 4-hr	BaP			16	0.2	µmol/animal	0.050	mg/animal	1	Higher of two values measured at 4 hrs
			ACEP			2.2	0.2	µmol/animal	0.046	mg/animal	0.15	Higher of two values measured at 4 hrs
			CPcdP			8.8	0.2	µmol/animal	0.045	mg/animal	0.61	Higher of two values measured at 24 hrs
18810	Hughes and Phillips, 1990	Sum of skin and lung	BaP			9	1	µmol	0.25	mg	1	RPFs based on peaks; digitizing not possible; peaks reached at different times postdosing
			DBaeP			Cannot determine	1	µmol			NA	
			DBahP			3.2	1	µmol	0.30	mg	0.30	
			DBaiP			0.85	1	µmol	0.30	mg	0.079	
			DBalP			65	1	µmol	0.30	mg	6.0	
11190	Mass et al., 1993	Lung	BaP		470			mg/kg			1	
			BjAC		464			mg/kg			0.99	Ratio of slopes of AUC versus dose; BjAC plot shows curvature
8010	Nesnow et al., 1993b	Total of lung, liver, and peripheral blood lymphocytes	BaP	52,084			100	mg/kg			1	
			BbF	11,314			100	mg/kg			0.22	Ratio of (sum of AUCs)/dose

Table E-7. In vivo DNA adducts: RPF calculations

Record number	Reference	Target organ(s)/route	PAH	Relative potency calculation								
				AUC	AUC versus dose	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
24590	Nesnow et al., 1998b	Lung	BaP		113			mg/kg			1	Ratio of slopes of AUC versus dose as reported by authors
			BbF		38			mg/kg			0.33	
			CPcdP		148			mg/kg			1.3	
			DBahA		219			mg/kg			1.9	
			DBalP		1,390			mg/kg			12	
22810	Phillips et al., 1979	Skin	BaP			27	1	µmol/animal	0.25	mg/animal	1	Ratio of peak levels; peaks reached at different times
			DBacA			10	1	µmol/animal	0.28	mg/animal	0.34	
			DBahA			15	1	µmol/animal	0.28	mg/animal	0.50	
24790	Kligerman et al., 2002	Mouse peripheral blood lymphocytes/ intraperitoneal	BaP			4,186	100	mg/kg			1	Ratio of single measure on d 7 postdosing
			BaA			93	100	mg/kg			0.022	
			BbF			516	100	mg/kg			0.12	
			CH			81	100	mg/kg			0.019	
		Mouse peripheral blood lymphocytes/ gavage	BaP			143	100	mg/kg			1	
			BaA			32	100	mg/kg			0.22	
			BbF			39	100	mg/kg			0.27	
			CH			37	100	mg/kg			0.26	
		Rat peripheral blood lymphocytes/ intraperitoneal	BaP			755	100	mg/kg			1	
			BaA			38	100	mg/kg			0.05	
			BbF			63	100	mg/kg			0.083	
			CH			24	100	mg/kg			0.032	
		Rat peripheral blood lymphocytes/ gavage	BaP			177	100	mg/kg			1	
			BaA			20	100	mg/kg			0.11	
			BbF			17	100	mg/kg			0.1	
			CH			10	100	mg/kg			0.056	

Table E-7. In vivo DNA adducts: RPF calculations

Record number	Reference	Target organ(s)/route	PAH	Relative potency calculation								
				AUC	AUC versus dose	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
24801	Weyand et al., 2004	Sum of adducts in lung amd forestomach/diet	BaP			0.117	230	mg/kg food			1	
			BcFE			0.191	197	mg/kg food			1.9	
		Lung/ intraperitoneal	BaP			0.776	100	mg/kg bw			1	
			BcFE			0.333	100	mg/kg bw			0.43	

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Table E-8. In vivo clastogenicity or sister chromatid exchange: RPF calculation

Record number	Reference	Route	Endpoint	Data type: quantal or continuous	PAH	Relative potency calculation						
						BMR	BMD	Point estimate response	Point estimate dose	Dose units	RPF	Comments
24740	Allen et al., 1999	Intraperitoneal	MN-PCEs in bone marrow (A/J mouse)	Q	BaP			0.0086	200	mg/kg	1	
					DBalP			0.0013	1.5	mg/kg	20	Model won't predict BaP BMR; RPF based on peak
		Intraperitoneal	MN-PCEs in peripheral blood (A/J mouse)	Q	BaP			0.0067	200	mg/kg	1	
					DBalP			0.0015	6	mg/kg	7.5	Model won't predict BaP BMR; RPF based on peak
		Intraperitoneal	MN-PCEs in bone marrow (p53 wt mouse)	Q	BaP			0.0019	200	mg/kg	1	
					DBalP			0.0042	12	mg/kg	37	Model won't predict BaP BMR; RPF based on peak
		Intraperitoneal	MN-PCEs in peripheral blood (p53 wt mouse)	Q	BaP			0.0022	200	mg/kg	1	
					DBalP			0.0011	18	mg/kg	5.6	BMD doesn't reflect selected BMR; RPF based on peak
14270	He and Baker, 1991	Dermal	Micronuclei	Q	BaP			0.064	50	µg/animal	1	No model fit; RPF based on peak
					CH			0.05	500	µg/animal	0.078	No model fit; RPF based on peak
17190	Bayer, 1978	Intraperitoneal	Sister chromatid exchanges	C	BaP			4.2	100	mg/kg	1	No model fit; RPF based on peak
					PH			0.9	100	mg/kg	0.21	No model fit; RPF based on peak
20950	Roszinsky-Kocher et al., 1979	Intraperitoneal	Sister chromatid exchanges	C	BaP			6.7	900	mg/kg	1	
					DBahA			1	900	mg/kg	0.15	
					CH			1.2	900	mg/kg	0.18	
					PH			1.6	900	mg/kg	0.24	
					BeP			1.6	900	mg/kg	0.24	
					BbF			1.7	900	mg/kg	0.25	

Table E-8. In vivo clastogenicity or sister chromatid exchange: RPF calculation

Record number	Reference	Route	Endpoint	Data type: quantal or continuous	PAH	Relative potency calculation						
						BMR	BMD	Point estimate response	Point estimate dose	Dose units	RPF	Comments
					BaA			2.2	900	mg/kg	0.33	
24720	Kligerman et al., 1986	Gavage	Sister chromatid exchanges	C	BaP			8	63	mg/kg	1	No SD for control
					BlAC			16	126	mg/kg	1.1	No SD for control; RPF based on lowest dose approaching peak
24790	Kligerman et al., 2002	Intraperitoneal	Sister chromatid exchanges	C	BaP			12.42	100	mg/kg	1	
					BaA			6.01	100	mg/kg	0.48	
					BbF			13.46	100	mg/kg	1.1	
					CH			3.17	100	mg/kg	0.26	
		Gavage	Sister chromatid exchanges	C	BaP			6.79	100	mg/kg	1	
					BaA			2.26	100	mg/kg	0.33	
		Gavage	Micronuclei	Q	BaP			0.0025	100	mg/kg	1	
					BbF			0.0017	100	mg/kg	0.68	

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Table E-9. In vitro bacterial mutagenicity: RPF calculations

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Slope	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
17030	Andrews et al., 1978	BaP	C				1,531	250	µg			1	
		DBacA	C				2,807	10	µg			46	
		DBajA	C				693	10	µg			11	
		DBahA	C				467	25	µg			3	
		AA	C				1,645	250	µg			1.1	
		BghiP	C				642	100	µg			1	
		BeP	C				492	1,000	µg			0.08	
23830	Baker et al., 1980	BaP	C				1,144	2.5	µg/plate			1	
		DBaiP	C				603	5	µg/plate			0.26	
		BaA	C				813	10	µg/plate			0.18	
		DBacA	C				1,604	2.5	µg/plate			1.4	
		DBahA	C				1,197	5	µg/plate			0.52	
23660	Bartsch et al., 1980	BaP	C				29,000	0.027	µmol/plate	0.007	mg/plate	1	
		BaA	C				6,000	0.067	µmol/plate	0.015	mg/plate	0.092	
17380	Bos et al., 1988	BaP	C				739	7.5	µg/plate			1	RPF based on peak response; BaP response well above range for other data sets; model fit required dropping high doses but not appropriate given BMR target
		PH	C				155	25	µg/plate			0.063	
		Pyr	C				193	25	µg/plate			0.078	
17590	Carver et al., 1986	BaP	C				895	50	µg/plate			1	Continuous data, no SD; RPF based on peak or lowest dose approaching peak
		BaA	C				1,123	50	µg/plate			1.3	
		BghiF	C				845	50	µg/plate			0.94	
		Pery	C				853	10	µg/plate			4.8	Uses S9 level with max BaP response; max Pery response at a different S9
17630	Cavalieri et al., 1981a	BaP	Q				0.00126	60	µM	15.1	mg/L	1	RPF based on peak; no model fit
		CPcdP	Q				0.0013	40	µM	9.1	mg/L	1.7	RPF based on peak; no model fit

Table E-9. In vitro bacterial mutagenicity: RPF calculations

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Slope	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
		ACEP	Q				0.0005	120	µM	27.4	mg/L	0.22	RPF based on peak; BMD doesn't coincide with selected BMR
9620	Chang et al., 2002	BaP	C				2,217	5	µg/plate			1	Continuous data, no SD; RPF based on peak or lowest dose approaching peak
		BghiF	C				1,304	5	µg/plate			0.59	
		BcPH	C				717	10	µg/plate			0.16	
24030	De Flora et al., 1984	BaP	NA			185			revertants/nmol	733,196	revertants/mg	1	RPFs based on potency estimates as reported by authors
		BaA	NA			12			revertants/nmol	52,565	revertants/mg	0.072	
		BeP	NA			1.6			revertants/nmol	6,341	revertants/mg	0.009	
		Pery	NA			21			revertants/nmol	83,229	revertants/mg	0.11	
18050	Eisenstadt and Gold, 1978	BaP	C				1,705	2	µg			1	Uses S9 level with max BaP response; CPcdP max at much lower S9
		CPcdP	C				134	1	µg			0.16	
18180	Florin et al., 1980	BaP	C				255	0.003	µmol/plate	0.001	mg/plate	1	TA100
		BaA	C				326	0.1	µmol/plate	0.023	mg/plate	0.042	
		CH	C				196	0.005	µmol/plate	0.001	mg/plate	0.51	
		BaP	C				235	0.003	µmol/plate	0.001	mg/plate	1	TA 98
		CO	C				82	0.07	µmol/plate	0.021	mg/plate	0.013	
		Pery	C				91	0.025	µmol/plate	0.006	mg/plate	0.046	
24080	Gibson et al., 1978	BaP	C				35	300	µg/plate			1	Continuous data, no SD; RPF based on peak or lowest dose approaching peak; metabolic activation by gamma radiation
		BaA	C				6.4	250	µg/plate			0.22	
		BghiP	C				4.2	400	µg/plate			0.090	
		CH	C				6.1	500	µg/plate			0.1	Lowest dose approaching peak
		FE	C				2.2	360	µg/plate			0.052	
		Pyr	C				28	160	µg/plate			1.5	

Table E-9. In vitro bacterial mutagenicity: RPF calculations

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Slope	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
14080	Gold and Eisenstadt, 1980	BaP	C				1,103	4	nmol	0.001	mg	1	
		CPcdP	C				281	4	nmol	0.001	mg	0.28	
18650	Hermann, 1981	BaP	NA			100			revertants/nmol	396,322	revertants/mg	1	RPFs based on potency estimates as reported by authors
		AA	NA			62			revertants/nmol	224,394	revertants/mg	0.57	
		BaA	NA			4			revertants/nmol	17,522	revertants/mg	0.044	
		BbA	NA			8			revertants/nmol	35,043	revertants/mg	0.088	
		BbF	NA			15			revertants/nmol	59,448	revertants/mg	0.15	
		BeP	NA			15			revertants/nmol	59,449	revertants/mg	0.15	
		CH	NA			2			revertants/nmol	8,761	revertants/mg	0.022	
		CO	NA			60			revertants/nmol	199,761	revertants/mg	0.50	
		DBacA	NA			42			revertants/nmol	150,888	revertants/mg	0.38	
		DBahA	NA			8			revertants/nmol	28,743	revertants/mg	0.073	
		DBaiP	NA			38			revertants/nmol	125,661	revertants/mg	0.32	
		DBalP	NA			21			revertants/nmol	69,451	revertants/mg	0.18	
		FA	NA			3			revertants/nmol	14,832	revertants/mg	0.037	
		Pery	NA			31			revertants/nmol	122,862	revertants/mg	0.31	
		Tphen	NA			13			revertants/nmol	56,944	revertants/mg	0.14	
10670	Johnsen et al., 1997	BaP	C				128	10	µg/plate			1	
		BjAC	C				192	10	µg/plate			1.5	RPF based on peak; no model fit
		BlAC	C				204	10	µg/plate			1.6	RPF based on peak; no model fit
19000	Kaden et al., 1979	BaP	NA									1	RPFs as reported by authors
		AA	NA									0.08	
		AN	NA									0.01	
		ANL	NA									0.07	
		BaA	NA									0.14	
		BbFE	NA									0.08	
		BeP	NA									0.11	
		BghiP	NA									0.08	
		CH	NA									0.2	
		CPcdP	NA									1.5	
		DBacA	NA									0.77	
		DBahA	NA									0.08	

Table E-9. In vitro bacterial mutagenicity: RPF calculations

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Slope	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
		DBbeF	NA									0.88	
		FA	NA									1	
		Pery	NA									6	
		Pyr	NA									0.07	
		Tphen	NA									0.07	
24680	Lafleur et al., 1993	BaP	Q				0.00026	8	µg/mL			1	RPF based on peak; BMD doesn't coincide with selected BMR
		BghiF	Q				0.00044	10	µg/mL			1.4	
		CPcdP	Q				0.00048	8	µg/mL			1.9	
		CPhiACEA	Q				0.00059	4	µg/mL			4.6	
		CPhiAPA	Q				0.00017	100	µg/mL			0.05	
		ACEA	Q				0.00059	35	µg/mL			0.53	
		APA	Q				0.00026	30	µg/mL			0.27	
19320	LaVoie et al., 1979	BaP	C				480	20	µg			1	Continuous data, no SD; RPF based on peak or lowest dose approaching peak
		BeP	C				20	10	µg			0.08	
		Pery	C				70	20	µg			0.15	
23650	McCann et al., 1975	BaP	NA			121			revertants/nmol	479,550	revertants/mg	1	RPFs based on potency estimates as reported by authors; authors caution that dose-response nonlinear
		BaA	NA			11			revertants/nmol	48,184	revertants/mg	0.10	
		BeP	NA			0.6			revertants/nmol	2,378	revertants/mg	0.005	
		CH	NA			38			revertants/nmol	166,455	revertants/mg	0.35	
		DBacA	NA			175			revertants/nmol	628,698	revertants/mg	1.3	
		DBahA	NA			11			revertants/nmol	39,521	revertants/mg	0.082	
		DBaiP	NA			20			revertants/nmol	66,138	revertants/mg	0.14	
20220	Pahlman and Pelkonen, 1987	BaP	NA			272			revertants/mg	1,077,996	revertants/mg	1	RPFs based on potency estimates as reported by authors
		BaA	NA			10			revertants/mg	43,804	revertants/mg	0.041	
		CH	NA			9.7			revertants/mg	42,490	revertants/mg	0.039	
		DBacA	NA			35			revertants/mg	125,740	revertants/mg	0.12	
		DBahA	NA			4			revertants/mg	14,371	revertants/mg	0.013	
		Tphen	NA			4			revertants/mg	17,521	revertants/mg	0.016	

Table E-9. In vitro bacterial mutagenicity: RPF calculations

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Slope	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
20450	Phillipson and Ioannides, 1989	BaP	C				119	10	µg/plate			1	No SD; RPFs based on peak or lowest dose approaching peak
		BaA	C				110	20	µg/plate			0.46	
		DBaiP	C				65	20	µg/plate			0.27	
		DBahA	C				51	10	µg/plate			0.43	
21000	Sakai et al., 1985	BaP	C				1,565	10	µg			1	No SD; RPFs based on peak or lowest dose approaching peak
		FE	C				65	5	µg			0.083	
		AC	C				320	10	µg			0.2	
		PH	C				345	10	µg			0.22	
		FA	C				835	10	µg			0.53	
		CH	C				638	10	µg			0.41	
		Pyr	C				2,400	10	µg			1.5	
		BeP	C				923	10	µg			0.59	
		Pery	C				2,607	4	µg			4.2	
		BghiP	C				814	20	µg			0.26	
		CO	C				223	10	µg			0.14	
11860	Sangaiah et al., 1983	BaP	C				384	6	µg/plate			1	No SD; RPFs based on peak or lowest dose approaching peak
		BjAC	C				940	10	µg/plate			1.4	
21360	Simmon, 1979a	BaP	C				1,141	5	µg			1	
		BaA	C				280	50	µg			0.025	
		BeP	C				57	50	µg			0.005	
21640	Teranishi et al., 1975	BaP	C				39	50	µg/plate			1	
		DBaiP	C				64	50	µg/plate			1.6	
		BaP					254	50	µg/plate			1	
		DBaeP					63	50	µg/plate			0.25	
16180	Utesch et al., 1987	BaP	C				839	6	µg/plate			1	No SD; RPF based on peak or lowest dose approaching peak
		BaA	C				3,347	25	µg/plate			1	

Table E-9. In vitro bacterial mutagenicity: RPF calculations

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Slope	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
16440	Wood et al., 1980	BaP	C				99	15	µg/plate			1	No SD; RPF based on peak or lowest dose approaching peak
		CPcdP	C				685	15	µg/plate			6.9	

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Table E-10. In vitro mammalian mutagenicity: RPF calculations

Record number	Reference	PAH	Relative potency calculation								
			BMR	BMD	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
16920	Amacher and Paillet, 1982	BaP			0.00023	10	µg/mL			1	No model fit; RPF based on peak
		BaA			0.000068	10	µg/mL			0.3	No model fit; RPF based on peak
16940	Amacher and Turner, 1980	BaP			0.00025	1.25×10^{-5}	M	3.15	mg/L	1	Control without S9 treatment
		BaA			0.00027	3.22×10^{-5}	M	7.35	mg/L	0.46	
16910	Amacher et al., 1980	BaP			0.00033	3.96×10^{-5}	M	9.99	mg/L	1	No model fit; RPF based on peak
		BaA			0.00007	4.3×10^{-5}	M	9.82	mg/L	0.22	BMD doesn't coincide with selected BMR; RPF based on peak
17140	Barfknecht et al., 1982	BaP	0.00001	1.8			µM	0.45	mg/L	1	
		BaA	0.00001	23			µM	5.25	mg/L	0.09	
		CH	0.00001	16			µM	3.65	mg/L	0.12	
		CPcdP			0.0000083	23	µM	5.20	mg/L	0.07	BMD doesn't coincide with selected BMR; RPF based on response closest to BMR of 0.00001
		FA	0.00001	3.9			µM	0.79	mg/L	0.58	
		Tphen	0.00001	54			µM	12.33	mg/L	0.04	
24670	Durant et al., 1999	BaP			0.00017	1,000	ng/mL			1	RPF based on peak response; single dose BaP response at upper end or above data range for most other data sets; model fit required dropping high doses but not appropriate given BMR target at BaP response level
		BaPery			0.00018	100	ng/mL			11	
		BbPery			0.000036	100	ng/mL			2.2	
		DBaeF			0.00017	100	ng/mL			10	
		DBafF			0.00017	1,000	ng/mL			1	
		DBahP			0.000061	100	ng/mL			3.7	
		DBaiP			0.00013	100	ng/mL			7.8	
		DBelP			0.000034	1,000	ng/mL			0.21	
		N23aP			0.000073	100	ng/mL			4.4	

Table E-10. In vitro mammalian mutagenicity: RPF calculations

Record number	Reference	PAH	Relative potency calculation								
			BMR	BMD	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
		N23eP			0.000079	1,000	ng/mL			0.48	
14250	Hass et al., 1982	BaP			0.00026	0.3	µg/mL			1	No model fit; response at low dose (approaching peak)
		DBaiP			0.0012	0.3	µg/mL			4.6	No model fit; RPF based on peak
		DBahP			0.00066	0.3	µg/mL			2.5	No model fit; RPF based on peak
18740	Huberman and Sachs, 1976	BaP			0.0042	1	µg/mL			1	
		DBacA			0.00016	1	µg/mL			0.04	
		DBahA			0.00011	1	µg/mL			0.03	
18990	Jotz and Mitchell, 1981	BaP			0.00014	4.5	µg/mL			1	With metabolic activation
		Pyr			0.000034	11	µg/mL			0.1	With metabolic activation
24720	Kligerman et al., 1986	BaP			0.00047	4	nmol/mL	0.001	mg/mL	1	No model fit; RPF based on peak
		BlAC			0.00028	5	nmol/mL	0.0013	mg/mL	0.48	No model fit; RPF based on peak
19180	Krahn and Heidelberger, 1977	BaP			0.00012	15.9	nmol/mL	0.004	mg/mL	1	3-MC S9; 40% survival
		BaA			0.00005	46.5	nmol/mL	0.011	mg/mL	0.16	3-MC S9; 40% survival
24680	Lafleur et al., 1993	BaP			0.000024	0.2	µg/mL			1	No model fit
		ACEA			0.000013	3	µg/mL			0.037	No model fit
		CPcdP			0.000015	2	µg/mL			0.061	No model fit
		CPhiACEA			0.000022	0.3	µg/mL			0.62	No model fit
7550	Li and Lin, 1996	BaP			0.00003	10	ng/mL			1	
		BaA			0.000036	10	ng/mL			1.2	
11450	Nesnow et al., 1984	BaP			0.00019	5	µg/mL			1	
		BeAC			0.00042	5	µg/mL			2.2	No model fit; RPF based on lowest dose approaching peak

Table E-10. In vitro mammalian mutagenicity: RPF calculations

Record number	Reference	PAH	Relative potency calculation								
			BMR	BMD	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
		BjAC			0.00025	5	µg/mL			1.3	No model fit; RPF based on lowest dose approaching peak
		BlAC			0.00044	2.5	µg/mL			4.6	No model fit; RPF based on lowest dose approaching peak
15630	Raveh and Huberman, 1983	BaP	0.0001	0.11			µg/mL			1	
		CPcdP	0.0001	0.58			µg/mL			0.18	Uses QL; MS didn't converge
15640	Raveh et al., 1982	BaP	0.00001	0.16			µg/mL			1	Uses QL, high dose dropped; MS didn't fit
		CPcdP	0.00001	1.1			µg/mL			0.14	Uses QL; MS didn't converge
21410	Slaga et al., 1978	BaP	0.0001	0.048			µM	0.012	mg/L	1	
		BaA	0.0001	32			µM	7.3	mg/L	0.001658	
16190	Vaca et al., 1992	BaP			0.00027	10	µM	2.5	mg/L	1	BMD doesn't coincide with selected BMR; RPF based on peak
		FA			0.00021	10	µM	2.02	mg/L	0.97	BMD doesn't coincide with selected BMR; RPF based on peak
21900	Wangenheim and Bolcsfoldi, 1988	BaP			0.0008	0.00001	mol/L	2.5	mg/L	1	BMD doesn't coincide with selected BMR; RPF based on peak
		FE			0.000086	0.00012	mol/L	19.9	mg/L	0.014	BMD doesn't coincide with selected BMR; RPF based on peak
		Pyr			0.00053	0.00003	mol/L	6.1	mg/L	0.28	BMD doesn't coincide with selected BMR; RPF based on peak

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Table E-11. In vitro morphological/malignant transformation: RPF calculation

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Point estimate response	Point estimate dose	Slope of dose-response curve	Dose units	Converted dose	Converted dose units	RPF	Comments
17610	Casto, 1979	BaP	Q	0.00001	0.1				µg/mL			1	
		DBahA	Q	0.00001	2.5				µg/mL			0.042	
17970	DiPaolo et al., 1969	BaP	Q			0.058	10		µg/mL			1	
		DBahA	Q			0.031	10		µg/mL			0.54	
		BaA	Q			0.011	10		µg/mL			0.18	
		BeP	Q			0.0058	10		µg/mL			0.1	
		DBacA	Q			0.011	10		µg/mL			0.19	
18080	Emura et al., 1980	BaP Expt I	Q	0.001	0.044				µg/mL			1	
		BbF	Q	0.001	0.75				µg/mL			0.059	
		BaA	Q	0.001	0.85				µg/mL			0.052	
		BaP Expt II	Q	0.001	0.046				µg/mL			1	
		IP	Q	0.001	0.82				µg/mL			0.056	
14130	Greb et al., 1980	BaP	NA					277	%/mmol	1.10	%/mg	1	Relative transformation potencies reported; RPFs are ratio of potencies
		BaA	NA					13.9	%/mmol	0.061	%/mg	0.055	
		BbF	NA					11.5	%/mmol	0.046	%/mg	0.042	
		BeP	NA					3.1	%/mmol	0.012	%/mg	0.011	
		CH	NA					37	%/mmol	0.16	%/mg	0.15	
		DBahA	NA					0.3	%/mmol	0.001	%/mg	0.000982	
14640	Krolewski et al., 1986	BaP	Q			0.0055	5		µM	1.3	mg/L	1	
		CPcdP	Q			0.0017	5		µM	1.1	mg/L	0.34	
14700	Laaksonen et al., 1983	BaP	Q			0.000009	10		µM	2.5	mg/L	1	RPF based on peak; inverse dose-response relationship possibly due to cytotoxicity
		BaA	Q			0.000018	11		µM	2.5	mg/L	2.0	
14850	Lubet et al., 1983	BaP	Q	0.1	1.9				µg/mL			1	
		BeP	Q	0.1	41				µg/mL			0.046	
24710	Mohapatra et al., 1987	BaP	Q			0.92	1		µg/mL			1	
		BjAC	Q	0.92	0.93				µg/mL			1.1	
		BaP	Q			0.83	1		µg/mL			1	
		BlAC	Q	0.83	7.5				µg/mL			0.13	
		BaP	Q			0.86	1		µg/mL			1	
		BeAC	Q	0.86	18				µg/mL			0.056	
24700	Nesnow et al., 1990	BaP	C			47	10		µg/mL			1	Based on peak response; no SD for control
		BlAC	C			120	10		µg/mL			2.5	
7980	Nesnow et al., 1997	BaP	C			2.5	4		µM	1.01	mg/L	1	Based on peak response; no SD for control
		DBalP	C			1.7	0.33		µM	0.10	mg/L	6.9	
7990	Nesnow et al., 1994	BaP	C			0.94	1		µg/mL			1	Based on peak response; no continuous linear model fit
		DBahA	C			0.37	1		µg/mL			0.39	
8000	Nesnow et al., 1993a	BaP	C			1.4	3		µg/mL			1	Based on peak response; no SD for control
		DBkmnoAPH	C			1.1	5		µg/mL			0.47	

Table E-11. In vitro morphological/malignant transformation: RPF calculation

Record number	Reference	PAH	Data type: quantal or continuous	Relative potency calculation									
				BMR	BMD	Point estimate response	Point estimate dose	Slope of dose-response curve	Dose units	Converted dose	Converted dose units	RPF	Comments
23720	Pienta et al., 1977	BaP	Q	0.01	15				µg/mL			1	High dose dropped
		BaA	Q	0.01	8.2				µg/mL			1.9	Caution: changing slope in region of BMR
		DBahA	Q	0.01	0.4				µg/mL			34	Two highest doses dropped

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Table E-12. In vitro DNA adducts: RPF calculations[a]

Record number	Reference[b]	PAH	Relative potency calculation						
			Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
16890	Allen and Coombs, 1980	BaP	7.5	0.24	µg/mL			1	Nuclear DNA
		BaA	0.44	0.64	µg/mL			0.021	
		BaP	413	0.24	µg/mL			1	Mitochondrial DNA
		BaA	104	0.64	µg/mL			0.092	
6300	Binkova et al., 2000	BaP	258	1	µM	0.25	mg/L	1	
		DBalP	2,317	0.1	µM	0.03	mg/L	75	
9510	Bryla and Weyand, 1992	BaP	5.5	600	nmol	0.15	mg	1	Light conditions
		BaA	1	600	nmol	0.14	mg	0.20	
		DBacA	1.8	600	nmol	0.17	mg	0.30	
22800	Grover and Sims, 1968	BaP	1.4	5	µg			1	
		DBahA	0.44	5	µg			0.31	
		DBacA	0.56	5	µg			0.40	
		BaA	0.7	5	µg			0.50	
		Pyr	0.31	5	µg			0.22	
		PH	0.05	5	µg			0.040	
10670	Johnsen et al., 1997	BaP	0.05	30	µg/mL			1	Clara cells
		BjAC	0.15	30	µg/mL			3	
		BlAC	0.24	30	µg/mL			4.8	
		BaP	0.02	30	µg/mL			1	Type 2 cells
		BjAC	0.06	30	µg/mL			3	
		BlAC	0.03	30	µg/mL			1.5	
10660	Johnsen et al., 1998	BaP	0.33	30	µg/mL			1	Human lymphocytes
		BjAC	0.11	30	µg/mL			0.33	
		BlAC	1.1	30	µg/mL			3.3	
		BaP	0.24	30	µg/mL			1	HL-60 cells
		BjAC	0.15	30	µg/mL			0.62	
		BlAC	0.94	30	µg/mL			3.9	
7870	Melendez-Colon et al., 2000	BaP	34	2	µM	0.50	mg/L	1	
		DBalP	348	2	µM	0.60	mg/L	8.5	

Table E-12. In vitro DNA adducts: RPF calculations[a]

Record number	Reference[b]	PAH	Relative potency calculation						
			Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
21200	Segerback and Vodicka, 1993	BaP	15	100	mM	25,232	mg/L	1	
		BaA	30	100	mM	22,829	mg/L	2.2	
		BbF	3.7	100	mM	25,232	mg/L	0.25	
		BghiP	0.5	100	mM	27,634	mg/L	0.03	
		CH	50	100	mM	22,829	mg/L	3.7	
		DBahA	2.8	100	mM	27,833	mg/L	0.17	
		FA	1.5	100	mM	20,226	mg/L	0.12	
		Pyr	0.14	100	mM	20,226	mg/L	0.012	

[a]All RPFs are point estimates based on peak response as adequate model fit was not achieved for any multidose dataset.
[b]No control data were available for any of these studies.

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Table E-13. In vitro DNA damage: RPF calculations

Record number	Reference	PAH	Relative potency calculation									
			BMR	BMD	Point estimate response	Point estimate dose	Slope of dose-response curve	Dose units	Converted dose	Converted dose units	RPF	Comments
16840	Agrelo and Amos, 1981	BaP			2,093	10		µg/mL			1	Control responses for BaP and Pyr differ by 10 times
		Pyr			548	100		µg/mL			0.026	RPF based on peak; continuous data without SD
23790	Ichinotsubo et al., 1977	BaP			6	70		µg/well			1	
		DBaiP			10	600		µg/well			0.19	
		DBahA			10	25		µg/well			4.7	
10660	Johnsen et al., 1998	BaP			7.9	3		µg/mL			1	Human lymphocytes; no model fit; lowest response point estimate
		BjAC	7.6	18				µg/mL			0.16	Human lymphocytes; BMR is BaP point estimate response
		BlAC			4.9	30		µg/mL			0.062	Human lymphocytes; no model fit; response point estimate closest to BaP response
		BaP			5.4	30		µg/mL			1	HL-60 cells
		BjAC			1.8	30		µg/mL			0.33	HL-60 cells
		BlAC			3.8	30		µg/mL			0.7	HL-60 cells
19740	Martin et al., 1978	BaP			210	1×10^{-5}		M	2.5	mg/L	1	Increase over background
		BaA			59	1×10^{-7}		M	0.023	mg/L	31	
		BeP			256	1×10^{-6}		M	0.25	mg/L	12	
		DBacA			97	1×10^{-5}		M	2.8	mg/L	0.42	
		DBahA			96	1×10^{-5}		M	2.8	mg/L	0.41	
19830	Mersch-Sundermann et al., 1992	BaP					0.61	µg/assay			1	SOS induction potential - slope of SOS induction dose-response curve as reported
		AA					0.14	µg/assay			0.23	
		BaA					0.1	µg/assay			0.17	
		BbF					0.045	µg/assay			0.074	
		BghiF					0.34	µg/assay			0.56	
		BjF					0.25	µg/assay			0.42	
		BbFE					0.024	µg/assay			0.04	
		BghiP					0.033	µg/assay			0.055	
		BeP					0.032	µg/assay			0.053	
		CH					0.22	µg/assay			0.37	
		DBacA					0.10	µg/assay			0.17	
		DBahA					0.039	µg/assay			0.064	

Table E-13. In vitro DNA damage: RPF calculations

Record number	Reference	PAH	Relative potency calculation									
			BMR	BMD	Point estimate response	Point estimate dose	Slope of dose-response curve	Dose units	Converted dose	Converted dose units	RPF	Comments
		DBalP					2.1	µg/assay			3.5	
		DBahP					0.12	µg/assay			0.19	
		DBaiP					0.17	µg/assay			0.29	
		FA					0.41	µg/assay			0.68	
		IP					0.036	µg/assay			0.06	
		PH					0.053	µg/assay			0.088	
		Tphen					0.26	µg/assay			0.43	
20810	Robinson and Mitchell, 1981	BaP			89	10		µg/mL			1	
		Pyr			63	7.2		µg/mL			0.98	
20940	Rossman et al., 1991	BaP			10.4	12.5		µg/mL			1	Enhancement over background
		AC			4.8	12.5		µg/mL			0.46	
		DBacA			8	1.44		µg/mL			6.7	
		DBahA			4	2		µg/mL			2.4	
		PH			4.5	25		µg/mL			0.22	
21730	Tong et al., 1981b	BaP			65.5	0.001		M	252	mg/L	1	
		BaA			17.1	0.0005		M	114	mg/L	0.58	Based on peak response; no model fit

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Table E-14. In vitro clastogenicity or sister chromatid exchange: RPF calculations

Record number	Reference	PAH	Endpoint	Data type: quantal or continuous	BMR	BMD	Point estimate response	Point estimate dose	Dose units	Converted dose	Converted dose units	RPF	Comments
14620	Kochhar, 1982	BaP	Aberrations	Q			0.53	5	µg/mL			1	BMD doesn't reflect selected BMR; RPF based on peak
		BaA					0.34	5	µg/mL			0.64	BMD doesn't reflect selected BMR; RPF based on peak
14640	Krolewski et al., 1986	BaP	Sister chromatid exchanges	C			0.79	5	µM	1.3	mg/L	1	
		CPcdP					0.29	5	µM	1.1	mg/L	0.41	No model fit; RPF based on peak response
19690	Mane et al., 1990	BaP	Sister chromatid exchanges	C			2.7	1	µg/mL			1	
		BaA					0.4	1	µg/mL			0.15	
21710	Tong et al., 1981a	BaP	Sister chromatid exchanges	C			92	1×10^{-4}	M	25.2	mg/L	1	
		BaA					13	1×10^{-4}	M	22.8	mg/L	0.16	No n provided; RPF based on peak response

APPENDIX F. EXAMPLE CALCULATION OF RPF DETECTION LIMIT

Table F-1. Example data for calculation of RPF detection limit

Group	Dose	Number with tumors	Number in group	Incidence	Extra risk response[a]
Actual responses					
Control	0	2	30	0.067	NA
Anthanthrene	0.25	2	29	0.069	NA
Benzo[a]pyrene	0.25	24	30	0.800	0.786
Theoretical statistically significant response[b]					
Anthanthrene	0.25	8	29	0.276	0.224

[a]Calculated as described below in Step 1.
[b]Calculated as described below in Step 2.

Source: Hoffmann and Wynder (1966).

Step 1. Estimate the number of tumor-bearing animals that would represent a statistically significant response (one-sided $p \leq 0.05$ using Fisher's exact test) in the number of animals exposed to anthanthrene (29) given the observed control response (2/30). In this case, 8/29 tumor-bearing animals (incidence of 0.276) would represent a statistically significant response to anthanthrene.

Step 2. Calculate the extra risk response associated with the theoretical statistically significant incidence for anthanthrene and the observed benzo[a]pyrene incidence as follows:

$$\text{Extra risk response} = \frac{P(d) - P(0)}{[1 - P(0)]}$$

For the theoretical statistically significant response to anthanthrene,

$$\text{Extra risk response} = (0.276 - 0.067)/(1 - 0.067) = 0.224$$

Step 3. Calculate the RPF detection limit as the ratio of the slopes associated with extra risk response and the actual doses of anthanthrene and benzo[a]pyrene as follows:

$$\text{RPF detection limit} = \frac{\text{(theoretical anthanthrene extra risk response/dose anthanthrene)}}{\text{(benzo[a]pyrene extra risk response/dose benzo[a]pyrene)}}$$

$$\text{RPF detection limit} = (0.224/0.25)/(0.786/0.25) = 0.28$$

APPENDIX G. EVALUATION OF ALTERNATIVES FOR RANKING RPFs

For many of the PAHs evaluated in this report, a number of datasets were available for use in calculating RPFs. The resulting RPFs are derived from tumor bioassays using different exposure routes, species, sexes, or tumor endpoints (incidence or multiplicity) and from a variety of different cancer-related endpoint assays. The various RPFs are derived from studies of varying design and quality (different numbers of animals, follow-up time, single or multiple dose groups, response levels low or high on the dose-response curve, etc.). In order to derive a single final RPF for each individual PAH, the various results from different datasets must be ranked or combined in some manner. This appendix details the options that were considered for ranking RPFs.

A series of options were considered for prioritizing RPFs for the purpose of selecting a single RPF for each PAH or exposure route. An a priori decision was made to consider tumor bioassay data to be preferable to cancer-related endpoint data because the tumor bioassay data are derived from whole animals and address the endpoint of interest for RPFs (tumorigenicity). Thus, options for ranking or combining tumor bioassays and for cancer-related endpoint data were considered separately; Section G.1 discusses options considered for use of tumor bioassay RPFs and Section G.2 discusses options considered for use of cancer-related endpoint RPFs.

G.1. OPTIONS FOR RANKING TUMOR BIOASSAY RPFs

Approaches considered for ranking tumor bioassay RPFs were: (1) ranking by exposure route, (2) ranking by target organ, and (3) preference for modeled data over point estimates.

Ranking by exposure route. One option for ranking RPFs derived from tumor bioassay data would be to order the datasets by exposure routes that are considered most relevant to environmental exposure routes (oral, dermal, and inhalation). RPFs for many PAHs were calculated from dermal tumor bioassays. The available database for PAHs included one oral and no inhalation studies that were suitable for RPF calculation; thus, route-to-route extrapolation is necessary to derive RPFs applicable to all routes of exposure.

Some earlier RPF approaches, primarily in the course of assessing risks from inhalation exposure to PAHs, have proposed hierarchies of bioassay types based on route of administration. Collins et al. (1998) proposed a hierarchy for PAH cancer potencies for use in assessing air contaminants. The hierarchy for inhalation potencies proposed by Collins et al. (1998) ordered the exposure routes as follows: intratracheal or intrapulmonary administration > oral administration > skin-painting studies > subcutaneous or intraperitoneal administration. However, Collins et al. (1998) did not provide any empirical data supporting the ordering of these exposure routes, other than the intuitive preference for intratracheal or intrapulmonary administration as a surrogate for inhalation. In another review of data available for relative potency assessment for PAHs as air contaminants, Pufulete et al. (2004) suggested that

intratracheal instillation of low doses of PAHs might be an appropriate surrogate exposure model for assessing relative potency of inhalation exposure. The basis for this suggestion was the authors' observation that clearance of PAHs administered in solution via intratracheal instillation exhibited a biphasic pattern similar to that observed after inhalation exposure to benzo[a]pyrene bound to particulates. However, the authors acknowledged that the high concentrations of PAHs used in intratracheal and intrapulmonary instillation studies may lead to major differences in pharmacokinetics compared with inhalation exposure (Pufulete et al., 2004). Further, the authors expressed this suggestion as a path for future research, rather than as a means of examining available data on PAHs; no intratracheal instillation studies were identified in the search for studies from which to calculate RPFs for PAHs. Pufulete et al. (2004) did not provide any specific information on the relevance of intrapulmonary administration (a route used in several of the bioassays used to calculate RPFs) to inhalation exposure.

To assess exposure-route differences in RPFs calculated in this review, a table comparing the average RPF for each PAH across exposure routes was prepared (Table G-1). Dermal studies are shown collectively as well as separated by study type (complete carcinogenesis or initiation only). Likewise, intraperitoneal studies are shown grouped as well as separated by target organ (lung and liver).

Table G-1. Comparisons among average nonzero tumor bioassay-based RPF values by exposure route

PAH	Dermal, target organ = skin		Dermal complete		Dermal initiation		Intraperitoneal		Intraperitoneal, target organ = lung		Intra-peritoneal, target organ = liver		Lung implantation, target organ = lung		Oral, target organ = lung	
	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average
AA	1	0.5	1	0.5	–	–	–	–	–	–	–	–	1	0.2	–	–
AC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
BaA	1	0.02	–	–	1	0.02	2	0.2[a]	1	0.08	1	0.4	–	–	–	–
BbcAC (1,12-MBA)	1	0.05	–	–	1	0.05	–	–	–	–	–	–	–	–	–	–
BbF	2	0.4	1	0.3	1	0.4	2[b]	1[c]	1	1	–	–	1	0.1	–	–
BcFE	–	–	–	–	–	–	1	1[d]	1	1	–	–	–	–	1	50
BeAC	2	0.8	–	–	2	0.8	–	–	–	–	–	–	–	–	–	–
BghiP	–	–	–	–	–	–	–	–	–	–	–	–	1	0.009	–	–
BjAC	–	–	–	–	–	–	1	60[d]	1	60	–	–	–	–	–	–
BjF	2	0.03	–	–	2	0.03	2[b]	0.7[a]	1	0.4	1	1	1	0.03	–	–
BkF	1	0.03	–	–	1	0.03	–	–	–	–	–	–	1	0.03	–	–
BlAC	2	5	–	–	2	5	–	–	–	–	–	–	–	–	–	–
CH	5	0.1	–	–	5	0.1	1	0.2[a]	–	–	1	0.2	1	0.04	–	–
CPcdP	4	0.3	2	0.4	2	0.2	1	1[d]	1	1	–	–	–	–	–	–
CPdefC	2	0.3	–	–	2	0.3	–	–	–	–	–	–	–	–	–	–
DBacA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
DBaeF	2	0.9	1	1	1	0.7	–	–	–	–	–	–	–	–	–	–
DBaeP	2	0.4	1	0.3	1	0.4	–	–	–	–	–	–	–	–	–	–
DBahA	1	1	–	–	1	1	1	40[d]	1	40	–	–	1	2	–	–
DBahP	1	0.9	–	–	1	0.9	–	–	–	–	–	–	–	–	–	–
DBaiP	2	0.6	1	0.7	1	0.5	–	–	–	–	–	–	–	–	–	–
DBalP	2	30	–	–	2	30	1	30[d]	1	30	–	–	–	–	–	–
FA	–	–	–	–	–	–	5	0.08[a]	4	0.05	1	0.2	–	–	–	–
IP	–	–	–	–	–	–	–	–	–	–	–	–	1	0.07	–	–
N23eP	1	0.3	–	–	1	0.3	–	–	–	–	–	–	–	–	–	–

Table G-1. Comparisons among average nonzero tumor bioassay-based RPF values by exposure route

PAH	Dermal, target organ = skin		Dermal complete		Dermal initiation		Intraperitoneal		Intraperitoneal, target organ = lung		Intra-peritoneal, target organ = liver		Lung implantation, target organ = lung		Oral, target organ = lung	
	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average	n	Average
PH	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pyr	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

[a]Newborn mouse model.
[b]Number of intraperitoneal RPFs includes those calculated for combined lung and liver incidence; these are not included in number of RPFs with lung or liver tumors.
[c]Includes both newborn mouse and adult A/J mouse models.
[d]Adult A/J mouse model.

The table shows a marked difference between the oral and intraperitoneal RPFs for benzo[c]fluorene (BcFE) (RPF = 50 for oral multiplicity and RPF = 1 for intraperitoneal incidence). However, as discussed earlier, this difference may result more from the use of a high tumor number to calculate the oral multiplicity RPF for this compound than route differences; if the oral incidence RPF is used for comparison, the two routes are more similar (RPF = 1 for intraperitoneal incidence versus RPF = 5 for oral incidence). Based on the latter comparison, which represents the only data with which to compare oral RPFs with those calculated from other routes, there appears to be fairly good correspondence between intraperitoneal and oral RPFs; however, this is based on only one PAH.

Based on the comparisons in the table, RPFs based on initiation and complete dermal carcinogenicity studies are similar (within a factor of 2). However, there are few PAHs with both types of dermal studies.

With respect to other route comparisons, the table generally shows that RPFs calculated from lung implantation and dermal studies are of the same order of magnitude, while RPFs calculated from intraperitoneal studies are higher for most compounds. Among PAHs with RPFs derived from intraperitoneal and dermal data, 6/7 showed higher RPF values from intraperitoneal data, compared with dermal data (benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, cyclopenta[c,d]pyrene, dibenz[a,h]anthracene; Table G-1). The intraperitoneal RPF for dibenzo[a,l]pyrene (DBalP) is similar to its dermal RPF.

At first glance, one might attribute the higher intraperitoneal RPFs calculated from newborn mouse assays (footnoted “a” in the table) to greater sensitivity of the newborn mouse, compared with an adolescent or adult mouse, to the carcinogenic action of PAHs. However, since the RPFs reflect potency of the PAH relative to benzo[a]pyrene, and not potency of the newborn mouse relative to other systems, the higher RPF cannot reflect a greater sensitivity of the system, since both the PAH of interest and benzo[a]pyrene have been tested in the same system. There is little information to evaluate whether RPFs from newborn mouse studies tend to be higher or lower than the adult A/J mouse model when both are exposed via intraperitoneal injection. Only one compound, benzo[b]fluoranthene (BbF), had RPFs calculated from both newborn mouse and adult A/J mouse models; the average newborn mouse RPF was 2, while the average A/J mouse RPF was 0.9. In summary, it is not clear whether the intraperitoneal RPFs are higher than dermal or lung implantation RPFs due to route-specific differences or animal model differences (for example, differential metabolism in various animal systems).

Ranking by target tissue. An alternative approach to ranking tumor bioassay RPFs would be to prefer target tissue-specific RPFs (for example, to prefer RPFs derived from lung tumor data for inhalation RPFs). An analysis was conducted to assess whether RPFs calculated from lung tumor potency in intraperitoneal studies (both newborn mouse and adult A/J mouse models) were consistent with RPFs from lung implantation studies. Table G-1 shows RPFs calculated for lung tumors (separate from liver tumors also observed in some intraperitoneal studies) after

intraperitoneal administration. Only four compounds (benzo[b]fluoranthene, benzo[j]fluoranthene, chrysene, and dibenz[a,h]anthracene) had RPFs for both intraperitoneal and lung implantation studies; for each of these, the intraperitoneal lung tumor RPF exceeded the lung implantation RPF. One compound, benzo[c]fluorene, also had lung tumor RPFs from both intraperitoneal and oral studies. In this case, the oral RPF for lung tumors exceeded the intraperitoneal RPF for lung tumors. No information assessing the concordance between lung tumor potency after intraperitoneal, lung implantation, or oral administration and inhalation cancer potency was identified in the literature.

Ranking by use of BMD. A third approach considered for ranking of tumor bioassay data was to prefer data amenable to BMD modeling (of either quantal or continuous data, depending on whether incidence or multiplicity was modeled) over an analysis of data based on point estimates. Table G-2 compares the average of RPFs for all bioassays with RPFs calculated using BMD modeling, and RPFs calculated using a point-estimate approach.

Table G-2. Comparisons among average nonzero tumor bioassay-based RPF values by calculation method

	All bioassays		BMD model		Point estimate	
	n	Average RPF	n	Average RPF	n	Average RPF
AA	2	0.4	1	0.2	1	0.5
AC	–	–	–	–	–	–
BaA	3	0.2	–	–	3	0.2
BbcAC	1	0.05	–	–	1	0.05
BbF	5	0.8	3	0.6	2	1.0
BcFE	2	20	–	–	2	20
BeAC	2	0.8	1	0.9	1	0.7
BghiP	1	0.009	1	0.009	–	–
BjAC	1	60	–	–	1	60
BjF	5	0.3	1	0.03	4	0.4
BkF	2	0.03	2	0.03	–	–
BlAC	2	5	2	5	–	–
CH	7	0.1	2	0.1	5	0.1
CPcdP	5	0.4	1	0.07	4	0.5
CPdefC	2	0.3	1	0.5	1	0.2
DBacA	–	–	–	–	–	–
DBaeF	2	0.9	1	1	1	0.7
DBaeP	2	0.4	1	0.3	1	0.4
DBahA	3	10	2	20	1	1
DBahP	1	0.9	–	–	1	0.9
DBaiP	2	0.6	1	0.7	1	0.5
DBalP	3	30	1	30	2	30
FA	5	0.08	4	0.08	1	0.09
IP	1	0.07	1	0.07	–	–
N23eP	1	0.3	–	–	1	0.3
PH	–	–	–	–	–	–
Pyr	–	–	–	–	–	–

While this ranking could be justified based on a general preference for multidose data and modeling to identify a point of departure, there are important limitations to this approach. First, RPFs based on BMD modeling may still use a point of departure high on the dose-response curve, if a single benzo[a]pyrene dose with an elevated response level (BMR)[1] was used to calculate the RPF. In some cases, an RPF based on a point estimate approach from a point of departure lower on the dose-response curve may be a better predictor of relative potency at environmental exposure levels. Second, unless RPFs based on BMD modeling are available for all of the relevant exposure routes (dermal initiation and complete carcinogenicity, lung implantation, and intraperitoneal), there may be differences between the RPFs calculated from BMD modeling and those calculated using a point estimate approach that are unrelated to study quality (i.e., route, species, sex differences). Thus, ranking RPFs based on a preference for modeled data over point estimate data would neglect other sources of variability in the estimates (exposure route, species, sex, target organ, dosing intervals, etc.)

In summary, the analysis of options for ranking bioassay RPFs does not suggest a clear basis for selecting among the available data types. As a consequence, none of the available data types were considered preferable to any other; all bioassay RPFs were considered equally relevant.

G.2. RANKING NONBIOASSAY DATA

In view of the fact that the present work created a large database of RPFs for multiple endpoints, an empirical approach to assigning ranks was explored. The database of PAH RPFs was analyzed to determine whether any individual cancer-related endpoint was more closely correlated with RPFs based on tumor bioassay data. The premise behind this analysis is that RPFs based on bioassay data represent the best available information, and that the genotoxicity endpoints that best predict bioassay RPFs should be preferred over those that show little relationship to tumor bioassay RPFs. The semiquantitative analysis was, of necessity, restricted to those PAHs for which at least one RPF based on bioassay data was available.

For each of the 23 PAHs with nonzero RPFs based on bioassay data, the average bioassay RPF was compared with the average RPF for several endpoints that could be correlated with cancer potency (in vivo DNA adducts, in vivo micronuclei and sister chromatid exchanges together, and in vitro mutagenicity). TIDAL values were not analyzed separately from other measures of DNA adducts because there were only four PAHs with both TIDAL and bioassay RPFs; similarly, micronuclei and sister chromatid exchange endpoints were grouped to increase the number of observations in the regression. In addition to analyzing these endpoints, analyses of several endpoints grouped across class (e.g., all in vivo nonbioassay endpoints, all in vitro endpoints, and all nonbioassay endpoints) were performed. Linear regression was performed on

[1]The BMR selected for multidose PAH data for studies with a single benzo[a]pyrene dose was the response level observed in the benzo[a]pyrene dose group.

the log-transformed average RPF values to assess the predictive power of each endpoint or grouping, and to assess whether there was a quantitative basis for ordering them.

Table G-3 shows the results of regression analyses assessing how well the average RPFs for several endpoints correlated with average bioassay RPFs. The table shows that neither in vivo clastogenicity RPFs (micronuclei and sister chromatid exchanges) nor in vitro mutagenicity RPFs were significantly correlated with bioassay RPFs for the dataset examined here. Among those showing a significant ($p < 0.05$) linear relationship, in vivo DNA adducts provided the best correlation ($r^2 = 0.64$), followed by all in vivo nonbioassay endpoints ($r^2 = 0.55$), all nonbioassay endpoints ($r^2 = 0.40$), and all in vitro nonbioassay endpoints ($r^2 = 0.39$). Although in vivo DNA adducts provided the strongest correlation, the slope for this regression was 1.22, indicating that RPFs for in vivo DNA adducts systematically underpredicted bioassay RPFs. Figure G-1 demonstrates this underprediction; as the figure shows, most of the average RPF values are to the left of the 1:1 correspondence line. The slope for in vivo nonbioassays and Figure G-2 shows a similar result for this endpoint. The slopes for all nonbioassays and all in vitro nonbioassays are somewhat closer to 1.0. Plots showing the average RPF comparisons for all nonbioassays and all in vitro nonbioassays are shown in Figures G-3 and G-4. These plots suggest that all nonbioassay RPFs slightly underpredict bioassay RPFs, while all in vitro nonbioassays tend toward overprediction.

Table G-3. Results of simple linear regression of log–transformed average genotoxicity RPF versus log average tumor bioassay RPF

Genotoxicity endpoint	r^2	Slope	*p*-Value	n
All in vivo DNA adducts	0.64	1.22	<0.01	10
All in vivo nonbioassays	0.55	1.16	<0.01	11
All nonbioassay endpoints (in vitro and in vivo)	0.40	1.10	<0.01	20
All in vitro nonbioassays	0.39	0.95	<0.01	19
All in vivo micronuclei and sister chromatid exchanges	0.39	0.81	>0.05 (nonsignificant)	6
All in vitro mutagenicity	0.032	0.33	>0.05 (nonsignificant)	17

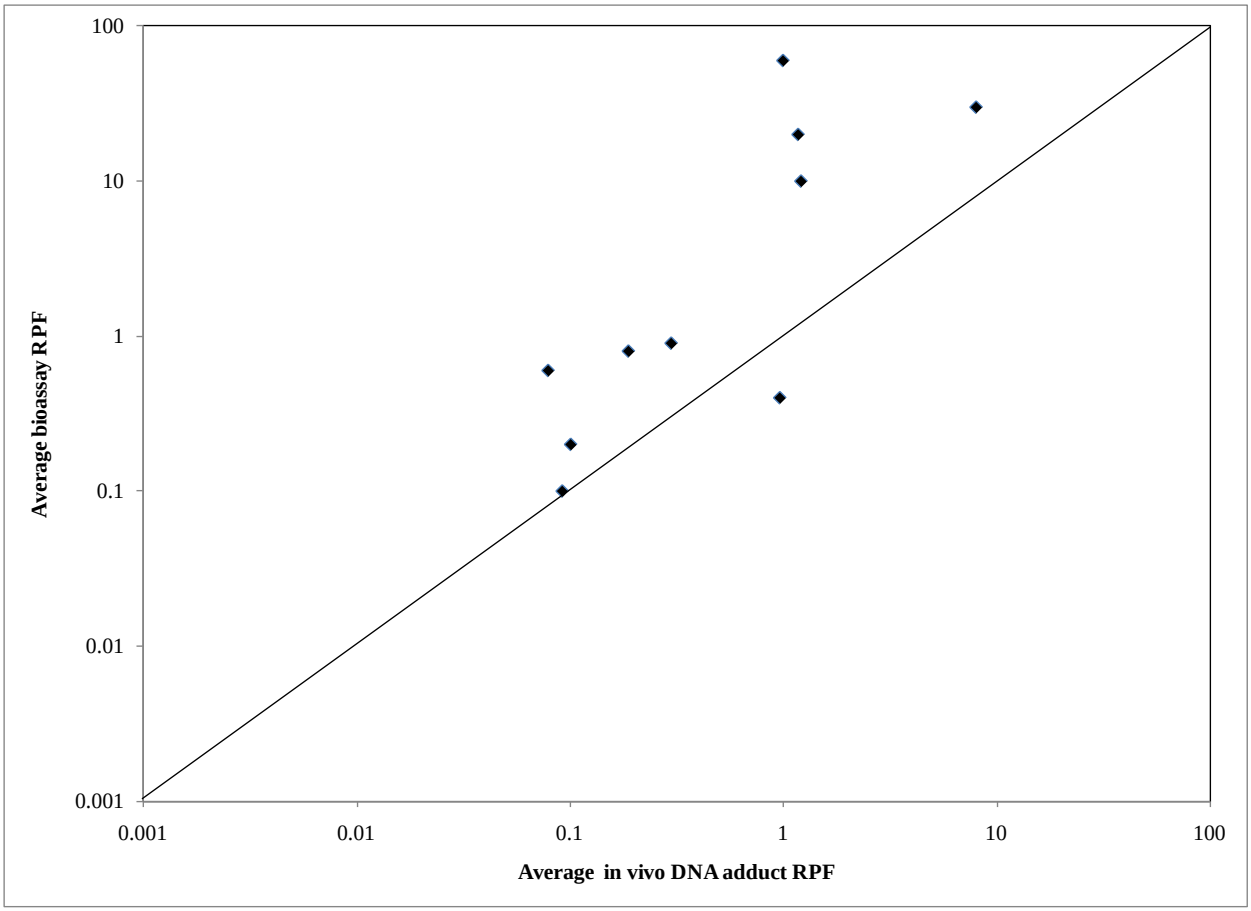

Figure G-1. Average bioassay RPF versus average in vivo DNA adduct RPF.

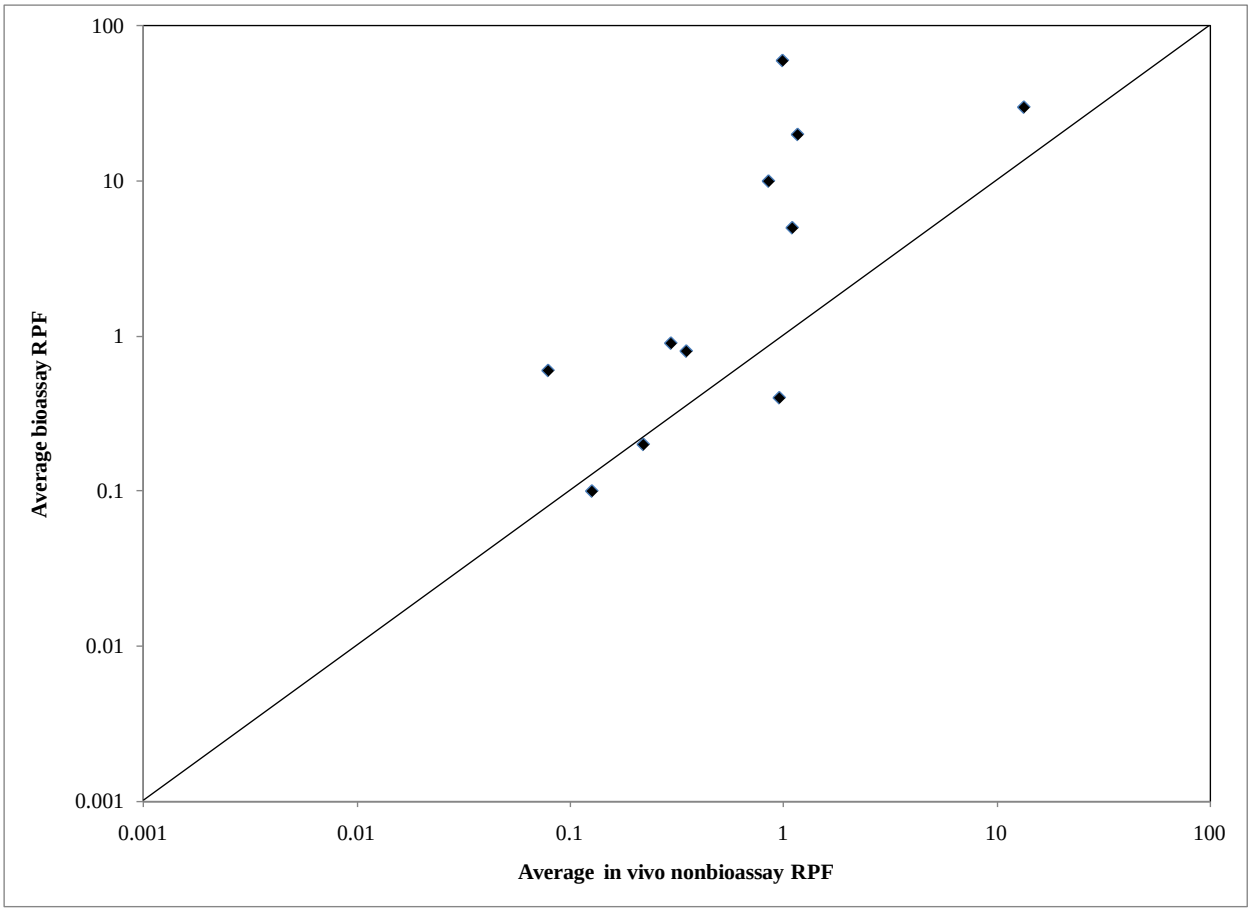

Figure G-2. Average bioassay RPF versus average in vivo nonbioassay RPF.

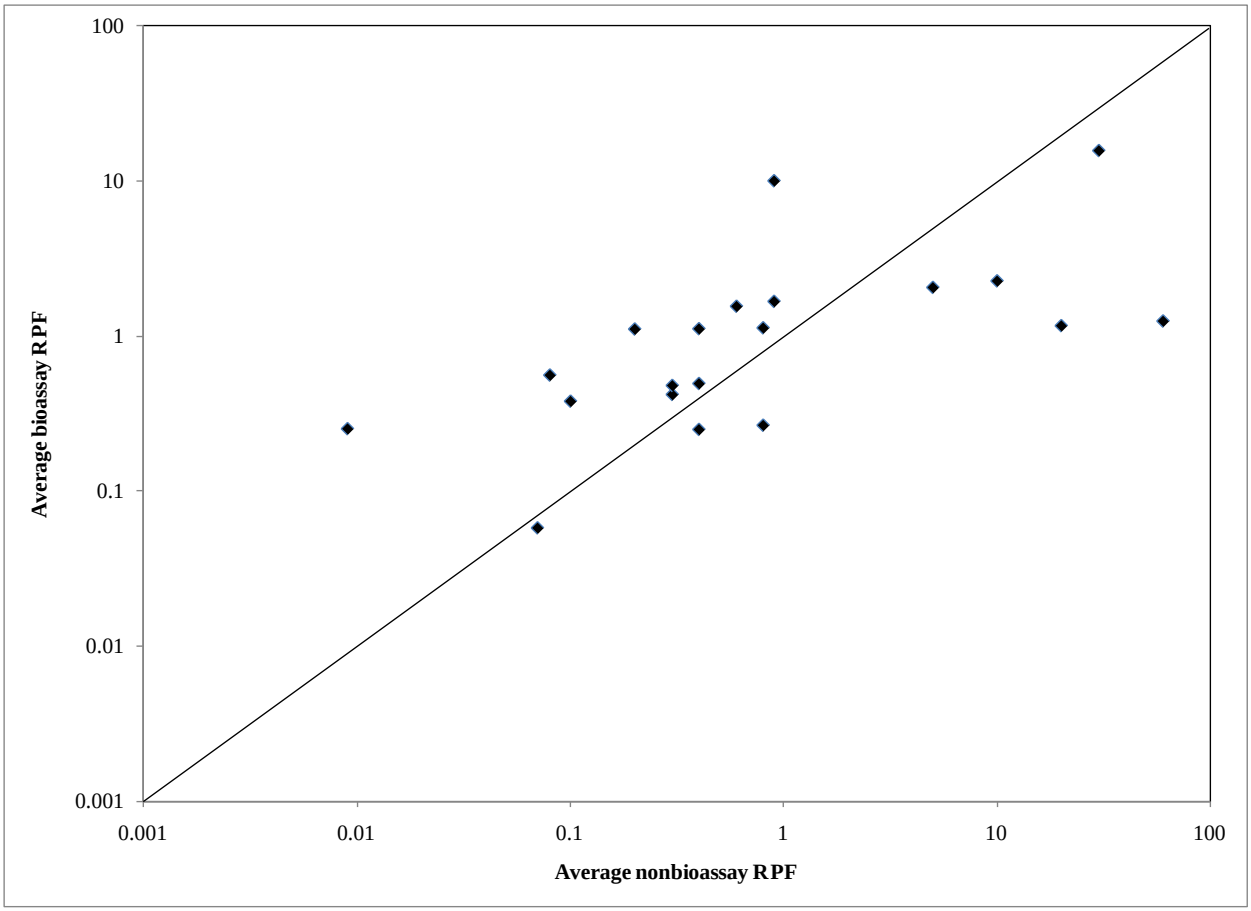

Figure G-3. Average bioassay RPF versus average nonbioassay RPF.

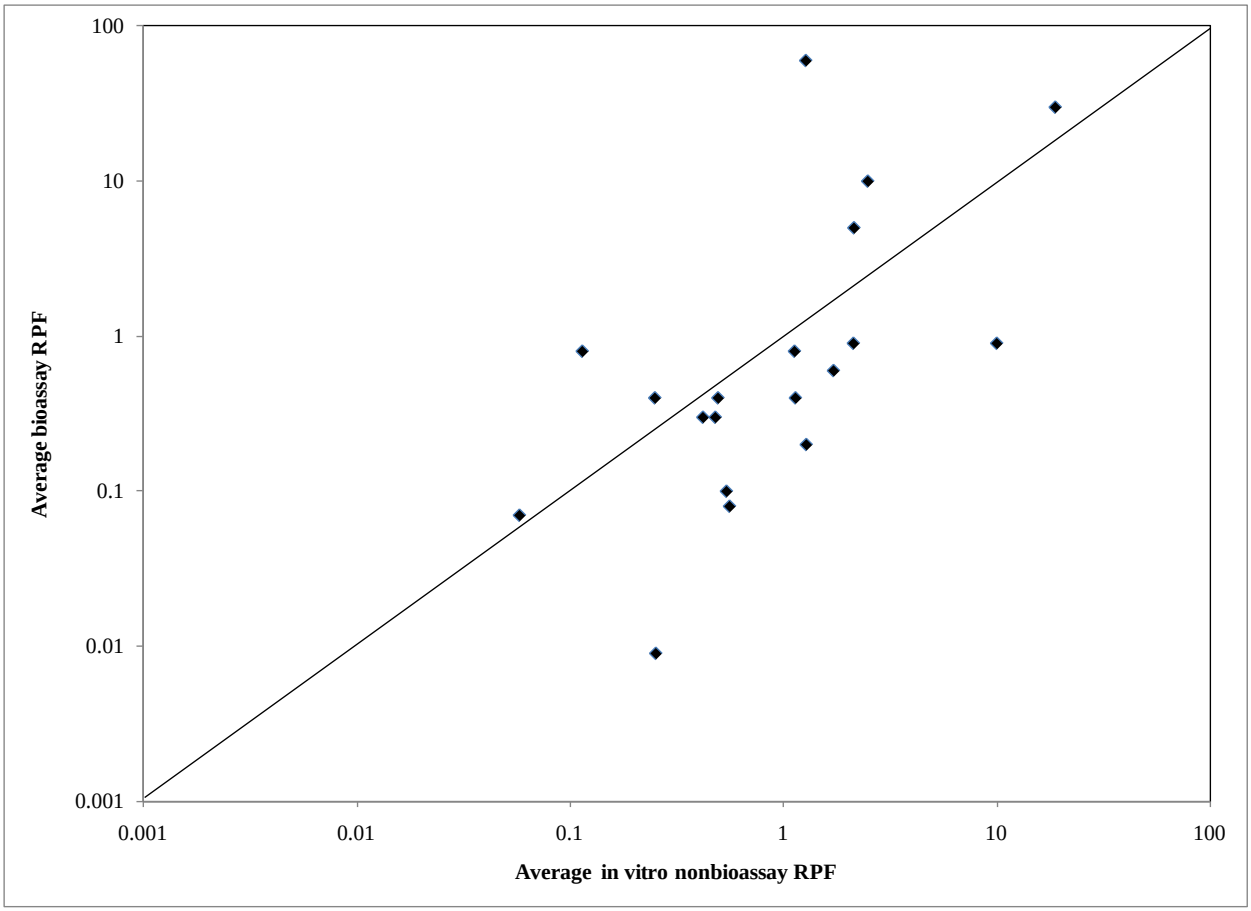

Figure G-4. Average bioassay RPF versus average in vitro nonbioassay RPF.

Based on the results of the linear regression analyses comparing PAH RPFs calculated for genotoxicity endpoints and RPFs calculated for bioassays (Table G-3), an argument could be made for the following ranking: (1) bioassays, (2) in vivo nonbioassays, and (3) in vitro nonbioassays. However, the improvement in correlation that is achieved with subdividing all nonbioassays into in vivo and in vitro endpoints is small, and the plot for in vivo nonbioassay RPFs (Figure G-2) shows that this grouping exhibits a slight tendency to underpredict bioassay RPFs.

In summary, as with the findings for tumor bioassay data, the analysis of options for ranking cancer-related endpoint RPFs did not suggest any clear basis for prioritizing the available data for the purpose of selecting RPFs. Thus, for PAHs without any tumor bioassay RPFs but with adequate information to suggest potential carcinogenicity, the cancer-related endpoint data were combined to calculate a final RPF as described in Chapter 7.