

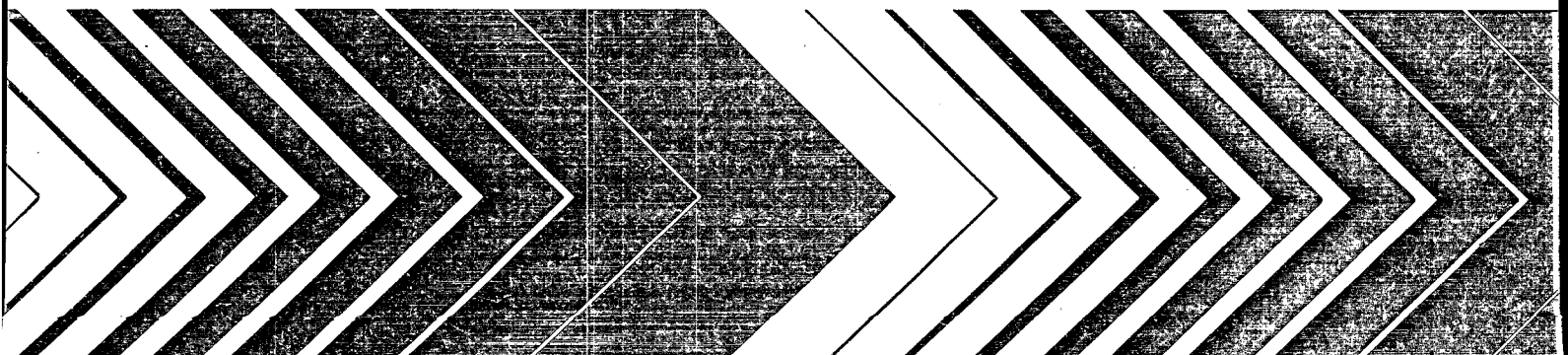
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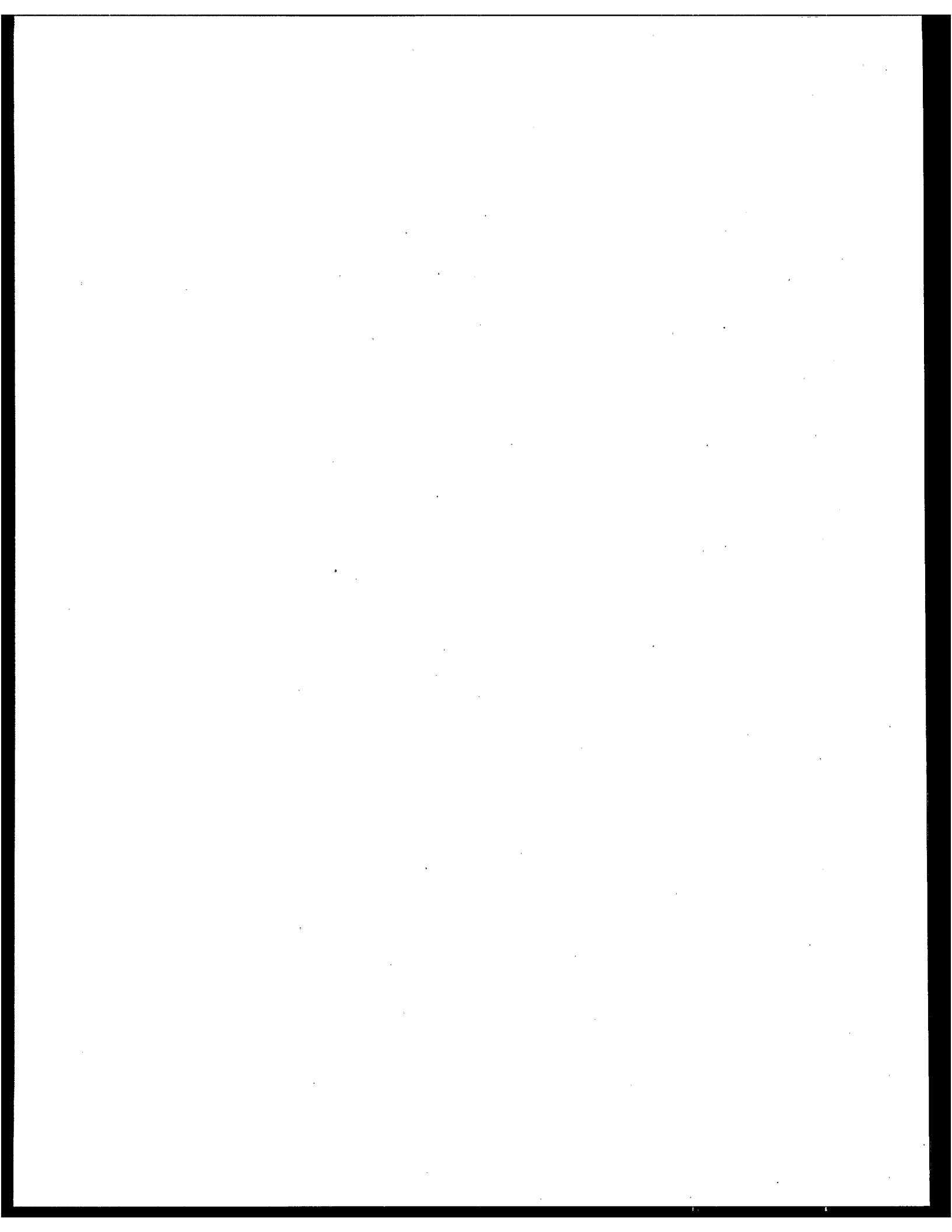
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July 1993



Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons





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**PROVISIONAL GUIDANCE FOR QUANTITATIVE RISK ASSESSMENT OF
POLYCYCLIC AROMATIC HYDROCARBONS**

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268



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PREFACE

The Office of Health and Environmental Assessment (OHEA) has prepared this Interim Guidance Document at the request of the Office of Emergency and Remedial Response. The purpose of this publication is to provide interim guidance for the quantitative risk assessment of polycyclic aromatic hydrocarbons (PAH).

For a more complete discussion of potential hazards from PAH exposure, the reader is referred to the 1992 Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAH). A literature search was not done in support of this short guidance document. A comprehensive, multimedia document for polycyclic aromatic hydrocarbons is in preparation by OHEA.

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INTRODUCTION

The Office of Health and Environmental Assessment (OHEA) recently completed an extensive document entitled "Drinking Water Criteria Document (DWCD) for Polycyclic Aromatic Hydrocarbons (PAHs)." In this document, weight-of-evidence judgments of Group B2, probable human carcinogen, are presented for seven PAHs; namely, benz[a]anthracene (BAA), benzo[b]fluoranthene (BBF), benzo[k]-fluoranthene (BKF), benzo[a]pyrene (BAP), chrysene (CHY), dibenz[a,h]anthracene (DBA), and indeno[1,2,3-cd]pyrene (IDP). All of these categorizations were found appropriate by the Carcinogen Risk Assessment Verification Endeavor (CRAVE), and files are available on the Agency's Integrated Risk Information System (IRIS) data base (U.S. EPA, 1993).

The 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986) support the calculation of quantitative risk estimates for those materials for which there is a reasonable concern for potential human health risk; for example, PAHs categorized as B2, probable human carcinogen. In the 1992 DWCD for PAHs, a quantitative risk estimate for oral exposure to BAP was given as a range of values from 4.5-9.0 per (mg/kg)/day with a geometric mean of 5.8 per (mg/kg)/day; the drinking water unit risk calculated from the mean was $1.7E-4$ per ($\mu\text{g/L}$) (U.S. EPA, 1992).

NOTE: At the June 1992 meeting of the CRAVE a revised risk estimate was verified. It was noted that an error had been made in the 1991 document "Dose-Response Analysis of Ingested Benzo[a]pyrene" which is cited in the DWCD for PAHs. In the calculation of the doses in the Brune et al. (1981) study it was erroneously concluded that doses were given in units of mg/year, whereas it was in fact mg/kg/year. When the doses are corrected the slope factor is correctly calculated as 11.7 per (mg/kg)/day as opposed to 4.7 per (mg/kg)/day as reported in the DWCD. The correct range of slope factors is 4.5-11.7 per (mg/kg)/day with a geometric mean of 7.3 per (mg/kg)/day. A drinking water unit risk based on the revised slope factor is $2.1E-4$ per ($\mu\text{g/L}$). These values are being changed on IRIS and an Erratum to the DWCD is being prepared.

Data were insufficient for the calculation of slope factors for any other PAHs discussed in the DWCD. While PAHs in general, and BAP in particular, are well-studied as carcinogens, data are by and large unsuitable for the calculation of quantitative risk estimates by conventional methods for one or more of the following reasons.

- Data were from exposures not typically used in deriving quantitative estimates for oral or inhalation exposure (e.g., skinpainting or subcutaneous exposure).
- Study populations were too small.
- Studies were done at only one exposure level.
- Dose-response data were not reported.

EPA quantitative risk estimates for mixtures of PAHs have often assumed that all carcinogenic PAHs are equipotent to BAP, and that the carcinogenic effect of the mixture can be estimated by the sum of the effects of each individual PAH (U.S. EPA, 1980). It has been recognized that some PAHs are less carcinogenic in animal studies than is BAP, so that application of this policy could result in an overestimation of the effect of those PAHs. On the other hand, PAH mixtures are likely to contain carcinogenic PAHs that are not considered indicator compounds and thus would not be measured. Some PAHs, moreover, have been shown to be more potent animal carcinogens than BAP.

This practice has been inconsistent; some risk assessments applied the BAP slope factor to all measured PAHs, rather than only those categorized as probable or possible human carcinogens. This would be expected to result in an overestimation of the mixture risk. Other risk assessments have used comparative potencies for PAHs published in the open literature, those cited in a contractor report to EPA (Clement Associates, 1988), or those based on ranking of PAHs presented in an Erratum to the Ambient Water Quality Criteria for PAHs (U.S. EPA, 1983).

This paper presents some comparative risk estimates for assessment of potentially carcinogenic PAHs. These are not proposed as toxicity equivalency factors

(TEF). A series of guiding criteria have been discussed for the application of a TEF to mixtures (U.S. EPA, 1991). They include the following:

1. A demonstrated need for the TEF. The PAHs meet this criterion. PAHs are found in all media; as a group they are among the most common contaminants at waste sites. PAHs are the subject of constant inquiry at the Superfund Technical Support Center. The lack of numerical estimates of risk for any PAH except BAP has had the potential for negative impacts on many risk-based regulatory decisions.
2. A well-defined group of chemicals. This criterion is also met. Any compound consisting of three or more fused aromatic rings qualifies as a PAH. At this time OHEA is limiting the definition to exclude all compounds with substituents on the ring or compounds with anything other than carbon and hydrogen in their composition. For purposes of this paper (and the Multimedia Document in preparation), only those PAHs classified as B2, probable human carcinogen, are being considered.
3. A broad base of toxicologic data. The data for PAHs are limited. Studies have, for the most part, been confined to carcinogenicity, genotoxicity and metabolism studies (generally concerned with the identification of metabolites that are genotoxic or carcinogenic). For this reason and others below, a weighting of potential potency is recommended only for carcinogenicity.
4. Consistency in the relative toxicity of congeners across toxicological endpoints, both *in vivo* and *in vitro*. As noted above there is not a broad toxicological data base. Consistency is observed among cancer bioassays in various animal models and by different routes. The point of congruency is in the generation of biologically active metabolites; if the PAH is administered to a system capable of "activating" metabolism, then tumors will be observed. If the site of administration is capable of metabolism (e.g., skin), contact point tumors will be observed. If the PAH can be absorbed and metabolized, then distant site tumors will also be observed. There are data which show that genotoxicity for individual PAHs and mixtures of PAHs are generally proportional to tumorigenicity. There are also

some limited data to indicate that immunotoxicity is roughly correlated with carcinogenic potency. Data for other noncancer effects are generally lacking but indicate that carcinogenicity is the most sensitive endpoint for PAH toxicity. The ranking of potential potency in this document is recommended only for PAH carcinogenicity.

5. Demonstrated additivity between the toxicity of individual congeners. Few studies have been reported which are an adequate test of an additivity assumption. In this regard the data bases for PAH, PCB congeners and dibenzo-p-dioxins and dibenzofurans are about of equal quality. Both additive and nonadditive effects have been observed for the carcinogenicity or genotoxicity of PAHs by various routes. Both inhibition and cocarcinogenicity have been observed for mixtures of PAHs; effects are dependent on route and proportion of materials and solvents (see U.S. EPA, 1992 for a review). It is logical to assume that in skin PAHs act as their own promoters; most B2, probable human carcinogens, in this group have been shown to be complete carcinogens in mouse skin. There have been few demonstrations that one PAH can serve as a promoter for a different PAH. According to the Guidelines for the Health Risk of Chemical Mixtures (U.S. EPA, 1986), ". . . none of the models for toxicant interactions can predict the magnitude of toxicant interactions in the absence of extensive data." The Guidelines make no recommendation as to the use of any risk model for promotion.

The guidelines further state the following:

Based on current information, additivity assumptions are expected to yield generally neutral risk estimates (i.e., neither conservative nor lenient) and are plausible for component compounds that induce similar types of effects at the same sites of action (U.S. EPA, 1986).

A National Research Council Report (NRC, 1988) notes that a consideration of the mathematical considerations of low-dose extrapolation shows that interactions which are demonstrable at high doses will not be detectable at low doses. All of the above indicates that the use of an additivity assumption for PAHs is not

contraindicated and is consistent with the practice of the Risk Assessment Guidelines.

6. Some mechanistic rationale as to why TEFs would be applicable to a particular group of chemicals. This criterion is met for PAHs assuming that one accepts the hypothesis that mutation or some DNA change is a necessary step in carcinogenesis. All the PAHs for which ranking of potential potency is proposed can be shown both to induce tumors in animals and genetic changes (generally mutations) in some systems.
7. Some method of gaining consensus as to what TEFs ought to be. This process has not yet been undertaken for PAHs. The proposed ranking of potential potency was developed by a small group of OHEA scientists and has received only OHEA review.

In summary, not all of the guiding criteria are met for TEF. For this reason OHEA has chosen not to label the risk assessment numbers in this document a "toxicity equivalency factor" but rather an "estimated order of potential potency." It should be recognized in the application of these risk estimates that there are many limitations. First, these risk estimates are applicable only to cancer evaluation. Second, additivity of PAH response has not been proved (or refuted). Last, the estimated order of potential potency described herein is an OHEA interim recommendation and does not constitute an Agency consensus.

ESTIMATED ORDERING OF POTENTIAL POTENCIES OF PAHS

In studies of rodents, wherein BAP was assayed for carcinogenicity in conjunction with other PAHs, a range of carcinogenic potencies were observed. For example, as seen in Table 1, several PAHs were less effective in tumor induction in a mouse lung adenoma assay than was BAP at smaller or equivalent doses (LaVoie et al., 1987). Likewise, ranges of potency have been observed in many species and by different routes; for example, intrapulmonary injection in rat lungs (Table 2) and skin painting in mice (Table 3).

Inspection of these data suggest that one should be able to estimate orders of potential carcinogenic potencies for various PAHs by comparison with the activity of a standard compound. If BAP is used as the standard, then estimates of individual slope factors could be done as a percentage of the calculated slope factor for BAP. This approach could be applied to estimating the amounts of group B2 (probable human carcinogen) PAHs in a particular exposure situation and calculating their weighted contribution (by comparison to BAP) to total carcinogenic activity of the mixture.

The choice of the data set or sets to be used for estimating the potency is important, as is the modeling procedure used to provide estimates of carcinogenic activity. A discussion of various approaches is given in the DWCD (U.S. EPA, 1992).

Previous work attempted to derive relative potencies for PAHs. One derivation was done by T. Thorslund of ICF-Clement Associates on contract to U.S. EPA. An interim report (Clement Associates, 1988) is described in some detail in U.S. EPA (1992). In this report data were used from studies wherein BAP and several other PAHs were administered in the same time frame by routes including skin painting, intraperitoneal or subcutaneous injection, and lung implantation. For each study considered, a comparison was made between BAP carcinogenic activity and the activity of a particular PAH in that same report.

Two forms of dose-response models were used: either $P(d) = 1 - \exp[-a(1+bd)]$; or $P(d) = 1 - \exp[-a(1+bd)^2]$, where a and b are background and exposure-related parameters, respectively (Clement Associates, 1988). The first equation is simply a one-hit model, which is a special case (one-stage) of the multistage model. The second equation is a special case of the multistage model with two stages and an additional assumption that the first and second transition rates are identical relative to their respective background rates. In the application of these models it was assumed that carcinomas can develop from papillomas. For studies which reported only combined tumors or did not classify tumors, the simple form, or one-stage model was used. The two-stage model was used for data in which malignant tumors were reported separately.

In deriving the potency for each PAH relative to BAP, it was assumed that the PAHs and BAP have similar dose-response curves, but that it takes a proportionally

larger concentration of non-BAP material to induce an equivalent tumor response. The relative potency of each PAH was calculated as the ratio of the estimated transition rates with the potency of BAP indexed as 1. Point estimates (maximum likelihood estimates) were compared rather than upper bounds. An example of relative potencies from one data set is given in Table 4. In this and all subsequent tables, transition rates and relative potencies for PAHs are given as reported in Clement Associates (1988). This is to allow the reader to follow derivation of the numbers; it is acknowledged that the number of significant figures is a reflection only of the precision of numerical calculations and does not accurately transmit the degree of experimental uncertainty.

The result of all calculations based on 11 separate studies is a range of comparative potencies; the ranges reported in Clement Associates (1988) for PAHs classified as B2, probable human carcinogen, are given in Table 5.

Clement Associates (1988) selected what they considered to be the most appropriate relative potency for each PAH based on a consideration of qualitative differences in studies. Their selections are presented in Table 6. It should be noted that the application of study selection criteria other than those described in the Clement Associates (1988) report could result in the selection of different "most appropriate" relative potencies. In this context, a peer review panel convened in 1988 to review the DWCD on PAHs and felt that potencies based on the Deutsch-Wenzel et al. (1983) study would be less reliable than those based on other bioassays because of the unusual route of exposure (surgical implantation of wax pellets in the lung). Arguments for the validity of this exposure method have also been presented, however.

Other approaches for obtaining a single estimate of relative potency are feasible; for example, taking a mean, a weighted mean, or some other measure of central tendency of the individual estimates comprising the range. Calculated means are given in Table 7 as well as order of magnitude potencies based on the following rounding scheme: $0.51-5.0 = 1.0$; $0.051-0.50 = 0.1$; $0.0051-0.050 = 0.01$.

The approach chosen here was to select a test system that provides a complete set of comparisons. Of the data sets modeled in Clement 1988, mouse skin painting

bioassays wherein PAHs were tested as complete carcinogens rather than as initiators only, meets this criterion. This data set is compiled from four reports with standard study protocols, using adequate numbers of test animals (20-36). These studies are not without deficiencies. For example, neither the Bingham and Falk (1969) paper nor Wynder and Hoffmann (1959) reported solvent control tumor incidences. Estimated orders of potential potencies based on skin painting tests as reported by Clement (1988) are given in Table 8. These are rounded to orders of magnitude using the rule presented above.

The values in Table 8 are recommended for interim use. They are based on well conducted studies using a standard, easily comparable endpoint well-known to be associated with exposure to PAHs; namely, complete carcinogenesis after repeated exposure to mouse skin. The potencies of PAH for comparison were calculated by Clement Associates (1988) using both forms of the model (one and two stages as indicated in Table 8). For this exercise no claim as to biological relevance is made for the modeling procedure; rather, it represents a convenient curve-fitting procedure, based on plausible assumptions. It is recommended that only the order of magnitude ranking be used. The quality of the data and the analysis thereof do not support any greater precision.

CONCLUSIONS

The values in Table 8 are provided for interim use. Research on relative potencies for PAHs and on the development of a TEF methodology is being undertaken by OHEA and other parts of the Agency. Areas of research include: the assumption of additivity of carcinogenic activity of PAHs; the basis for choice of studies and data sets; and the choice of modeling procedures.

In summary, a series of relative potency values (orders of magnitude) is provided as temporary guidance for the risk evaluation of PAHs. It is recognized that the list of PAHs in Table 8 is not sufficiently extensive to meet the needs of Programs and Regions; part of the continuing work on PAHs will be the consideration of the expert panel approach of ranking PAH hazards undertaken by OERR. Also in progress is

work to expand the series to include PAH for which there are animal carcinogenicity studies that did not include BAP as a positive control.

The guidance in this paper should be applied only to assessment of carcinogenic hazard from oral exposure to PAHs. There is currently no inhalation unit risk for BAP that has been found acceptable by the CRAVE. At this time, there is no basis for judgment that BAP or other PAHs will be equipotent by oral and inhalation routes. The documented effects of particulate matter and other cocarcinogens on BAP carcinogenic effects in animal lungs are confounding issues for the derivation of an inhalation unit risk for BAP and the establishment of potencies for inhalation vs. oral exposure to other PAHs.

In order to apply this guidance of relative potencies to mixtures, empirical data are needed on the additivity (or lack thereof) of carcinogenic effects of PAHs. Results of testing simple mixtures of PAHs and mixture components must be compared to assessments made from bioassays of complex environmental mixtures. Research of this nature is being undertaken by the U.S. EPA Health Effects Research Laboratory and by several research groups under contract to the Electrical Power Research Institute.

TABLE 1			
Incidence of Lung Adenomas Observed in Newborn Mice for Various PAHs ^a			
Treatment	Total Dose (μmol)	Lung Adenomas	
		Incidence	% Response
Control ^b	0	0/35	0
Benzo[a]pyrene	1.1	23/31	74.2
Benzo[b]fluoranthene	0.5	5/32	15.6
Benzo[j]fluoranthene	1.1	15/39	38.5
Benzo[k]fluoranthene	2.1	4/34	11.8
Indeno[1,2,3-cd]pyrene	2.1	1/20	5.0

^aSource: Adapted from LaVoie et al., 1987

^bDimethylsulfoxide was used as the vehicle control.

TABLE 2

Tumor Incidence in Female Osborne-Mendel Rats Administered PAHs by Intrapulmonary Injection^a

Treatment	Total Dose (mg)	Epidermoid Carcinomas	
		Incidence	% Response
CONTROL ^b	0	0/35	0
Benzo[a]pyrene	1.0	33/35	94.3
Benzo[b]fluoranthene	1.0	9/35	25.7
Benzo[e]pyrene	5.0	1/35	2.9
Benzo[k]fluoranthene	4.15	12/27	44.4
Indeno[1,2,3-cd]pyrene	4.15	21/35	60.0
Benzo[g,h,i]perylene	4.15	4/34	11.8

^aSource: adapted from Deutsch-Wenzel et al., 1983

^bNeither untreated nor vehicle (beeswax and trioctanoin pellets) controls were observed to develop epidermoid carcinomas.

TABLE 3

Tumor Initiating Activity of PAHs in Female CD-1 Mouse Skin^a

Treatment	Total Initiating Dose (μg)	Incidence	Tumor Response ^b % Response	# Tumors/ Animal
Control ^c	0	0/20	0	0
Benzo[a]pyrene	30	17/20	85.0	4.9
Benzo[b]fluoranthene	30	12/20	60.0	2.3
Benzo[j]fluoranthene	30	6/20	30.0	0.6
Benzo[k]fluoranthene	30	1/20	5.0	0.1

^aData from LaVoie et al., 1982. Initiating doses were applied in 10 doses, one every other day followed by applications of TPA 3 times/week for 20 weeks.

^bTumors were largely papillomas.

^cAcetone was used as the vehicle control.

TABLE 4

Relative Potency Estimates for PAH Based on Skin Tumor Data^a

Treatment	Total Dose (mg/animal)	Tumor Incidence	Estimated Transition Rate	Relative Potency ^b
DMSO	0	0/35	—	—
Acetone	0	0/36	—	—
BAP	1.7 2.8 4.6	8/43 24/35 22/36	3.92	1.0
BBF	3.4 5.6 9.2	2/38 5/34 20/37	0.656	0.167
BJF	3.4 5.6 9.2	1/38 1/35 2/38	0.241	0.241
BKF	3.4 5.6 9.2	1/39 0/38 0/38	0.078	0.020
IDP	3.4 5.6 9.2	1/35 0/37 0/37	0.081	0.021

^aSource: Data from Habs et al. (1980); transition rates and relative potencies from Clement Assoc. (1988).

^bModel: $P(d)=1-\exp[-a(1+bd^2)]$

TABLE 5

Summary of Relative Potency Estimates for Indicator PAHs^a

Compound	Test System				
	Mouse Skin Carcinogenesis	Subcutaneous Injection into Mice	Intrapulmonary Administration to Rats ^b	Initiation-Promotion on Mouse Skin	Intraperitoneal Injection in Newborn Mice
Benzo[a]pyrene	1.0	1.0	1.0	1.0	1.0
Benz[a]anthracene	0.145 ^c				0.057, 0.524, 0.496 ^d
Benzo[b]fluoranthene	0.167 ^e		0.140	0.258 ^f , 0.125 ^g	0.232, 1.067, 0.874 ^h
Benzo[k]fluoranthene	0.020 ^e		0.066	0.022 ^f	0.040, 0.097, 0.044 ^h
Chrysene	0.0044 ⁱ			0.040 ^g	0.125, 0.33 ^d
Dibenz[ah]anthracene	1.11 ⁱ	2.82 ^j , 4.50 ^k			
Indeno[1,2,3-cd]pyrene	0.021 ^e , 0.089 ^l		0.232	0.074 ^l	0.013 ^h

^aWhere more than one potency estimate is shown, they were derived from the same study using different tumor types as endpoints. Both forms of the dose-response model in the text were used.

^bDeutsch-Wenzel et al., 1983

^cBingham and Falk, 1969

^dWislocki et al., 1986

^eHabs et al., 1980

^fLaVoie et al., 1982

^gVan Duuren et al., 1966

^hLaVoie et al., 1987

ⁱWynder and Hoffmann, 1959

^jPfeiffer, 1977

^kBryan and Shimkin, 1943

^lHoffmann and Wynder, 1966

TABLE 6

Comparative Potency Estimates Based on Single Data Sets as Calculated by
Clement Associates, 1988

Compound	Relative Potency	Reference
Benzo[a]pyrene	1.0	
Benzo[a]anthracene	0.145 ^a	Bingham and Falk, 1969
Benzo[b]fluoranthene	0.140 ^a	Deutsch-Wenzel et al., 1983
Benzo[k]fluoranthene	0.066 ^a	Deutsch-Wenzel et al., 1983
Chrysene	0.0044 ^a	Wynder and Hoffmann, 1959
Dibenzo[a,h]anthracene	1.11 ^a	Wynder and Hoffmann, 1959
Indeno[1,2,3-cd]pyrene	0.232 ^b	Deutsch-Wenzel et al., 1983

^aModel: $P(d)=1-\exp[-a(1+bd)^2]$

^bModel: $P(d)=1-\exp[-a(1+bd)]$

TABLE 7

Ranges and Combined Potencies for Seven PAHs*

Compound	Range	Potency Relative to BAP		
		Simple Mean	Geometric Mean	Order of Magnitude
Benzo[a]pyrene	—	—	—	1.0
Benzo[a]anthracene	0.057-0.524	0.31	0.22	0.1
Benzo[b]fluoranthene	0.125-1.067	0.41	0.29	0.1
Benzo[k]fluoranthene	0.020-0.097	0.05	0.04	0.01
Chrysene	0.0044-0.33	0.12	0.05	0.01
Dibenz[a,h]anthracene	1.11-4.5	2.81	2.42	1.0
Indeno[1,2,3-cd]pyrene	0.013-0.232	0.08	0.08	0.1

*Relative potencies given in the range are from Clement Associates, 1988. Both forms of the dose-response model in the text were used.

TABLE 8

Estimated Order of Potential Potencies of Selected PAH Based
on Mouse Skin Carcinogenesis

Compound	Relative Potency ^a		Reference
Benzo[a]pyrene	1.0	1.0	
Benz[a]anthracene	0.145	0.1	Bingham and Falk, 1969
Benzo[b]fluoranthene	0.167	0.1	Habs et al., 1980
Benzo[k]fluoranthene	0.020	0.01	Habs et al., 1980
Chrysene	0.0044	0.001	Wynder and Hoffmann, 1959
Dibenz[a,h]anthracene	1.11	1.0	Wynder and Hoffmann, 1959
Indeno[1,2,3-cd]pyrene	0.055 ^b	0.1	Habs et al., 1980; Hoffmann and Wynder, 1966

^aModel was $P(d)=1-\exp[-a(1+bd)^2]$ for all but indeno[1,2,3-cd]pyrene

^bSimple mean of relative potencies (0.021 and 0.089) the latter of which was derived using the one-hit model.

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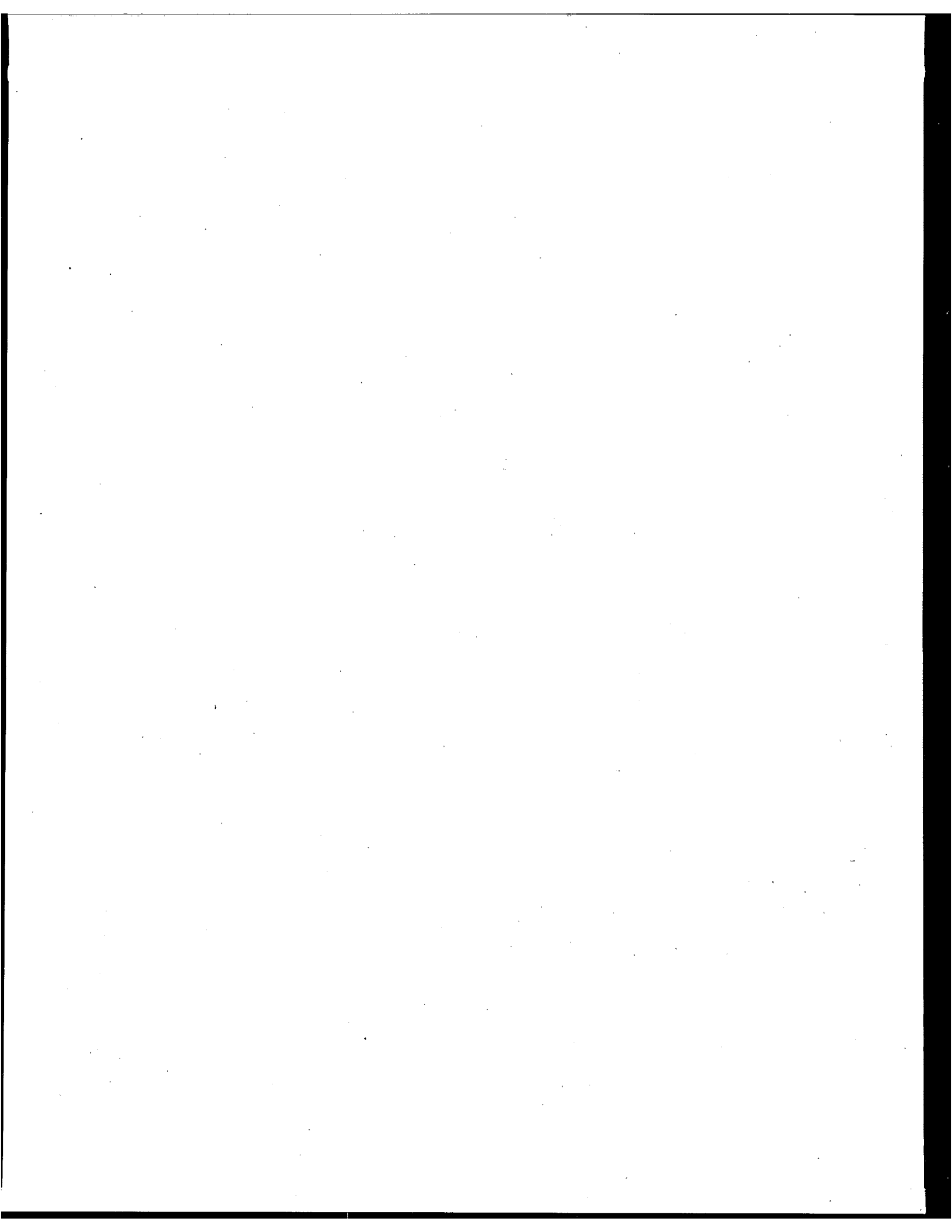
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