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THE EVALUATION AND ESTIMATION OF POTENTIAL CARCINOGENIC

RISKS OF POLYNUCLEAR AROMATIC HYDROCARBONS (PAH)

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EVALUATION AND ESTIMATION OF POTENTIAL CARCINOGENIC RISKS OF POLYNUCLEAR AROMATIC HYDROCARBONS*

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INTRODUCTION

The evaluation and estimation of potential risks of human exposures to hazardous chemicals such as polynuclear aromatic hydrocarbons (PAHs) can be useful in the setting of permissible levels of hazardous chemicals in the workplace and the environment, or in the setting of regulatory priorities. The hazard potential can be evaluated by considering all of the parameters related to the fate, effects, and dose-response characteristics of the hazardous substance in question. Important parameters for assessing such hazards are chemical structure; physical-chemical properties; mechanisms of action; chemical, biological, and environmental transformation and transport; and toxicity indices. Some of these parameters can be estimated directly from experimental data, while others may be estimated indirectly through the use of modeling techniques.

Risk can be conceptualized as a composite function of the hazard and exposure potentials. In order to estimate the potential risk of human exposure to a hazardous chemical, exposure parameters such as level, duration, frequency, and route are needed. Exposure parameters can be derived using monitoring or modeling results. The ability of the chemical to induce the potential effect (i.e., a "potency" factor) can then be coupled to the magnitude of exposure to give an estimate of the potential risk.

The assessment of human cancer risk is a complicated scientific undertaking. It relies heavily upon available data,

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*The views expressed in this paper are those of the authors and not necessarily those of the U.S. Environmental Protection Agency.

scientific assumptions, and judgments to bridge data gaps. Thus there is great uncertainty in every step of the process. The extent and the form of a risk assessment also depends upon the uses for which it is designed.

This paper presents the general framework of current approaches useful in the assessment of potential carcinogenic risks; problems associated with these approaches with emphasis related to the assessment of specific individual PAHs; and, finally, alternatives that can be developed as more data gaps are filled in the near future.

EVALUATION OF POTENTIAL CARCINOGENIC HAZARDS

Substances suspected of being carcinogenic hazards can be evaluated by considering available chemical, biological, and toxicologic data. This process, called hazard identification (25), relies heavily on three types of information: (1) epidemiologic and clinical studies of human populations, (2) long-term experimental animal studies, and (3) short-term *in vivo* and *in vitro* tests, comparative metabolism, pharmacokinetics, and other biochemical and mechanistic studies, including structure-activity correlations.

The types and volume of information available, and their contribution to such assessments, vary from compound to compound. The weight-of-evidence approach can be used to organize this information in formulating a judgment of the potential carcinogenic hazard of the compound at hand (1, 18, 40, 41). The weight-of-evidence is defined as the degree of evidence for carcinogenicity in humans, and not the relative carcinogenic activity or "potency" of the agent.

The most complete form of weight-of-evidence determination is made from a consideration of the validity, quality and relevance of each epidemiologic and long-term animal study, as well as all short-term toxicologic, biological, chemical, and mechanistic information.

Epidemiologic Studies

Epidemiologic studies can, under certain conditions, provide direct evidence of the association of increases in tumor incidence in humans with exposure to specific chemicals. Consistent results in independent studies, freedom from bias and confounding factors, reliable exposure data, sufficient follow-up time, and high levels of statistical significance are impor-

tant factors leading to increased confidence in the determination of a causal relationship.

Long-Term Animal Studies (Carcinogenesis Bioassays)

While human data provide the most direct evidence for the carcinogenicity of a compound, usually such data either do not exist or are inadequate. In the absence of human data, reliance is placed on information from long-term animal studies in assessing the potential carcinogenic risk to humans. It should be noted that information compiled and evaluated by the International Agency for Research on Cancer (IARC) shows that chemicals or groups of chemicals that are known to be human carcinogens and have been tested appropriately, produce cancer in animals. This certainly supports the use of animal data as indicators of potential human carcinogenicity.

The general factors considered in evaluating the carcinogenicity of chemicals using animal studies are the induction of rare tumors, the earlier induction of tumors, and the induction of higher incidences of tumors when compared to control animals. Confidence in the results of animal experiments is gained when the carcinogenic effects have been confirmed in repeated experiments, and have been observed in different strains or species, in different dose groups or sexes, or in multiple organs or tissues, with high degrees of malignancy and dose-related trends.

Short-Term Tests, Structure-Activity Relationships, and Metabolic, Pharmacokinetic, and Mechanistic Studies

Results from short-term tests, structure-activity analyses, and metabolic, pharmacokinetic, and mechanistic studies are currently being used as supportive evidence in modifying judgments based on epidemiologic and long-term animal studies. By far the largest volume of information recently generated is in the area of short-term tests for mutagenicity. While the IARC has not formally incorporated mutagenesis testing results in its classification system, an evaluation scheme for analyzing mutagenicity testing data has been developed (18, 19). Short-term *in vivo* carcinogenesis testing (sometimes referred to as "limited-bioassay") such as skin-painting experiments with mice, and mouse-skin initiation-promotion studies, are not given the same status as the conventional carcinogenesis bioassay. Structure-activity analyses and metabolic, pharmacokinetic, and mechanistic studies are evaluated on a case-by-case basis, since their availability is variable.

The results of the analysis of epidemiologic evidence and evidence from long-term animal studies are combined to determine the human carcinogenic hazard potential of the chemical being evaluated. This determination is modified on the basis of data from short-term tests and other supportive information (18, 41)

ESTIMATION OF POTENTIAL CARCINOGENIC RISKS

After qualitative evaluations of the data bearing on a chemical's ability to induce a carcinogenic effect, and the relevance of such data to humans, it is desirable to estimate the magnitude of the potential human risks. Two additional categories of data are usually needed to provide such an estimate: (1) dose-response data from which a "potency factor" can be derived; (2) information on the number of humans and the types, levels, and durations of potential human exposures. The results of coupling the potency factor with the magnitude of exposure will provide a numerical estimate of potential human risk.

This paper is concerned mainly with estimating the carcinogenic potential of a compound. The evaluation of potential human exposures and the estimation of risks based on potential exposures will not be considered here.

Estimating Carcinogenic Potency

The carcinogenic potency of a compound can be defined as the probability of an individual's developing cancer in his or her lifetime following exposure to a unit dose, if the unit dose is sufficiently small.

The carcinogenic potency of a known or suspect carcinogen cannot be estimated with accuracy because it is not possible to determine the shape of the dose-response curve beyond experimental exposure levels. In the absence of knowledge regarding the shape of the dose-response curve, the multistage model is used for low-dose extrapolation to provide an upper-bound estimate of carcinogenic potency when animal bioassay data are used. The reasons for selecting the multistage model and using the upper-bound estimate are given in the following section. When human data are used, the procedure for estimating carcinogenic potency, and the accuracy of such estimates, depend on the availability and the quality of the data. The data reported in an epidemiologic study may range from a simple relative risk estimate associated with a rough estimation of average exposure to a full report on each individual in the cohort, including information such as age, cause of death, detailed work history,

smoking habits, and length of exposure.

Choice of the Extrapolation Model

Because the procedure for estimating risk from human data varies depending on the availability and quality of data, we concentrate our discussion on the procedure for estimating carcinogenic potency where animal bioassay data are used. Several dose-response models are available for low-dose extrapolation. These include the probit, the multi-hit, the logit, and the multistage models. These models are generally statistical in character, and are not derived from biological arguments, except for the multistage model, which has been used to support the somatic mutation hypothesis of carcinogenesis (3, 42, 43). The main difference among these models is the rate at which the response function, P(d), approaches P(0) as dose d decreases. For instance, the probit model would usually predict a smaller risk at low doses than the multistage model because of the difference of the decreasing rate in the low-dose region. However, it should be noted that one could always artificially make the multistage model have the same or even greater rate of decrease as the probit model by transforming the dose rate and/or by assuming that some of the parameters in the multistage model are zero. This, of course, is not reasonable without knowing, a priori, what the carcinogenic process for the agent is. The multistage model is used for the extrapolation because it is the most general model, with other models approximating some form of the multistage model according to the values of the parameters. Although the multistage model appears to be a reasonable (at least the most general) model to use, the point estimate generated from the model is not used because a question remains as to the shape of the dose-response curve beyond the experimental exposure level. Therefore, the upper-bound estimate of the carcinogenic potency is derived when animal bioassay data are used. This upper-bound estimate can be taken as a plausible estimate if the true dose-response curve is actually linear at low doses. Upper-bound estimation means that the risks are unlikely to be higher but could be lower if the compound has a concave dose-response curve or if there is a threshold at lower doses. The other reason why the upper-bound estimate is used instead of the point estimate is that, in some cases, the point estimate is extremely unstable, depending on where the lowest experimental dose is, while the upper-bound estimate is much more stable.

THE EVALUATION OF CARCINOGENIC POTENTIAL AND ESTIMATION OF CARCINOGENIC POTENCIES OF SOME PAHs

Epidemiologic Evidence for Carcinogenicity of PAHs

Humans are exposed to PAHs in the form of complex mixtures rather than single compounds. For this reason, human data for exposure to specific PAHs are not available. The evaluation of human evidence for carcinogenic risks of exposure to PAHs thus must rely largely on experimental evidence from animal studies.

Where available, human data can be classified as follows, using the IARC criteria (18). Sufficient evidence for carcinogenicity in humans requires the finding of causal association between chemical exposure and cancer in humans on the basis of analytical epidemiologic studies. Limited evidence indicates that a causal relationship is credible but that alternative explanations cannot be excluded, and inadequate evidence indicates that there are few pertinent data, that the data do not show association, or that the data do not exclude chance, bias, or confounding.

Evidence from Animal Studies

Very few long-term animal studies have been conducted on PAHs (with the exception of benzo(a)pyrene). Table 1 summarizes the results of the studies in which PAHs were administered to animals orally.

PAHs were the first class of compounds shown to be carcinogenic in experimental animals (17, 19). Although numerous routes of administration, in several animal species, have been used in the study of benzo(a)pyrene, the majority of the animal studies on other PAHs have been mouse skin assays. The IARC stated that data from mouse skin assays may contribute to sufficient evidence of carcinogenicity because certain PAHs initially established as carcinogenic by application to mouse skin have been shown to produce malignant tumors at other sites following administration via other routes (19). Table 2 gives the results of the evaluation of the animal evidence for carcinogenicity of the 30 non-substituted PAHs evaluated by the IARC that have been shown to occur in the environment.

Using IARC criteria (18), animal evidence is classified as sufficient when a carcinogenic effect is observed in more than one strain or species, in more than one experiment, or via more than one route of administration; or in which the degree of

TABLE 1.

CARCINOGENICITY OF PAH BY ORAL ADMINISTRATION.

PAH[a]	Species	Dose	Route of administration	Tumorigenic effects
B[a]P	Mouse	0.2 mg in polyethylene glycol	Intragastric	14 tumors of the forestomach in 5 animals out of 11
	Rat (Sprague-Dawley; age 105 days)	2.5 mg per day	Oral	Papillomas developed in the esophagus and forestomach in 3 out 40 animals
	Hamster	2-5 mg biweekly	Intragastric	5 stomach papillomas developed in 67 animals treated for 1-5 months; 7 papillomas and 2 carcinomas in 18 animals treated for 6-9 months; 5 papillomas in 8 animals treated for 10-11 months
	Hamster	500 ppm	Dietary (4 days per week for up to 14 months)	12 tumors (2 esophagus, 8 forestomach, 2 intestinal) in 8 animals
DB[a,h]A	Mouse	9-19 mg (total dose)	Dietary (5-7 months)	Forestomach tumors in 7 of 22 survivors after one year; one tumor was a carcinoma

[a]Abbreviations for PAHs are as follows: B[a]P = Benzo[a]pyrene; DB[a,h]A = Dibenzo[a,h]anthracene; B[a]A = Benzo[a]anthracene.

(continued on the following page)

TABLE 1. (continued)

PAH	Species	Dose	Route of administration	Tumorigenic effects
DB[a,h]A (cont.)	Mouse (A backcross)	0.4 mg per day	Oil emulsion (drinking water replacement)	11 papillomas of the forestomach in 20 animals within 406 days
	Mouse (DBA/2)	0.76-0.85 mg per day	Oil emulsion (drinking water replacement)	Pulmonary adenomatosis in all 27 survivors at 200 days; 24 animals had alveologenic carcinomas; 16 had hemangio-endothelimoas; 12 of 13 females had mammary carcinomas; 2 pulmonary adenomatoses seen among 25 controls
	Mouse (Swiss, male)	1.5 mg in polyethylene glycol	Oral (single dose)	Papillomas of the forestomach in 2 out of 42 animals within 30 weeks
	Mouse (BALB/c, female)	15 mg total dose in almond oil	Intragastric (twice weekly for 15 weeks)	Mammary carcinomas in 1 out of 20 intact animals and 13 out of 24 pseudo-pregnant animals
B[a]A	Mouse	0.5 mg in mineral oil	Stomach tube (single dose)	No tumors in 13 mice in 16 months

(continued on the following page)

TABLE 1. (continued)

PAH	Species	Dose	Route of administration	Tumorigenic effects
B[a]A (cont.)	Mouse	0.5 mg in mineral oil	Stomach tube (8 or 16 administrations at 3- to 7-day intervals)	Papillomas in 2 out of 27 mice; no tumors in mineral oil group
	Mouse (B6AF1/J)	1.5 mg as a 3% solution in methocelaerosol OF	Stomach tube (15 times in five weeks)	Lung adenomas in 56 of 59; hepatomas in 38 of 59; papillomas of the stomach in 2
			2 times 3 days apart	Lung adenomas in 17 of 20; hepatomas in 16 of 20
				Controls: Lung adenomas in 10 of 59; hepatomas in 2 of 59

SOURCE: IARC Monographs, Vol. 3, 1973.

TABLE 2.

DEGREE OF EVIDENCE OF CARCINOGENICITY FOR EXPERIMENTAL ANIMALS OF NON-SUBSTITUTED PAHs.

Chemical	Degree of evidence of carcinogenicity for experimental animals
Anthanthrene	Limited
Antnracene	No evidence
Benz[a]anthracene[a]	Sufficient
Benzo[b]fluoranthene	Sufficient
Benzo[j]fluoranthene	Sufficient
Benzo[k]fluoranthene	Sufficient
Benzo[ghi]fluoranthene	Inadequate
Benzo[a]fluorene	Inadequate
Benzo[b]fluorene	Inadequate
Benzo[c]fluorene	Inadequate
Benzo[ghi]perylene	Inadequate
Benzo[c]phenanthrene	Inadequate
Benzo[a]pyrene[a]	Sufficient
Benzo[e]pyrene	Inadequate
Chrysene	Limited
Cyclopental[cd]pyrene	Limited
Dibenz[a,c]antnracene	Limited
Dibenz[a,n]anthracene[a]	Sufficient
Dibenz[a,l]anthracene	Limited
Dibenzo[a,e]fluoranthene	Limited
Dibenzo[a,e]pyrene	Sufficient
Dibenzo[a,h]pyrene	Sufficient
Dibenzo[a,i]pyrene	Sufficient
Dibenzo[a,l]pyrene	Sufficient
Fluoranthene	No evidence
Fluorene	Inadequate
Indeno[1,2,3-cd]pyrene	Sufficient
Perylene	Inadequate
Phenanthrene	Inadequate
Pyrene	No evidence

[a]Chemicals which also have oral and/or inhalation studies.

SOURCE: Adapted from IARC Volume 33, 1984.

tumor incidence, site, type or latency-shortening is unusual. A limited-evidence classification signifies limitation in the quality or reporting of the studies, and a limited number of species or strains tested or experiments performed. Evidence is judged to be inadequate when the results of the studies cannot be interpreted as showing the presence or absence of a carcinogenic effect. A no-evidence category is used for chemicals with no observed carcinogenic effects in several animal studies.

Evidence from Short-Term Tests

The extent of short-term tests on individual PAHs varies (19). A summary of the IARC's conclusions is tabulated in Table 3. The IARC first proposed and considered the results of short-term tests in making an overall evaluation of carcinogenic risk of chemicals to humans in 1982 (18). The scheme proposed by the IARC is as follows:

i. Sufficient evidence: When there were a total of at least three positive results in at least two of three test systems measuring DNA damage, mutagenicity, or chromosal anomalies. When two of the positive results were for the same biological endpoint, they had to be derived from systems of different complexity.

ii. Limited evidence: When there were at least two positive results, either for different endpoints or in systems representing two levels of biological complexity.

iii. Inadequate evidence: When there were too few data for an adequate evaluation, or when there were contradictory data.

iv. No evidence: When there were many negative results from a variety of short-term tests with different endpoints, and at different levels of biological complexity. If certain biological endpoints are not adequately covered, this is indicated.

Overall Evidence for Carcinogenicity

Table 4 is a summary of the overall evidence for carcinogenicity of the 30 non-substituted PAHs, incorporating human, animal and short-term test results. Two categorization schemes (18, 41) are used in the evaluation. For the IARC grouping scheme, Group 1 (human carcinogen) is reserved for compounds with sufficient evidence from epidemiologic studies; Group 2

TABLE 3.

DEGREE OF EVIDENCE IN SHORT-TERM MUTAGENICITY TESTS OF NON-SUBSTITUTED PAHs EVALUATED BY AN IARC WORKING GROUP IN FEBRUARY 1983.

Chemical	Degree of evidence in short-term mutagenicity tests
Antnanthrene	Inadequate
Anthracene	No evidence
Benz[a]anthracene	Sufficient
Benzo[b]fluoranthene	Inadequate
Benzo[j]fluoranthene	Inadequate
Benzo[k]fluoranthene	Inadequate
Benzo[ghi]fluoranthene	Inadequate
Benzo[a]fluorene	Inadequate
Benzo[b]fluorene	Inadequate
Benzo[c]fluorene	Inadequate
Benzo[ghi]perylene	Inadequate
Benzo[c]phenanthrene	Inadequate
Benzo[a]pyrene	Sufficient
Benzo[e]pyrene	Limited
Chrysene	Limited
Cyclopenta[cd]pyrene	Sufficient
Dibenz[a,c]anthracene	Sufficient
Dibenz[a,h]anthracene	Sufficient
Dibenz[a,j]anthracene	Inadequate
Dibenzo[a,e]fluoranthene	No data
Dibenzo[a,e]pyrene	Inadequate
Dibenzo[a,h]pyrene	Inadequate
Dibenzo[a,i]pyrene	Inadequate
Dibenzo[a,l]pyrene	No data
Fluoranthene	Limited
Fluorene	Inadequate
Indeno[1,2,3-cd]pyrene	Inadequate
Perylene	Inadequate
Phenanthrene	Limited
Pyrene	Limited

SOURCE: IARC Monographs, Vol. 32, 1983.

TABLE 4.

SUMMARY OF THE DEGREE OF EVIDENCE FROM HUMAN, ANIMAL AND SHORT-TERM TESTS OF NON-SUBSTITUTED PAHs EVALUATED BY AN IARC WORKING GROUP IN FEBRUARY 1983.

PAH	Human evidence	Degree of evidence of carcinogenicity for experimental animals	Degree of evidence in short-term mutagenicity tests	Overall evidence of carcinogenicity based on IARC groups[a]	Overall evidence of carcinogenicity based on EPA groups[b]
Anthanthrene	No data	Limited	Inadequate	3	C
Anthracene	No data	No evidence	No evidence	--	E
Benz[a]anthracene	No data	Sufficient	Sufficient	2B	B2
Benzo[b]fluoranthene	No data	Sufficient	Inadequate	2B	B2
Benzo[j]fluoranthene	No data	Sufficient	Inadequate	2B	B2
Benzo[k]fluoranthene	No data	Sufficient	Inadequate	2B	B2
Benzo[ghi]fluoranthene	No data	Inadequate	Inadequate	3	D
Benzo[a]fluorene	No data	Inadequate	Inadequate	3	D
Benzo[b]fluorene	No data	Inadequate	Inadequate	3	D
Benzo[c]fluorene	No data	Inadequate	Inadequate	3	D
Benzo[ghi]perylene	No data	Inadequate	Inadequate	3	D
Benzo[c]phenanthrene	No data	Inadequate	Inadequate	3	D
Benzo[a]pyrene	No data	Sufficient	Sufficient	2B	B2
Benzo[e]pyrene	No data	Inadequate	Limited	3	D
Chrysene	No data	Limited	Limited	3	C
Cyclopenta[cd]pyrene	No data	Limited	Sufficient	3	C
Dibenz[a,c]anthracene	No data	Limited	Sufficient	3	C
Dibenz[a,h]anthracene	No data	Sufficient	Sufficient	2B	B2
Dibenz[a,j]anthracene	No data	Limited	Inadequate	3	C
Dibenzo[a,e]fluoranthene	No data	Limited	No data	3	C
Dibenzo[a,e]pyrene	No data	Sufficient	Inadequate	2B	B2
Dibenzo[a,h]pyrene	No data	Sufficient	Inadequate	2B	B2
Dibenzo[a,i]pyrene	No data	Sufficient	Inadequate	2B	B2
Dibenzo[a,l]pyrene	No data	Sufficient	No data	2B	B2
Fluoranthene	No data	No evidence	Limited	--	D
Fluorene	No data	Inadequate	Inadequate	3	D
Indeno[1,2,3-cd]pyrene	No data	Sufficient	Inadequate	2B	B2
Perylene	No data	Inadequate	Inadequate	3	D
Phenanthrene	No data	Inadequate	Limited	3	D
Pyrene	No data	No evidence	Limited	--	D

[a] IARC Groups: 1, human carcinogen; 2A and 2B, probable human carcinogen; 3, carcinogenicity to humans cannot be classified.

[b] EPA Groups: A, human carcinogen; B1 and B2, probable human carcinogen; C, possible human carcinogen; D, not classified; E, no evidence for human carcinogenicity.

SOURCE: IARC Monographs, Vol. 32, 1983.

(probable human carcinogen) is subdivided into 2A (at least limited human evidence) and 2B (sufficient evidence from animal studies). Group 3 (not classified) includes chemicals with limited, inadequate, or no evidence in animal studies.

The proposed EPA grouping scheme for categorizing the overall evidence is similar to the IARC grouping scheme. The proposed EPA Group A is equivalent to IARC Group 1, and EPA Groups B1 and B2 are equivalent to IARC Groups 2A and 2B. In the EPA scheme, Group C is restricted to chemicals with limited animal evidence, Group D is for chemicals with inadequate human and/or animal data, and Group E is for chemicals with no human and/or animal evidence.

Estimation of Carcinogenic Potency of PAHs

The first paper on the relative potencies of a series of PAHs was published in 1939 (14). In this study, the investigator collected the results of mouse-skin carcinogenesis tests on PAHs and derived a method to compare potencies. The carcinogenic potency index is commonly referred to as the Iball index (percent tumor incidence x 100/mean latency period in days). The deficiencies of this index are that it does not reflect the dosage administered, and it assumes that the tumor response is linearly related to age, while it is known that tumor response is exponentially related to age.

Inhalation and ingestion are important routes of human exposure to PAHs. It is desirable to estimate potency factors for these routes of exposure. For benzo[a]pyrene, because data are available from inhalation and oral routes of administration, potency estimates can be derived by means of the data in Tables 5 and 6.

Using data from Table 5 and the linearized multistage model (1), the carcinogenic potency of B[a]P by oral exposure is estimated to be $q_1^* = 11/(mg/kg/day)$. The value q_1^* is the 95% upper confidence limit of the linear component q_1 in the multistage model

$$P(d) = 1 - \exp[- q_1 d - q_2 d^2 \ldots - q_k d^k]$$

Under the multistage model, the cancer risk p(d) at a constant exposure d can be calculated by $p(d) = q_1 \times d$ when d is sufficiently small and when $q_1 \neq 0$. However, the maximum likelihood estimate (MLE) for the linear component q_1 is very unstable and may be estimated to be zero even if the true dose-response model contains both non-zero linear and higher order

TABLE 5.

B[a]P POTENCY BY ORAL ROUTE: INCIDENCE RATE OF STOMACH PAPILLOMA/CARCINOMA[a]

Dose (ppm in diet)	Dose (mg/kg/day)	Incidence rate of stomach papilloma/carcinoma
0	0.00	0/289
1	0.13	0/25
10	1.30	0/24
30	3.90	0/37
40	5.20	1/40
45	5.85	4/40

[a]This table contains only those groups that are comparable with respect to age at exposure, number of days exposed, and age killed.

SOURCE: Neal and Rigdon, 1967.

TABLE 6.

B[a]P POTENCY BY INHALATION: INCIDENCE RATE OF RESPIRATORY TRACT TUMORS IN SYRIAN GOLDEN HAMSTER.

Dose (mg/m^3)	Incidence rates
0	0/27
2.2	0/27
9.5	9/26
46.5[a]	13/25

[a]Because of the higher mortality rate in the highest dose group, the data from this group is excluded in the calculation of potency.

SOURCE: Thyssen et al., 1981.

polynomial terms. This can easily be seen by observing that two response models (one containing only a quadratic term and the other containing both linear and quadratic terms) can adequately fit a set of experimental tumor incidence data. This is because the dose-response model is dominated by higher order polynomial terms at the high-dose range, as in the experimental data. However, a dose-response model that contains a linear component predicts significantly larger risk, at low doses, than does a model without a linear component. Since the upper confidence limit for the linear component, q_{1*}, is always positive and its estimate is "robust," the value q_1^* is used to represent the carcinogenic potency of a compound. At low doses, the risk is calculated by $q_1^* \times d$.

Using data from Table 6 and the linearized multistage model (1), the carcinogenic potency of B[a]P by inhalation exposure is estimated to be $q_1^* = 4 \times 10^{-7}/(ug/m^3)$.

The carcinogenic potency of other PAHs can be estimated by reference to the potency of benzo[a]pyrene as a function of the relative potency index using mouse-skin painting data. The potency of PAH_1 can be expressed as the following equations:

$$(1)\quad \text{potency } PAH_1 \text{ (oral)} = \frac{\text{potency } PAH_1 \text{ (skin)}}{\text{potency B[a]P (skin)}} \times \text{potency of B[a]P (oral)}$$

$$(2)\quad \text{potency } PAH_1 \text{ (inhalation)} = \frac{\text{potency } PAH_1 \text{ (skin)}}{\text{potency B[a]P (skin)}} \times \text{potency of B[a]P (inhalation)}$$

Listed below are seven PAHs for which sufficient information is available to apply this approach. The results are presented in Tables 7 and 8.

	PAH (abbreviation)	Carcinogenicity evidence from animal studies
1.	Benzo[a]anthracene (B[a]A)	Sufficient
2.	Benzo[a]pyrene (B[a]P)	Sufficient
3.	Chrysene	Limited
4.	Benzo[k]fluoranthene (B[k]F)	Sufficient
5.	Dibenzo[a,h]anthrancene (DB[a,h]A)	Sufficient
6.	Indeno[1,2,3-c,d]pyrene (I[1,2,3-c,d]P)	Sufficient
7.	Benzo[b]fluoranthene (B[b]F)	Sufficient

TABLE 7.

INDICES USED TO RANK 7 PAHS.

PAHs	Q_1^*	ED_{10} and 95% C.L.	q_1^*	ed_{10} and 95% C.L.	References
B[a]P	470	2.98×10^{-3} (8.62×10^{-4}, 5.98×10^{-3})	152.49	9.33×10^{-4} (6.54×10^{-4}, 1.21×10^{-3})	(44)
B[aP	435	1.43×10^{-3} (3.68×10^{-4}, 1.43×10^{-3})	67.62	1.71×10^{-3} (8.51×10^{-4}, 2.57×10^{-3})	(46)
B[a]P	N.A.	N.A.	20.83	1.43×10^{-2} (4.24×10^{-3}, 2.44×10^{-2})	(5)
DB[a,h]A	299.62	6.34×10^{-4} (3.24×10^{-4}, 9.44×10^{-4})	292.81	6.16×10^{-4} (3.28×10^{-4}, 9.04×10^{-4})	(45)
B[k]F	N.A.	N.A.	0.30	No point est. (0.35, none)	(46)
B[b]F	35.64	5.0×10^{-3} (2.75×10^{-3}, 7.25×10^{-3})	11.57	1.29×10^{-2} (8.54×10^{-3}, 1.73×10^{-2})	(46)
Chrysene	0.53	0.35 (0.23, 0.47)	0.88	0.21 (0.11, 0.31)	(45)
B[a]A (0.34, 1.12)	N.A.	N.A.	0.28	0.73 (0.34, 1.12)	(5)
I[1,2,3,-c,d]P (0.08, 0.22)	N.A	N.A.	1.16	0.15 (0.08, 0.22)	(45)

Remarks: 1. Q_1^* is the 95% upper confidence limit for the linear component in a multistage model and ED_{10} is the dose level corresponding to the 10% incremental tumor response when time-to-tumor data are used. The values of q_1^* and ed_{10} are similarly defined when incidence data are used.

2. N.A.: Not available.

3. Since there is only one dose group for Chrysene, Q_1^* is calculated by using Kaplan-Meier survival analysis and the assumption that the control group has a zero response.

TABLE 8.

RELATIVE POTENCY IN REFERENCE TO B[a]P AND 95% CONFIDENCE LIMIT

Compounds	Based on Q_1^* (or q_1^*) compound/B[a]P	Based on ED_{10} (or ed_{10}) B[a]P compound and 95% confidence limits
DB[a,h]A	0.69	2.26 (0.56, 5.36)
B[b]F	0.08	0.29 (0.07, 0.65)
Chrysene	1.22×10^{-3}	4.09×10^{-3} (1.06×10^{-3}, 7.12×10^{-3})
I[1,2,3-c,d]P	1.71×10^{-2}	1.14×10^{-2} (5.09×10^{-3}, 2.63×10^{-2})
B[a]A	1.34×10^{-2}	1.96×10^{-2} (5.48×10^{-3}, 4.96×10^{-2})
B[k]F	4.44×10^{-3}	none none

Remarks:

1. When available, Q_1^* and ED_{10} are preferred to q_1^* and ed_{10} in deriving the relative potency.
2. The confidence limits of the ratio are constructed using Geary's theorem.

The appropriateness of this approach, however, is uncertain at the present time. Further investigation and analysis using information from mechanistic, pharmacokinetic, and macromolecular binding studies may provide additional insight for the estimation of oral and inhalation potencies using skin-painting carcinogenicity data.

LIMITATIONS OF CURRENT ASSESSMENT APPROACHES AND POTENTIAL ALTERNATIVES

While there is general agreement within the scientific community about the general approach (15, 16, 29) that should be used in carcinogen risk assessment, judgments and assumptions made to fill data gaps are often controversial. With the advancement of research, the scientific data base will grow and the uncertainties involved in risk assessment will be reduced. Ideally, testing data based on the knowledge of the mechanism of carcinogenesis would increase the certainty of the results in assessing human risks. However, our current understanding of the mechanism of carcinogenesis is very limited. Major advancements have been made in the understanding of the initiation steps of carcinogenesis, but events related to promotion and progression to tumor formation are largely unexplored. Thus, assessments of carcinogenic risks to humans are based on observational and correlative data and plausible assumptions and judgments. The following sections summarize some of the limitations of current assessment approaches and present a forward look at potential alternatives.

Evaluation of Potential Carcinogenic Hazards

(1) Epidemiologic studies. While epidemiologic studies can provide direct evidence for carcinogenicity in humans, the following limitations are inherent in such studies:

a) They are expensive and time-consuming.
b) Their sensitivity may be limited because of small numbers of persons exposed.
c) Individuals in such studies have often been exposed to several carcinogenic compounds.
d) The duration of follow-up may not be sufficiently long for cancer manifestation.
e) Such studies provide associative evidence only, and usually provide limited information on exposure for specific agents.

(2) Rodent Long-Term Carcinogenesis Bioassays. Although at present the carcinogenesis bioassay is the most reliable method for carcinogen identification, the bioassay presents certain limitations in assessing human carcinogenicity.

a) Besides being expensive, the standard bioassay (24) of a single compound requires about 600 rodents and takes two years for the experiment and at least an additional year for pathology, statistical analysis, and preparation of the report.
b) Such studies provide data only at two dose levels and a control level.
c) Because of the inherent insensitivity of these studies, they often involve high doses which are usually several orders of magnitude above potential human exposures. Thus, they do not provide linearity and threshold information on dose-response behavior at low doses.
d) Negative results in such studies are difficult to interpret because only small numbers (50) of animals are tested per dose, and the species tested are usually only rats and mice.

(3) Short-Term Mutagenesis Tests. The use of these tests to predict animal and human response relies heavily upon our knowledge about the mechanisms of carcinogenesis, which is very incomplete at this time.

a) Mutagenesis testing is based on the observation that many carcinogens either directly or indirectly generate electrophilic metabolites that bind to DNA. Thus, one of the weaknesses of the test system is the requirement of an activation system, which contributes to the variability of test results, depending on the source of the activation factor.
b) Since no single test will detect all potential carcinogens, it is necessary to develop an appropriate battery of short-term tests based on the predictive values of specific tests with specific classes of compounds.
c) Short-term tests for the study of agents which affect the carcinogenesis process by mechanisms other than genotoxicity are not available.
d) The carcinogenesis process progresses in multiple stages. Short-term mutagenicity tests, with the exception of cell transformation assays, detect only initiation activities.

Exposure Evaluations

The exposures measured by selective monitoring measurements or estimated through modeling may not correlate well with actual experience in larger populations. There is uncertainty in monitored levels of chemicals at trace levels in the workplace or environment. In addition, high-risk populations are usually not identified. Monitored data generally tend to be crude estimates relying on modeling in which assumptions have to be made.

The relationship of exposure level to biological dose depends on information such as absorption and excretion; environmental transformation; bioaccumulation, and thus bio-magnification via the food chain; frequency, duration, intensity and route differences; and chemical interactions. Such data are usually unavailable in exposure evaluations.

Estimation of Carcinogenic Risks

The major limitation in the estimation of potential carcinogenic risks to humans is the lack of a mechanistic understanding of the process of carcinogenesis, and the paucity of scientific data that can be used in quantitative evaluation. This limitation contributes to the high degree of uncertainty associated with the estimation of potential human carcinogenic risks.

Some of the key contributors to the uncertainty of risk estimates are: uncertainty of low-dose behavior because the shape of the dose-response curve is unknown; uncertainty about the relevance of available biological data with respect to humans; uncertainty of species differences in sensitivity to carcinogens; and uncertainty about the relationship between exposure level and biological effective dose.

Limitations of Current Approaches to the Estimation of the Carcinogenic Risks of PAHs

As stated above, in estimating carcinogenic risks, heavy reliance is placed on human epidemiologic studies and the results of long-term animal carcinogenesis testing. Since, in the case of specific PAHs, human data are not available, reliance must be placed on long-term animal studies. However, of the 30 nonsubstituted PAHs evaluated, only benzo[a]pyrene, benz[a]anthrene and dibenzo[a,h]anthracene have been tested by the oral or respiratory route. Benzo[a]pyrene, because it has received the most thorough study, has frequently been used as a surrogate

PAH in the estimation of carcinogenic risks of mixtures containing PAHs. This approach has added uncertainty in that other PAHs can be either more or less potent than benzo[a]pyrene. Uncertainties also exist with relation to the potential chemical, biochemical, and toxicologic interactions among components in the mixture.

The major routes of human exposure to PAHs are via the gastrointestinal tract and the respiratory tract (26). However, animal experiments have been performed with skin-painting and subcutaneous injection as routes of administration. The validity of extrapolating from one route of administration to another is uncertain. The relative potency approach presented in this paper seems reasonable, particularly for ranking the hazards of the different PAHs. Its applicability to setting permissible exposure levels, however, is highly uncertain.

A Forward Look at Potential Alternatives

The magnitude of the limitations and uncertainties relating to the form of the dose-response curve can be easily seen in reference to the inability of the "ED_{01}" bioassay experiment with 2-AAF to resolve these problems. The current approach emphasizes the use of animal bioassay data; short-term test results take a supportive role.

However, short-term *in vitro* biochemical and toxicologic studies could provide information about mechanisms of action, metabolic pathways, macromolecular (DNA, RNA, and protein) adduct formation, DNA repair, and cell proliferation. Some of these studies can be performed at dose levels much closer to potential human exposures, and all can be performed in shorter time periods than the conventional carcinogenesis bioassay. Additional research should be performed to determine if short-term tests are viable alternatives.

(1) Mutagenesis Tests. The attractiveness of *in vitro* tests as potential alternatives for long-term carcinogenesis tests is demonstrated by the proliferation of the mutagenesis test. The genetic toxicology (Gene-Tox) program of EPA has conducted panel reviews of the validity of the different test systems. The results are published in several volumes of "Mutation Research." The International Commission for Protection Against Environmental Mutagens and Carcinogens (21) has reviewed the potential of using mutagenesis as an indicator of carcinogenesis. Recently, the National Toxicology Program convened an ad-hoc panel to review their testing procedure, including the potential uses of the different short-term mutagenesis tests and macromolecular

binding studies (27). Bartsch, Tomatis, and Malaveille (4) reviewed the literature and qualitatively and quantitatively compared mutagenic and carcinogenic activities of chemicals. It could be concluded that currently mutagenesis tests are appropriate both for screening chemicals under development and for screening existing chemicals for further testing. They could be used in biological monitoring of exposure to mutagenic carciinogens. Qualitatively, carcinogenesis and mutagenesis seemed to correlate well for a few PAHs (anthracene, benz[a]anthracene, benzo[a]pyrene, dibenzo[a,h]anthracene) that are adequately studied in both systems. Further research is needed to fill data gaps before potential quantitative relationships can be established. The lack of quantitative correlation can be illustrated by the results of the two PAH studies that are reviewed below.

Combs et al. (7) measured the liver microsome-mediated mutagenicity of 35 PAHs which are derivatives of cyclopentaphenanthrene and chrysene, using Aroclor-pretreated rats and S. typhimurium TA100 strain. The results were compared with carcinogenicity expressed as Iball indices, using results from skin-painting experiments in mice. The authors reported little quantitative correspondence between mutagenic activity and carcinogenic potency. However, Huberman and Sachs (13) found that the carcinogenicity of 10 PAHs paralled their mutagenicity, measured as 8-azaquanine or ouabain resistance, in cell-mediated mutagenicity assays on Chinese hamster V79 cells co-cultivated with lethally irradiated rat embryo cells for metabolic activation.

(2) Pharmacokinetics and Metabolism. Pharmacokinetic studies (both experimental and computational) and metabolism studies provide parameters for deriving a human biological effective dose from exposure data. These studies can be performed at lower doses and more dose levels and dose-rate schedules than the carcinogenesis bioassay, and can provide important insights about dose-response behavior at low exposure levels in humans. In 1980, Anderson et al. (2), published a general scheme for the incorporation of pharmacokinetics in low-dose risk estimation for chemcial carcinogenesis. However, adequate data for quantitative analysis are usually unavailable. Recently, Ramsey and Anderson (34) developed physiologically based pharmacokinetic models. These models may have promise for estimating human tissue dose.

Metabolic studies on PAHs are numerous. E.C. Miller (23) first reported evidence of metabolic activation of PAHs in 1951. She found covalent binding of metabolites of benzo[a]pyrene when

that substance was applied to mouse skin. Since then, many investigations of PAH metabolites, particularly metabolites of benzo[a]pyrene, and their ability to bind DNA, RNA, and protein, have been reported. Cooper et al. (9) have extensively reviewed the metabolism and activation of benzo[a]pyrene. Other reviews also contain sections on the metabolism of PAHs (8, 26, 33, 36). A reading of these reviews will show the complexity of the metabolic processes involved in the activation of a PAH to its ultimate carcinogenic intermediate. Because of this complexity, mathematical modeling studies of PAH metabolites as a function of exposure levels are not available. With the physiologically based model developed by Anderson and Ramsey (34) and Hoel et al. (11), it may be useful to re-review the metabolic and pharmacokinetic studies on benzo[a]pyrene and investigate the feasibility of such modeling.

(3) Macromolecular Binding. Macromolecular binding, particularly to DNA, as a quantitative indicator in the process of chemical carcinogenesis, has been most extensively reviewed by Lutz (22).

Carcinogen metabolite DNA binding provides the most direct measure of the biological effective dose. Carcinogen-DNA adduct can be an effective biological monitoring tool for human exposure. Factors limiting such use are the small quantity of DNA present in cells and uncertainty as to the appropriate tissue or body fluid to be used for monitoring. An additional limitation is that this measure is only useful for studying carcinogens that act through a genotoxic mechanism.

The importance of DNA binding for assessing the carcinogenicity of PAHs to mouse skin was suggested by Brooks and Lawley in 1964 (6). They found a correlation between the carcinogenicity of several PAHs to mouse skin and the covalent binding of these hydrocarbons on mouse skin DNA. This finding is supported by the results of Goshmand and Heidelberger (10) with 10 PAHs on DNA binding and carcinogenesis in mouse skin. Since then, numerous studies have demonstrated benzo[a]pyrene metabolite-DNA adduct formation in different in vitro animal and human systems (for review see Conney [8], Cooper [9], Perera [30], and Selkirk [17]).

Analytical techniques are available to quantify benzo[a]pyrene metabolite-DNA adducts by immunologic methods (12, 31, 32). Monoclonal antibodies were developed to benzo[a]pyrene diol-epoxide-DNA adducts (33). The use of these antibodies and immunoassays makes possible the detection of femtomole levels of carcinogen in µg quantities of DNA (i.e., 1 adduct/10^6 nucleotides) (12, 35).

At this level of sensitivity, human tissue or body fluids can be monitored for exposure.

In summary, while molecular biochemical studies cannot currently replace conventional toxicologic testing, they provide information that can be used for better estimates of biological effective dose and dose-response characteristics at low levels of exposure, and for improvement in interspecies scaling.

In spite of these improvements, it would be unrealistic to expect the development of a complete set of risk assessment information for all chemicals in the near future. What is possible is the development of complete sets of information for specific exposures that are well studied in both humans and animals. These examples could be used to derive a more realistic set of quantitative parameters for chemicals predicted to have similar carcinogenic mechanisms. Benzo[a]pyrene should be a good model compound for developing a set of parameters for the assessment of other carcinogenic PAHs.

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16. ABSTRACT

The evaluation and estimation of the potential risk of human exposures to a hazardous substance requires the analysis of all relevant data to answer two questions (1) does the agent cause the effect; (2) what is the relationship between dose (exposure) and incidence of the effect in humans? For polynuclear aromatic hydrocarbons (PAH), carcinogenicity is the effect of concern. Three types of evidence can be used to evaluate the likelihood that a PAH is carcinogenic to humans. They are (1) epidemiologic evidence, (2) experimental evidence derived from long-term animal bioassays, (3) supportive or suggestive evidence from short-term tests, metabolism, pharmacokinetics and structure-activity correlations. Mathematical modeling can be used to estimate the potential human risks. The approaches and the problems associated with these approaches for estimating cancer risk to humans are addressed with special emphasis on problems related to PAH.

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