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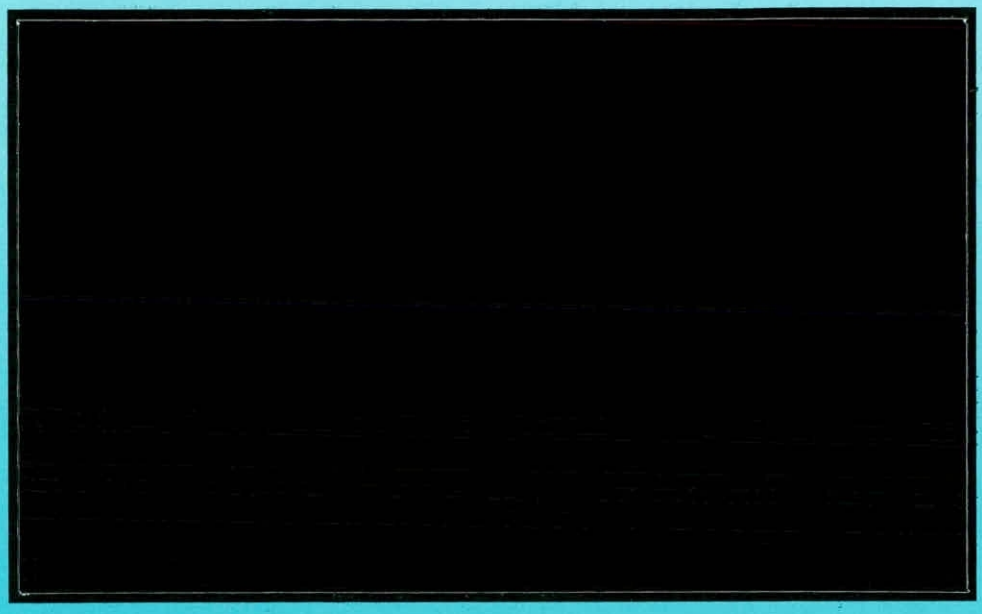

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(NATURAL ENVIRONMENT RESEARCH COUNCIL)

ITE Project TO7061i1
Report to the Her Majesty's Inspectorate of Pollution

The calculation of a Regulatory Assessment Level (RAL) for atmospheric PAHs based on relative potencies

FIRST DRAFT

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The calculation of a Regulatory Assessment Level (RAL) for atmospheric PAHs based on relative potencies.

Polycyclic aromatic hydrocarbons are compounds which are formed during the incomplete combustion of organic compounds such as coal, oil, gas, wood, refuse and tobacco. The group comprises more than 100 different compounds, although this report will only cover 23 compounds, namely

naphthalene	pyrene
fluoranthene	benzo(a)pyrene
chyrsene	benzo(e)pyrene
anthracene	cyclopenta(c,d)pyrene
dibenz(a,h)anthracene	indeno(1,2,3-c,d)pyrene
dibenz(a,c)anthracene	perylene
benz(a)anthracene	benzo(g,h,i)perylene
phenanthrene	fluorene
1-methylphenanthrene	acenaphthylene
benzo(b)fluoranthene	acenaphthene
benzo(j)fluoranthene	coronene
benzo(k)fluoranthene	

Table 1 lists the empirical formulae, CAS numbers and PAH grouping of these compounds. The physical-chemical properties which may be of relevance to the behaviour of these compounds in the atmosphere are listed in Table 2.

The relationship between cancer and exposure to coal tar, soot, coke oven emisions and cigarette smoke has been well documented. Coal soots, coal tar, pitch and coal tar fumes (all of which contain benz(a)anthracene, benzo(b)fluoranthene, benzo(j)fluoranthene, benzo(k)fluoranthene and benzo(a)pyrene) have been classified by the International Agency for Research on Cancer (IARC) as group 1, "carcinogenic to humans". Cancer is the most significant endpoint of PAH toxicity. US Department of Health & Human Services (1993b) reported an increased incidence of cancers of the lung, skin, gastro-intestinal tract and bladder following exposure to PAHs. Chronic exposure increases the likelihood of cancer initiation, as well as the potential for metabolism of a PAH procarcinogen to a carcinogen (Holbrook, 1990). Many of the studies on both laboratory animals and occupationally exposed humans have been based on PAH mixtures. The relationship between individual PAH compounds and carcinogenicity is not a straightforward one. Carcinogenicity increases with the number of rings in the compound, however some 6 ring PAH compounds such as benzo(g,h,i)perylene are classified as non-carcinogenic. Carcinogenicity is also determined by the shape of the molecule; benz(a)pyrene is classified as strongly carcinogenic, whereas its isomer benz(e)pyrene is classified as non-carcinogenic. PAH compounds with a "bay region", the area between three aromatic rings arranged in a crescent formation, are known to be carcinogens. However some "bay region" compounds such as benzo(e)pyrene and benzo(g,h,i)perylene are classified as non-carcinogenic

This report will detail carcinogenicity studies of exposure of laboratory mammals to individual PAH compounds via the inhalation route. Where such information exists, the relative potency

of each compound with reference to the carcinogenisity of benz(a)pyrene will be calculated. The relative potency can then be used to set a regulatory assessment level (RAL) for either individual PAH compounds, or as total PAH.

The carcinogenicity of PAHs has been reported in the following reviews, Harvey, (1991); US Department of Health & Human Services, (1993b); US Department of Health & Human Services, (1990f).

Comparison of separate carcinogenicity studies is generally more difficult than the methods used to compare acute toxicity studies which have standard end-points such as LC_{50} or NOELs. Different researchers measure different carcinogenicity endpoints, e.g. number of tumour bearing animals, number of tumours per affected animal, percentage response rate, incidence of a specific tumour type, lowest dose causing tumour development, or highest dose which did not induce tumour development. Comparison can only be made between different PAH compounds when they were tested using identical methodologies, which normally consists of a single study with separate exposure groups for each individual compound.

Table:1 Identity of PAH compounds

Name	Empirical Formula	CAS No.	No. Rings	PAH group
naphthalene	C10 H8	91-20-3	2	
fluoranthene	C16 H10	206-44-0	4	nonalterant polyarene
chrysene	C18 H12	218-01-9	4	alterant tetracyclic polyarene
anthracene	C14 H10	120-12-7	3	
dibenz(a,h)anthracene	C22 H14	53-70-3	5	alternant pentacyclic polyarene
dibenz(a,c)anthracene	C22 H14	215-58-7	5	alternant pentacyclic polyarene
benz(a)anthracene	C18 H12	56-55-3	5	alternant tetracyclic polyarene
phenanthrene	C14 H10	85-01-8	3	
1-methylphenanthrene	C15 H12	832-69-9	3	
benzo(b)fluoranthene	C20 H12	205-99-2	5	nonalterant polyarene
benzo(j)fluoranthene	C20 H12	205-82-3	5	nonalterant polyarene
benzo(k)fluoranthene	C20 H12	207-08-9	5	nonalterant polyarene
pyrene	C16 H10	129-00-00	4	alternant tetracyclic polyarenes
benzo(a)pyrene	C20 H12	50-32-8	5	alternant pentacyclic polyarene
benzo(e)pyrene	C20 H12	192-97-2	5	alternant pentacyclic polyarene
cyclopenta(c,d)pyrene	C18 H10	27208-37-3	5	nonalterant polyarene
indeno(1,2,3-cd) pyrene	C22 H12	193-39-5	6	nonalterant polyarene
perylene	C20 H12	198-55-0	5	alternant pentacyclic polyarenes
benzo(ghi)perylene	C22 H12	191-24-2	6	alternant hexacyclic polyarenes
fluorene	C13 H10	86-73-7	3	nonalterant polyarenes
acenaphthylene	C12 H8	208-96-8	3	
acenaphtene	C12 H10	83-32-9	3	
coronene	C24 H12	191-07-1		

3 rings vapour phase
4 rings vapour or particulate phase
5 rings particulate phase

Table 2: Physical-chemical properties of PAH compounds

Name	Molecular weight (g)	1 ppm = _ mg/m^3	Vapour Pressure at 20 °C (kPa)	Henry's Law Constant (atm /m^3/mol)
naphthalene	128.16	5.238	0.01 [a]	4.6 x 10^{-4}
fluoranthene	202.26	8.267	1.3 x 10^{-3}	6.5 x 10^{-6}
chrysene	228.28	9.331	8.4 x 10^{-9} b	1.05 x 10^{-6}
anthracene	178.22	7.285	2.27 x 10^{-6} b	8.6 x 10^{-5}
dibenz(a,h)anthracene	278.36	11.378	1.3 x 10^{-9}	7.3 x 10^{-8}
dibenz(a,c)anthracene	278.36	11.378		
benz(a)anthracene	228.30	9.332	2.9 x 10^{-7}	1 x 10^{-6}
phenanthrene	178.24	7.285	1.3 x 10^{-4} b	2.26 x 10^{-4}
1-methylphenanthrene	192.27	7.859		
benzo(b)fluoranthene	252.32	10.313	6.7 x 10^{-6}	1.22 x 10^{-5}
benzo(j)fluoranthene	252.32	10.313	2 x 10^{-7} b	7.39 x 10^{-7}
benzo(k)fluoranthene	252.32	10.313	6.7 x 10^{-7}	3.87 x 10^{-5}
pyrene	202.26	8.267	3.3 x 10^{-5} b	5.1 x 10^{-6}
benzo(a)pyrene	252.32	10.313	7.5 x 10^{-8} a	4.9 x 10-7
benzo(e)pyrene	252.32	10.313		
cyclopenta(c,d)pyrene	226.28	9.249		
indeno(1,2,3-cd) pyrene	276.34	11.295	~1.3 x 10^{-9}	6.95 x 10^{-8}
perylene	252.32	10.313		
benzo(ghi)perylene	276.34	11.295	1.3 x 10^{-9}	1.44 x 10^{-7}
fluorene	166.23	6.795		0.6-7.1 x 10^{-4}
acenaphthylene	152.20	6.221	3.8 x 10^{-3}	1.45 x 10^{-3}
acenaphtene	154.22	6.304	6.0 x 10^{-4}	
coronene	300.36	12.277		

a temperature not specified
b calculated at 25 °C

NAPHTHALENE

Two year inhalation studies showed no evidence of carcinogenicity of naphthalene following exposure of male mice (strain B6C3F1) to 10 or 30 ppm (NTP, 1992). Carcinogenicity was evident in female mice of the same strain chronically exposed to 30 ppm (157 mg/m^3). Carcinogenicity was based on an increased incidence of pulmonary alveolar/bronchiolar adenomas. However the incidence of tumours in the mice exposed to 10 ppm (52 mg/m^3) was lower than that of the controls. It was concluded that there was some evidence of naphthalene carcinogenicity in female mice.

US EPA, (1990) reported no carcinogenic activity in female mice (strain A/J) following exposure to 10 or 30 ppm (52 or 157 mg/m^3) naphthalene. Exposure periods were 6h/day, 5d/week for 6 months.

Adkins, *et al.*, (1986) exposed mice to 30 ppm (157 mg/m^3) naphthalene for 6h/day, 5d/week for 6 months. No effect on the number of tumour-bearing mice was reported, although an increase in the number of tumours per tumour bearing mouse was reported.

US EPA Classification of human carcinogenicity: D "not classifiable as to human carcinogenicity". This is due to the lack of human data and inadequate data from animal bioassays.

IARC classification: 3

Additional studies on the carcinogenicity of naphthalene (non-inhalation exposures) are listed in US Department of Health & Human Services, (1993).

FLUORANTHENE

US EPA Classification of human carcinogenicity: D "not classifiable as to human carcinogenicity". This is due to the lack of human data and inadequate data from animal bioassays.

No information available for inhalation exposure.

CHRYSENE

Wenzel-Hartung, *et al.*, (1990) reported a dose-related increase in the incidence of squamous cell carcinomas in rats given an intra-pulmonary implant of 1 or 3 mg chrysene. Chrysene has been implicated as an etiological determinant of chemical carcinogenesis. Chrysene has been reported to induce aryl hydrocarbon hydroxylase in cultured human lymphocytes (Snodgrass, 1979). Aryl hydrocarbon hydroxylase was not induced in mitogen-activated cultured human lymphocytes from healthy donors (Gurtoo, 1979).

Classified by US EPA as B2, "probable human carcinogen" (classifiction was based on non-inhalation studies).

Details of other carcinogenicity studies (non-inhalation exposure routes) are reported in (US Department of Health & Human Services, 1990d).

ANTHRACENE

US EPA Classification of human carcinogenicity: D "not classifiable as to human carcinogenicity" .This is due to the lack of human data and inadequate data from animal bioassays.

Details of carcinogenicity studies are available, but not from inhalation exposure.

DIBENZ(a,h)ANTHRACENE

Wenzel-Hartung, et al., (1990) reported over 50% of rats given an intrapulmonary implant of 0.1 mg dibenz(a,h)anthracene developed squamous cell carcinomas (one rat developed a begnign squamous cell tumour). Only one dose of dibenz(a,h)anthracene was used in this study.

A slight increase in repiratory tract tumours was reported in male hamsters given a weekly dose of 0.25 mg for 24 to 30 weeks (Sellakumar & Shubik, 1974). Dibenz(a,h)anthracene was reported to be a weak to moderate respiratory carcinogen.
Yanysheva & Balenko, (1966) reported a dose-related increase in the number of rats developing squamous cell carcinomas within 30 months of intratracheal instillation of 0.5, 2, 10 or 20 mg dibenz(a,h)anthracene. The lowest dose which induced tumours was 2 mg.

US EPA Classification of human carcinogenicity: B2 "probable human carcinogen". There are no human data, but sufficient data from animal bioassays (none listed are from inhalation exposure).

Details of other carcinogenicity studies (non-inhalation exposures) are listed in (US Department of Health & Human Services, 1990e).

DIBENZ(a,c)ANTHRACENE (BENZO(b)TRIPHENYLENE)

IARC classification: 2B "possibly carcinogenic to humans" Classification was based on limited animal evidence, and no adequate human data. No inhalation studies listed.

BENZ(a)ANTHRACENE

US EPA Classification of human carcinogenicity: B2 "probable human carcinogen". There are no human data, but sufficient data from animal bioassays (none listed are from inhalation exposure).

IARC classification: 2A, "probably carcinogenic to humans". There are sufficient animal data, no human data

Details of other carcinogenicity studies (non-inhalation exposure) are reported in US Department of Health & Human Services, (1990a).

PHENANTHRENE

Wenzel-Hartung, *et al.*, (1990) reported a squamous cell carcinoma in a single rat given an intrapulmonary implant of 10 mg phenanthrene. No carcinomas were reported in the other rats in this dose group, or in rats given 1 or 3 mg implants. The authors suggested that the single carcinoma reported may have been spontaneous since there was no increase in the incidence of squamous cell metaplasias (pre-neoplastic lesions) in any of the exposure groups with reference to the vehicle or untreated controls.

US EPA Classification of human carcinogenicity: D "not classifiable as to human carcinogenicity" .This is due to the lack of human data and inadequate data from animal bioassays. (No data for inhalation exposure listed).

IARC classification: 3 "not classifiable as to carcinogenicity to humans", due to lack of human data and inadequate animal data.

1-METHYLPHENANTHRENE

IARC classification: 3, "not classifiable as to its carcinogenicity to humans". Due to lack of human data, and inadequate animal data.

BENZO(b)FLUORANTHENE

Deutsch-Wenzel, *et al.*, (1983b) reported a dose-related increase in the number of rats with epidermoid carcinomas or pleomorphic sarcomas following intra-tracheal injection of 0.3 or 1.0 mg (0.4, 1.2 or 4.1 mg/kg). Rats given 0.1 mg did not develop tumours. Benzo(b)fluoranthene was classified as a moderately active respiratory carcinogen.

Classification of human carcinogenicity: B2 "probable human carcinogen". There is no human data, but sufficient animal data.

IARC classification: 2B "possibly carcinogenic to humans. No human data is available, but there are sufficient data on the carcinogenicity in animals.

Details of other carcinogenicity studies (non-inhalation exposure) are reported in US Department of Health & Human Services, (1990c).

> *Unlike other PAHs benzo(b)fluoranthene does not form bay region diol epoxides, but it does form reactive metabolites which may form DNA adducts.*

BENZO(j)FLUORANTHENE

Deutsch-Wenzel, et al., 1983b) reported a dose-related increase in epidermoid carcinomas in rats given a pulmonary implant of 0.2, 1.0 or 5.0 mg. The dose 1.0 mg (25 mg/kg) was reported to be carcinogenic by RTECS criteria.
Grimmer, *et al.*, 1982) reported that 5 mg/kg benzo(j)fluoranthene applied as a pulmonary implant to rats gave an equivocal tumourogenic response, based on RTECS criteria.

IARC classification: 2B, "possibly carcinogenic to humans". There are no human data, but sufficient animal data.

BENZO(k)FLUORANTHENE

Deutsch-Wenzel, et al., (1983b) reported a dose-related increase in epidermoid carcinomas in rats given a pulmonary implant of 0.83 or 4.15 mg. No carcinomas were reported in rats given a 0.16 mg implant.
Grimmer, et al., (1982) reported that 5 mg/kg benzo(k)fluoranthene applied as a pulmonary implant to rats gave an equivocal tumourogenic response, based on RTECS criteria.

US EPA Classification of human carcinogenicity: B2, "probable human carcinogen". There is no human data, but sufficient animal data.

IARC classification: 2B, "possibly carcinogenic to humans". There are no human data, but sufficient animal data.

PYRENE

US EPA Classificaton of human carcinogenicity: D, "not classifiable as to human carcinogenicity" . Classification based on no human data, and inadequate animal data.

IARC cassification: 3, "not classifiable as to its carcinogenicity to humans". There are no human data, and inadequate animal data.

BENZO(a)PYRENE

Increased lung neoplasms (10 fold) reported in rats and mice exposed to 50 to 90 µg/m^3 for 16h/day, 5 days/week for 22 months (Heinrich, *et al.*, 1986). Anon (1982) reported tumours in mice exposed to benzo(a)pyrene at 200 ng/m3 for 6 hours / day for 13 weeks. Benzo(a)pyrene was classified as an equivocal tumourogenic agent. A dose-related increased incidince of both respiratory tract and upper gastro-intestinal tract tumours was reported in Golden hamsters exposed to benzo(a)pyrene at 2.2, 9.5 or 46.5 mg/m^3 for 4 hours per day x 96 weeks (Thyssen et al., 1981).

Deutsch-Wenzel, et al., (1983b) reported a dose-related increase in epidermoid carcinomas in rats given a pulmonary implant of 0.1, 0.3 or 1.0 mg.
Grimmer, *et al.*, (1984) reported 150 µg/kg benzo(a)pyrene implanted in rat lungs was carcinogenic by RTECS criteria. Tumours were noted at the site of application. Deutsch-Wenzel, *et al.*, (1983a) reported 500 µg/kg benzo(a)pyrene implanted in rat lungs was carcinogenic by RTECS criteria.

A pulmonary implant of 200 mg/kg benzo(a)pyrene was reported to be carcinogenic to mice, based on RTECS criteria (Anon, 1979a).

Intra-tracheal administration of 200 mg/kg benzo(a)pyrene at 10 week intervals was reported to be neoplastic, according to RTECS criteria (Anon, 1979b).
Benzo(a)pyrene is classified as B2, probable human carcinogen. There are no data specifically linking benzo(a)pyrene to human carcinogenicity, but much data is available on carcinogenicity to animals following exposure to benzo(a)pyrene via a variety of routes, including inhalation. Benzo(a)pyrene has been used as a positive control in carcinogenicity assays of other chemicals. Such studies tend to use single dose of benzo(a)pyrene, and are therefore of limited use in establishing a dose-response relationship.

IARC classification: 2A "probably carcinogenic to humans".
US EPA classification: B2 "probably carcinogenic to humans"

Details of other carcinogenicity studies (non-inhalation exposure) are listed in US Department of Health & Human Services, (1990b).

BENZO(e)PYRENE

Deutsch-Wenzel, et al., (1983b) did not report a dose-related increase in carcinogenicity following application of benzo(e)pyrene as a pulmonary implant. The highest dose tested, 5.0 mg produced only one rat with a epidermoid carcinoma. One rat in the 1.0 mg dose group developed a pleomorphic sarcoma.

IARC classification:3, "not classifiable as to its carcinogenicity to humans". There are no human data, and inadequate animal data.

Other studies listed, but not for inhalation exposure.

CYCLOPENTA(c,d)PYRENE

IARC classification: 3, "not classifiable as to its carcinogenicity to humans". There are limited animal data, and no adequate human data

INDENO(1,2,3-CD)PYRENE

Deutsch-Wenzel, et al., (1983b) reported a dose-related increase in the number of rats developing epidermoid carcinomas. The rats were given pulmonary implants containing 0.16, 0.83 or 4.15 mg indeno(1,2,3-CD)pyrene (0.65, 3.4 and 17 mg/kg, respectively). Tumours were reported in rats from each dose group. The 4.15 mg dose was classified as carcinogenic, with reference to RTECS criteria.
Grimmer, et al., (1982) reported that a pulmonary implant of 5 mg/kg indeno(1,2,3-CD)pyrene hgave an equivocal tumourogenic response, based on RTECS criteria, in rats.

US EPA Classification B2, "probable human carcinogen". There are no human data, but sufficient animal data, including lung implants. No inhalation studies listed.

IARC classification: 2B, "possiby carcinogenic to humans". There are no human data, but sufficient animal data.

PERYLENE

IARC classification: 3, "not classifiable as to its carcinogenicity to humans". There are no human data, and inadequate animal data.

BENZO(ghi)PERYLENE

Benzo(ghi)perylene implants of 0.16, 0.83, or 4.15mg (0.65, 3.4 or 17 mg/kg, respectively) in rat lungs showed a weak (non-significant) tumourigenic effect (Deutsch-Wenzel, et al., 1983b). The authors reported that a dose-response relationship for this individual PAH compound was not significant. The small number of tumours produced may have been caused by impurities in the benzo(g,h,i)perylene implant.

IARC classification: 3, "not classsifiable as to its carcinogenicity to humans". There are no human data and inadequate animal data.

FLUORENE

US EPA classification: D, "not classifiable as to its human carcinogenicity". This is based on no human data, and inadequate data from bioassays.

IARC classification: 3, "not classifiable as to its carcinogenicity to humans". There are no human data, and inadequate animal data.

No studies with inhalation exposure listed.

ACENAPHTHYLENE

US EPA classification: D, "not classifiable as to its carcinogenicity to humans". This is based on no human data, and inadequate animal data.

No inhalation studies listed.

ACENAPHTHENE

Reshetyuk, (1970) reported no malignant growths in rats exposed to acenaphthene at 12 ±1.5 mg/m^3 for four hours per day, six days per week for eight months.

CORONENE

IARC classification: 3 "not classifiable as to its carcinogenicity to humans". There is a lack of adequate human data, and inadequate evidence of carcinogenicity to animals.

Table 3 Carcinogenicity classifications of PAH compounds

Name	Gerde, *et al.*, (1991)	IARC classification	US EPA Classification	Eisler, (1987)
naphthalene		3	D	non carcinogenic
fluoranthene	tumourigenic in new born mouse lung bioassay. No activity on mouse skin or *sc. inj.*		D	non carcinogenic
chrysene	inactive as complete carcinogen, although a weak initiator-promoter (IARC, 1983)		B2	weak carcinogen
anthracene			D	non carcinogenic
dibenz(a,h)anthracene	moderate carcinogen, activity lies between BA and BaP.		B2	strong carcinogen
dibenz(a,c)anthracene	inactive, or weak carcinogen in mouse skin, but shows significant tumour-initiating activity with TPA promotion.	2B		weak carcinogen
benz(a)anthracene	weakly carcinogenic compared to BaP in most test systems	2A	B2	weak carcinogen / co-carcinogen - tumourogen
phenanthrene		3	D	non-carcinogen
1-methylphenanthrene		3		
benzo(b)fluoranthene		2B	B2	carcinogen
benzo(j)fluoranthene	weak tumour-initiating agent. Less active than benzo(b)fluoranthene	2B		carcinogen
benzo(k)fluoranthene	Inactive as complete carcinogen on mouse skin, or lung or liver in newborn mice. Acts as tumour initiator on mouse skin and induces fibrosarcomas following *sc inj* to mice.	2B	B2	non-carcinogen
pyrene	generally considered non-carcinogenic	3	D	non-carcinogen
benzo(a)pyrene	potent carcinogen, used as reference for other PAHs.	2A	B2	strong carcinogen

Name	Gerde, *et al.*, (1991)	IARC classification	US EPA Classification	Eisler, (1987)
benzo(e)pyrene	Inactive as a complete carcinogen, but a weak tumour initiator with TPA promotion (IARC, 1983)	3		non carcinogen
cyclopenta(c,d)pyrene	Much less active than BaP as a cpmplete carcinogen or tumour initiator. Potent tumourigen in the newborn mouse assay.			
indeno(1,2,3-cd) pyrene	Lower activity than BaP as a complete carcinogen on mouse skin.	2B	B2	weak carcinogen / co-carcinogen / tumourogen
perylene	No activity as a complete carcinogen or tumour initiator	3		
benzo(ghi)perylene	Non-carcinogenic (IARC, 1983)	3	2 (Limited)	non-carcinogenic
fluorene	No tumours in rats or mice (IARC, 1983)	3	D	non-carcinogenic
acenaphthylene			D	
acenaphtene				
coronene		3		

Table 4: Relative Potency (RP) of PAH compounds reported in the literature, with reference to benzo(a)pyrene.

Name	RP (1)	RP (2)	RP (3)	RP (4)	RP (5)	RP (6)	RP (7)
naphthalene	0.001			0			
fluoranthene	0.001			0			
chrysene	0.001			1		0.03	
anthracene	0.01			0	0.19		
dibenz(a,h)anthracene	5	1.1	0.69	1		1.908	0.59
dibenz(a,c)anthracene							
benz(a)anthracene	0.1	0.145	0.013	1			0.16
phenanthrene	0.001			0		0.001	
1-methylphenanthrene							
benzo(b)fluoranthene	0.1	0.140	0.08	1	0.11		0.024
benzo(j)fluoranthene					0.03		0.08
benzo(k)fluoranthene	0.1	0.066	0.004	1	0.03		
pyrene	0.001	0.081		0			
benzo(a)pyrene	1	1	1	1	1.00	1	
benzo(e)pyrene					0.003		
cyclopenta(c,d)pyrene							
indeno(1,2,3-cd) pyrene	0.1	0.232	0.017	1	0.08		0.006
perylene							
benzo(ghi)perylene	0.01	0.022		0	0.01		
fluorene	0.001			0			
acenaphthylene	0.001			0			
acenaphtene	0.001			0			
coronene							

(1) (Nisbet & LaGoy, 1992)
(2) Clement (1988) cited in (Nisbet & LaGoy, 1992)
(3) Chu & Chen (1984) cited in (Nisbet & LaGoy, 1992)
(4) US EPA (1984) cited in (Nisbet & LaGoy, 1992)
(5) (Deutsch-Wenzel, et al., 1983b)
(6) (Wenzel-Hartung, et al., 1990)
(7) (Rugen, *et al.*, 1989)

Table 5 RALs calculated from highest reported RP

Name	Relative Potency based on highest reported value	RAL $\mu g/m^3$
naphthalene	0.001	1×10^{-2}
fluoranthene	0.001	1×10^{-2}
chrysene	0.03	3×10^{-4}
anthracene	0.32	3×10^{-5}
dibenz(a,h)anthracene	5	2×10^{-6}
dibenz(a,c)anthracene	0.1	1×10^{-4}
benz(a)anthracene	0.1	1×10^{-4}
phenanthrene	0.001	1×10^{-2}
1-methylphenanthrene	0.001	1×10^{-2}
benzo(b)fluoranthene	0.1	1×10^{-4}
benzo(j)fluoranthene	0.01	1×10^{-3}
benzo(k)fluoranthene	0.1	1×10^{-4}
pyrene	0.081	1×10^{-4}
benzo(a)pyrene	1.0	1×10^{-5}
benzo(e)pyrene	0.003	3×10^{-3}
cyclopenta(c,d)pyrene	0.001	1×10^{-2}
indeno(1,2,3-cd) pyrene	0.232	4×10^{-5}
perylene	0.001	1×10^{-2}
benzo(ghi)perylene	0.022	4×10^{-4}
fluorene	0.001	$1x\ 10^{-2}$
acenaphthylene	0.001	1×10^{-2}
acenaphtene	0.001	1×10^{-2}
coronene	0.001	1×10^{-2}

Table 6 RALs calculated from RP using solely pulmonary exposure data (Deutsch-Wenzel, et al., 1983b; Wenzel-Hartung, et al., 1990)

Name	Relative Potency based on highest reported value	RAL $\mu g/m^3$
naphthalene		
fluoranthene		
chrysene	0.03	3×10^{-4}
anthracene	0.19	5×10^{-5}
dibenz(a,h)anthracene	1.908	5×10^{-6}
dibenz(a,c)anthracene		
benz(a)anthracene		
phenanthrene	0.001	1×10^{-2}
1-methylphenanthrene		
benzo(b)fluoranthene	0.11	1×10^{-4}
benzo(j)fluoranthene	0.03	3×10^{-4}
benzo(k)fluoranthene	0.03	3×10^{-4}
pyrene		
benzo(a)pyrene	1.00	1×10^{-5}
benzo(e)pyrene	0.003	3×10^{-3}
cyclopenta(c,d)pyrene		
indeno(1,2,3-cd) pyrene	0.08	1×10^{-4}
perylene		
benzo(ghi)perylene	0.01	1×10^{-3}
fluorene		
acenaphthylene		
acenaphtene		
coronene		

Table 7: Percentage contribution of different PAHs of a total PAH in typical air sample, as in TOMPS programme

Name	Percentage contribution of different PAHs to a typical total PAH (%)
naphthalene	0.001
fluoranthene	7.4
chrysene	7
anthracene	25.7
dibenz(a,h)anthracene	0.1
dibenz(a,c)anthracene	0.1
benz(a)anthracene	12.8
phenanthrene	46.2
1-methylphenanthrene	0.1
benzo(b)fluoranthene	15.8
benzo(j)fluoranthene	0.001
benzo(k)fluoranthene	6.1
pyrene	6.9
benzo(a)pyrene	0.1
benzo(e)pyrene	0.001
cyclopenta(c,d)pyrene	0.001
indeno(1,2,3-cd) pyrene	0.001
perylene	0.001
benzo(ghi)perylene	3.0
fluorene	17.6
acenaphthylene	5.9
acenaphtene	0.1
coronene	0.1

DISCUSSION

There is a paucity of data available on the carcinogenicity of individual PAH compounds to experimental animals following inhalation exposure. With the exception of benz(a)pyrene, naphthalene, and acenaphthene, the potential carcinogenic activity of individual PAH compounds has not been reported following inhalation exposure. Details on the carcinogenic activity of some these compounds are available from bioassasys with non-inhalation exposure routes, including pulmonary implants. Care must be taken when interpreting these studies since this route is not directly relevant to inhalation exposure. However this route was used by Wenzel-Hartung, et al., (1990) and Deutsch-Wenzel, et al., (1983b) to determine the relative potency of individual PAH compounds, with reference to benz(a)pyrene. The toxic equivalence factors (TEFs) calculated in these studies are listed in Table 4. Table 4 also lists TEFs which have been calculated in other studies using data from all exposure routes including pulmonary implant, dermal, subcutaneous and *in vitro* administrations

The TEFs used to calculate the RALs are listed in Table 4. The RALs listed in Table 6 are based upon the worst case scenario, i.e. the highest TEF value, without reference to the route of exposure. The RALs listed in Table 7 are based upon the two pulmonary implant studies (Deutsch-Wenzel, et al., 1983b; Wenzel-Hartung, et al., 1990). TEFs were assigned to compounds which did not have a value reported in the literature according to their carcinogenicity classifications, with reference to the carcinogenicity classifications of compounds for which TEFs had been reported.

Nisbet & LaGoy, (1992) reported that the use of TEFs requires several assumptions. These are as follows:

1. A reasonably well-characterised compound can be selected to serve as a reference compound for other compounds in the group.
2. The toxic effects of all members of the group are qualitativley similar to those of the reference compound, and may therefore be characterised quantitatively by means of a relative potency or TEF.
3. TEFs for diferent toxic endpoints are similar, so that limited information on reative toxic potencies in one or a few assay systems can be used to assign TEFS to single compounds or subclasses for other end points.
4. The toxic effects of different compounds of the mixtures are additive.

For PAHs, assumption one is satisfied by use of benzo(a)pyrene as the reference compound. Benzo(a)pyrene is one of the most potent carcinogens, and its carcinogenicity and related effects in several different assay systems have been well studied. Assumption two is satisfied since the primary concern for risk assessment of PAHs is carcinogenicity. Many of the individual PAH compounds have been tested for carcinogenicity for at least one route of exposure, and subsequently classified by IARC or the US EPA. Assumption three is not relevant to the scope of this report, which is aimed at carcinogenicity following inhalation exposure. However it should be considered when examining TEFs calculated from other studies, although those listed are all based on carcinogenicity. (Nisbet & LaGoy, 1992) cited studies which they claim demonstrated similarities in relative potencies for different end points. Assumption four is satisfied by data cited in Nisbet & LaGoy, (1992). This data was derived from studies where mice were exposed to individual PAH compounds and mixtures of PAH compounds via dermal or sub-cutaneous exposure. The data provided demonstrated that the

carcinogenicity of individual PAH compounds is additive. This is an important consideration, as it allows a RAL to be calculated for Total PAH, based on the existing RAL for benzo(a)pyrene.

Tables 5 and 6 demonstrate that the RALs calculated for four of the seven individual PAH compounds administered via pulmonary implant (Deutsch-Wenzel, et al., 1983b; Wenzel-Hartung, et al., 1990) do not vary by more than an order of magnitude between relative potencies calculated by other studies. This suggests that the carcinogenicity of PAH compounds is not affected by the route of exposure,

The data in table 7 can be used to calculate an RAL for total PAH. The sum of the percentages given in this table is greater than 100%, so the the proportions need to be altered accordingly, to allow the RAL to be calculated. (Peter Douben to supply data).

The TEFs previously published (Deutsch-Wenzel, et al., 1983b; Rugen, et al., 1989; Wenzel-Hartung, et al., 1990) did not appear to take into account the molecular weight of the individual PAH compounds. The method of calculation used in these papers was not reported, other than that probit analysis was used. Calculations of TEFs should take into account molar ratios, since it is indicative of the number of molecules present which can form DNA adducts; the inducer of the carcinogenic effects.

There are limitations in the calculation of a RAL for total PAHs based on the sum of the RALs of individual PAH compounds. A RAL for Total PAH is likely to be of greater relevance to environmental exposure since exposure to single PAH compounds is unlikely. However there are limitations in the studies involoving exposure to individual PAH compounds, as some PAHs have been classified as having co-carcinogenicity (Eisler, 1987). This means that although no carcinogenicity was reported following exposure to the compound on its own, the compound may contribute to carcinogenicity in a PAH mixture. The assumption that the toxic effects of individual PAH compounds are additive underestimates this risk.

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ANNEX 1 CLASSIFICATION OF CARCINOGENS (IARC / US EPA)

The classification scheme used by the International Agency for Research on Cancer (IARC) consists of five categories:

Group	Description	Basis of classification
1	carcinogenic to humans	sufficient human evidence
2A	probably carcinogenic to humans	limited human evidence and sufficient animal evidence
2B	possibly carcinogenic to humans	limited human evidence or sufficient animal evidence
3	not classifiable as to carcinogenicity to humans	agents which do not fit into any other group
4	probably not carcinogenic to humans	lack of carcinogenicity in humans and animals

The following definitions are used in the IARC carcinogenicity classification:

sufficient evidence — a positive causal relationship between exposure to the agent and cancer has been established in which chance, bias and confounding factors could be ruled out with reasonable confidence. Experimental evidence may demonstrate an increased incidence of malignant neoplasms (or a combination of benign and malignant neoplasms) in either a) two or more species of animal, b) two or more independant studies on one species, or c) in exceptional cases, one species with a high incidence.

limited evidence — a credible positive causal relationshiphas been established, but chance, bias and confounding factors could not be ruled out with resonable confidence. Experimental data suggest carcinogenicity but definite classification is not possible because of one or more of the following factors: a) single experiment available, b) there are unresolved questions regarding experimental design or interpretation, c) only benign tumours were reported.

inadequate evidence — available studies of insufficient quality, consistency or statistical power to permit a conclusion to be reached. Experimental data show qualitative or quantitative limitations

evidence suggesting lack of carcinogenicity — several adequate studies, covering the full range of doses to which humans are known to be exposed, fail to show a positive association between exposure to the agent, and any studied cancer at any observed level of exposure. The possibility of a very small risk at the levels of exposure studied in not excluded. Experimental data should be avaialble for at least two species. This conclusion is neccessarily limited to the species, tumour sites and doses of exposure studied.

The classification scheme used by the US Environmental Protection Agency (US EPA) is similar to the one used by IARC, although it consists of six categories. These are as follows:

Group	description
A	human carcinogen
B1	probably carcinogenic to humans (limited human evidence)
B2	probably carcinogenic to humans (no or inadequate human evidence and sufficient animal evidence)
C	possible human carcinogen
D	not classifiable as to carcinogenicity to humans
E	non-carcinogenic to humans.

Natural Environment Research Council