BaP and PAH from coal-derived sources

Health-based calculated occupational cancer risk values
of benzo[a]pyrene and unsubstituted non-heterocyclic
polycyclic aromatic hydrocarbons from coal-derived sources

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'BaP and PAH from coal-derived sources'
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Mijnheer de staatssecretaris,

Bij brief van 3 december, nr DGV/BMO/U-932542, verzocht de staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

In dat kader bied ik u hierbij een advies aan over benzo(a)pyreen en PAK afkomstig van steenkool. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport, de minister van Sociale Zaken en Werkgelegenheid en de staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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polycyclic aromatic hydrocarbons from coal-derived sources

Dutch Expert Committee on Occupational Standards
a committee of the Health Council of the Netherlands

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2006/01OSH, The Hague, 21 February 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

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Samenvatting

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid berekent de Commissie WGD van de Gezondheidsraad de concentratieniveaus in de lucht (HBC-OCRV's*) die samenhangen met een extra kans op overlijden aan kanker van 4 per 1 000 en 4 per 100 000 door beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor de door de EU aangemerkte genotoxische kankerverwekkende stoffen benzo(a)pyreen (BaP) en polycyclische aromatische koolwaterstoffen (PAK) afkomstig van steenkool; door de onvolledige verbranding van steenkool komen PAK vrij. Beroepsmatige blootstelling vindt vooral plaats bij industriële activiteiten, zoals cokes-, aluminium-, ijzer- en koolstofelektrodenproducerende bedrijven en staalgieterijen.

Hoewel dit advies zich beperkt tot steenkool is dit niet de enige bron waaruit PAK door onvolledige verbranding vrij kunnen komen: andere voorbeelden zijn hout en petroleum. Bij verbranding van deze materialen komen echter relatief veel meer andere stoffen vrij dan PAK. Sommige van die stoffen zijn eveneens kankerverwekkend net als PAK. Daardoor is het niet mogelijk om de gegevens van deze zo verschillende bronnen te combineren voor de berekening van con-

* HBC-OCRV's: health-based calculated occupational cancer risk values.

centratieniveaus van PAK gebaseerd op één gezamelijke blootstellingsparameter. Deze gegevens heeft de Commissie WGD daarom in dit advies buiten beschouwing gelaten.

Voor de berekening van concentraties in de lucht bij de bovengenoemde extra kansen op kankersterfte gebruikt de commissie normaliter een standaardmethode van lineaire extrapolatie, die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06 WGD)[50]. In dit advies is zij daarvan afgeweken, omdat wetenschappelijke gegevens aangeven dat een log-lineair model geschikter is.

Fysisch-chemische eigenschappen

Polycyclische aromatische koolwaterstoffen vormen een grote groep verbindingen, bestaande uit ten minste twee geconjugeerde aromatische ringen die uitsluitend uit koolstof en waterstof bestaan. Benzo(a)pyreen bestaat uit vijf van deze aromatische ringen. PAK moeten niet verward worden met polynucleaire aromatische verbindingen. Deze laatste groep verbindingen bevatten namelijk behalve de ongesubstitueerde PAK ook gesubstitueerde PAK en heterocyclische aromatische verbindingen.

Door verschillen in de chemische structuur kunnen de fysisch-chemische eigenschappen van PAK aanzienlijk variëren. PAK zijn in het algemeen niet tot matig vluchtig, en in de lucht komen zij voor zowel geadsorbeerd aan stofdeeltjes als in de vorm van damp. PAK lossen niet op in water, maar wel in benzeen en andere organische oplosmiddelen.

PAK komen altijd als mengsel voor, waarvan de onderlinge verhouding van de componenten afhangt van de bron, de wijze van ontstaan (o.a. verbrandingstemperatuur) en de verdere lotgevallen van de stoffen.

Monitoring

Luchtmonsters van benzo(a)pyreen (BaP) en andere PAK worden in het algemeen op filters verzameld met behulp van pompsystemen. Na extractie en zuivering van het filter wordt de hoeveelheid BaP en PAK bepaald met behulp van chromatografie of spectrofotometrie.

Voor het berekenen van de concentraties van PAK behorend bij bepaalde extra risico's op kankersterfte heeft de commissie gekozen voor benzo(a)pyreen als indicatieve verbinding voor de totale PAK blootstelling. Deze keuze is op praktische gronden gemaakt. Idealiter zouden alle PAK verbindingen moeten worden gemonitord, of tenminste een deel van deze verbindingen. Benzo(a)pyr-

een heeft het voordeel dat voor deze stof veel blootstellings- en effectgegevens beschikbaar zijn. Tot op heden wordt ze bovendien als één van de meest kankerverwekkende PAK verbindingen beschouwd. Daarnaast wordt benzo(a)pyreen op dit moment ook door vele andere (internationale) instanties als een geschikte indicatieve verbinding voor PAK beschouwd.

Dit advies geldt voor BaP en PAK afkomstig van steenkool. Diverse metingen hebben aangegeven dat bij gangbaar industrieel gebruik van steenkool de variatie in verhouding maar in beperkte mate bijdraagt in het geheel van onzekerheden. Deze verhouding kan echter worden verstoord doordat bijvoorbeeld BaP wel maar andere PAK niet worden uitgefilterd vóórdat emissie van verbrandingsproducten in de lucht plaatsvindt. In die gevallen is herziening van de op BaP gebaseerde risicoconcentraties nodig.

De belasting van het lichaam met PAK (interne blootstelling) kan worden vastgesteld door middel van biomonitoring, zoals de bepaling van 1-hydroxypyreen in urine. Hoewel deze parameter geschikt is om de totale lichaamsbelasting vast te stellen, is op dit moment onvoldoende bekend hoe deze zich verhoudt tot de luchtblootstelling.

Opname, verdeling en uitscheiding

Benzo(a)pyreen en andere PAK worden geabsorbeerd door het epitheel van de luchtwegen en het maagdarmstelsel. Ze worden door verschillende enzymen afgebroken tot wateroplosbare producten. De meeste van deze producten zijn onschadelijk, maar een aantal veroorzaken kanker. Dit zijn vooral PAK met ten minste vijf aromatische ringen, zoals benzo(a)pyreen. PAK met minder ringen zijn in het algemeen minder potent of zelfs niet kankerverwekkend, zoals pyreen.

Na opname via de longen of het maagdarmkanaal worden PAK en zijn afbraakproducten via het bloed naar alle delen van het lichaam getransporteerd, met name naar de vetrijke delen. Uiteindelijk verlaten PAK en zijn afbraakproducten het lichaam via de urine en ontlasting.

Kankerverwekkendheid

Er zijn vele mens- en dieronderzoeken gepubliceerd over de kankerverwekkende eigenschappen van benzo(a)pyreen en PAK. Daaruit kwam naar voren dat de kankerverwekkende PAK vooral lokaal kanker veroorzaken, dat wil zeggen op de plaats waar direct contact is met de PAK, bijvoorbeeld huidkanker bij huidcontact en longkanker bij inademing. Er bestaat echter ook onderzoek dat niet uitsluit dat PAK ook elders in het lichaam kanker kan doen ontstaan. Bijvoor-

beeld, enkele onderzoekers associeerden blootstelling aan PAK met het ontstaan van blaaskanker. Maar aangezien in veel van deze gevallen ook sprake was van blootstelling aan onder andere 2-naftylamine, een stof waarvan bekend is dat het blaaskanker veroorzaakt, blijft onzeker of de gevonden associatie een oorzakelijk verband weerspiegelt. Bij enkele dieronderzoeken zijn verder longtumoren gevonden na chronische inname van PAK via de voeding. De gegevens van deze dieronderzoeken zijn echter beperkt, zowel in kwantiteit als in kwaliteit, zodat een duidelijke uitspraak over systemische kankerverwekkende effecten van PAK niet mogelijk is.

Het vergelijken en interpreteren van de epidemiologische gegevens wordt deels bemoeilijkt door de grote diversiteit in onderzoeksopzet, verschillen in methoden van blootstellingsmeting, het niet of wel rekening houden met rookgewoonten en gelijktijdige blootstelling aan andere stoffen en soms de incomplete beschrijving van onderzoeksresultaten. Desondanks is de conclusie gerechtvaardigd dat een groot deel van deze onderzoeken een duidelijke associatie aantoont tussen beroepsmatige blootstelling aan benzo(a)pyreen en andere PAK en het optreden van longkanker. Dit geldt ook voor huidkanker bij blootstelling via de huid.

Enkele onderzoekers hebben het risico van longkanker bij een bepaalde blootstelling aan PAK geschat. Zo zijn recent de resultaten van een meta-analyse gepubliceerd, waarin 39 verschillende cohorten zijn betrokken. De beroepsmatige blootstelling in deze cohorten ontstond door verwerking van uit steenkool afgeleide producten in verschillende industrieën, waaronder bedrijven die cokes en aluminium produceren. Met behulp van een log-lineair rekenmodel hebben de desbetreffende onderzoekers berekend dat er een extra risico van 20% is (relatief longkankerrisico van 1,2 (95% betrouwbaarheidsinterval 1,11-1,29)) bij een gemiddelde benzo(a)pyreen blootstelling van 2,5 $\mu g/m^3$ (microgram per kubieke meter) gedurende 40 arbeidsjaren ten opzichte van de niet-blootgestelde mensen.

Evaluatie en berekende concentraties in de lucht

Omdat inhalatoire blootstelling aan BaP en PAK duidelijk tot longkanker kan leiden, en daarvoor een grote hoeveelheid gegevens beschikbaar is, heeft de commissie besloten concentratieniveaus in de lucht te berekenen op basis van deze longkankergegevens.

Voor de berekening van de concentraties in de lucht behorende bij de referentiewaarden voor de extra kans op kankersterfte gaat de voorkeur uit naar mensgegevens afkomstig van epidemiologisch onderzoek. De meta-analyse waarin 39 verschillende epidemiologische onderzoeken zijn betrokken vormt volgens de

commissie het beste uitgangspunt, ondanks de onzekerheden die inherent zijn aan de onderzoeksopzet van de afzonderlijke onderzoeken. De onderzoekers van deze meta-analyse stelden vast dat de relatie tussen concentratie in de lucht en de kans op kanker het beste beschreven kan worden met een log-lineair model in plaats van een lineaire model. De commissie heeft daarom het log-lineaire model overgenomen en gebruikt om de concentraties behorende bij de referentiewaarden te berekenen. De commissie voegt daaraan toe dat bij de lage blootstellingsconcentraties waarop HBC-OCRV's worden berekend, het lineaire model vergelijkbare uitkomsten oplevert als het log-lineaire model. Daarnaast heeft zij gebruik gemaakt van de Nederlandse algemene sterftecijfers aan longkanker onder mannen, zodat de berekening op de Nederlandse situatie is gebaseerd.

Naar schatting van de commissie is de concentratie in de lucht die samenhangt met een extra kans op overlijden aan kanker van*

- 4 per 1 000 sterfgevallen aan kanker ($4x10^{-3}$) bij 40 jaar beroepsmatige blootstelling aan benzo(a)pyreen en polycyclische aromatische koolwaterstoffen afkomstig van steenkool gelijk aan 550 ng BaP/m^3
- 4 per 100 000 sterfgevallen aan kanker ($4x10^{-5}$) bij 40 jaar beroepsmatige blootstelling aan benzo(a)pyreen en polycyclische aromatische koolwaterstoffen afkomstig van steenkool gelijk aan 5,7 ng BaP/m^3.

Huidnotatie

De commissie heeft tevens beoordeeld of voor benzo(a)pyreen en polycyclische aromatische koolwaterstoffen afkomstig van steenkool een huidnotatie nodig is. Hoewel er geen bewijs is dat huidblootstelling tot effecten elders in het lichaam kan leiden, beveelt de commissie toch een huidnotatie aan, omdat direct contact met de huid tot huidkanker kan leiden.

Schatting van concentratieniveaus

Naar schatting van de commissie is de concentratie in de lucht die samenhangt met een extra kans op overlijden aan kanker van

- 4 per 1 000 sterfgevallen aan kanker ($4x10^{-3}$) bij 40 jaar beroepsmatige blootstelling aan benzo(a)pyreen en polycyclische aromatische koolwaterstoffen afkomstig van steenkool, gelijk aan 550 ng BaP/m^3

* Berekening is gebasseerd op het log-linear model van Armstrong *et al*. (2003).

- 4 per 100 000 sterfgevallen aan kanker ($4x10^{-5}$) bij 40 jaar beroepsmatige blootstelling aan benzo(a)pyreen en polycyclische aromatische koolwaterstoffen afkomstig van steenkool, gelijk aan 5,7 ng BaP/m^3.

Executive summary

Scope and procedure

At the request of the Minister of Social Affairs and Employment, the Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, derives so-called health-based calculated – occupational cancer risk values (HBC-OCRVs) associated with excess mortality levels of 4 per 1,000 and 4 per 100,000 as a result of working life exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen.

In this report the committee derives HBC-OCRVs for benzo[a]pyrene (BaP) and unsubstituted non-heterocyclic polycyclic aromatic hydrocarbons (PAH) from coal-derived sources. PAH (and BaP) are formed by incomplete combustion of these coal-derived sources. Occupational exposure may occur in several industries, such as in: coke ovens and power plants; petroleum refining; aluminium production using Söderberg anodes; manufacture of anodes; and, steel and iron foundries.

Although this report is limited to coal-derived sources, it is not the only source at which PAH may be formed by incomplete combustion; other examples are wood, petroleum, and gas oil. However, a main problem with these sources is that they contain relatively high concentrations of other substances than PAH. Some of these are carcinogenic, just as PAH. Therefore, the committee is not able to combine data from these different sources to estimate reliable cancer risk values for PAH, and thus left these data aside this evaluation.

HBC-OCRVs associated with the reference cancer risks are derived by using a standard linear non-threshold extrapolation model, unless scientific data indicate otherwise. This model is described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06 WGD)[50].

Identity and physical-chemical properties

Polycyclic aromatic hydrocarbons constitute a large class of organic compounds consisting of at least two fused aromatic rings of carbon and hydrogen atoms. Concerning benzo[a]pyrene, this PAH consists of 5 benzene rings. PAH are not to be confused with polycyclic or polynuclear aromatic compounds (PAC), which contain not only unsubstituted non-heterocyclic PAH, but also substituted and/or heterocyclic PAH-derivates.

Due to differences in number of rings and molecular mass, the physical and chemical properties of a single PAH may differ. However, in general PAH are solids having high melting (~60-450°C) and boiling (~200-600°C) points. In addition, PAH are very little to moderately volatile, in particular the high molecular PAH. This means that PAH can occur in the air as inhalable particles and vapour. Furthermore, PAH are rather inert lipophilic compounds, which easily dissolve in organic solvents.

PAH always occur as complex mixtures, of which the composition may differ by source (*e.g.,* coal-derived *versus* non-coal derived), physical circumstances, and the way these sources are handled in the workplace.

Monitoring

Airborne benzo[a]pyrene and PAH are collected using pumping systems, filters (for particle-bound PAH) and absorbents (for gaseous PAH). After extraction and purification, BaP and PAH are analysed by chromatographic or spectrophotometric techniques.

Although it is desirable to monitor total PAH or a selection of PAH, considering the vast and consistent amount of data presented for benzo[a]pyrene and the fact that BaP is believed to be one of the more potent PAH carcinogens, the committee prefers the use of BaP as a marker for the overall PAH exposure. Similarly, various other national and international regulatory authorities consider BaP as a suitable marker for PAH exposure in the air.

The recommendation in this report is valid for BaP and PAH derived from coal. Various measurements have pointed out that by current industrial use of coal the variation between BaP and other PAH contributes to a limited degree in

the whole set of uncertainties. This relationship will be disturbed when, for instance, BaP (but not the other PAH) is filtered out before the PAH mixture is emitted in the air. In those cases, a readjustment of the recommendation is needed.

Internal benzo[a]pyrene and PAH exposure can be assessed using biological monitoring techniques (*e.g.*, 1-hydroxypyrene in urine, and DNA- and protein-adducts in blood and tissues). Biological monitoring is not only useful in protecting worker health and minimising exposure, but also for quantitative occupational cancer risk estimation. However, since biological monitoring represents total body burden, and thus dermal, oral and inhalation exposure cannot be separated, it cannot readily used for the risk estimation in this document, which is based on inhalation exposure alone.

Kinetics

PAH are absorbed through the epithelia of the respiratory and gastrointestinal tract. In these epithelia, PAH are metabolised by phase I and II enzymes into various polar and water soluble metabolites. Most of these metabolites are inactive and do not cause harm, but some do and are able to initiate cancer (*e.g.*, diol epoxides and cations). Of all PAH investigated, BaP (five aromatic rings) is considered as one of the more potent carcinogens, whereas PAH with less than five aromatic rings are considered less potent or even non-carcinogenic (*e.g.*, pyrene). After absorption, PAH and its metabolites are distributed via the bloodstream throughout all internal organs, with a preference for organs or tissues that contain high amounts of fat. Finally, they are released from the body in the urine and faeces.

Carcinogenicity

To cope with the vast amount of data and considering the purpose of this report, the committee extensively evaluated only what it judged to be the most relevant studies, with a main focus on epidemiological studies. Below a summary of the findings is given.

Numerous human and animal studies have been published on the carcinogenic effects of PAH, as a single compound (in animal studies only) or as a mixture, by various routes of exposure. These studies revealed that PAH act mainly as local carcinogens (*e.g.*, lung cancer by inhalation, skin cancer by dermal exposure). Some authors reported also on the risk of systemic cancer, such as bladder cancer in humans after inhalation. However, in none of these studies the presence

of specific bladder carcinogens could be ruled out (*e.g.,* 2-naphtylamine). Data on cancer at other sites of the body were inconclusive, due to limitations in data presentation and the low number of cases.

Concerning animal studies, in a few carcinogenicity studies lung tumours were reported after chronic feeding of coal tar pitch volatiles. Also other animal data are published on systemic cancer after oral, intraperitoneal and intrarectal administration of single PAH, but the quality of these studies was insufficient to make a final conclusion about systemic carcinogenicity. Overall, no consistent evidence was found that PAH might induce or enhance the development of systemic cancer by inhalation or dermal exposure.

In the literature a vast amount of epidemiological data is presented associating lung cancer with work-related PAH exposure (expressed by job-title or airborne PAH concentrations). However, interpretation and comparison of these data is partly hampered due to: differences in study design (case control *versus* cohort); differences in exposure measurements; not taking into account lifestyle factors; unawareness of co-exposure; and, incomplete data presentation. Nevertheless, despite these confounding factors, the majority of the epidemiological data associated airborne PAH exposures with increased lung cancer risk. In addition, skin cancer has been reported to be positively associated with dermal PAH exposure, but not with inhalation exposure.

Some investigators estimated (excess) lifetime lung cancer risk. For instance, the results of a well-performed meta-analysis have been published recently, which included 39 different cohorts. Exposure in all these cohorts concerned coal-derived PAH sources from various industries (*e.g.,* coke oven, gas works, aluminium production). The unit relative lung cancer risk (URR) at 100 $\mu g/m^3$ years BaP was estimated at 1.20 (95% CI, 1.11-1.29, $p<0.001$; log-linear model). This risk value was not driven by any particular cohort and was not dependent on analysis method.

Evaluation and HBC-OCRVs

Since lung cancer is strongly associated with airborne BaP and PAH exposure, and a vast amount of data is available on PAH exposure and lung cancer, the excess lifetime cancer risk values are based on lung cancer data.

In selecting the suitable study for estimating HBC-OCRVs, in principle the committee prefers epidemiological studies. According to the committee the meta-analysis constitutes the best starting-point. The committee has thoroughly evaluated this analysis and despite some uncertainties inherent to the design of the single epidemiological studies, none of the 39 cohorts were excluded. The

authors of this meta-analysis concluded that a log-linear model instead of a linear model best described the relationship between exposure and cancer risk. Therefore, to derive HBC-OCRVs, the committee adopted the log-linear model. The committee likes to add that at the low exposure concentrations, at which cancer risk values are based, the models just differ very little from each other, and the use of the linear model yields comparable outcomes as the log-linear model. Furthermore, lung cancer death values of the general population were adapted to the situation in the Netherlands.

In considering the above, the committee derived HBC-OCRVs corresponding to an excess cancer mortality level of*

- 4 per 1,000 ($4x10^{-3}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 550 ng BaP/m^3
- 4 per 100,000 ($4x10^{-5}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 5,7 ng BaP/m^3.

Skin notation

At the request of the Minister of Social Affairs and Employment, the committee judged whether for benzo[a]pyrene and polycyclic aromatic hydrocarbons (PAH) from coal-derived sources a skin notation is needed. Although the committee did not find proof that BaP or other PAH compounds add substantially to systemic non-carcinogenic adverse health effects by dermal exposure, the committee does recommend a skin notation, because direct skin contact may cause skin cancer.

Recommendation of Health-Based Occupational Cancer Risk Values

The committee derived HBC-OCRVs corresponding to an excess cancer mortality level of

- 4 per 1,000 ($4x10^{-3}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 550 ng BaP/m^3
- per 100,000 ($4x10^{-5}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 5,7 ng BaP/m^3.

* Calculation is based on the log-linear model of Armstrong *et al*. (2003).

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (Annex A). This evaluation should lead to a health-based recommended occupational exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with genotoxic carcinogenic properties.

In this case an exposure-response relationship is recommended for use in regulatory standard setting, *i.e.,* the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The committee calculates HBC-OCRVs for compounds, which are classified as genotoxic carcinogens by the European Union or by the present committee.

For the establishment of the HBC-OCRVs the committee generally uses a linear extrapolation method, as described in the committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens'[50]. The linear

model to calculate occupational cancer risk values is used as a default method, unless scientific data indicates that this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

This document contains the derivation of HBC-OCRVs for benzo[a]pyrene (BaP) and polycyclic aromatic hydrocarbons (PAH) from coal-derived sources.

The members of the committee are listed in Annex B. The first draft of this report was prepared by Dr WK de Raat, from the OpdenKamp, Registration & Notification in The Hague, by contract with the Ministry of Social Affairs and Employment. The Health Council further adapted the draft.

In 2005, the president of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The committee's calculations on HBC-OCRVs are based on scientific data, which are publicly available. A number of comprehensive and up to date studies and evaluations are available on the occurrence and health effects of PAH. It is beyond the scope of this document to evaluate all these publications. Consequently, the committee has made restrictions. Only references concerning dose-response relationships between cancer and PAH exposure were extensively consulted. In addition, because of the complexity of PAH composition references concerning this subject were more closely studied. For detailed information on the sources, exposures, kinetics and metabolism, and other toxicological effects, the reader is referred to evaluations published by other international authorities and reviewers. In addition, the following most relevant reviews were consulted and used as starting point for the present document:

- International Program on Chemical Safety (IPCS). Environmental health Criteria 202: Selected non-heterocyclic polycyclic aromatic hydrocarbons. World Health Organization 1998[70];

- Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for polycyclic aromatic hydrocarbons. US Department of Health and Human Services, Public Health Service August 1995[128];
- International Agency for Research on Cancer (IARC). Evaluation of the carcinogenic risk of chemicals to humans. A series of IARC Monographs concerning polynuclear aromatic compounds, including volumes 32 (1983)[57], 33 (1984)[58,59], 34 (1984)[58,59], and 35 (1985)[60].

Finally, additional data were obtained from the online database Toxline of the National Institute of Health in the USA, using: benzo[a]pyrene, polycyclic aromatic hydrocarbons, and human as key words.

The last search was performed in September 2005.

A list of abbreviations and symbols used in this report can be found in annex L.

Chapter 2

Identity

2.1 Identity

Polycyclic aromatic hydrocarbons (PAH; in this document, the abbreviation is used as both plural and singular) are a large class of organic compounds consisting of two or more fused aromatic rings of carbon and hydrogen atoms. Besides aromatic rings, some PAH also contain pentacyclic rings. The simplest PAH is the rather volatile solid naphthalene, consisting of two fused aromatic rings. However, the number of rings may be larger and the molecules can form large graphite-like aggregates[18]. Between these two extremes, numerous configurations of conjugated aromatic (and pentacyclic) rings are possible. Benzo[a]pyrene is a PAH that consists of five aromatic benzene rings.

In the literature, various terms are used for PAH and related compounds, and this may be confusing. Both the IPCS[70] and IARC[57] refer to the term PAH as unsubstituted non-heterocyclic PAH (including alkyl-substituted derivates). The general terms 'polycyclic aromatic compounds', 'polycyclic organic matter' or 'polynuclear aromatic compounds', not only includes PAH, but also: functional PAH derivates, in which hydrogen atoms are replaced by other atoms or functional groups (*e.g.,* chlorine, alkyl, nitro and amino groups); and/or, heterocyclic analogues, in which one or more carbon atoms in the rings are replaced by nitrogen, oxygen or sulphur atoms. The committee follows the terminology used by

IPCS and IARC. This means that in this evaluation only unsubstituted non-heterocyclic PAH (including alkyl-substituted derivates) are considered.

At the moment there are more than 100 single PAH identified. Only a minor fraction of these have been studied in environmental research and toxicology. The names, molecular weights, and CAS registry numbers of those evaluated by the IPCS[70] are listed in annex D1 (33 different PAH). Seventeen of these were also described and evaluated by the ATSDR[128].

In practice, PAH do not exist isolated, but as components of a complex mixtures that contain many different PAH and related compounds. This is due to the way they are naturally or artificially produced or processed (see Chapter 3). A number of these mixtures, which may exist in an industrial or occupational environment, are described and also given CAS registry numbers (see annex D2).

2.2 Physical and chemical properties

The physical and chemical properties of PAH vary and are largely determined by the number of rings and molecular masses[142]. Annex D3 shows a list of chemical and physical properties of the 33 single PAH substances evaluated by IPCS[70].

Overall, PAH are solids (at room temperature) with relatively high melting (66-439°C) and boiling (218–596°C) points. In particular high molecular PAH are very little to moderately volatile. In addition, they can occur in air as inhalable particles and vapour. Their water solubility is low and tends to decrease with increasing molecular mass. However, PAH are highly lipophilic and, therefore, soluble in many organic solvents. Finally, PAH are chemically rather inert, although they show chemical and photochemical reactions in the atmosphere[70,128].

2.3 Environmental monitoring

2.3.1 Validated analytical methods

Various techniques have been developed for the collection of the samples, their preparation and analysis of PAH in the air[70,128]. Most of these techniques have been evaluated as to recovery, sensitivity and artefacts[15,16,39,44]. Some examples of the analytic methods of PAH in the air are described by IPCS and shown in annex D4. The intent of this section is not to provide an exhaustive list of analytical methods. Rather, a brief summary of the sampling, preparation and analysis techniques is given.

Depending on the temperature at the sampling site and the molecular weight (*i.e.*, the number of aromatic rings), PAH may be present in the air as a gas or absorbed on airborne suspended particulate matter. The particle-bound PAH are collected by pumping the air through a filter or an impactor followed by a back-up filter, after which the gaseous PAH are absorbed from the air stream passing this filter by an adsorbent. Various filters (*e.g.*, quartz filters, glass-fibre filters, Teflon filters and Teflon-coated glass-fibre filters) and adsorbents (*e.g.*, XAD-2 resins and polyurethane foam) may be used for sampling.

Concerning the filters used to trap particle-bound PAH, all the available filters enable a virtual complete retention of particulate-bound PAH. In the literature, some investigators reported that some filter materials affect the decomposition of PAH during sampling more than other filters. However, for ambient air the influence of the filter material was found to be limited. To avoid sample decomposition and loss, it is recommended to restrict the sampling time to 24 hours.

There are some sampling factors that may influence the outcome of the analysis in such a way that results are difficult to compare. When PAH are emitted into the air, the composition of the mixture may change rapidly. For instance, PAH may evaporate, condensate or adsorb, so that PAH are transferred from the gas to the particulate phase and vice versa. In addition, some PAH are removed from the air by gravitation, impaction, dry deposition and adsorption to surfaces, or by chemical conversion. All these factors may lead to under- or overestimation of the presence of PAH in the gas phase or particulate matter. This makes clear that the composition of different PAH mixtures may vary by sampling site (near source, (static) environmental or personal air sampling, outdoor and indoor sampling), and duration of sampling.

In general, after sampling, the filters and the sorbents are extracted with organic solvents (*e.g.,* benzene, toluene, cyclohexane, dichloromethane, acetone and methanol). Standard extraction techniques, such as soxhlet and ultrasonic techniques, and solid-phase extraction may be used. After extraction, samples are cleaned-up or purified. Several techniques may be used for this, including liquid-liquid partition and (semi) preparative normal-phase chromatography (open column, HPLC or TLC).

Three analytical-chemical methods are routinely used to determine the concentrations of PAH in environmental samples. These include: separation of single PAH compounds with thin-layer chromatography (TLC) combined with visual fluorescence detection and identification by reference spots; separation by gas chromatography (GC) combined with flame ionisation detection (FID) and/

or mass spectrometry (MS) for detection or/and identification; and, separation by reversed-phase high-performance chromatography (HPLC), combined with ultraviolet and/or fluorescence detection and/or MS for detection and identification.

2.3.2 *Selections of PAH as marker for exposure assessment*

By definition, PAH exposure in the workplace concerns exposure to a mixture. The composition of these mixtures is complex and variable. Due to this complexity, research on the presence, fate and hazardous effects of PAH has been difficult and necessarily focussed on a limited number of PAH, with a preference for those PAH which are of interest concerning cancer risk assessment, and for which relatively easy and sensitive analysis techniques are available. Nevertheless, attempts have been made to assess occupational PAH exposure in the air by using mixtures as a whole or a selection of single PAH. The following paragraphs contain short evaluations and considerations on the use of the most used markers in exposure assessment.

Benzo[a]pyrene as surrogate for PAH exposure

The most extensively studied PAH as surrogate for total PAH exposure is benzo[a]pyrene. It is released from a great variety of different PAH-sources. In the thirties, BaP was identified as the predominant carcinogenic compound in coal tar[75,76,92,140]. Since then and up to now, exposure assessment and health effect studies were mainly focussed on this particular compound. In addition, various national and international authorities have used BaP as an indicator for total PAH exposure. At present, the compound is considered as one of the strongest genotoxic known carcinogens, which significantly contributes to the carcinogenic potency of PAH-rich mixtures (see Section 5.3 and Chapter 6).

Various validated analytic techniques are available to measure BaP in air[57,81,87,88]. At ambient temperatures, BaP is virtually exclusively present in the form of airborne particulate matter. This means, that no significant fluctuation due to condensation, absorption and evaporation has to be expected, when the compound is in the air or during sampling. However, it also means that BaP is a poor predictive marker for the effects of gaseous PAH compounds. This should be kept in mind, because the environmental fate between gaseous and particle–bound PAH may differ. On the other hand, none of the more volatile PAH substances (less than 5 rings) have been shown to be carcinogenic (see Chapter 5). Another point that should be taken into account in considering BaP as reliable

marker for total PAH exposure, is the stability of the compound and thus its chemical reactivity. BaP may react and decompose during sampling time. However, BaP has been found in particles from long-range transport, which shows that its instability does not lead to a complete decomposition. Furthermore, concentrations of BaP are always strongly correlated with those of its less reactive counterparts. As a result, in the literature it is pointed out that the influence of chemical reactivity will most probably be slight.

Recently, Sanderson *et al*. (2005)[112], and earlier Farant and Gariepy (1998)[38] reported that there was a strong relationship between BaP, and individual and total PAH in the air (the particulate phase PAH); and, that BaP was a good indicator for other PAH in two different types of Söderberg aluminium smelters.

A selection of PAH

In many studies, BaP is the only PAH compound measured. However, quantification of a series of single PAH gives a clearer picture of the overall PAH exposure and the composition of the mixture than one PAH alone. Such a PAH profile should contain a selection of carcinogenic PAH (keeping in mind that it is impossible to cover all carcinogenic PAH) that is representative for the overall chemical and physical properties of PAH (*e.g.,* vapour pressure and chemical reactivity), and are present in (all) PAH-sources. In the late sixties, Borneff and Kunte[24] introduced a selection of six different PAH (benzo[a]pyrene, benzo[ghi]perylene, benzo[k]fluoranthene, fluoranthene, indeno[1,2,3-cd]pyrene and benzo[b]fluoranthene). In addition, at the moment, various authorities require or recommend a selection of PAH to assess overall PAH exposure in the (occupational) environment. Examples are shown in annex D5.

A main disadvantage in using a selection of PAH is that at present no accepted selection of PAH is available as a marker for PAH exposure. Furthermore, only a limited number of data is available in which a selection of PAH is used for health risk assessment. Consequently, comparisons among different investigations are hampered.

Total PAH / Benzene Soluble Matter (BSM)

PAH mixtures contain non-carcinogenic PAH as well as substituted and/or heterocyclic PAH and non-related PAH compounds. All these substances are simultaneously released during processing and heating of PAH-rich sources and thus always occur together. As a result, the carcinogenic effects observed in epidemi-

ological studies due to exposure to PAH-rich sources, are in fact an overall effect of all those (non-) carcinogenic substances present in the mixture. Since the total mixture determines the final carcinogenic potency, it is of interest to monitor PAH-mixtures as a whole.

A possibility to assess total PAH exposure is sampling of benzene soluble matter or particulate (BSM). BSM is prepared from airborne particles and has often been used in the past. It not only contains all unsubstituted and non-heterocyclic PAH, but also other PAH and non-PAH substances that resemble the polarity of PAH. However, a main disadvantage of using BSM as exposure parameter is that it may include non-PAH substances released from sources other than the typical PAH-sources. As a result, BSM values are source dependent and may strongly be influenced by additional non-PAH sources in the vicinity of the sampling site. This makes the marker less attractive for risk assessment.

Conclusion

In conclusion, although it is desirable to monitor total PAH or a selection of PAH, considering the vast and consistent amount of data presented for benzo[a]pyrene and the fact that BaP is considered as one of the more potent PAH carcinogens, the committee prefers the use of BaP as a marker for the overall PAH exposure.

2.4 Summary

Polycyclic aromatic hydrocarbons (PAH) constitute a large class of organic compounds, consisting of at least two aromatic rings, which are sometimes replaced by pentacyclic rings. They are not to be confused with polycyclic or polynuclear aromatic compounds (PACs) that also contain substituted and/or heterocyclic PAH-derivates.

The physical and chemical properties of the single PAH are largely determined by the number of rings and molecular mass. Overall, at ambient temperature PAH are solids. The melting and boiling points are high. Furthermore, PAH are highly lipophilic and thus easily dissolve in organic solvents.

Several methods of sampling and analysis have been published. In short, after sampling on filters (particle-bound PAH) and sorbents (gaseous PAH), PAH are extracted and purified before the amount is determined chromatographically or spectrophotometrically.

PAH always exist as mixtures of various single PAH and (un)related compounds. Although, attempts are made to assess occupational PAH exposure in the

air by using mixtures as a whole or a selection of single PAH, the committee prefers using benzo[a]pyrene (BaP) as exposure marker in estimating cancer risk values for several reasons. One is that the amount of data on BaP exposure is vast and consistent, and another that BaP is one of the more potent PAH carcinogens.

Chapter 3

Sources

PAH are formed by pyrolysis or incomplete combustion of organic material, such as coal and wood. Formation of PAH by this process occurs quickly and at high temperatures[18]. At lower temperatures (100-150°C) PAH may be formed from organic material. Yet, this geochemical synthesis may take millions of years. In this way, PAH in coal and crude oils are formed in sediments. Up to now, evidence of biosynthesis of PAH compounds has not been found. As a result, the main environmental PAH sources are material from incomplete combustion of gases and organic substances[10,16,18,39,87], and subsequent release of PAH present in fossil fuels[18,47,133,136].

In general, both the temperature and the duration of PAH formation influence the PAH profiles[30,45,46,128]. For instance, at higher temperatures more low molecular weight PAH are formed than at lower temperatures[17,18,121]. In addition, geochemical synthesis results in more pentacyclic rings in the PAH molecules than rapid pyrolysis. The latter is interesting to know, because formation of pentacyclic rings blocks the formation of (carcinogenic) aromatic rings.

3.1 Natural sources

The main natural, non-anthropogenic sources of PAH release in the environment include forest fires and volcanic activity[11,65,66,88]. However, releases from these

sources constitute only a minor part of the total emission of PAH in the environment.

3.2 Man-made sources[70,128]

3.2.1 *Daily human activities*

Since PAH are present throughout the environment, exposure to these substances may take place at home or outside. Primary sources of environmental exposure include: cigarette smoke, vehicle exhaust, smoke from open fireplaces and cooking, and ingestion of contaminated food and drinking water.

3.2.2 *Occupational and industrial sources*

As is clear form the previous sections, sources of occupational exposure may be divided in sources of heating and incomplete combustion of organic substances, and sources of processing organic material that contain PAH. Concerning heating, examples are power plants heated with wood, coal and mineral oils, and waste incinerations. Other important contributions to occupational exposure are commercial industrial processes of coal and petroleum products, such as: the production of coke, petroleum refining, manufacture of anodes, aluminium, iron and steel production, and foundries.

Combustion products of petroleum or gas oil (vehicle exhaust), and asphalting may contain other toxic substances in much greater quantities than PAH. For this reason the committee excluded these mixtures from the present risk assessment, and focussed on coal-derived PAH sources (see Table 3.1). As a result, sections 3.3 and 3.4 give mainly information on PAH release and emission profiles from these coal-derived sources. The reader is referred to the IPCS document (1998)[70] and the EC position paper (2001)[36] for information on PAH release and emission profiles from sources other than the coal-derived ones.

Table 3.1 A number of occupational PAH coal sources (EPA, 2001)[127].

Coal sources
• coal fired industrial boilers
• primary aluminium producers – various processes
• secondary lead smelters
• coke ovens
• carbon black manufacturing

3.2.3 *Commercial production and use*

Some single PAH are commercially produced in Western Europe, Japan and the USA. These include: naphthalene, acenaphthene, acenaphthylene, fluorene, anthracene, phenanthrene, fluoranthene and pyrene. Of those, only naphthalene, acenaphthene, acenaphthylene and anthracene are produced in significant quantities.

Commercially produced PAH are mainly used for research goals. In addition, some PAH are used as (chemical) intermediates, such as: anthracene in dye production and in the synthesis of the chemotherapeutic agent Amsacrine; acenaphtalene in the manufacture of pharmaceuticals and plastics; and, fluorene in resin production.

3.3 Overall PAH release into the atmosphere

PAH release during production and processing of PAH, and during the use of single PAH. IPCS (1998) reported that no data are available on PAH emissions during industrial production and processing in developed countries. Therefore, IPCS concluded that these emissions are not thought to be important in comparison with the PAH release from incomplete combustion processes. Concerning single PAH, only naphthalene is used directly without further processing. IPCS assumed that about 15,000 tonnes per year was emitted in the atmosphere in Western Europe in 1986, and about 5,500 tonnes per year in the USA in 1987.

PAH release during processing and use of coal products. Much information is publicly available on PAH emissions during industrial processes and uses, such as during coal coking, coal conversion and liquefaction, and production of carbon anodes. It should be kept in mind that several factors may influence the concentration of PAH emitted. These factors include not only the source, but also the physical circumstances, the handling of the sources during processing and use, and the location of sampling. As a result, the emissions reported in various publications give only a rough idea of the situation (IPCS, 1998). Table E1 in the annex of this report shows some data on BaP emission in the United Kingdom by coal-derived sources. For comparison, Table E2 shows PAH and BaP emissions into the atmosphere of a few European countries from all anthropogenic sources together. Other examples of coal-derived PAH emissions can be found in the IPCS document (1998) and in the EC position paper (2001).

PAH release due to incomplete combustion. The most important PAH release into the ambient and industrial atmosphere is from incomplete combustion pro-

cesses. Of the total PAH release into the environment, it is estimated that about 80% is released from stationary sources and the rest from mobile sources (*e.g.*, vehicle exhaust). Concerning stationary point sources, these include aluminium production with use of Söderberg electrodes, iron and steel production, foundries, and power plants (IPCS, 1998). See also Table E1 and E2, and the IPCS and EC documents.

3.4 PAH emission profiles

3.4.1 PAH profiles in the ambient air

De Raat *et al*. (1988, 1994)[96,97] undertook a series of measurements to study PAH profiles and possible fluctuations within these profiles in one rural (coast), one urban (Delft), and two urban and industrialized (Rijnmond) areas in the Netherlands. Twenty-four hour samples were collected once a week for one year. These samples were analysed on the presence of 14 different PAH. The concentrations of these PAH were expressed as the ratio relative to BaP. The results are shown in Table E3 in the annex of this report. From the table it is clear that in particular the more volatile PAH (*e.g.,* pyrene, phenanthrene) are underestimated. In Figure E1 (see annex) E, also a frequency histogram and a calculated distribution for benzo[b]fluoranthene are depicted. This figure shows that the ratios obtained from about 200 samples is log normally distributed.

Muller and his colleagues[83,84] evaluated mean PAH profiles in ambient air in Canada emitted from different sources (point source, near mobile source, home heating and transport; presented in IPCS). The concentrations of 11 different PAH relative to BaP and their corresponding confidence ranges are shown in Table E4 (see annex E). From these data, IPCS concluded that the confidence ranges for most types of ambient air are similar. The committee noted that the Canadian profiles differed somewhat with the ambient air profiles found in the Netherlands. However, these differences are well explained by differences in sampling site (nearby sources *versus* random samples in ambient air) and method of analysis.

3.4.2 PAH profiles emitted into the occupational environment

Coal-derived PAH sources produce a characteristic PAH profile, of which the composition may differ by the way the source of PAH is handled in the workplace. Below, a few examples are given of these profiles of PAH emitted into the atmosphere. The committee emphasizes that these profiles serve as an indicator

of PAH exposure and are not intended to be complete. In addition, in most of the studies, the concentrations of PAH are expressed as the ratios of the levels of each PAH relative to BaP. Quantitative BaP concentrations released in the air by coal-derived sources are given by Bjørseth and Ramdahl (1985)[17]: 1,500 g/kg coal by coal furnaces; 15,000 µg/kg (range, 10,000-38,000 µg/kg) by aluminium smelting; 66 g/kg by anode baking; 1,6 µg/kg (range, 1.1-2.7 µg/kg) by pulverized coal-fired power plants; and, 0.93 µg/kg by coal-fired industrial boilers.

Table E5 and Figure E2 (see annex E) show the profiles of the most commonly measured PAH emitted by incomplete combustion of coal in a variety of industrial activities. In addition, IPCS presented the confidence ranges for various types of combustion mixtures, including those from coke ovens, coal tar, coal-fired power plants and coal stoves, which were analysed by Muller *et al*. (1995, 1996)[83,85] (see Table E6 in annex E). The authors concluded that "given the degree of uncertainty usually associated with risk assessment, the uncertainty presented by the variation in PAH profile was relatively small". Furthermore, they stated that "These factors are unlikely to generate large enough differences in the PAH profiles of mixtures to significantly alter the estimate of risk for a given mixture". 'These factors' are factors that may alter the PAH profile, such as source, use, aerial transport of PAH and degradation in sunlight.

3.5 Summary

PAH are mainly formed by incomplete combustion of organic material, such as coal and wood. The main part of the PAH released into the environment is the result of human activity. These include daily activities, such as cigarette smoke and vehicle exhaust, and industrial activities, such as coal coking in coke ovens, carbon electrode production, aluminium production, and iron and steel foundries. In some of those industrial activities, the source of PAH exposure is not heating and incomplete combustion, but the use of organic material that contains PAH. Commercial production of PAH does not play a major role as source of exposure.

Studies on the composition of PAH profiles, emitted in the air, revealed variations in composition of commonly measured PAH, although the confidence ranges of these compositions relative to BaP were relatively narrow. These variations could be well explained by differences in source and use, and by different monitor conditions. As to source differences, combustion mixtures of petroleum and gas oil, and asphalt contain other toxic substances in much greater quantities than PAH. Therefore, in assessing cancer risk values, these combustion mixtures were not taken into account. As a result, the committee considered only coal-

derived sources, although it is of the opinion that co-exposure to non-PAH substances from any source cannot be excluded.

Various measurements have pointed out that by current industrial use of coal the variation of emission profiles between BaP and other PAH contributes to a limited degree in the whole set of uncertainties.

Chapter 4

Exposure

4.1 General population

In the position paper, the EC (2001)[36] reported that in the 1990s typical annual mean levels of BaP in rural background varied between 0.1 and 1 ng/m^3; for urban areas between 0.5 and 3 ng/m^3; and up to 30 ng/m^3 in the vicinity of certain industrial installations. In the Netherlands, annual background concentrations of airborne BaP were below 1 ng/m^3 (period: 1988-2002; rural, urban industrial areas) (RIVM, Milieu & Natuurcompendium, 2004)[125].

In the USA, background levels were measured in rural and urban areas of 0.02-1.2 ng/m^3 and 0.15-19.3 ng/m^3, respectively[128].

4.2 Working population

The main route of occupational exposure to PAH is inhalation, although there is also potential for significant dermal exposure. In addition, exposure to PAH is possible in all operations involved in processing and using coal. A brief evaluation on airborne PAH exposure by the most relevant types of industry is given below.

4.2.1 Coke production

In various occupations in coke production substantial PAH exposure may occur, in particular in operations at the top of the ovens. This was illustrated by several investigators, such as: Romundstad *et al*. (1998)[106], who undertook exposure measurements in a Norwegian coke plant (see Table 4.1); and, Armstrong *et al*. (2004)[8] (see Table 4.2).

Table 4.1 Exposure to PAH in a Norwegian coke plant by job exposure matrix (from Romundstad *et al*. 1998).

Exposure category		PAH[a] (μg/m^3)	Carbonaceous particulates (mg/m^3)
Top oven	1964-1970	45	2
	1971-1976	300	16
	1977-1988	65	3
Side oven	1964-1977	45	8
	1978-1988	35	5
Stamper and ram car	1964-1970	45	8
	1971-1976	30	6
	1977-1988	6	1
Heater and quenching car	1964-1988	2	1
Wharf station	1964-1988	2	4

[a] Total PAH (sum of at least 30 different PAH).

Table 4.2 Occupational exposure to BaP and dust during coke production (data obtained from Armstrong *et al*. 2004).

Industry	Job category	BaP (μg/m^3)	Dust classification
Coke ovens	Top	20	H
	Side	10	M
	Other	0.5	M
	Typical plant mean	10	H/M[a]

[a] M, 1-5 mg/m^3; H, 5-10 mg/m^3.

Levin *et al*. (1995)[79] measured air concentrations of BaP of 0.9-37 μg/m^3 (median 4 μg/m^3), and 0.1-6.8 μg/m^3 (median 0.7 μg/m^3) in a Swedish coke oven, before and after a renovation, respectively. Total PAH was in the range of 20-480 μg/m^3 and below 10 μg/m^3 before and after the renovation, respectively. Total PAH was the sum of phenanthrene, anthracene, fluoranthene, pyrene, benzo[a]anthracene, chrysene and benzo[a]pyrene. The samples were obtained by stationary sampling. Marczynski *et al*. (2002)[80] determined mean personal exposure levels of 2.77 μg/m^3 BaP (range, 0.12-16.26 μg/m^3) and of 54.26 μg/m^3 total PAH (sum of 16 PAH; range, 4.51-316.45 μg/m^3) in a German coke-oven

plant (20 subjects) during an 8 h working shift. Also Strunk *et al*. (2002)[123] measured personal air concentrations of PAH in a German Coke plant. The concentrations of total PAH (sum 16 different PAH) and of BaP was higher on the topside of the ovens (mean total PAH, 491,2 μg/m^3 (range 82.8-1,679 μg/m^3); BaP, 7.4 μg/m^3 (range 0.9-29.3 μg/m^3)) than in the other workplaces (bench side: total PAH, 26.6 μg/m^3 (range 1.7-88.5 μg/m^3); BaP, 1.3 μg/m^3 (range below detection limit-4.6 μg/m^3)). Winker *et al*. (1996)[137] presented air concentrations of PAH in a new and an old coke-oven plant of the same company. In the coal charging car department of the old facility BaP levels of 5.4 μg/m^3 were measured, whereas in the new facility lower levels were found (0.6 μg/m^3).

In the Netherlands, Van Rooij *et al*. (1993)[108] measured mean personal air concentrations among twelve coke-oven workers. Concentrations of BaP ranged between 0.01 and 13.0 μg/m^3, and concentrations of pyrene between 0.1 and 5.4 μg/m^3. In addition, Jongeneelen *et al*. (1990)[73] measured total PAH concentrations (11 different PAH) in the breathing zone air of Dutch coke-oven workers of up to 186 g/m^3. The concentrations of pyrene ranged up to 24 μg/m^3. Also, these investigators reported that the highest concentrations were found among topside workers.

Overall, ATSDR (1995)[128] summarised that depending on work site or area airborne concentrations of BaP ranged from 0 to 383 μg/m^3 in coke oven operations.

IPCS (1998)[70] presented some airborne exposure concentrations of various single PAH in coke-ovens (see Table F1 in annex). The reader is referred to IPCS for further details on these exposure data.

4.2.2 *Coal gasification and liquefaction.*

In the production of town or industrial gas from destructive distillation of coal, exposure to PAH occur in both old and modern processes. In modern gasification systems, the stationary and personal total PAH air concentrations are usually below 1 μg/m^3 (IPCS, 1998)[70]. Armstrong *et al*. (2004)[8] reported airborne BaP levels of 3 μg/m^3 in retorts, and 0.5 μg/m^3 in by-products departments. Based on various epidemiological studies in the coal gasification industry, Boffetta *et al*. (1997)[21] reported ranges of 1,000-10,000 μg/m^3 BaP when old processes were used.

4.2.3 *Aluminium production*

Workers in the aluminium industry are exposed to PAH from evaporation of carbon electrode materials used in the electrolysis process. These anodes are usually made from coal tar pitch and coke (Boffetta *et al*. 1997)[21]. Boffetta *et al*. (1997) summarized that PAH exposure was particularly high in Söderberg electrolysis departments (range 1,000-10,000 μg/m^3 BaP), whereas in other departments the BaP air concentrations are lower (other main types of electrolysis, prebake, carbon plants: 100-1,000 μg/m^3).

However, others reported lower air concentrations. For instance, Levin *et al*. (1995)[79] reported on BaP and total PAH levels in a Swedish aluminium smelter with Söderberg pots from stationary air samples. The BaP concentrations ranged from 1.9 to 36 μg/m^3 (median 2.8 μg/m^3); total PAH ranged from 30 to 400 μg/m^3 (total PAH: the sum of phenanthrene, anthracene, fluoranthene, pyrene, benzo[a]anthracene, chrysene and benzo[a]pyrene). Armstrong *et al*. (2004)[8] reported mean airborne BaP concentrations of 3 μg/m^3 in Söderberg potrooms, and of 0.5 μg/m^3 in prebake areas.

IPCS[70] stated that PAH concentrations in the air of aluminium plants is reduced dramatically using tempered anodes instead of Söderberg anodes. For instance, Barat (1991)[12] reported BaP levels in a French factory of 1 to 36 μg/m^3 in potrooms with Söderberg anodes and 0.004 to 0.6 μg/m^3 in potrooms with tempered anodes.

Overall, ATSDR (1995) summarised that depending on work site or area airborne concentrations of BaP ranged from: 'not detected' to 975 μg/m^3 in aluminium production facilities (period 1959-1982); and, 0.03 to 53 μg/m^3 in aluminium reduction plants.

IPCS (1998) presented some airborne exposure concentrations of various single PAH in aluminium production plants (see Table F2 in annex). The reader is referred to IPCS for further details on these exposure data.

4.2.4 *Carbon and graphite electrode manufacture*

Petry *et al*. (1996)[91] measured personal air exposure to total PAH and to BaP for six workers in a carbon anode producing plant. BaP concentrations ranged from 0.16 to 4.88 μg/m^3, and total PAH from 3.99 to 120.6 μg/m^3 (total PAH: 26 different PAH). Furthermore, Marczynski *et al*. (2002)[80] determined mean personal exposure levels of 2.77 μg/m^3 BaP (range, 0.02-46.22 μg/m^3) and of 143.08 μg/m^3 total PAH (sum of 16 PAH; range, 0.97-1,848.37 μg/m^3) in a German graph-

ite-electrode producing plant (30 subjects) during an 8 h working shift. Armstrong *et al*. (2004) reported air concentrations of BaP of 1 μg/m^3 in carbon anode plants.

4.2.5 *Iron and Steel foundries*

Workers in the iron and steel foundries are exposed to PAH by the use of coal powder or coal tar pitch as a binder material, during thermal decomposition. Based on the results of epidemiological studies published by others, Boffetta *et al*. (1997)[21] reported concentrations of BaP in the range of 0.1-1.1 μg/m^3. Recently, Apostoli *et al*. (2003)[5] measured airborne concentrations of 7 different PAH in the work environment of two Italian electric steel plants and one iron foundry. The areas were classified as low (iron foundry and continuous casting area), high (oven, continuous furnace and refractory areas) or very high exposure (oven area of electric steel plant). Regarding BaP, concentrations of 26.3, 49.0 and 106.5 ng/m^3 were found, respectively.

IPCS (1998) presented some airborne exposure concentrations of various single PAH in steel foundries (see Table F3 in annex). The reader is referred to IPCS for further details on these exposure data.

Chapter 5

Kinetics

The general principles of the kinetics of PAH, in particular BaP, have been covered exhaustively in the published literature (for an overview see also IPCS[70], ATSDR[128], and IARC[57]). In this chapter, only a very brief summary is given, with special attention to dermal absorption and the carcinogenic pathway.

5.1 Absorption and distribution[70]

PAH are lipophilic compounds and, therefore, they are easily absorbed through the epithelia of the respiratory, gastrointestinal tract and the skin. When absorbed, PAH are distributed via the bloodstream throughout all internal organs, and particularly in those with high fat contents. However, in the literature it is suggested that only a minor portion will reach the circulation, because PAH are metabolised (see section 5.2). It is assumed that the absorption of PAH in the gastrointestinal tract is more rapid than in the lungs and the skin. Hence, a larger portion may reach the internal system by oral exposure[90]. Furthermore, PAH are able to pass the placental barrier.

5.1.1 Absorption by the lungs

Following inhalation exposure, PAH attached to particulate matter are partly cleared from the lungs by desorption and uptake in the blood, and by particle

clearance mechanisms. The desorption maybe rapid but incomplete and depends on the loading of the particles. The clearance rate of particles with-bound PAH is slow (Gerde *et al*. 2001)[41] and depends on lung burden and size of the particles. Some animal studies have been performed on the bioavailability of PAH bound to particles (Gallagher *et al*. 1994[40]; Borm *et al*. 2005[22]). Although further research is needed, these studies suggest that PAH attached to high surface particles are not bioavailable based on the absence of detectable PAH-DNA adducts *in vivo*.

5.1.2 Dermal absorption

The fact that PAH are absorbed through the skin, raises the question whether dermal exposure leads to a significant additional cancer risk at other sites than the skin, such as in the lungs. To answer this question evidence is needed that dermal exposure to PAH contributes significantly to the total PAH body burden of exposed workers, when dermal exposure is present.

Observations in humans

Occupational exposure studies, in which the urinary excretion of 1-hydroxypyrene was determined together with external exposure to pyrene, clearly indicate that a large part of the amount excreted had entered the body through the skin[13,33,51,71-73,107,108]. For instance, Van Rooij *et al*. (1993)[108] estimated that on average 75% (range 28-95%, 12 coke-oven workers) of the total absorbed amount of pyrene (indicator: urinary 1-hydroxypyrene concentration) enters the body through the skin.

Concerning controlled clinical studies, Van Rooij *et al*. (1993)[109] applied coal-tar ointment to the skin of seven healthy volunteers. The ointments were applied three times for 6 hours on various anatomical sites (foreheads, shoulders, volar forearms, palms of the hands, groins, and ankles). Dermal absorption and urinary 1-hydroxypyrene levels were measured up to 72 hours after application. PAH were clearly absorbed through the skin (20-56%, 6 hours after application and dependent on anatomical site). In addition, the authors estimated that 0.3-1.4% of the pyrene dose that was applied (about 2 μg pyrene/cm^2) became systemically available.

In another study, Viau *et al*. (1995)[130] applied a single dose of 500 μg pyrene (dissolved in 200 μL toluene) on 100 cm^2 of the inner face of each forearm of two healthy male volunteers for 1 hour for five consecutive days. Urinary 1-hydroxypyrene levels were measured up to 48 hours after the last application. As

a result of the exposure, urinary 1-hydroxypyrene levels increased. The authors did not perform any statistical analysis.

Storer *et al*. (1984)[122] applied 2% crude coal tar (in petrolatum) to the skin of five healthy non-smoking volunteers for 8 hours per day on two consecutive days. After completion of the exposure, analysis revealed the presence of at least eleven different PAH (*e.g.,* naphthalene, acenaphthalene, phenanthrene) in the blood.

Observations in animals

Withey *et al*. (1993)[138] exposed male Wistar rats (n=3/group/time point) to radiolabelled pyrene (in acetone vehicle) at doses of 2, 6 and 15 mg/kg bw. The substance was applied to 4 cm^2 of a shaved area of the mid back and wiped off 24 hours later. At 1, 2, 4 and 6 days postdosing, all organs, and including blood and urine, were investigated for the presence of radiolabelled and non-radiolabelled pyrene. The results of the analyses are shown in Table G1 and G2 (see annex G). About 50% of the applied doses were excreted over the study period of 6 days. Furthermore, levels of pyrene were highest in the liver, kidneys and fat tissue. In addition, metabolites of pyrene were found in the lungs.

Potter *et al*. (1999)[94] studied the influence of the viscosity of the vehicle on the bioavailability of BaP. A final concentration of 0.1% of radiolabelled BaP was dissolved in several vehicles with different viscosities (from mineral oil (low viscosity) to residual aromatic extracts (high viscosity)). These solutions (50 µL/mouse) were applied on the shaved dorsal skin of female CF1 mice (n= 5/group) for a maximum of 6 hours. This was done by inserting a pipette under the aluminium foil using a spreading motion. The aluminium foil (4.0x2.5 cm) was taped (polythene adhesive tape) on the shaved area two days before exposure. Blood analysis on the presence of total radioactivity and free radiolabelled BaP revealed that the uptake of BaP was reduced by about a fivefold when the viscosity increased from 32 to more than 5000 cSt. Also other investigators studied the influence of viscosity of the vehicle on the bioavailability of BaP after dermal application. For instance, Ingram and his colleagues[67,68] used skin painting studies with mice to show that binding of radiolabelled BaP to both epidermal DNA and protein decreased when viscosity of the vehicle increased. These results suggest that the bioavailability of BaP depends on the viscosity of the vehicle.

Schoket *et al*. (1990)[116] found persistent levels of DNA-adducts in the skin and lungs of mice, which were dermally exposed to coal (lungs, less than 0.03 fmol/µg DNA) and juniper tar (lungs, 0.7 fmol/µg DNA) ointments. Comparable

results were found for lubricating oils from petrol and diesel engine oils applied to the skin of mice (40-150 amol adducts/µg DNA) (Schoket *et al*. 1989)[115]. When petrol engine oil was used, twenty-two percent of the adducts corresponded to the major BaP-DNA adduct. However, diesel engine oil did not produce significant amounts of this type of DNA adduct. In addition, in an earlier study by Schoket *et al.* (1988)[114] also DNA-adducts were found in the lungs of male Parkes mice (n=4/group), which were dermally exposed to crude coal tar. The coal tar (6 mg per mouse, dissolved in 150 µL ethanol) was applied to the shaved dorsal skin on the first and fourth day of each week for up to 5 weeks. The levels of DNA-adducts in the lungs increased over the first three weeks of treatment after which a plateau was reached (5^{th} week: 0.5 fmol adducts/ µg DNA). In the skin, DNA-adducts reached a maximum level at five weeks of treatment (1.4 fmol adducts/µg DNA).

Evans *et al*. (2004)[37] topically applied 200 nMol BaP (in 25 µL acetone; corresponding to 2 mg/kg bw) on the shaved dorsal region to fifteen female C57BL/6 mice, once daily for 4 consecutive days. On the fifth day the mice were sacrificed. A total of 300 BaP-DNA adducts/10^9 nucleotides were found in the skin, and 13 BaP-DNA adducts/10^9 nucleotides in the lungs. No adducts were found in control animals.

Hughes *et al*. (1990)[55] used male Parkes mice (n=4/group/time point) for a single topical application of 1 µMol BaP (in 200 µL tetrahydrofuran) on the shaved dorsal skin. The animals were sacrificed at 6 hours, 1, 2, 4, 7, 21, and 84 days after the application. In the skin the amount of DNA-adducts reached a maximum of 7.9 fmol/µg DNA (1 fmol/µg DNA = 33 adducts/10^8 nucleotides) after one day. One week later 70% of the damage was removed. In the lungs, a maximum amount of adducts of 1.2 fmol/µg DNA was reached after two days. Seventy percent of it was removed within four days.

In vitro skin penetration models

Kao *et al*. (1985)[74] found that of the dermally applied dose (2 µg/cm^2 BaP), 10% crossed the mouse skin *in vitro*, 3% the human skin, and less than 0.5% the guinea pig skin. These findings suggest that percutaneous absorption strongly depends on species-specific diffusion and metabolic processes.

Van Rooij *et al*. (1995)[110] investigated the dermal absorption of a series of single PAH in the blood-perfused pig ear model (n=5). After 30 minutes of blood perfusion, industrial coal tar was applied on a skin area of 6x4 cm^2 with an average dose of 11 mg/cm^2 (7.7-17.5 mg/cm^2) for a maximum of about 250 minutes.

Less than 0.2% of PAH in the coal tar was absorbed through the skin in the perfusion blood after 200 minutes. This indicates that the amount of coal tar applied was strongly overdosed. The absorbed amount of 10 single PAH is shown in Table G3 (see annex G). The data in this table clearly show that lower molecular weight PAH (*e.g.,* phenanthrene) are absorbed in larger quantities than pyrene, and that higher molecular weight PAH (*e.g.,* BaP) are absorbed in smaller quantities than pyrene.

Sartorelli *et al*. (1999)[113] used a static diffusion cell system with full-thickness monkey abdominal skin to investigate the influence of the vehicle in which PAH is applied. A mixture of 13 PAH was applied in a vehicle of acetone solution with artificial sweat or in a vehicle of lubricating oil. The permeability constants (K_p), maximum penetration rates (flux) and lag times of PAH in acetone with artificial sweat are shown in Table G4 (see annex G). The penetration of most PAH was clearly slower in lubricating oil than in acetone/artificial sweat. For instance BaP only passed the skin when applied in acetone/artificial sweat.

Wester *et al*. (1990)[131] studied the penetration of BaP into and through human skin. Donor skin, obtained from two different humans, was put in diffusion cells with a flow-through design (1 cm^2 surface area; human plasma as receptor fluid). BaP was applied in acetone solution or as soil particles (artificially contaminated with BaP) for 24 hours. Although BaP was absorbed through the skin (23.7% in acetone, 1.4% as soil particle), it did not reach the receptor fluid (surrogate for human plasma).

Yang and his colleagues (1989)[141] evaluated the percutaneous absorption of BaP in petroleum crude oil sorbed on soil. Full thickness dorsal skin from rats was put in diffusion cells (aqueous antibacterial solution as receptor fluid). Radiolabelled BaP in petroleum crude oil sorbed on soil (9 mg/cm^2 of fortified soil) was once applied. Also, radiolabelled BaP in crude oil (not sorbed on soil; 90 $\mu g/cm^2$, administered in 70-145 µL acetone-carbon disulfide (1:1, v/v)) was applied for comparison reasons. The absorption rate was determined by analysis of the receptor fluid, which was sampled every 24 hours for four days. The penetration rate of BaP in soil-sorbed crude oil was much lower than of BaP in crude oil only (see Figure G1, annex G).

Evaluation and conclusion

Both human and animal studies clearly showed that PAH penetrate the skin and reach the circulation. The absorption rates were affected by the viscosity of the vehicle of administration[67,68,94,113], the anatomical site of application[109], and the

molecular weight of the single PAH[110]. Concerning the distribution of PAH in the body following dermal exposure, no data were found in humans. From the few animal data that are available, it is reasonable to conclude that PAH after dermal exposure are distributed through various internal organs, including the lungs.

5.2 Biotransformation[70]

The biotransformation of PAH starts at the moment they are absorbed through the epithelia of the lungs and the skin. The longer the retention time in the epithelium of the respiratory tract, the more PAH will be metabolised[28].

The metabolism of PAH is complex. In a first step, PAH are oxidized to form epoxides, phenols and dihydrophenols (phase-I metabolites). In a second step, these metabolites are conjugated with either glutathione, sulphate or glucuronic acid to form much more polar and water-soluble metabolites (phase-II metabolites). Most PAH metabolised in this way are deactivated. However, some of them are activated to DNA-binding species, which can initiate cancer[42].

5.2.1 Carcinogenic pathway

Most information on the carcinogenic metabolism of PAH is obtained from *in vivo* and *in vitro* studies with benzo[a]pyrene as model compound. For this reason, the committee paid particular attention to BaP metabolism as an illustration. Other carcinogenic PAH compounds are metabolized in a comparable way (see also IPCS document).

In the first step, BaP is oxidized by the enzyme aryl hydrocarbon hydroxylase (AHH, an enzyme of the cytochrome P450 family) resulting in epoxide and phenol groups at several sites in its ring structure. These epoxides may be hydrated by epoxide hydrolase to dihydrodiols, or spontaneously rearrange to phenols. Also quinone structures can be formed. The epoxides may be conjugated with glutathione, while the phenols are conjugated with glucuronate or sulfate. All conjugates are detoxification products.

The specific route of bioactivation of BaP to its ultimate DNA-reactive carcinogenic metabolite is shown in Figure 5.1. After the initial formation of the (+) BaP-7,8-epoxide and its subsequent epoxide hydrolase dihydrodiol product, it is activated to the ultimate reactive intermediate (+) anti BaP-7,8-dhydrodiol-9,10-epoxide. This is an extremely reactive species that covalently interacts with cellular DNA. The DNA adducts formed may lead to mutations.

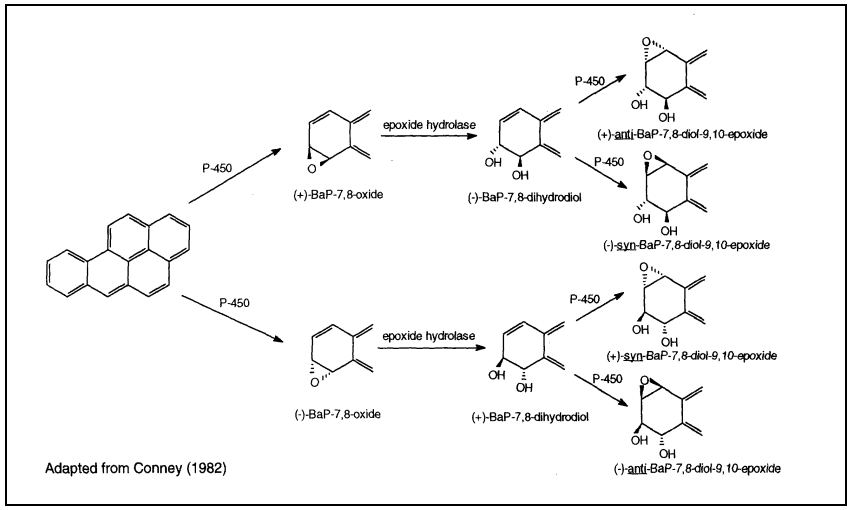

Figure 5.1 Stereoselective pathways involved in the formation of 'bay-region' vicinal diol epoxides of benzo[a]pyrene (reproduced from IPCS, 1998).

An additional complexity of PAH metabolism is the stereoselectivity in the metabolism as shown for BaP in Figure 5.1. Depending on the location of the epoxide in de PAH ring system the epoxide displays more or less chemical reactivity towards DNA.

IPCS[70] reported that in recent years, several investigators suggested that also other mechanisms than the diol epoxide mechanism play a role. These include the radical-cation, the quinone and the benzylic oxidation mechanisms, which may occur simultaneously for the various PAH components (see IPCS for a detailed overview).

The extent to which PAH will express carcinogenic effects in certain persons are thought to be partly genetically controlled. Although similar enzyme systems are involved in PAH metabolism, the inducibility and activity of these enzymes may differ per species, within one species and per organ[104,120]. Since the inducibility determines the extent of the carcinogenic susceptibility, it is clear that the ultimate carcinogenic risk may vary per person. However, to what extent genetic variability may have contributed to the variations in cancer mortality ratios, which were found when epidemiological studies were compared, remains unclear.

5.3 Carcinogenic potency of selected PAH in relation to BaP

Many investigators have ranked the carcinogenic and mutagenic potencies of single PAH compared to BaP in order to provide more reliable estimates of the carcinogenicity of PAH mixtures. To rank, a toxicity equivalence factor approach was used. Examples are those made by Collins *et al*.[26] (see annex H1) and by the IPCS[70] (see annex H2). These rankings are based on comparative studies, in which BaP and other PAH were assayed by the same protocol and within the same time frame. Overall, these comparisons show that the genotoxic potency increases with the number of rings; the carcinogenic 3- or 4-ring PAH are clearly less potent than their 5 and 6-ring counterparts (see IARC Monographs). Concerning dibenz[a,h]anthracene, this 5-ring PAH appears to be equipotent or somewhat more potent than BaP, whereas other 5-ring PAH tested (*e.g.,* benzofluoranthenes, benzo[e]pyrene) are less or much less potent. In addition, Pufulete *et al*. (2004)[95] reported on the high carcinogenic potency (higher than BaP) of dibenzo[a,l]pyrene, dibenzo[a,i]pyrene, dibenzo[a,h]pyrene, dibenz[a,h]anthracene, and 5-methylchrysene. As a result, in estimating cancer risk of complex PAH mixtures in which BaP is used as exposure indicator for PAH, values may be over- or underestimated. However, until more data on the potency of other carcinogenic PAH become available, the committee considers BaP as the best genotoxic indicator for PAH mixtures.

5.4 Elimination and excretion[70,128]

PAH metabolites and their conjugates do not persist in the body. They are rapidly excreted in the urine and faeces.

5.5 Possibilities for biological monitoring

5.5.1 PAH and their metabolites (1-hydroxypyrene)

PAH and their metabolites can be measured in the urine of humans and animals as a biological indicator of PAH exposure, since these substances do not occur endogenously. A substantial number of investigations on internal PAH exposure using urinary 1-hydroxypyrene have been published.

To assess whether urinary 1-hydroxypyrene is a reliable biomarker for PAH exposure it is of paramount importance to demonstrate that the concentration of the metabolite correlates well with the environmental PAH concentration. The

presence of 1-hydroxypyrene in the urine of workers exposed to PAH in several occupational environments has been demonstrated (see for instance Table 5.1 and 5.2). Although the concentrations of urinary 1-hydroxypyrene correlated very well with parameters such as DNA adducts in peripheral lymphocytes it did not always correlate well with airborne PAH exposure.

One of the most obvious reasons that may account for this observation is that 1-hydroxypyrene not only represents inhalation exposure but also dermal and oral exposure. Thus, other exposure routes may have influenced the outcome. In addition, exposure from non-occupational activities may have confounded the correlation.

Table 5.1 Comparison of air and biological PAH exposure monitoring in non-smoking aluminium workers (Van Schooten *et al*. 1995)[118].

Job category	Total PAH (sum of 12 PAH, μg/m^3) geometric mean	BaP (μg/m^3) geometric mean	Pyrene (μg/m^3) geometric mean	Urinary 1-hydroxy-pyrene (μmol/mol creatinin) ± SD	DNA adducts in leu-kocytes (adducts/10^8 nucleotides) ± SD
Bake oven	8.7	0.35	1.5	3.65 ± 2.11	0.1 ± 42.1
Anode factory	23.0	1.51	5.6	3.25 ± 1.89	26.2 ± 15.0
Pot relining	150.0	1.05	32.3	6.20 ± 8.44	47.3 ± 39.1
Electrolysis	1.0	0.03	0.12	0.48 ± 0.27	12.8 ± 10.0
Foundry	0.4	0.02	0.04	0.47 ± 0.20	7.4 ± 9.6

Table 5.2 Comparison of air and biological PAH exposure monitoring in non-smoking carbon-electrode workers (Van Delft *et al.* 1998)[31]. Values expressed as median (range).

Exposure	Total PAH (sum of 16 PAH, μg/m^3)	BAP (μg/m^3)	Pyrene (μg/m^3)	1-hydroxypyrene in 24-h urine (μg/day)	DNA adducts in lymphocytes (adducts/10^9 nucle-otides)
High	32 (2.3-185)	1.2 (0.43-3.2)	2.45 (0.28-46)	13.9 (7.7-38.8)	510 (260-1700)
Intermediate	8.4 (1.8- 80)	0.37 (0.09-5.0)	0.51 (0.10- 4.4)	4.7 (2.2-19.2)	503 (260-1500)
Low	-	-	-	1.5 (0.7- 3.5)	650 (340-2500)

Moreover, the concentration of urinary 1-hydroxypyrene may also depend on the metabolic activity at the site of entry into the body, and on the distribution of PAH over the body. These factors are subject to interindividual variation resulting in variations in for instance half-life of pyrene between 6 to 35 hours[73].

Another point to take into account considering the usefulness of urinary 1-hydroxypyrene as a biological exposure parameter in cancer risk assessment is the location where cancer develops following exposure to PAH. Human and animal data on PAH exposure indicate that cancer develops mainly at the site of contact, that is lung cancer following inhalation and skin cancer following dermal exposure (see Chapter 6). However, urinary 1-hydroxypyrene reflects total body burden rather than the exposure of the lungs. Furthermore, carcinogenic

PAH are of primary interest, whilst 1-hydroxypyrene is a metabolite of pyrene, which is not considered to be carcinogenic. This is no problem if pyrene is a reliable indicator of carcinogenic PAH exposure. However, as discussed in previous chapters (Chapter 2 and 3), pyrene is more volatile than most carcinogenic PAH compounds. This implicates differences in fate between pyrene and carcinogenic PAH, such as differences in absorption rates (see Table G3 and G4 in annex). The most important reason, however, is that the exposure parameters used in dose-response studies on the carcinogenic effects of PAH mainly concern measurements of BaP or a selection of PAH, whereas the number of studies using 1-hydroxypyrene is very limited.

Overall, urinary 1-hydroxypyrene (1-HP) is positively correlated with PAH exposure in occupational environments, and may serve as a reliable parameter for the total body burden. However, recently, ACGIH (2005)[3] did not recommend a Biological Exposure Indices (BEI), although it suggested that a benchmark value of 1 μg 1-HP/L in urine be considered a post shift level indicating occupational exposure to PAH. The committee emphasizes that the value of 1 μg 1-HP/L in urine expresses the sum of inhalation, dermal and oral exposure, and that a reliable quantitative relationship between airborne PAH concentrations (upon which cancer risk values are based) and urinary 1-hydroxypyrene is not determined yet.

5.5.2 PAH-DNA and -protein adducts

PAH may form adducts with DNA, proteins or other macromolecules, such as haemoglobin and serum proteins[1,70]. For instance, DNA adducts were found in the skin and the lungs of mice after dermal application of BaP or coal tar (see section 5.1.2)[37,55,115-117]. Also DNA-adducts in the lungs were found after inhalation. For example, Wolff *et al*. (1989)[139] exposed male F344/N rats (n=4/group/time point) to filtered air, 2 mg BaP/m^3, or 2 mg [^{14}C]BaP absorbed onto 98 mg carbon back/m^3, for 4 hours/day, 1 day/week for 12 weeks. The animals were killed at various time points during and after the last exposure day. At 12 weeks, in the lungs the quantity of DNA-adducts/10^9 nucleotides amounted to 1-2, 2-15, and 10-12, respectively. In addition, Binková *et al*. (1994)[14] put male Wistar rats (n=3/group) on top of a coke-oven battery for 24 hours (temperature approximately 40 °C). The animals were killed two hours after ending the exposure. The mean 24-hour concentration of total particulate matter (containing 26% extractable organic matter) was 1.42 mg/m^3 (total carcinogenic PAH 892 ng/m^3, of which 118 ng/m^3 was BaP). In the lungs, approximately 16.3 BaP-adducts/10^9 nucleotides and 48 total-adducts/10^9 nucleotides were found (control values were

1-3 and 5-15 adducts/10^9 nucleotides, respectively). Also in the heart, the liver and in white blood cells DNA-adducts were found.

Measurement of DNA-adducts in easily accessible body tissue may have advantages over traditional exposure determinations, in that it is an internal endpoint which accounts for all exposure routes and inter-individual differences in PAH metabolism[43,129]. However, in predicting cancer risk a clear quantitative relationship should be present between the concentration of DNA-adducts and tumour development. Overall, indirect evidence points to a tendency towards a positive relationship between DNA-adduct content, in for instance white blood cells, and increased cancer risk, but further investigations are needed to verify and quantify these findings[43,129].

For protein adducts, data is very limited[1,70].

5.6 Summary and evaluation

PAH are lipophilic compounds that are absorbed through the epithelia of the lungs, gastrointestinal tract and the skin. When absorbed, they are distributed via the bloodstream throughout all internal organs. The metabolism of PAH is complex. In a first step, PAH are oxidized to form epoxides, phenols and dihydrodiols. In a second step, these metabolites are conjugated with, for instance, glutathione, to form more water-soluble metabolites. Some of these metabolites, such as diol epoxides and radical cations, can initiate cancer. Finally, PAH and its metabolites are excreted in the urine and faeces. Whether PAH will express carcinogenic effects, not only depends on the PAH and the route of metabolism, but also on the genetic factors of the person who is exposed to these substances. Of all PAH investigated, BaP is considered as one of the more potent carcinogenic PAH compounds.

Concerning skin absorption, human and animal studies have clearly shown that PAH penetrates the skin into the circulation. However, the absorption rate is strongly affected by various factors, such as the anatomical site, the composition of the vehicle of administration, the molecular weight of the single PAH and the dose applied.

PAH exposure can be biologically monitored (*e.g.,* 1-hydroxypyrene in urine, DNA- and protein-adducts in white blood cells). In particular 1-hydroxypyrene can easily be measured in the urine and serves as a reliable parameter for total body burden. Also an increase in PAH-DNA-adducts, in for instance white blood cells, indicate internal or systemic exposure to PAH. For these reasons, the committee is of the opinion that biological monitoring may be useful in protecting worker health and minimizing worker exposure. However, in setting occupa-

tional exposure limits it is of concern how well these biomarkers quantitatively correlate with airborne PAH exposure and cancer risk. Data on this matter are still inconclusive, and further investigations are needed to answer this question.

Chapter 6

Carcinogenicity

Numerous human and animal studies have been published on the carcinogenic effects of single PAH and complex PAH mixtures by various routes of exposure. Since the purpose of this evaluation is to estimate the additional lifetime cancer risk associated with exposure to carcinogenic PAH present in the air in the workplace, the committee limited this evaluation by showing only an overall picture of the carcinogenicity of PAH. In addition, details are only given of those studies, which are useful for quantitative risk estimation. Finally, the committee derived data on the carcinogenicity primarily from the IPCS evaluation[70] and IARC monographs[56-64], supplemented with recent publications.

PAH act mainly as local carcinogens. This means that they induce (malignant) tumours at the site of contact (*i.e.,* skin tumours by dermal exposure, lung tumours by inhalation). Limited evidence exists that PAH may also induce tumours at other sites of the body than at the site of application. For instance, lung tumours were found after oral[29,100,101], intrarectal[4] and intraperitoneal administration[89,111] of BaP. However, the committee noted the insufficient quality of the studies (*i.e.*, limited number of animals in experiment, high spontaneous tumour incidence, single exposure or short-duration of experiment, no statistical analysis). Therefore, no reliable conclusion can be drawn from these findings. In two animal studies, lung tumours were also found in mice, which were chronically fed coal tar mixtures or gas plant residues (see also section 6.2.2). However, the committee finds these data too limited to make a conclusion on systemic

effects. No data are published suggesting that inhalation or dermal exposure to single PAH or PAH-mixtures may lead to cancer at other sites than the lungs and skin, respectively[70].

6.1 Human data

6.1.1 Carcinogenicity of single PAH

No human data were available to the committee on exposure to BaP or other single PAH compounds.

6.1.2 Carcinogenicity of PAH mixtures

A number of epidemiological studies have been performed on the carcinogenesis of complex PAH mixtures due to occupational exposure. These include cohort and case-control studies with various PAH-rich sources (*e.g.,* evaporation of carbon electrode materials, coal tar distillation and purification, coke production, thermal decomposition of organic materials) in various industries (*e.g.,* aluminium production, coal gasification, coke production, iron and steel foundry).

It is evident that in none of these industries PAH is the only substance to which workers are exposed. This not only concerns organic solvents, nitro-PAH, aromatic amines and metals, but also dust particles and in some cases asbestos. Some of these substances are carcinogens, such as 2-naphtylamine and 4-aminobiphenyl, which are known to cause bladder cancer. Also airborne particles are suspected to elicit genotoxicity and carcinogenicity by directly generating reactive oxygen (ROS) and nitrogen species (RNS), and indirectly by activating pathways of inflammation and proliferation (Knaapen *et al*. 2004[77]; Borm *et al*. 2004[23]). Particle induced ROS and RNS may interfere with the carcinogenic potency of PAH. Although the committee is aware that co-exposure cannot be excluded, in particular to airborne particles, it limited its evaluation to those studies in which PAH were the main carcinogenic substances to which workers were exposed.

Cohort studies

In the search for evidence of the relationship between occupational PAH exposure and cancer in humans, Armstrong *et al*. (2003, 2004)[7,8], the IPCS[70] and Boffetta *et al*. (1997)[21] evaluated a series of epidemiological studies based on a cohort design.

Armstrong *et al*. (2003, 2004))[7,8] published the results of a well-performed meta-analysis study on lung and bladder cancer risk following PAH-exposure funded by the Health and Safety Executive (the UK). The meta-analysis was based on published reports, in which relationships between occupational PAH-exposure and lung and bladder cancer was studied quantitatively. All the exposures concerned airborne PAH, emitted from incomplete combustion of organic matter. Risk estimates on lung and bladder cancer were determined because of the clear positive or highly suggestive association between these cancers and occupational PAH-exposure.

In the analysis only studies were included that did meet certain criteria. These criteria included: original epidemiological studies of occupational exposure by inhalation; studies of workplaces in which PAH was considered the predominant carcinogen (this meant exclusion of rubber industry, diesel exhaust, foundries and part of steel works); studies in which misclassification of exposure was not to be likely; and, only the most recently reported results from the same workforce reported in several papers. From the 744 references screened, only 36 papers fully met these criteria. These papers covered 39 distinct cohorts (35 cohorts, 1 case-cohort and 3 nested case-control samples from within a cohort). Annex I1 shows the details of the studies.

For the meta-analysis, it is essential that the PAH exposures in the included studies were determined or estimated by the same exposure parameter. For this reason, Armstrong and his colleagues converted total PAH and BSM concentrations to BaP concentrations by using conversion ratios. These conversion ratios differed for each study (for details see the original publications). Furthermore, for those studies with no exposure measurements, a job-exposure matrix indicating estimated mean concentrations of BaP exposure for each industry and occupation was estimated with the collaboration of industrial hygienists and by using published reviews on workplace exposure (proxy measures). Concerning studies with cumulative exposure, the mean cumulative exposure in each group or the midpoint of interval was chosen as an estimate for the average cumulative BaP exposure. Overall, the cumulative exposure in the highest exposure groups ranged across three orders of magnitude, from 0.75 to 805 $\mu g/m^3$ BaP years ($\approx$ average air concentration of 0.04 to 40 $\mu g/m^3$ BaP).

For each cohort, unit relative risks (URRs) were calculated. URRs refer to increments in relative risk per 100 $\mu g/m^3$ BaP years, in which 100 $\mu g/m^3$ BaP years corresponds to a concentration of 2.5 $\mu g/m^3$ BaP over 40 years. For determining URRs two models were used: the log-linear relative risk model ($RR=\exp(b_{loglin}x)$ and the linear relative risk model ($RR=1+b_{lin}x$), where 'x' is

cumulative exposure (μg/m^3-years) and 'b' the slope of the exposure-response relationship. Concerning data on effects, the authors preferred mortality outcomes over morbidity outcomes within a same study. Furthermore, other preferences were formulated, such as smoking-adjusted data over unadjusted data.

The meta-analysis was performed with standard methods. These methods allow for variation in precision by which URRs are estimated in different studies, but allow also for random effects. To obtain an average URR, weights were implicitly given to each study reflecting these two effects. In addition, to identify cohort or exposure characteristics that explained variation in URRs (*e.g.,* industry, source of exposure information), each was considered as a dependent variable in a meta-regression analysis.

The relative risks for lung cancer, predicted at 100 μg/m^3 BaP years from the log-linear models, ranged from 0 to over 1,000 among the studies, with standard errors ranging between 0.02 and 1,000. This is a substantial variation in precision, which is well explained by variations in the degree of exposure in the studies (some studies have only low exposures) and by variations in size of cohort populations and duration of follow-up. The overall mean URR for lung cancer was 1.20 (95% CI, 1.11-1.29, p<0.001). In general, repeating analyses using the linear model revealed similar rankings of URRs for lung cancer as those obtained from the log-linear model, with some acceptable variation in URRs of the cohorts.

None of the cohorts dominated the estimate. In addition, it was little changed after removal of less precise cohorts. Furthermore, meta-regression analysis revealed that the URRs for coke ovens, gas works and aluminium production were consistent and relatively precisely estimated (combined URR 1.17, 95% CI: 1.12-1.22), whereas mean URRs for other industries (*e.g.*, chimney sweeps, asphalt, carbon black) were rather imprecise. After allowing for differences *across* industries by including industry in the meta-regression analysis, no difference more than could be explained by chance (p<0.02) was found when studies were grouped according to several heterogenic factors (*e.g.,* source of exposure, smoking habits, study design, duration, dust exposure). However, whether the differences *between* industries are caused by chance or by true unknown variations is not exactly known, because scientific data that reported on the presence of true variations is not available or insufficient to draw conclusions.

Overall, lung cancer risk at other exposures can be estimated from URRs under log-linear model assumptions: $URR_{cum\ exp\ X} = [URR_{cum\ exp\ 100}]^{(x/100)}$. In the United Kingdom, the lifetime lung cancer risk in males from the general population is 8% (year 1997). This means a lifetime excess risk for coke oven workers

(URR 1.17), who were 40 years exposed to 1.5 μg/m^3 BaP of 1.9x10^{-4} (8 cases among 1,000 coke oven workers).

Bladder cancer was reported in 27 cohorts. The overall mean URR was 1.33 (95% CI: 1.16-1.52), with no statistically significant variation by industry or other putative determinants. In addition, the mean URR was strongly dependent on results of two large aluminium production industries, one that was performed by Tremblay *et al*. (1995)[126] and the other by Romunstad *et al*. (2000)[105]; only the Tremblay results were statistically significant. There was little evidence of a relationship between bladder cancer and PAH exposure in coke ovens and other industries. Though the URR of bladder cancer (URR 1.33) is higher than that for lung cancer (URR 1.17) Armstrong *et al*. (2003, 2004)[7,8] considered the causal relationship between PAH exposure and bladder cancer weak for several reasons. Firstly, in epidemiological studies less cases of bladder (and renal) cancer than lung cancer were reported. This limits the power of the analysis and results in a less precise estimate than the estimates for lung cancer. Secondly, bladder cancer mortality in the general population is much lower than for lung cancer. Thirdly, it cannot be excluded that bladder cancer is induced by substances (not PAH), which are suspected to be specific bladder carcinogens (*e.g*., 2-naphthylamine), and are found in the types of industries under investigation. The investigators estimated that the number of expected bladder cancer cases after 40 years of occupational exposure to 1.5 μg/m^3 corresponds with 3.3 cases among 1,000 coke-oven workers.

Finally, Armstrong *et al*. (2003, 2004)[7,8] discussed in detail the uncertainties as to the exposure-response relationship. In summary, by comparing their results with those of others, the authors concluded that the results for coke-ovens, gas-works, and aluminium production are relatively well supported by others, although potential biases should be considered. These biases include; smoking, which was uncontrolled in most studies; confounding by other occupational exposures, although the authors excluded studies in which PAH was judged unlikely to be the predominant carcinogen (except dust); and inaccurate exposure measurement estimates (uncertainty in past exposure).

Regarding smoking habits, data from four cohorts were adjusted for smoking habits. Pooling data of these cohorts revealed a higher unit relative risk for lung cancer than the pooled data from the other cohorts (1.31 (95%CI 1.16-1.48), and 1.16 (95%CI 1.11-1.21), respectively). Comparable results were found for bladder cancer risk. However, Armstrong *et al*. considered the data on smoking habits too small to base the meta-analysis on these four studies only, and thus they included all other cohorts as well.

True variations in URRs between industries were explained by confounding, such as: inaccurate exposure estimation; smoking habits; uncertainty about the right metric (cumulative versus average exposure); and, variations in carcinogenic potency of the PAH mixture across industries.

The committee has evaluated the meta-analysis to assess its usefulness for risk assessment and deriving cancer risk values. A meta-analysis is aimed to combine study results based on comparable data in order to derive one overall risk estimate and to increase the power of pooled data to better clarify, in this case, the relationship between occupational PAH exposure and cancer risk. A critical point was whether inclusion of all cohorts was acceptable for the committee, since not always exposure measurements were available, nor exposure duration was known, and not all cohort-studies concerned exposure to PAH only.

In the meta-analysis, cohorts without exposure data could have been excluded from the evaluation. In that case the unit relative risks for lung cancer increases (URR 1.29 (95%CI, 1.11-1.49) versus URR 1.17 (95%CI, 1.03-1.33) for cohorts with and without exposure data on BaP, respectively). It also means that 16 cohorts with limited exposure data remained for the analysis, whereas 23 cohorts with useful data on cancer would have been excluded. To take this into account, Armstrong *et al*. used supplementary exposure estimates for the studies for which no exposure data were available, and included the respective cohorts in the meta-analysis. For the estimates they used a large database of exposure measurements and data obtained from industrial hygienists. These data showed rather stable exposure patterns by job title and type of industry. However, as a consequence of using exposure estimates, not all studies are completely independent with respect to exposure, and this may have influenced the outcome (smaller exposure variation among studies). On the other hand, they are independent concerning effect data, and observations showed merely a marginal heterogeneity among the studies. Therefore, according to the committee, the use of supplementary exposure estimates is justified.

The committee noticed that for some studies no data on exposure duration were available. This was overcome by Armstrong *et al*. by estimating exposure duration by using an average value from external data. In general, this could have led to an overestimation as well as to an underestimation of the relative risk in the duration-response analysis.

In a few cohorts, co-exposure was likely (*i.e.*, bitumen (asphalt) industry, power plants). It is therefore well possible that in those studies other substances have contributed to the observed excesses in lung cancer. On the other hand, Boffetta *et al*. (2001, 2003)[19,20] did not find associations between lung cancer risk

among asphalt road pavers and roofers, and co-exposure to other substances (*i.e.*, silica, organ vapour, diesel exhaust). Furthermore, in the majority of the cohorts (*i.e.*, coke-ovens, gas works, carbon black, and aluminium industry) co-exposure to other substances than PAH was marginal, and PAH is the predominant exposure leading to lung cancer. Based on this information, the committee takes the position that co-exposure only played a minor role in the overall uncertainties introduced by performing a meta-analysis.

In conclusion, the committee is of the opinion that the meta-analysis study is well performed and useful for estimating cancer risk values. Taking into account both the uncertainties and the strength of this meta-analysis, the committee has found no serious constraints to exclude certain cohorts with no or limited exposure data.

In an earlier publication, Armstrong *et al*. (1994)[9] estimated the quantitative lung cancer risk for aluminium production workers from a large cohort study in Quebec, Canada. The study was performed in one plant that used two types of pots to melt aluminium, namely Söderberg and prebake pots. In particular in the Söderberg process high amounts of coal tar pitch volatiles are emitted in the air. The workers were exposed to substantial quantities of coal tar pitch volatiles, expressed as cumulative exposure to BSM or BaP. The follow-up period started in 1950 and continued through 1988. Both linear and (supra-linear) curved relationships were computed between rate ratios and cumulative exposure. As a result, the best fit was obtained using the supra-linear curve model, expressed as rate ratio (RR) = 1 + (0.098 x mg/m^3 BSM-$yr^{0.7}$) or 1 + (0.012 x $\mu g/m^3$ BaP-$yr^{0.6}$). This means that the model predicts a rate ratio for lung cancer in aluminium production workers of 1.42 and a lifelong excess risk of 3.8% after 40 years exposure to 0.2 mg/m^3 BSM. The authors advised to be cautious in extrapolating their results to modern aluminium plants, because exposure to coal tar pitch volatiles have been substantially reduced in this industry.

In the review by Boffetta *et al*. (1997)[21], several industries and occupations were included of which data were published before 1997. Parts of these data are shown in annex I2 and I3. According to them, heavy exposure to PAH entailed a substantial risk for lung, skin and bladder cancer. These substantial risks were not likely to be explained by other carcinogenic exposure present in the same industries. The major target organ of PAH carcinogenicity was found to be the lung. The increased risk for lung cancer was present in most industries and occupations studied. Furthermore, they concluded that an increased risk for skin cancer

was related to high dermal exposure. However, increased risk for bladder cancer was less consistent; positive associations were mainly found in industries where workers were exposed to coal tars and coal tar pitch volatiles (*e.g.*, aluminium production, coal gasification and tar distillation). Evidence of increased risk for cancer in other organs (*e.g.,* the larynx, the kidney) was inconclusive. The authors did not estimate cancer risk quantitatively.

Moolgavkar *et al*. (1998)[82] estimated the unit risk for lung cancer due to exposure to coke oven emissions. The risk assessment was based on information described by Costantino *et al.* (1995)[27] (for study details see annex I1). In short, two cohorts, called the Allegheny County and the non-Allegheny County cohort, were followed-up for 30 years. The cohorts included coke-oven workers from steel plants within those counties. The workers were grouped into three exposure categories: topside full-time (average, 3.25 mg/m^3 BSM*), topside part-time (average, 1.99 mg/m^3 BSM) and side oven (average, 0.88 mg/m^3 BSM). During the follow-up mortality was registered. Moolgavkar *et al*. analysed the data from the non-Allegheny County non-white cohort, using standard techniques of survival analysis and the two-mutation expansion model of carcinogenesis. The best estimate for unit risk for lung cancer at 70 years of age for continuous exposure to coke oven emissions at a concentration of 1 μg/m^3 starting at birth was 1.5x10^{-4} (exponential dose-response model without birth cohort effects, adjusted for competing causes of mortality; 95% confidence interval, 1.2-1.8x10^{-4}).

IPCS[70] summarized that occupational exposure may induce lung and skin cancer after inhalatory and dermal exposure, respectively. Increased lung tumour rates due to PAH-exposure were found in coke-oven workers, and workers in Söderberg pot room of aluminium reduction plants (for some data, see annex I2). IPCS also mentioned that asphalt workers had excess lung cancer risk. However, IPCS noticed that it is not clear whether this excess risk is due to PAH exposure, as it could not be determined whether carcinogenicity was due to coal tar (high amount of PAH) or bitumen fume (low amount of PAH) exposure. Confounding by smoking habits could not explain the observed increased lung tumour rates. On the basis of the epidemiological study by Costantino *et al*. (1995)[27] the risk for the general population for developing lung cancer over a lifetime has been calculated to be 10^{-4} to 10^{-5} per ng/m^3 BaP. Furthermore, IPCS noted the inconsistent findings that PAH exposure induces bladder cancer. The inconsistency

* In this study, BSM refers to coal tar pitch volatiles, which contain PAH present in the benzene soluble fraction of the total particulate matter.

was partly explained by the presence of known bladder carcinogens in the working environment, such as 2-naphtylamine, and the fact that less data were available concerning the occurrence of bladder cancer.

A few cohort-based studies reported on cancer in the liver, kidneys, the larynx and stomach (see annex I2 and I3). However, as Boffetta *et al*. (1997)[21] indicated these data were limited and inconclusive. Therefore, it is unclear to the committee whether inhalation or dermal exposure of PAH may lead to tumours at other sites of the body than the lungs or skin, respectively, or possibly the bladder.

Case-control studies

The number of case-control studies on the relationship between cancer and PAH exposure is vast. The IPCS[70] and Boffetta *et al*. (1997)[21] summarized most of these studies (for some of them see annex I4). The committee emphasizes that the data presented in this annex are not intended to be complete. However, it shows an overall picture on the relationship between occupation, at which substantial exposure to PAH is assumed, and cancer risk. Overall, the same conclusions are made from case-control studies as from cohort studies: increased risk for lung cancer and skin cancer following inhalation and dermal exposure, respectively; and, inconclusive results on the relation between bladder cancer and other types of cancer.

6.2 Animal data

In the study on the carcinogenicity of PAH in experimental animals, both the effects of single PAH, as well as effects of various complex PAH-containing mixtures to which humans can be exposed during their work, have been investigated.

6.2.1 Carcinogenicity of single PAH

In a great number of animal studies, the carcinogenic properties of single PAH have been investigated. An overall view of these studies shows a strong preponderance of studies with benzo[a]pyrene and of studies with dermal exposure (see annex J1). It is beyond the scope of this evaluation to discuss all these studies in detail. However, those evaluated by IPCS[70] are summarized in annex J2 through J7 (categorized by route of exposure). The reader is further referred to the IARC[57,62] and ATSDR[128] evaluations. In addition, ATSDR made short summaries on the carcinogenic effects of single PAH (see annex J8).

6.2.2 *Carcinogenicity of complex PAH mixtures*

Various complex PAH-containing mixtures to which humans can be exposed during work have been investigated for carcinogenic properties with experimental animals. In most of these studies the animals were dermally exposed to extracts, tars or condensates. Exposure via the respiratory tract was applied in a much smaller number of studies, due to the technically complex nature of these mixtures.

Exposure by inhalation

In Germany, a group of scientists performed a series of chronic animal studies with PAH-containing mixtures, of which the (preliminary) results were published in various scientific journals or books[52-54,102,103,119]. Concerning the possible use for calculating additional cancer risk values, the most relevant ones are briefly discussed in the following paragraphs.

Heinrich *et al*. (1986)[52] exposed female Wistar rats (n=108/group) to coal oven exhaust gas (containing 0.3 μg/m^3 BaP) for 9 months, followed by exposure to a combination of pyrolized pitch and coal oven exhaust gas (containing approximately 90 μg/m^3 BaP) for another 12 months, with a gap of one month between the two exposures. Exposure was on average 16 h per day and 5 days per week. After exposure, about 50% of the exposed animals had died, which was comparable with the mortality in the clean air exposed control group. Furthermore, preliminary results showed that of the exposed animals that died, 12 developed lung tumours (mainly squamous cell carcinomas), whereas no lung tumours were detected in the control group.

In the same study and with the same exposure regimen, also female NMRI mice (n=28-31/group) were exposed to clean air or pyrolized pitch/coal oven exhaust (month 1-9, average 0.3 μg/m^3 BaP; from 10 months, average ca. 60 μg/m^3 BaP) for 16 h/day, 5 d/week for 2 years. Macroscopically evaluation revealed lung tumour incidences of 32% and 79% for control and exposed animals, respectively. In addition, the tumour multiplicity (average number of tumours ± SD per lung) was 0.7 ± 1.7 and 7.0 ± 7.9, respectively. Histological examinations were not performed yet. Tumours in organs other than the lung were not studied.

Table 6.1 Macroscopic and microscopic results of long-term exposure to PAH-rich exhaust (Schulte *et al*. 1994)[119].

Exposure	Lung cancer mortality (%)	Average no. of nodules per lung	No. of adenomas	No. of adenocarc.	No. of squa-mous cell carc.	No. of adeno-squa-mous carc.
Control	0.0 (0/40)	0.1	5	0	0	0
50 μg/m^3 BaP	2.5 (1/40)	24.7	***40	**10	0	0
90 μg/m^3 BaP	10.0 (4/40)	37.1	***40	***33	*6	1

*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$ (compared to controls, pair wise Fisher test).

Table 6.2 Lung tumour incidence in rats chronically exposed to PAH-rich exhausts (Heinrich *et al*. 1994)[54].

Average Exposure	Exposure: clean air time (months)	Cumulative exposure	Lung tumour incidence
Clean air	0:30	0	0.0%
20 μg/m^3 BaP	10:20	71 mg/m^3 BaPxh	4.2%
	20:10	142 mg/m^3 BaPxh	33.3%
46 μg/m^3 BaP	10:20	158 mg/m^3 BaPxh	38.9%
	20:10	321 mg/m^3 BaPxh	97.2%

In 1993, Schulte *et al*. (1994)[119] used newborn female NMRI/BR mice to study carcinogenesis of PAH-rich exhausts. The authors explained the use of newborn animals by the lower spontaneous lung tumour incidence of newborn and a greater susceptibility to tumour induction. Exposure started at the first day after birth. The animals (n=40/group) were exposed to filtered room air or coal tar pitch volatile aerosols (mass median aerodynamic diameter of 0.55 ± 0.03 μm), containing 50 or 90 μg/m^3 BaP, for 16 hours per day, 5 days per week during 44 weeks. The results of the macroscopic and microscopic analysis of the lung are shown in Table 6.1. From this table, it is clear that exposure to PAH-rich exhausts caused a dose-dependent increase in lung tumours. As in the previous study, tumours in organs other than the lung were not investigated.

In another study, Heinrich and his colleagues (1994)[54] exposed rats to coal tar/pitch condensation aerosols, free of any carbon black carrier particles, to estimate lifetime unit lung cancer risk for BaP. Female Wistar rats (n=72/group) were exposed to filtered clean air or the aerosols, with a concentration of BaP of 20 or 46 μg/m^3, for 17 hours per day, 5 days per week for 10 or 20 months. After exposure, the animals were left in a clean air room for 20 or 10 months, respectively, making a total experimental time of 30 months for all groups. As shown in Table 6.2, a clear dose-dependent increase in lung tumour incidence was observed. Most tumours were classified as keratinising squamous cell tumours,

but also some broncho-alveolar adenomas and adenocarcinomas were found. No exposure related tumours were observed in organs other than the lung.

Intratracheal instillation

A few studies comprised intratracheal instillation of PAH-rich mixtures in Syrian Golden hamsters. In short, in the Pott and Stöber study[93], hamsters received 30 intratracheal instillations of PAH fraction of extracts of urban particulate air pollution, containing 12.5 μg BaP. Nine out of the 46 examined animals showed tumours in the respiratory tract. The authors stated that when pure BaP would be given at the same concentration as in the extract, the tumour incidence rate would have been considerably lower. In another study, performed by Künstler[78], hamsters (n=25-30/group) received intratracheal instillations with different doses of automobile exhaust condensate fractions. Some of these fractions were recombined with a synthetic mixture of pure carcinogenic PAH, resulting in doses between 5.3 and 42.8 μg BaP equivalents. The instillations took place at 2-week intervals until their natural death. The treatments did not result in any malignant neoplasia in the respiratory tract. However, Reznik-Schüller and Mohr[99] did find multiple pulmonary adenomas in Syrian golden hamsters, which were exposed by intratracheal instillations to automobile exhaust condensates containing 340 μg/g BaP, once every two weeks for life.

Concerning the choice of animals, the committee noted the comment of Pott and Stöber[93] that for unknown reasons, strains of Syrian Golden hamster may differ in response to PAH exposure. Furthermore, the committee noted that for intratracheal instillations, PAH was always applied as particles or extracts. This means that effects of PAH may be influenced by possible effects of particles themselves. Therefore, the committee considers these types of studies not relevant for estimating additional lifetime risks of PAH.

Dermal application

A number of chronic animal studies used dermal application of condensates containing various PAH compounds[59,60]. These condensates included those obtained from tobacco smoking, diesel and gasoline engine exhaust, carbon blacks, cool tar and coal gasification derived products, etc. Overall, these mixtures caused dermal tumours, mainly of benign origin, after repeated dermal exposure. However, for estimating additional lifetime cancer risk values for PAH, these studies are not useful for several reasons. Firstly, the mixtures and condensates contain

also potential carcinogenic substances other than PAH[58,60]. Furthermore, not always the amount of substance applied could be reproduced. Lastly, the committee prefers using inhalation data in estimating cancer risk values.

Oral application

Culp *et al*. (1998)[29] fed coal tar mixtures to female B6C3F1 mice (n= 48/group) for 2 years. Mixture one (coal tar from seven coal gasification plant waste sites) was given at doses of 0.0, 0.01, 0.03, 0.1, 0.3, 0.6 and 1.0% in diet; mixture two (coal tar from two of the seven waste sites plus another site having a high BaP content) at doses of 0.0, 0.03, 0.1, and 0.3% in diet.

A significant decrease in food consumption was observed in animals fed the highest doses. In addition, the body weights of these animals were significantly less than those of the control animals fed normal diets without coal tar mixtures. Also the survival period in the group of animals fed the highest amounts of coal tar mixtures was shortened; none of the animals fed a diet with 1% of mixture one survived the two-year period.

The coal tar mixtures induced a variety of tumours. The incidence of the following neoplasms were statistically significantly increased: hepatocellular adenomas and/or carcinomas (Mix one, 0.3%; Mix two, 0.3%); alveolar/bronchiolar adenomas and or carcinomas (Mix one, 0.3, 0.6, and 1.0%; Mix two, 0.1 and 0.3%); papillomas and/or carcinomas in the forestomach (Mix one, 0.3 and 0.6%; Mix two, 0.3%); adenocarcinomas in the small intestines (Mix one, 0.6 and 1.0%); hemangiosarcomas in various organs (Mix one, 0.3 and 0.6%; Mix two, 0.3%); and, histiocytic sarcomas (Mix two, 0.3%). The *p*-values for dose-related trends for these tumours were 0.006 or lower.

A few years earlier, Weyand *et al*. (1995)[132] reported on the tumorigenic activity of manufactured gas plant residues (MGP) in female A/J mice (n=30/group) using a F0927 basal gel diet system. These animals were chosen because of their sensitivity to chemical induction of pulmonary adenomas. The mice were fed the diets, containing 0.0, 0.1 or 0.25% of MGP, for 260 days. After the last exposure day the animals were sacrificed and their lungs and stomach removed for histologic examination.

The investigators observed an unexpected and unexplained lower intake of diet and body weight in control animals. Also the intake of diet and body weight of animals fed the highest amount of MGP was lower compared to the other exposed group.

The percentage of mice with lung tumours was statistically significantly increased in groups fed MGP compared to controls (29/29 (0.25% MGP), 19/27 (0.1% MGP), 4/21 (controls)). However in none of the animals fed MGP or in controls, forestomach tumours were found.

6.3 Toxicity profile

Both the IPCS[70] and the ATSDR[128] evaluated the non-carcinogenic toxicity of single PAH and complex PAH mixtures. A short summary of their findings is given below. For those interested in the original publications the reader is referred to the IPCS and ATSDR documents.

6.3.1 Observations in humans

Reliable health-based information on the non-carcinogenic toxicity of single PAH compounds is very limited, because in the environment PAH occur as mixtures and not as single compounds. The typical acute systemic effect after accidental dermal, oral or inhalation exposure to naphthalene is acute haemolytic anaemia. In addition, after dermal application, anthracene, fluoranthene and phenanthrene may induce specific skin reactions.

Although a considerable number of epidemiological studies on complex PAH mixtures have been published, the end-point of most of these studies has been carcinogenicity. No data are available on human death and on systemic effects, such as cardiovascular, gastrointestinal, hepatic effects, dermal effects, and effects on reproduction, following inhalation exposure to PAH. In one study, workers in a rubber factory showed reduced lung function, abnormal chest X-ray, cough, and throat and chest irritation (Gupta *et al*. 1993; source ATSDR). However, the authors did not make clear whether the observed effects were due to PAH-exposure or to other toxic chemicals. In addition, coke oven workers showed reduced levels of serum immunoglobulin and decreased immune function (Lei, 1993, and Szczeklik *et al*. 1994; source IPCS and ATSDR, respectively). However, the biological significance of these findings is uncertain.

6.3.2 Observations in animals

Most of the experiments have addressed the carcinogenicity of PAH. The number of studies on the non-carcinogenic short- and long-term toxicity is limited. Moreover, these studies are for a large part restricted to non-carcinogenic PAH, such as acenaphthene, anthracene, fluoranthene, fluorene, and pyrene. Furthermore,

data on the non-carcinogenic effects are only available for single PAH and not for complex PAH mixtures.

Acute toxicity. The main routes of exposure were oral, intraperitoneal and dermal. In general, single doses of PAH (*e.g.,* anthracene, BaP, naphthalene) have moderate to low toxicity (LD_{50} values > 500 mg/kg bw after oral administration). For non-lethal doses, the database is very limited, and mainly concerns naphthalene. Intraperitoneal injections of this compound at a dose of at least 200 mg/kg bw resulted in bronchiolar necrosis and cytotoxicity of the olfactory epithelium in mice, rats and hamsters. Earlier reports on dogs, given naphthalene orally, revealed diarrhoea. Moreover, dermal and ocular irritation and dermal sensitisation were described in various animal species.

Short-term exposure. Subacute and subchronic toxicity of various PAH compounds (*e.g.,* anthracene, BaP, fluorene, naphthalene, pyrene) were mainly described in animals that were exposed by gavage. No treatment-related pathological effects were observed in mice fed up to 1,000 mg/kg bw anthracene per day for 90 days. In mice fed up to 500 mg/kg bw fluorene per day for 16 weeks, increased weights were observed of the liver, spleen and kidneys. In addition, at 250 mg/kg bw, haematological effects were reported. Comparable effects were observed in mice fed naphthalene. Data on inhalation exposure is limited to BaP. Rats and hamsters did not show any sign of respiratory tract lesions, when exposed to 7.7 mg/m^3 BaP (2h/d, 5d/w, 4 weeks) or 9.8-44.8 mg/m^3 BaP (4.5h/d, 5d/w, 16 weeks), respectively.

Long-term exposure. No data on inhalation exposure is available to the committee. Mice who were exposed subcutaneously to anthracene, benz[a]anthracene or dibenz[a]anthracene for 40 weeks showed signs of iron deposition in lymph glands and a reduced number of lymphoid cells.

Mutagenicity and genotoxicity. Benzo[a]pyrene has been extensively studied in various *in vitro* and *in vivo* mutagenicity tests. It scored positive in many endpoints, such as: bacterial DNA repair and mutation; mutations in *Drosophila melanogaster*; DNA binding in various species; DNA repair; sister chromatid exchange; chromosomal aberration; point mutation; transformation in mammalian cells *in vitro*; *in vivo* sperm abnormalities; and, *in vivo* somatic mutations at specific loci.

Regarding other PAH, IPCS reported that anthracene, fluorene and naphthalene were inactive in various short-term mutagenicity tests. Inconsistent results were found for phenanthrene and pyrene. In addition, data on acenaphthalene, acenaphthylene, benzo[*a*]fluorine, and corone were inadequate. Other PAH were positive or showed a tendency for mutagenic activity.

Reproductive effects, embryotoxicity and teratogenicity. The main routes of exposure in evaluating these types of effects were by diet, intraperitoneal or subcutaneous injections. No data on inhalation exposure is available to the committee. Whether PAH compounds express reproductive and embryotoxic effects depends on the genotype of mice (induction of the cytochrome P450 monooxygenase receptor) and the ability to transform PAH into active PAH metabolites. These metabolites can cross the placenta and, therefore, may produce adverse effects in the embryo and foetus. Indeed, in female mice, which can induce monooxygenase receptors, benz[a]anthracene, benzo[a]pyrene, dibenz[a,h]anthracene, and naphthalene were found to be embryotoxic. Concerning BaP, it is suggested that the route of exposure affects also the magnitude of effects; the teratogenicity being worse in orally exposed animals than in animals exposed intraperitoneally. Further, a single intraperitoneal injection of BaP in mice reduced fertility and destroyed primordial oocytes in a dose-dependent manner.

6.4 Summary

Exposure to a single PAH and carcinogenicity

No data are available on the carcinogenic effects of single PAH in humans. On the other hand, a vast amount of studies are available in which animals were exposed to a single PAH. However, most of these animal studies were addressed to BaP and to dermal and oral exposure; only a few have been published on inhalation exposure. Overall, these animal data clearly showed that carcinogenic PAH act as local carcinogens. Thus, concerning occupational exposure, cancer in the lungs and skin presents the main risks.

Some investigators reported systemic effects of BaP after oral, intrarectal and intraperitoneal exposure. However, these reports were of insufficient quality to conclude that BaP acts as a systemic carcinogen.

Exposure to PAH mixtures and carcinogenicity

In contrast to animal studies, a vast amount of epidemiological data has been published on the carcinogenicity of PAH mixtures. Interpretation of these data is hampered by the many variables present in assessing work-related health effects in humans. These include the study design, exposure measurements, lifestyle factors, co-exposure to other toxic compounds and data presentation. Nevertheless, taking these shortcomings into account, a majority of the epidemiological data revealed a positive association between airborne PAH exposure and lung cancer risk. In addition, some investigators estimated the (excess) lifetime lung cancer risk. For instance, Armstrong *et al*. (2003, 2004)[7,8] estimated that coke-oven workers in the United Kingdom, who worked for 40 years and were exposed to an average of 1.5 $\mu g/m^3$ BaP had an excess lifetime risk of 8 extra cases per 1,000 coke-oven workers.

Some investigators reported also on the risk for cancer at other sites of the body of humans. For instance, skin cancer is strongly associated with dermal exposure. Also, some investigators reported on bladder cancer. However, concerning bladder cancer they could not rule out possible co-exposure to other carcinogenic compounds, such as 2-naphtylamine, which are known to induce bladder cancer. Overall, evidence of increased risk for cancer in other organs in humans was inconclusive. Therefore, it is unclear to the committee whether inhalation or dermal exposure of PAH may lead to tumours at other sites of the body than the lungs or skin, respectively.

In a few animal carcinogenicity studies lung tumours were reported after chronic inhalation of coal tar pitch volatiles. In two animal studies, lung tumours were also found in mice, which were chronically fed coal tar mixtures or gas plant residues. However, the committee finds these data too limited to make a conclusion on systemic effects.

General toxicity

Most of the human and animal studies have addressed the carcinogenicity of PAH. Hence, the number of studies on short- and long-term toxicity is small. In short, the limited amount of data indicates that certain PAH may induce effects on the haematopoietic system (*e.g*., anaemia). Furthermore, some PAH may have immunotoxic potential or may cause skin or eye irritation. Finally, PAH can cross the placenta and may induce adverse effects on the embryo and foetus.

Chapter 7

Existing guidelines, standards and evaluations

7.1 General population

The WHO based its cancer risk estimate for PAH on data obtained from occupational epidemiology[135]. The unit risk for BaP as indicator air constituent for PAH is estimated to be 8.7 x 10^{-5} per ng/m^3, which is the same as that established by WHO in 1987[134]. The estimate is based on data from studies in coke-oven workers by Redmond *et al*. (1979)[98], using a linearized multistage model. The corresponding concentrations of BaP producing excess lifetime cancer risks of $1x10^{-4}$, $1x10^{-5}$ and $1x10^{-6}$ are 1.2, 0.12 and 0.012 ng/m^3, respectively.

In the Netherlands[49], the concentration of PAH producing an excess lifetime lung cancer risk of $1x10^{-6}$ was estimated to be 0.01 ng BaP/m^3.

7.2 Working population

Table 7.1 summarizes the occupational exposure limits of PAH established by regulatory authorities of the Netherlands and various other counties. Table 7.2 summarizes the occupational exposure limits of some single PAH compounds.

Table 7.1 OELs of PAH established in various countries.

Country	OEL mg/m^3	TWA	Comments	Reference
The Netherlands				
- Min SZW	0.2	8-h	Administrative OEL; PAH as soluble in cyclohexane; only valid for noncarcinogenic PAH	69
- DECOS	-	-	-	-
Germany				
- DFG	-	-	No OEL, because PAH is classified as carcinogenic (category 1)	32
- AGS	-	-	-	124
The UK (HSE)	-	-	-	48
Sweden (SNB)	-	-	-	86
Denmark	0.2	8-h	PAH; benzene soluble fraction	6
The USA - ACGIH	0.2	8-h	TLV; coal tar pitch volatiles as benzene soluble aerosol	2
- OSHA	0.2	8-h	PEL; coal tar pitch volatiles as benzene soluble aerosol	2
- NIOSH	0.1	8-h	REL; coal tar pitch volatiles as cyclohexane extractable fraction	35
EU (SCOEL)	-	-	-	2

-, no OEL established, no information available.

Table 7.2 OELs of some single PAH.

Country	OEL (mg/m^3)	TWA	Comments	Reference
Benzo[a]pyrene				
The Netherlands	-	-		69
Germany - DFG and AGS	0.005	8-h	TRK, carcinogenicity cat. 2 (cookeries, oven area)	32,124
	0.002	8-h	TRK, carcinogenicity cat. 2 (other workplaces)	32,124
Sweden	0.002	8-h	LLV, set in 1993	86
	0.020	15-min	STV, set in 1993	
The USA - OSHA	0.200	8-h	see coal tar pitch volatiles (Table 7.1)	2
- NIOSH	0.100	8-h	see coal tar pitch volatiles (Table 7.1)	2
Naphthalene				
The Netherlands	50	8-h	MAC: administrative OEL	69
	80	15-min	STEL: administrative OEL	
Germany - DFG and AGS	50	8-h	TRK; carcinogenic; skin notation	32,124
Sweden	50	8-h	HLV; set in 2000	86
	80	15-min	STV; set in 2000	
Denmark	50	8-h	-	6
The UK	53	8-h	OES: chemical hazard alert notice (CHAN)	48
	80	15-min	OES: chemical hazard alert notice (CHAN)	
The USA - ACGIH	52	8-hr	TLV: skin notation	2
	79	15-min	STEL: skin notation	
- OSHA	50	8-h	PEL	2
- NIOSH	50	8-h	REL	2
	75	15-min	STEL	

-, no OEL established, no information available. CHAN: Chemical Hazard Alert Notice, current scientific information indicates that it is not possible to identify with confidence a level of exposure which is judged to offer a reasonable certainty of health protection; HLV, hygienic limit value; LLV, level limit value; MAC, maximum allowable concentration; MAK, maximum workplace concentration; OES, occupational exposure standard; TRK, Technische Richtkonzentrationen (technical exposure limit); TWA, time-weighted average; STEL, short-time exposure level; STV, short-term value; TLV, threshold limit value.

7.3 Carcinogenic classification

The European Community, IARC[57,62] and the American Environmental Protection Agency[127] have classified several single PAH for their carcinogenic potency (see annex H3). Also in the Netherlands some PAH were classified as a carcinogen (annex H3). Overall, due to a lack of human data, the classifications of single PAH compounds were based on animal data.

In addition, the HSE (the UK)[48], DFG (Germany)[32], ACGIH (the USA)[2] and NIOSH (the USA)[2] classified coal tar pitch (volatiles), which contain high amounts of PAH, as carcinogenic. The DFG also considers coke oven emissions as carcinogenic[32]. The European Community has classified various PAH mixture from coal-derived sources (see annex H3).

Chapter 8

Hazard assessment

PAH are a group of non-heterocyclic non-substituted aromatic hydrocarbons that are mainly formed by incomplete combustion of organic materials. They are not to be confused with polycyclic or polynuclear aromatic compounds (PACs) that also comprise substituted and/or heterocyclic PAH-derivates. PAH occur as complex mixtures, of which the composition depends on the source of organic material (*e.g.*, coal, wood) and the way by which these materials are handled in the workplace. Also, certain sources may contain substantial levels of non-PAH substances that contribute to the total cancer risk, such as petroleum and gasoline exhaust or asphalt. To avoid uncertainties such as co-exposure as much as possible, the committee limited the current risk assessment to coal-derived PAH sources only. Therefore, it used only epidemiological data in which coal-derived sources were the main source of PAH exposure.

8.1 Benzo[a]pyrene as a risk indicator for PAH exposure

The complex composition of PAH mixtures raises the question of the best indicator for PAH exposure in ambient air. Of the several possibilities (BaP, benzene soluble matter (BSM), profile of selected PAH), the committee prefers BaP, because i) validated and standardized analysis techniques are available for this compound, ii) in the past thirty years most exposure data have been presented with BaP as exposure indicator, and iii) BaP is considered as one of the more

potent PAH carcinogens. As a result, the excess cancer risk estimated for PAH exposure is expressed as the concentration of BaP in the air.

As indicated in the previous section, the recommendation in this report is valid for BaP and other PAH derived from coal. Various measurements have pointed out that by current industrial use of coal the variation between BaP and other PAH contributes to a limited degree in the whole set of uncertainties. However, this relationship will be disturbed when, for instance, BaP (but not the other PAH) is filtered out before the PAH mixture is emitted in the air. In those cases, a readjustment of the recommendation is advised.

8.2 Health-based calculated - occupational cancer risk values (HBC-OCRVs)

8.2.1 Carcinogenicity studies and selection of the suitable study for risk estimation in the occupational situation

The committee estimates the excess lifetime cancer risk values for PAH from coal-derived sources from epidemiological studies, not only because for risk assessment human data are preferred over animal data, but also because a substantial amount of epidemiological data is available on occupational PAH exposure and cancer risk. In addition, the number of animal studies involving inhalation exposure to PAH mixtures – the most relevant route of exposure concerning occupational exposure – is very limited and includes intratracheal instillations.

Various epidemiological studies revealed that PAH act mainly as local carcinogens, leading to lung cancer after inhalation and skin cancer after dermal contact. This positive association is consistent, despite the differences in industries, PAH sources, possible co-exposure with non-PAH substances, and confounding or information bias in many studies[7,8,21,70,82].

Few data suggest that PAH may act as systemic carcinogens. For instance, some investigators found a weak association for bladder cancer after occupational exposure. The problem, however, is that in none of these situations co-exposure with specific bladder carcinogens (*e.g.*, 2-naphthylamine) could be ruled out. In all other cases, such as liver and stomach cancer, an association for cancer risk was found to be weak, absent or inconclusive, due to the small number of these types of cancers and reporting bias. Evidence for systemic carcinogenesis of natural PAH mixtures in animal studies is limited to oral exposure. In those studies lung tumours were found after chronic feeding of diets containing natural PAH-rich sources. On the other hand, in an occupational situation, oral

exposure is not or less relevant in deriving HBC-OCRVs than inhalation exposure.

From the previous, the committee is of the opinion that data on lung cancer are the best data available on cancer risk related to PAH exposure, due to its consistency and the large data set available. For this reason, the committee decided to base its estimation of cancer risk values on preventing this type of cancer. Furthermore, by reducing the risk of lung cancer, the committee expects that the development of other types of cancer will be reduced as well, at least after inhalation exposure.

In calculating cancer risk values quantitative exposure-response relationships are needed. Regarding PAH exposure and lung cancer risk, the relationships are hampered by many variables. These include differences in study design, industry, PAH source, presence of non-PAH carcinogens, variations in lifestyle factors and incomplete data presentation. In these circumstances, a meta-analysis can help. A meta-analysis integrates the findings and uncertainties of the individual studies to obtain a more powerful and reliable exposure-response relationship and to identify sources of variation in this relationship.

One large meta-analysis study has been performed, of which the results were recently published by Armstrong *et al*. (2003, 2004)[7,8]. In this well-performed study, unit relative risks and lifetime excess lung cancer risks for workers, who were mainly exposed to PAH, were calculated. Unit relative risk values refer to increments in relative lung cancer risk per 100 $\mu g/m^3$ BaP years, in which 100 $\mu g/m^3$ BaP years corresponds to a concentration of 2.5 g/m^3 BaP over 40 years. Based on data obtained from 39 distinct cohorts, the overall mean unit relative risk for lung cancer was calculated at 1.20 (95% CI, 1.11-1.29; $p<0.001$; log-linear model). The cohorts included various industries in which PAH were considered the predominant carcinogens. All these industries concerned coal-derived PAH. Although none of the cohorts dominated the estimate, significant differences across industries were found. After allowing for these differences in the analysis, differences could only be explained by chance or by unknown true variations. Differences across industries could be explained by problems of exposure estimation and small number of cases in some studies. For the committee, these uncertainties and variability within the cohorts were no reason to reject any of the included cohorts.

Recognizing the limitations and uncertainties, which are present in the meta-analysis, the committee is of the opinion that this analysis is the best starting point in estimating HBC-OCRVs in humans, who are occupationally exposed to carcinogenic PAH.

8.2.2 Calculation of the HBC-OCRV

The HBC-OCRV is defined as the additional lifetime cancer risk value, usually expressed per ng/m^3, under occupational conditions. To derive an HBC-OCRV for lung cancer in humans under workplace exposure conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day during 5 days per week, 48 weeks per year, for 40 years, and inhales 10 m^3 air per 8-hour-working day. These assumptions were taken into account in the meta-analysis[7,8]. Furthermore, the analysis showed that the relationship between exposure and cancer risk was best described by a log-linear model instead of a linear model. Therefore, the committee used the formula obtained from this log-linear model to derive HBC-OCRVs. The committee likes to add that at low exposure concentrations (at which cancer risk values are based), the models just differ very little, and the use of the linear model would result in comparable outcomes as the log-linear model.

The log-linear equation was expressed as follows:

$$URR_{cum\ exp\ X} = [URR_{cum\ exp\ 100}]^{(X/100)}$$

in which X represents the exposure concentration of BaP, 100 the benchmark of 100 μg/m^3 BaP years, the $URR_{cum\ exp\ X}$ the relative risk on exposure to X, and $URR_{cum\ exp\ 100}$ the relative risk of 1.20 on exposure to 100 μg/m^3 BaP years (2.5 μg BaP /m^3 40 years). According to Armstrong *et al*. (2003, 2004), at moderate-low relative risks, the log-linear interpolation is close to the linear interpolation.

The excess lifetime cancer risk depends on the background rate of lung cancer. In the Netherlands, of the 250 death cases in the general male population (age>15 years), on average 24.21 are caused by lung cancer (source: Statline, a databank of Statistics Netherlands, period 1996-2002)[25]. For the derivation of an HBC-OCRV, an additional risk of one extra cancer death due to occupational exposure per 250 death cases is taken into account (= 4x10^{-3}; corresponds to 1 excess death per 1,000). As a result, the unit relative risk is calculated at 1.041 (calculation: (24.21+1)/24.21). Using the non-linear formula, this corresponds with a concentration of 22.03 μg BaP/m^3-40 years (1.041 = [1.20]$^{(X/100)}$). This means over a period of 40 working years an average exposure of 550 ng/m^3 BaP. In case of an additional risk of one cancer death per 250,000 death cases, the unit relative risk is 1.0004131 ((2421+1)/2421), and the equivalent concentration 0.227 μg BaP/m^3-40 years. This corresponds to an average exposure of 5.7 ng/m^3 BaP over 40 working years. Comparable results were obtained with two chronic animal studies (see annex K). Although in one of these animal studies the HBC-

OCRV was rather low, this could be well explained by the fact that the mice were exposed as early as the first day after birth.

In conclusion, the committee derived HBC-OCRVs corresponding to an excess cancer mortality level of*:

- 4 per 1,000 ($4x10^{-3}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 550 ng BaP/m^3;
- 4 per 100,000 ($4x10^{-5}$) for 40 years of occupational exposure to benzo[a]pyrene and polycyclic aromatic hydrocarbons from coal-derived sources of 5,7 ng BaP/m^3.

Based on the limited data available on the non-carcinogenic toxicity of PAH, the committee concludes that a health-based occupational exposure limit for PAH in the air, derived from data other than on genotoxicity or carcinogenicity, is expected to be well above the concentration level (550 ng/m^3 BaP) associated with the referential lifetime cancer risk level of $4x10^{-3}$.

8.3 Skin notation

At the request of the Minister of Social Affairs and Employment, the committee judged whether for benzo[a]pyrene and polycyclic aromatic hydrocarbons (PAH) from coal-derived sources a skin notation is needed.

A skin notation is recommended for those substances 'where the amount absorbed by both hands and forearms in 1 hour could amount to more then 10% of the amount that can be absorbed via the lungs on exposure to the OEL (8-h TWA), provided that this OEL is set on the basis of *systemic* toxicity rather than on sensory or irritant effects or direct effects in the respiratory tract' (ECETOC 1998)[34]. Furthermore, ECETOC pointed out that although 'carcinogens should not automatically be allocated a skin notation … carcinogenicity will only play a role in assigning a skin notation when skin absorption is important or when skin cancer is considered a relevant end-point'.

From the available human data, the committee concludes that skin penetration of PAH does occur in significant amounts. For instance, coke oven workers, who are dermally exposed to a mixture of various PAH, had considerable amounts of hydroxypyrene (a non-carcinogenic metabolite of pyrene) in their urine (see section 5.1.2). However, although skin absorption does occur and PAH

* Calculation is based on the log-linear model of Armstrong *et al*. (2003).

metabolites are found in several internal organs, including the lungs, the committee did not find proof from human or animal data indicating that BaP or other PAH compounds adds substantially to systemic non-carcinogenic adverse health effects by dermal exposure.

Yet, human and animal studies have clearly shown a positive association between dermal exposures to PAH, by direct contact on the skin, and skin cancer risk. This is a relevant endpoint, and therefore a skin notation is justified.

In conclusion, the committee recommends a skin notation for benzo[a]pyrene and other polycyclic aromatic hydrocarbons (PAH) from coal-derived sources.

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Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances in the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality in the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10-4 and 10-6 per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
  epidemiologist; Environ, Terneuzen
- PJ Boogaard
  toxicologist; Shell International Petroleum Company, The Hague
- PJ Borm
  professor of inhalation toxicology; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  professor of risk assessment in occupational epidemiology; IRAS, Utrecht University, Utrecht
- TM Pal
  occupational physician; Netherlands Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; the Dow Chemical Company, Terneuzen
- RA Woutersen,
  toxicologic pathologist; TNO Quality of Life, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- TMM Coenen, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared by WK de Raat, PhD, from OpdenKamp, Registration & Notifiction in The Hague, the Netherlands, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: Ms F Smith and Ms M Javanmardi.
Lay-out: Ms J van Kan.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist

involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Comments on the public review draft

A draft of the present report was released in 2005 for public review. The following organisations and persons have commented on the draft document:

- T scheffers, Dohsbase v.o.f., the Netherlands
- F Jongeneelen, IndusTox Consult, the Netherlands
- M Bakker, ArboNed, the Netherlands
- K de Raat, Environ Netherlands BV, the Netherlands
- H Roos, VBW Asfalt, the Netherlands
- W Kat, Corus Staal BV, the Netherlands
- E González-Fernández, Ministerio de Trabajo y Asuntos Sociales, Spain
- D Zumwalde, National Institute for Occupational Safety and Health, the USA

Annex **D**

Physical and chemical properties

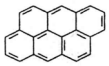
D1 Identity and structural formulae of PAH covered in this evaluation (IPCS, 1998)[70]

Acenaphthene (Mw=154.2)
CAS Reg. no.83-32-9

Acenaphthylene (Mw=152.2)
CAS Reg. no. 208-96-8

Anthracene (Mw=178.2)
CAS Reg. no. 120-12-7

Anthanthrene (Mw=276.3)
CAS Reg. no. 191-26-4



Benz[a]anthracene (Mw=228.3)
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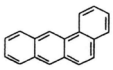

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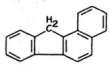

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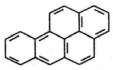

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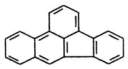

Benzo[b]fluorene (Mw=216.3)
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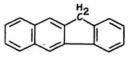

Benzo[c]phenanthrene (Mw=228.3)
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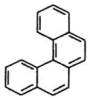

Benzo[e]pyrene (Mw=252.3)
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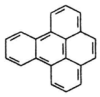

Benzo[ghi]fluoranthene (Mw=226.3)
CAS Reg. no. 203-12-3

Benzo[ghi]perylene (Mw=276.3)
CAS Reg. no. 191-24-2

Benzo[j]fluoranthene (Mw=252.3)
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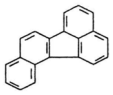

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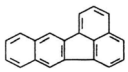

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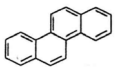
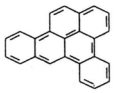


Coronene (Mw=300.4)
CAS Reg. no. 191-07-1

Cyclopenta[cd]pyrene (Mw=226.3)
CAS Reg. no. 27208-37-3

Dibenzo[a,e]pyrene (Mw=302.4)
CAS Reg. no. 192-65-4



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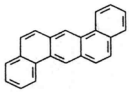

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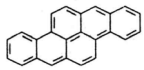

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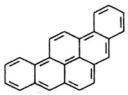

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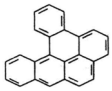
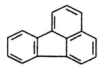
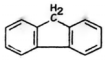


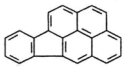
Fluoranthene (Mw=202.3)
CAS Reg. no. 206-44-0



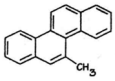
Fluorene (Mw=166.2)
CAS Reg. no. 86-73-7



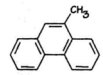
Indeno[1,2,3-cd]pyrene (Mw=276.3)
CAS Reg. no. 193-39-5



5-Methylchrysene (Mw=242.3)
CAS Reg. no. 3697-24-3



1-Methylphenanthrene (Mw=192.3)
CAS Reg. no. 832-69-9



Naphtalene (Mw = 128.2)
CAS Reg. no. 91-20-3

Perylene (Mw=252.3)
CAS Reg. no. 198-55-0

Phenanthrene (Mw=178.2)
CAS Reg. no. 85-01-8

Pyrene (Mw=202.3)
CAS Reg. no. 129-00-0

Triphenylene (Mw=228.3)
CAS Reg. no. 217-59-4

D2 Industrial mixtures of PAH (reproduced from EPA, 2001)[127]

CAS Reg. No.	Industrial mixtures with polycyclic aromatic hydrocarbons
101794-76-7	Aromatic hydrocarbons, C-20-28, polycyclic, mixed coal-tar pitch-polystyrene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polystyrene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a softening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
101794-75-6	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polyethylene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polyethylene pyrolysis. Combined primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a sof tening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
101794-74-5	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polyethylene-polypropylene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polyethylene-polypropylene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having a sof tening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
94113-85-6	Aromatic hydrocarbons, polycyclic, from decompn. of solvent extd. coal tar pitch-2,4,6-tricnitrophenol-reaction products. Definition: A complex combination of organic compounds obtained by addition of a picric acid solution to the solvent extract of a bitumineus coal tar pitch and decomposition of the precipitated pitch-picric acid reaction product with bases. Composed primarily of high molecular weight polycyclic aromatic compounds.
94113-84-5	Aromatic hydrocarbons, polycyclic, from decompn. of iodine-solvent extd. coal-tar pitch cargo-transfer complexes. Definition: A complex combination of organic compounds obtained by addition of iodine solution to the solvent extract of a bitumineus coal tar pitch and decomposition of the precipitated pitch iodine reaction products. Composed primarily of high molecular weight polycyclic aromatic compounds.
68409-74-5	Aromatic hydrocarbons, polycyclic, cyclohexanone, ext. residues. Definition: A complex residuum from the cyclohexanone extraction of anthracene salts. It consists predominantly of polynuclear aromatic hydrocarbons such as anthracene.
90640-80-5	Anthracene oil. Definition: A complex combination of polycyclic aromatic hydrocarbons obtained from coal tar having an approximate distillation range of 300°C to 400°C (572°F to 752°F). Composed primarily of phenanthrene, anthracene, and carbazole.
141785-66-2	Tar bases, coal, low-temperature, crude. Definition: The reaction product obtained by neutralizing the acidic extract of alkali-washed low-temperature coal tar middie oil with an alkaline solution, such as aqueous sodium hydroxide, to obtain the free bases. Composed primarily of a complex mixture of aromatic nitrogen bases.
130576-63-5	Extracts (coal), coal tar pitch solvent. Definition: Solvent extract of bituminous coal tar pitch. Composed primarily of polycyclic aromatic hydrocarbons.
94113-98-1	Extracts (coal), coal tar pitch solvent, reaction products with 2,4,6-trinitrophenol.Definition: Insoluble reaction product obtained by addition of apicric acid solution to the solvent extract of a bitumineus coal tar pitch. Composed primarily of polycyclic aromatic hydrocarbons.
94113-97-0	Extracts (coal), coal tar pitch solvent, reaction products with iodine. Definition: Extract obtained by adding an iodine solution to the solvent extract of a bitumineus coal tar pitch. Composed primarily of polycyclic aromatic hydrocarbons.
94113-96-9	Extract residues (coal), liquefaction heavy acid, alkaline extracts. Definition: The neutral oil obtained by debasing and dephenolating the heavy oil from the high pressure hydrogenation of bituminous coal. Composed primarily of unsubstituted and alkyl-substituted aromatic polynuclear hydrocarbons that are partially hydrogenated and may contain heteroatoms.
94113-95-8	Extract residues (coal), naphthalene oil acid, alkaline extracts. Definition: The neutral oil obtained by debasing and dephenolating the middie oil from the low temperature carbonization of bituminous coal. Composed primarily of a mixture of mono- and polynuclear, substituted and unsubstituted aromatic and naphthenic hydrocarbons and heterocycles as well as paraffinic hydrocarbons.

CAS Reg. No.	Industrial mixtures with polycyclic aromatic hydrocarbons
101794-76-7	Aromatic hydrocarbons, C-20-28, polycyclic, mixed coal-tar pitch-polystyrene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polystyrene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a softening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
140413-63-4	Distillates (coal tar), low-temperature, pitch. Definition: The distillate obtained during the heat treatment of low temperature coal tar pitch having an approximate distillation range of 100°C to 400°C (212°F to 752°F). Composed primarily of a complex mixture of aromatic compounds.
140203-27-6	Distillates (coal tar), upper, fluorene-low. Definition: A complex combination of hydrocarbons obtained by the crystallization of the fractional distillates from tar oil. It consists of aromatic polycyclic hydrocarbons, primarily diphenyl, dibenzof üran, and acenaphthene.
140203-21-0	Distillates (coal tar), gasification, pitch, full range. Definition: The distillate obtained during the heat treatment of pitch obtained from coal gasification tar having an approximate distillation range of 100°C to 400°C (212°F to 752°F). Composed primarily of aromatic and other hydrocarbons, phenolic compounds, and aromatic nitrogen compounds.
140203-19-6	Distillates (coal tar), gasification, heavy oils, pyrene fraction. Definition: The distillate from the fractional distillation of coal gasification tar having an approximate boiling range of 350°C to 450°C (662°F to 842°F). Composed primarily of phenanthrene and anthracene homologs, tetranuclear aromatic hydrocarbons which may also contain heteroatoms, high-boiling aliphatic and naphthenic hydrocarbons, and polynuclear phenols.
91995-52-7	Distillates (coal tar), pitch, pyrene fraction. Definition: The redistillate obtained from the fractional distillation of pitch distillate and boiling in the range of approximately 380°C to 410°C (716°F to 770°F). Composed primarily of tri- and polynuclear aromatic hydrocarbons and heterocyclic compounds.
91995-51-6	Distillates (coal tar), pitch, heavy oils. Definition: The distillate from the distillation of the pitch obtained from bitumineus high temperature tar. Composed primarily of tri- and polynuclear aromatic hydrocarbons and boiling in the range of approximately 300°C to 470°C (572°F to 878°F). The product may also contain heteroatoms.
91995-42-5	Distillates (coal tar), heavy oils, pyrene fraction. Definition: The redistillate obtained from the fractional distillation of pitch distillate boiling in the range of approximately 350°C to 400°C (662°F to 752°F). Consists predominantly of tri- and polynuclear aromatics and heterocyclic hydrocarbons.
91995-25-4	Distillates (coal), liquefaction, heavy. Definition: the heavy oil obtained by distillation in the range of approximately 300°C to 550°C (572°F to 1022°F) of coal oil from the catalytic hydrogenation of coal and coal-derived products. Composed primarily of polynuclear aromatics and naphthenes. The product contains sulfür, oxygen, and nitrogen compounds.
90640-86-1	Distillates (coal tar), heavy oils. Definition: The distillate from the fractional distillation of coal tar having an approximate distillation range of 300°C to 400°C (572°F to 752°F). Composed primarily of tri-and polynuclear aromatic hydrocarbons and heterocyclic compounds.
84989-11-7	Distillates (coal tar), upper, fluorene-rich. Definition: A complex combination of hydrocarbons obtained by the crystallization of the fractional distillates from coal tar. It consists of aromatic and polycyclic hydrocarbons, primarily fluorene and acenaphthene.
84989-10-6	Distillates (coal tar), upper, fluorene-free. Definition: A complex combination of hydrocarbons obtained by the crystallization of tar oil. It consists of aromatic polycyclic hydrocarbons, primarily diphenyl, dibenzof üran, and acenaphthene.
121575-60-8	Pitch, coal tar, high-temperature, heat-treated. Definition: The heat-treated residue from the distillation of high temperature coal tar. A black solid with an approximate sof tening point from 80°C to 180°C (176°F to 356°F). Composed primarily of a complex mixture of three or more membered condensed ring aromatic hydrocarbons.
100403-59-6	Pitch, mixed brown-coal tar-ethylene manufacturing pyrolysis oil distillation. Definition: The residue from the joint distillation of brown coal tar and pyrolysis residu^ oil from ethylene plants. Composed primarily of polynuclear aromatic and naphthenic hydrocarbons, which can be alkyl- and vinyl-substituted and can contain heteroatoms, paraffin hydrocarbons, and high-boiling mono- and dinuclear phenols. It is a black solid with a sof tening point of 60°C (140°F) according to DIN 52025.

CAS Reg. No.	Industrial mixtures with polycyclic aromatic hydrocarbons
101794-76-7	Aromatic hydrocarbons, C-20-28, polycyclic, mixed coal-tar pitch-polystyrene pyrolysis-derived. Definition: A complex combination of hydrocarbons obtained from mixed coal tar pitch-polystyrene pyrolysis. Composed primarily of polycyclic aromatic hydrocarbons having carbon numbers predominantly in the range of C20 through C28 and having a softening point of 100°C to 220°C (212°F to 428°F) according to DIN 52025.
100403-58-5	Pitch, brown-coal tar. Definition: The residue from the distillation of brown coal tar formed by carbonization up to 1250°C (2282°F). Composed primarily of polynuclear aromatic and naphthenic hydrocarbons and heterocycles, paraffin hydrocarbons, and high-boiling mono- and dinuclear phenols. It is a black solid with a sof tening point of 50°C to 120°C (l 22°F to 248°F) according to DIN 52025.
94114-13-3	Pitch, coal tar, high-temperature, secondary. Definition: The residue obtained during the distillation of high boiling fractions from bituminous coal high temperature tar and/or pitch coke oil, with a sof tening point of 140°C to 170°C (284°F to 338°F) according to DIN 52025. Composed primarily of tri- and polynuclear aromatic compounds, which also contain heteroatoms.
94114-12-2	Pitch, coal gasification tar, low-temperature. Definition: The residue from the distillation of bituminous coal pressure gasification tar. A black solid with a sof tening point of greater than 60°C (140°F) according to DIN 52025 and composed primarily of a complex mixture of polynuclear aromatic and naphthenic hydrocarbons that may be alkyl substituted and may contain heteroatoms, high boiling aliphatic hydrocarbons and polynuclear phenols.
92061-94-4	Residues (coal tar), pitch distillation. Definition: Residue from the fractional distillation of pitch distillate boiling in the range of approximately 400°C to 470°C (752°F to 878°F). Composed primarily of polynuclear aromatic hydrocarbons, and heterocyclic compounds.
92061-92-2	Residues (coal tar), anthracene oil distillation. Definition: The residue from the fraction distillation of crude anthracene boiling in the approximate range of 340°C to 400°C (644°F to 752°F). It consists predominantly of tri- and polynuclear aromatic and heterocyclic hydrocarbons.
92061-88-6	Residues (coal), coke-oven gas-polycyclic aromatic hydrocarbons reaction products distillation. Definition: The residue from the distillation of a complex reaction product, obtained by reaction of gases obtained by the dry distillation of bitumineus coal with a distillate, consisting of di- and trinuclear aromatic hydrocarbons and their alkyl derivatives, with a sof tening point of 30°C to 50°C (86°F to 122°F). The residue consists predominantly of substituted aromatic di- and polynuclear hydrocarbons and sulfür-containing compounds.

D3 Physical-chemical properties of some PAH (adapted from IPCS, 1998)[70]

Compound	Colour	Melting-Point (°C)	Boiling-Point (°C)	Vapour Pressure (Pa; 25°C)	Density[a]	log K_{ow}[b]	Solubility in water (25°C; µg/L)
Acenaphthene	White	95	279	2.9×10^{-1}	$1.024^{90/4}$	3.92	3.93×10^{3}
Acenaphthylene		92-93		8.9×10^{-1}	$0.899^{16/2}$	4.07	
Anthracene	Colourless	216.4	342	8.0×10^{-4}	$1.283^{25/4}$	4.5	73
Anthanthrene	Golden yellow	264	547		1.39		
Benz[a]anthracene	Colourless	160.7	400	2.8×10^{-5}	1.226	5.61	14
Benzo[a]fluorene	Colourless	189-190	399-400			5.32	45
Benzo[a]pyreneBenzo[b]	Yellowish	178.1	496	7.3×10^{-7}	1.351	6.5	3.8
fluoranthene	Colourless	168.3	481	6.7×10^{-5} (20°C)		6.12	1.2 (20 °C)
Benzo[b]fluorene	Colourless	213.5	401-402		1.226	5.75	2
Benzo[c]phenanthrene	Colourless	66.1			1.265		
Benzo[e]pyrene	Pale yellow	178.7	493	7.4×10^{-7}		6.44	5.07 (23 °C)
Benzo[ghi]fluoranthene	Yellow	128.4	432		1.345^{23}		
Benzo[ghi]perylene	Pale yellow-green	278.3	545	1.4×10^{-8}	1.329^{20}	7.1	0.26
Benzo[j]fluoranthene	Yellow	165.4	480	2.0×10^{-6}		6.12	2.5
Benzo[k]fluoranthene	Pale yellow	215.7	480	1.3×10^{-8}		6.84	0.76
Chrysene	Colourless with blue fluoresence	253.8	448	8.4×10^{-5} (20°C)	$1.274^{20/4}$	5.91	2
Coronene	Yellow	439	525	2.0×10^{-10}	1.371		5.4
Cyclopenta[cd]pyrene	Orange	170	439				
Dibenzo[ae]pyrene	Pale yellow	244.4	592				
Dibenz[ah]anthracene	Colourless	266.6	524	1.3×10^{-8} (20°C)	1.282	6.5	0.5 (27 °C)
Dibenzo[ah]pyrene	Golden yellow	317	596				
Dibenzo[ai]pyrene	Greenish-yellowish	282	594	3.2×10^{-10}		7.3	0.17
Fluoranthene	Pale yellow	108.8	375	1.2×10^{-3}	$1.252^{0/4}$	5.22	260
Fluorene	White	115-116	295	9.0×10^{-2}	$1.203^{0/4}$	4.18	1.98×10^{3}
Indeno[l,2,3-cd]pyrene	Yellow	163.6	536	1.3×10^{-8} (20°C)		6.58	62
5Methylchrysene		117.1	458				62 (27 °C)
1-Methyl-phenanthrene	Colourless	123	354-355			5.07	255 (24 °C)
Naphthalene	White	81	217.9	10.4	1.154^{25}	3.4	3.17×10^{4}
Perylene	Yellow - colourless	277.5	503		1.35	5.3	0.4
Phenanthrene	Colourless	100.5	340	1.6×10^{-2}	0.98^{4}	4.6	1.29×10^{3}
Pyrene	Colourless	150.4	393	6.0×10^{-4}	$1.271^{23/4}$	5.18	135
Triphenylene	Colourless	199	425		1.3	5.45	43

a When two temperatures are given as superscript, they indicate the specific gravity (the density of the substance at the first reported temperature relative to the density of water at the second reported temperature. When there is no value, or only one, for temperature, the datum is in gram/mL, at the indicated temperatur, if any.

b log K_{ow}, n-octanol:water partition coefficient.

D4 Methods of analysis for determining PAH in the air (reproduced from IPCS, 1998)[70]

Matrix	Sampling, extraction	Clean-up	Analysis	Limit of detection[a]	References
Ambient air	Sampling on GF+PUF, at 45 m^3/h; Soxhiet extraction with cyclohexane	Liquid-liquid partition with cyclohexane: H_2O:DMSO, then CC with SiO_2	GC/MS		Yamasaki *et al*. 1982
	Sampling on GF+PUF, at 30 m^3/h; Soxhiet extraction with petroleum ether (GF) and DCM (PUF)	CC with Al_2O_3 + SiO_2	HPLC/FL	0.01-0.7 ng/m^3	Keller and Biddleman, 1984
	Sampling on GF (particle diameter < 15 mm), at 68 m^3/h; Soxhiet extraction with cyclohexane, DCM, and acetone	TLC with SiO_2	HPLC/UV + FL	0.01-0.3 ng/m^3	Greenberg *et al*. 1985
	Sampling on GF at 83 m^3/h; sonication (cyclohexane)	TLC with SiO_2	GC/FID		Valerio *et al*. 1992
Indoor air	Sampling on GF (particle diameter <10 μm) at 10 L/min; sonication (cyclohexane)	TLC with acetyloxylated cellulose	Spectrofluo-rescence only (benzo[a]yrene)		Lioy *et al*. 1988
	Sampling on quartz-fibre filtre and XAD-4 at 226 L/min; Soxhlet extraction with DCM		GC/MS		Chuang *et al*. 1991
	Sampling on PTFE-coated GF at 20 L/min for 24 h; Soxhlet extraction with DCM	Filtration; then CC	HPLC/FL	0.02-0.12 ng/m^3 [b]	Daisey and Gundel, 1993
	Sampling on GF and PUF, at 20 L/min for 24 h; Soxhlet extraction (10% ether: n-hexane)		GC/FID, GC/MS or HPLC/UV + FL		US EPA, 1990
Workplace air	Sampling on PTFE filter and XAD-2 at 2 L/min; sonication or Soxhlet extraction of filter[c], extraction of XAD-2 with toluene (for GC) or acetonitrile (for HPLC)		GC/FID HPLC/UV + FL	0.3-0.5 μg per sample 0.05-0.8 μg per sample	NIOSH, 1994
	Sampling on filter (GF, quartz fibre, PTFE or silver membrane) at 2 L/min; sonication or Soxhlet extraction with cyclohexane or toluene	CC (XAD-2)	GC/FID	approx 0.5 μg/m^3	GRC, 1991

GC glass fibre; PUF, polyurethane foam; DMSO, dimethyl sulfoxide; CC, column chromatography; GC, gas chromatography;MS, mass spectrometry; DCM, dichloromethane; HPLC, high-performance liquid chromatography; FL, fluorescence detection; TLC, thin-layer chromatography; UV, ultraviolet detection; FID, flame-ionization detection; DMF, N-dimethylformamide; PTFE, polytetrafluoroethylene.

[a] Various PAH.

[b] The following PAH can be determined: fluoranthene, pyrene, chrysene, benzo[e]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[ghi]perylene, indeno[l,2,3-cd]pyrene.

[c] Appropriate solvent must be determined by recovery tests on specific samples.

D5 Some polycyclic aromatic hydrocarbons required or recommended for determination by various authorities (partly reproduced from IPCS, 1998)[70]

PAH	A	B	C	D	E	F	G	
					Health	Environ-ment		
Acenapthene		X					X	X
Acenapthylene		X					X	
Anthracene		X	X			X	X	
Anthanthrene					X	X		X
Benz[a]anthracene		X	X	X	X	X	X	
Benzo[a]fluorene			X					X
Benzo[a]pyrene	X		X	X	X	X	X	
Benzo[b]fluoranthene	X	X	X	X	X	X	X	X
Benzo[b]fluorene			X					X
Benzo[c]phenanthrene					X	X		
Benzo[e]pyrene			X				X	
Benzo[ghi]perylene	X	X	X		X	X	X	
Benzo[j]fluoranthene		X		X	X	X	X	
Benzo[k]fluoranthene	X	X	X	X	X	X	X	
Chrysene		X	X		X	X	X	X
Cyclopenta[a]pyrene					X	X		X
Dibenzo[a,e]pyrene			X		X	X		
Dibenz[a,h]anthracene		X	X	X	X	X	X	
Dibenzo[a,h]pyrene			X		X	X		X
Dibenzo[a,i]pyrene			X		X	X		
Dibenzo[a,l]pyrene						X		
Fluoranthene	X	X	X			X	X	
Fluorene		X					X	X
Indeno[1,2,3-cd]pyrene	X	X	X	X	X	X	X	X
Naphthalene		X				X		X
Phenanthrene		X	X			X	X	
Pyrene		X	X			X	X	X
Triphenylene								X

A Recommended by WHO and required by an EEC Directive.
B Required by the US Environmental Protection Agency for the analysis of municipal and industrial wastewater
C Recommended by the European Aluminium Association, Environmental Health and Safety Secretariat.
D Recommended by the Italian National Advisory Toxicological Committee for health-related studies.
E Recommended at the International Workshop on polycyclic aromatic hydrocarbons (State Pollution Control Authority and Norwegian Food Control Authority, 1992) for studies on health and environment.
F Selected by the US Agency for Toxic Substances and Disease Registry.
G Routinely monitored by the Rijksinstituut voor de Volksgezondheid en Milieuhygiene (Dutch State Institute for Public Health and Environmental Hygiene). The method required by the US Environmental Protection Agency for the analysis of municipal and industrial wastewater covers the determination of 16 ‘priority pollutant PAH’ considered to be representative of the class. Outside the USA, this list of compounds is often taken as a reference list for the analysis of various environmental matrices.

For complete references, see IPCS (1998)[70].

Annex **E**

PAH release and emission profiles

Table E1 Benzo[a]pyrene emissions from coal-derived sources in the United Kingdom (1990-2010; data retrieved from EC, 2001)[36].

	1990		2010 (estimated)	
	emission (tonnes)	% contribution to total BaP	emission (tonnes)	% contribution to total BaP
Aluminium production	1.9	2.4	0.03	0.2
Anoda baking	22.7	28.3	1.0	5.9
Coke production	1.3	1.6	1.1	6.7
Industrial coal combustion	6.3	7.8	3.8	23.3
Domestic coal combustion	5.3	6.6	1.9	11.3

% contribution of total BaP is based on emission data from various souces (coal-, petroleum-, and wood-derived sources), as presented in the EC position paper).

Table E2 Anthropogenic PAH and BaP emission estimates from a few European countries (tonnes/ year; data retrieved from EC, 2001)[36]. The anthropogenic sources include domestic, mobile, industrial and agricultural sources.

	PAH[a]	BaP[b]
The Netherlands	184	2.29
France	3.479	26.4
Germany	420	26.4
Italy	694	13.9
United Kingdom	1.437	12.0

a PAH refers to the "Borneff six" (*i.e.*, BaP, benzo[*b*]fluoranthene, benzo[*ghi*]perylene, benzo[*k*]fluoranthene, fluoranthene, and indeno[1,2,3-*c,d*]perylene). Source: UBA Berlin 1997.

b The reference year is 1995, or for some countries 1993 or 1994. Source: Pacyna *et al*. 1999.

Tabel E3 Correlation between the concentrations of benzo[a]pyrene and the concentrations of other PAH, and the confidence interval of the ratio's between these concentrations assuming a log-normal distribution (De Raat *et al*. 1994)[96,97].

PAH	r	5%	m	95%	95%/μ
phenanthrene	0.83	0.4	2.33	13.69	5.9
anthracene	0.83	0.05	0.12	0.31	2.6
pyrene	0.71	0.14	1.51	15.64	10.4
fluoranthene	0.57	1.39	3.89	10.83	2.8
benzo[e]pyrene	0.84	0.21	1.07	5.47	5.1
benzo[k]fluoranthene	0.97	0.49	0.77	1.22	1.6
benzo[b]fluoranthene	0.96	1.14	1.93	3.25	1.7
chrysene	0.88	1.03	2.13	4.4	2.1
anthanthrene	0.9	0.06	0.15	0.39	2.6
benzo[ghi]perylene	0.95	0.96	1.84	3.52	1.9
perylene	0.98	0.13	0.19	0.28	1.5
indeno[c,d]pyrene	0.98	0.84	1.43	2.44	1.7
trifenylene	0.81	0.64	1.71	4.58	2.7

The expression 95%/μ indicates a factor by which the concentration of each PAH would be over- or underestimated at the limits of the confidence intervals (95%).

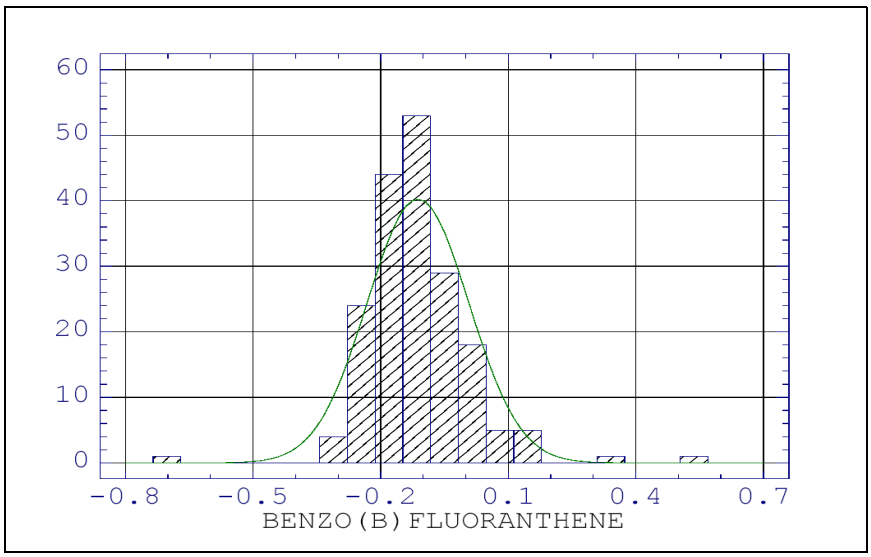


Figure E1. The distribution of the ratios between the concentrations of benzo[b]-fluoranthene and benzo[a]pyrene in about 200 samples taken outdoor (De Raat *et al*. 1994)[96,97].

Table E4 Mean PAH profiles in ambient air and corresponding confidence ranges (CR) relative to benzo[a]pyrene (reproduced from IPCS, 1998)[70].

compound	point source		near mobile source		home heating		transport		geometric mean	
		CR		CR		CR		CR		CR
anthracene	5.5	2.8	7.6	5.7	1.0	6.7	1.8	2.0	2.9	6.2
phenanthrene	38.0	2.3	200.0	1.7	39.0	2.6	43.0	1.4	60.0	34.2
fluoranthene	14.0	2.2	48.0	1.5	12.0	1.7	13.0	1.4	18.0	7.8
pyrene	9.3	2.4	28.0	1.4	11.0	1.7	7.1	1.4	12.0	111.7
benz[a]anthracene	1.4	2.0	0.8	1.4	1.0	1.5	0.8	1.2	1.0	
perylene	0.3	2.7	0.3	1.3	0.2	1.2	0.2	1.9	0.3	1.6
benzo[e]pyrene	1.5	2.8	1.3	1.3	1.6	1.6	1.4	1.1	1.4	26.0
benzo[ghi]perylene	1.4	2.5	1.5	1.5	2.4	1.6	1.3	1.2	1.6	3.7
indeno[c,d]pyrene	1.5	1.3	1.3	1.4	1.5	1.8	1.4	1.2	1.4	2.9
anthanthrene chrysene	0.2	2.0	0.2	3.4	0.1	1.8	0.2	41.0	0.2	6.5
and triphenylene	3.0	2.1	2.7	1.3	3.5	2.0	2.9	1.3	3.0	0.04/7.2
benzofluoranthenes	3.6	2.5	2.9	1.3	3.6	1.9	4.4	1.3	3.6	2.5/2.9

Table E5 PAH profiles of a number of emissions relative to benzo[a]pyrene from coal-derived sources.

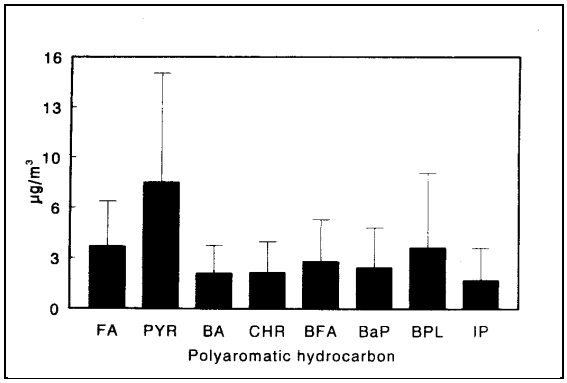
Sample	A	B	C
phenanthrene	0.5	1.4	50
anthracene	0.2	0.8	5
fluoranthene	4.5	0.1	267
chrysene	0.1	0.8	83
pyrene	0.4	6.2	20
benz[a]anthracene		0.4	62
benzo[e]pyrene	0.2	0.6	17
benzo[a]pyrene	1.0	1.0	1
perylene			
benzo[k]fluoranthene	0.0	1.0	72
benzo[b]fluoranthene	0.9	1.4	
indeno[c,d]pyrene	0.0	0.9	1
benzo[ghi]perylene	3.8	5.7	5
anthanthrene			2

Values indicate a relative measure, which is determined by dividing the concentration of the PAH by the concentration of benzo[a]pyrene.

A flue gas of a coal-fired power plant, particulate matter, condensate, and volatiles (Olsen *et al*. 1984).

B flue gas of a coal-fired power plant, particulate matter, condensate, and volatiles (Olsen *et al*. 1984).

C anthracite-fired residential furnac; no information about sampling (Baek *et al.* 1991)[11].



Abbreviations:
FA, fluoranthene;
PYR, pyrene;
BA, benzo[a]anthracene;
CHR, chrysene;
BFA, benzo[bjk]fluoranthene;
BaP, benzo[a]pyrene;
BPL, benzo[ghi]perylene;
IP, indeno[1,2,3-c,d]pyrene.

Figure E2 Average PAH profile of the particulate phase of the air in an aluminium plant anode factory. The columns represent averages and the bars standard deviations (reproduced from Van Schooten, 1995[118].

Table E6 Confidence ranges[a] for polycyclic aromatic hydrocarbons in various combustion mixtures relative to benzo[a]pyrene (reproduced from IPCS, 1998)[70].

Compound	Coke ovens	Coal-tar	Coal-fired power plant	Coal stove
Anthracene	3.2	440	830	
Phenanthrene	1.3	32	27	
Fluoranthene	2.7	4.5	3.2	43
Pyrene	2.6	280	37	18
Benz[a]anthracene	19		2.8	32
Perylene	2.3	27		23
Benzo[e]pyrene	1.3	5.5	3.3	35
Benzo[ghi]perylene	8.8			12
Dibenz[a,h]anthracene				310
Coronene	7.8			7.1
Indeno[l,2,3-cd]pyrene				7.4
Anthanthrene	8.7			
Chrysene and triphenylene	2.1	12	430	42
Benzofluoranthenes	5.7		2.0	28

[a] Confidence ranges are a measure of the range of the means of the relative levels (95% confidence). The range is determined by dividing the upper confidence limit by the lower confidence limit.

Annex **F**

Occupational exposure

Table F1 Exposure data of PAH in coke-ovens from stationary and personal air sampling. Exposure levels are expressed in µg/m^3.

Sampling	Stationary	Personal	Personal	Personal	Personal	Personal	Personal
Country	Germany	Finland	Italy	Italy	Sweden	UK	USA
Year of publication	1983	1995	1993	1993	1983	1986	1986
Source	[1]	[2]	[3]	[4]	[5]	[6]	[7]
BaP	0.9 - 89	0.01 - 23	0.03 -13	0.9 - 46	38	0.1 - 29	7.3
anthanthrene	0.2 - 17						2.4
anthracene					55		16
benz[a]anthracene	1.2 - 120		0.11 - 33		96		7.5
benzo[a]fluorene					70		3.7
benzo[b]fluorene						4.3	
benzo[b]fluoranthene					42		
benzo[c]phenanthrene	0.4 - 37					1.4	
benzo[c]pyrene	0.7 - 79						
benzo[ghi]perylene	0.4 - 27						4.4
benzo[k]fluoranthene					42		
chrysene			0.08 -13		72		
cyclopenta[cd]pyrene	0.2 - 21						1.9
fluoranthene	2.7				144		22
fluorene					109		14
naphtalene					650		
perylene	0.2 - 14						1.8
phenanthrene					195		49
pyrene	1.9 - 170			2.4 - 99			17

[1] Manz *et al*. 1983 ; [2] Yrjänheikki *et al*. 1995; [3] Assennato *et al*. 1993; [4] Cenni *et al*. 1993; [5] Andersson *et al.* 1983, one sample; [6] Davies *et al.* 1986; [7] Haugen et al. 1986). Data adapted from IPCS, 1998[70].

Table F2 Exposure data of PAH in aluminium production from stationary and personal air sampling. Exposure levels are expressed in μg/m^3.

Sampling	Stationary	Personal	Personal
Industry	Smelter	Söderberg	Söderberg
Country	N Zealand	Sweden	?
Year of publication	1985	1983	1993
Source	[1]	[2]	[3]
BaP	0.19 - 4.4		< 1.0 - 48
anthracene		2.8	
benzo[a]fluorene		2.8	
benzo[e]pyrene	0.1 - 2.6		
benzo[ghi]perylene	0.12 - 3.3		
fluoranthene		20	
fluorene		28	
naphtalene		<1.0	
perylene	0.05 - 1.5		
phenanthrene		27	
pyrene			3.5 - 130

[1] Swallow and van Noort 1985; [2] Andersson *et al.* 1983; [3] Ny *et al.* 1993. Adapted from IPCS (1998)[70].

Table F3 Exposure data of PAH in steel foundries from stationary and personal air sampling. Exposure levels are expressed in μg/m^3.

Sampling	stationary	stationary	personal	personal
Country	Canada	Germany	Denmark	Finland
Year of publication	1977	1986	1994	1994
Source	[1]	[2]	[3]	[4]
BaP	0.05 - 0.15	0.47	0.02	0.002 - 0.06
anthanthrene		0.64		
anthracene		2.31	0.05	
benz[a]anthracene	0.01 - 0.22	0.67	0.01	
benzo[a]fluorene		0.48		
benzo[b]fluorene		0.41		
benzo[b]fluoranthene			0.003	
benzo[e]pyrene		0.48		
benzo[ghi]perylene		0.72	0.05	
benzo[k]fluoranthene	0.04 - 0.46		0.02	
chrysene			0.02	
fluoranthene		1.56	0.13	
fluorene			0.08	
naphtalene			9.68	
perylene		0.21		
phenanthrene		4.46	0.32	
pyrene		1.74	0.01	

[1] Gibson *et al*. 1977; [2] Knecht *et al.* 1977; [3] Omland *et al*. 1994; [4] Perera *et al.* 1994; Adapted from IPCS (1998)[70].

Annex **G**

Dermal absorption

Withey *et al.* (1993)[138]

Table G1 Cumulative excretion (mean SD) of pyrene equivalents following dermal uptake by rats of ^{14}C-labelled pyrene.

Route	Dose (mg/kg bw)	Days post dosing / Mean percentage applied dose excreted (± SD)					
		1	2	3	4	5	6
Urine	2	6.6 (2.3)	16.8 (1.0)	20.0 (1.2)	21.6 (1.0)	22.3 (1.1)	22.7 (1.2)
	6	6.8 (2.8)	15.9 (4.4)	19.4 (3.5)	21.1 (3.1)	22.4 (2.8)	22.9 (2.6)
	12	3.7 (0.3)	9.0 (1.4)	14.3 (2.5)	17.2 (2.6)	18.9 (2.9)	19.6 (3.0)
Feces	2	1.8 (0.8)	14.3 (0.3)	19.0 (0.5)	22.1 (0.9)	23.6 (1.7)	24.0 (1.9)
	6	6.3 (1.5)	17.2 (2.3)	20.6 (1.9)	22.7 (1.9)	23.6 (1.7)	23.9 (1.8)
	15	3.6 (1.3)	17.8 (0.6)	25.1 (2.9)	28.9 (2.8)	31.3 (2.9)	32.6 (3.0)
Combined	2	8.4 (1.8)	31.0 (1.3)	39.1 (1.7)	43.6 (1.8)	45.9 (2.8)	46.7 (3.1)
	6	13.1 (2.6)	33.1 (3.8)	40.0 (2.5)	43.8 (2.3)	45.9 (2.1)	46.8 (1.8)
	15	7.3 (1.6)	26.8 (1.0)	39.3 (1.4)	46.1 (2.2)	50.2 (2.1)	52.2 (1.9)

Three rats were used for each dose group and each time group.

Table G2. Percent ratio of metabolites to total [^{14}C]pyrene concentrations in the tissues of dermally exposed rats.

Time (days)	Dose (mg/kg)	Mean values (± SD) for the percent ratio									
		Blood	Brain	Heart	Lungs	Liver	Spleen	Kidneys	Testes	Fat	Muscle
1	2	46.9 (2.4)	60.3 (5.2)	60.1 (0.9)	63.8 (3.6)	70.6 (3.9)	49.8 (4.2)	85.3 (3.3)	61.4 (6.1)	46.3 (4.5)	69.9 (5.4)
	6	21.8 (9.6)	52.7 (9.3)	61.9 (5.7)	61.6 (4.4)	65.3 (2.9)	41.0 (7.7)	76.2 (3.0)	60.2 (9.8)	19.7 (10.6)	66.3 (7.2)
	15	50.0 (3.9)	47.6 (13.5)	52.2 (13.1)	38.4 (4.3)	59.8 (0.9)	54.6 (13.7)	78.5 (2.0)	49.2 (2.6)	21.6 (5.4)	59.4 (3.3)
2	2	42.3 (7.4)	71.7 (7.2)	74.7 (11.9)	71.1 (5.0)	81.9 (1.9)	73.1 (1.7)	84.7 (1.8)	67.6 (6.9)	45.9 (0.0)	71.1 (6.3)
	6	44.9 (11.1)	74.8 (4.0)	75.2 (5.8)	75.9 (12.7)	68.7 (13.6)	73.9 (4.5)	85.0 (6.0)	71.2 (6.8)	30.4 (4.4)	86.9 (2.8)
	15	42.8 (1.6)	36.1 (8.1)	77.0 (2.8)	59.6 (0.8)	61.8 (2.4)	53.2 (5.7)	82.6 (3.6)	43.5 (8.8)	17.3 (4.8)	53.3 (10.4)
4	2	55.3 (7.4)	83.4 (2.9)	83.8 (1.3)	85.9 (0.9)	84.5 (3.6)	72.0 (6.3)	87.5 (1.7)	87.1 (——)	45.9 (5.2)	69.4 (——)
	6	43.0 (3.1)	76.7 (5.8)	82.6 (3.5)	75.8 (5.0)	83.9 (4.8)	77.8 (6.0)	83.0 (6.2)	84.1 (2.2)	49.4 (5.3)	88.6 (2.4)
	15	42.2 (9.1)	72.5 (8.4)	72.2 (5.7)	66.8 (5.8)	64.6 (5.4)	47.2 (13.0)	77.0 (2.7)	76.0 (1.2)	27.8 (3.0)	62.2 (10.1)
6	2	-	-	-	-	-	-	-	-	39.6 (3.2)	-
	6	62.8 (1.9)	-	-	84.5 (1.9)	85.9 (2.7)	88.1 (1.2)	86.5 (2.8)	-	25.0 (9.1)	86.3 (6.3)
	15	74.2 (1.9)	19.4 (2.5)	52.9 (7.5)	63.3 (2.9)	65.0 (4.2)	59.1 (2.6)	64.0 (2.4)	75.9 (14.1)	16.9 (8.5)	61.3 (6.3)

Table lists means and, between brackets, standard deviations. Metabolite concentrations were assumed to be equal to the difference between [^{14}C]pyrene and "free" pyrene. —— Fewer than three values or pyrene concentration below detectable levels.

Van Rooij *et al.* (1995)[110]

Table G3 The absorbed amount of 10 PAH through pig ear skin (in pmol/cm^2) during 200 min after coal tar application[a].

PAH	Ear 1	Ear 2	Ear 3	Ear 4	Ear 5	Relative amount[b]	SD
Fluorene	384	222	489	2377	566	9.5[c]	3.9
Phenanthrene	439	334	915	1623	929	12.0[c]	3.8
Anthracene	55	47	131	302	157	1.8[c]	0.5
Fluoranthene	36	23	122	59	164	1.6	0.7
Pyrene	26	43	67	193	70	1	
Benzo[b]fluoranthene	4	13	5	<0.1	<0.1	<0.11[c]	0.1
Benzo[k]luoranthene	1	1	<0.4	<0.1	<0.1	<0.02	0.02
Benzo[a]pyrene	9	13	<1	<0.1	<0.1	<0.13[c]	0.2
lndeno[1,2,3-cd]pyrene	<1	<0.2	<0.7	<0.3	<0.1	<0.01[c]	0.02
Dibenz[a,h]anthracene	<2	<2	<2	<2	<0.1	<0.03[c]	0.03

[a] Dose: 7.7, 8.3, 17.5, 10.1 and 17.5 mg/cm^2 on ears 1, 2, 3, 4 and 5, respectively.
[b] Related to pyrene, mean value (n = 5).
[c] Statistically different from 1 (p<0.01).

Sartorelli *et al.* (1999)[113]

Table G4 K_p values, steady state fluxes and lag time of PAH (mean SD) applied in acetone solution with artificial sweat.

	Dose applied (nmol/cm^2)	K_p (cm/h)	Flux (nmol cm^2 h^{-1})	Lag time (h)
In aceton solution with artifical sweat				
Naphthalene	160.0	(6.31 ± 2.49) x 10^{-3}	1.0107 ± 0.3981	1.18 ± 0.01
Acenaphthene	120.0	(7.80 ± 4.10) x 10^{-3}	0.9684 ± 0.5996	2.34 ± 2.31
Fluorene	23.1	(6.56 ± 5.33) x 10^{-3}	0.1455 ± 0.1138	4.23 ± 3.99
Anthracene	15.1	(3.97 ± 2.82) x 10^{-3}	0.0526 ± 0.0297	12.85 ± 7.18
Phenanthrene	12.1	(2.63 ± 0.74) x 10^{-3}	0.0319 ± 0.0089	10.95 ± 7.62
Pyrene	9.3	(4.13 ± 4.36) x 10^{-3}	0.0387 ± 0.0416	24.46 ± 2.68
Benzo[a]anthracene	8.5	(1.72 ± 2.60) x 10^{-3}	0.0142 ± 0.0215	27.14 ± 8.28
Chrysene	6.5	(0.57 ± 0.43) x 10^{-3}	0.0035 ± 0.0025	23.79 ± 2.25
Benzo[b]fluoranthene	16.5	(0.09 ± 0.04) x 10^{-3}	0.0014 ± 0.0006	22.46 ± 21.12
Benzo[k]fluoranthene	6.3	(0.09 ± 0.04) x 10^{-3}	0.0006 ± 0.0002	23.80 ± 25.70
Benzo[a]pyrene	6.1	(0.23 ± 0.20) x 10^{-3}	0.0014 ± 0.0012	31.21 ± 10.81
Dibenz[a,h]anthracene	7.5	*	*	*
Benzo[ghi]perylene	6.9	*	*	*
In lubricating oil				
Naphthalene	160.0	(1.87 ± 0.31) x 10^{-3}	0.2740 ± 0.2189	4.86 ± 7.99
Acenaphthene	120.0	(1.72 ± 1.76) x 10^{-3}	0.2255 ± 0.2432	8.37 ± 3.44
Fluorene	23.1	(1.64 ± 1.66) x 10^{-3}	0.0363 ± 0.0355	5.70 ± 3.02
Anthracene	15.1	(0.93 ± 0.98) x 10^{-3}	0.0120 ± 0.0112	17.55 ± 4.73
Phenanthrene	12.1	(0.50 ± 0.28) x 10^{-3}	0.0060 ± 0.0035	15.15 ± 3.10
Pyrene	9.3	(0.17 ± 0.04) x 10^{-3}	0.0015 ± 0.0003	13.38 ± 8.91
Benzo[a]anthracene	8.5	*	*	*
Chrysene	6.5	(0.22 ± 0.12) x 10^{-3}	0.0015 ± 0.0008	26.12 ± 3.34
Benzo[b]fluoranthene	16.5	*	*	*
Benzo[k]fluoranthene	6.3	*	*	*
Benzo[a]pyrene	6.1	*	*	*
Dibenz[a,h]anthracene	7.5	*	*	*
Benzo[ghi]perylene	6.9	*	*	*

* Below the detection limit.

Yang *et al.* (1989)[141]

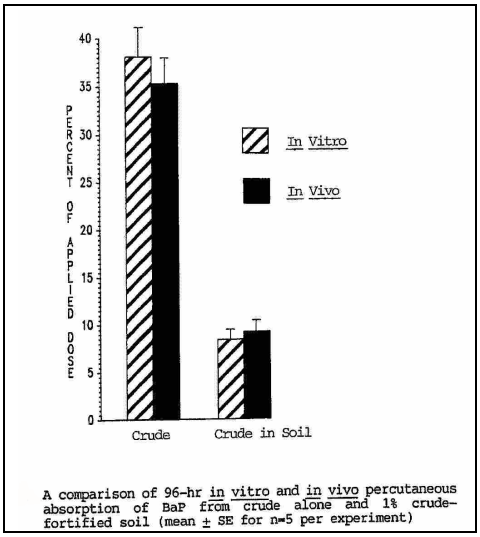


Figure G1 A comparison of 4 days in vitro and in vivo percutaneous absorption of BaP from crude alone and 1% crude-fortified soil (mean ± SE; n=5/experiment).

Annex **H**

Carcinogenicity of single PAH

H1 Relative carcinogenic and mutagenic potencies of single PAH

PAH	Carcinogenicity[a]	Mutagenicity[a]
Dibenz[a,h]anthracene	1.11	0.47
Benzo[a]pyrene	1.00	1.00
Anthanthrene	0.320	0.06
Indeno[1,2,3,-cd]pyrene	0.232	0.14
Benz[a]anthracene	0.145	0.62
Benzo[b]fluoranthene	0.141	0.20
Benzo[k]fluoranthene	0.066	
Benzo[j]fluoranthene	0.061	
Pyrene	0.081	0.20
Cyclopentadieno[cd]pyrene	0.023	0.26
Benzo[ghi]perylene	0.022	0.08
Chrysene	0.0044	0.37
Benzo[e]pyrene	0.004	0.42

[a] BaP set equal to 1.00, other PAH were scaled to BaP. Adapted from Collins *et al*. (1991)[26].

H2 Relative potencies of single PAH (benzo[a]pyrene=1.0)

Compound	[1]	[2]	[3]	[4]	[5]	[6]	[7]
1-Methylphenanthrene	-	-	0.001	-	-	-	-
Acenaphthene	-	0.001	0.001	0.001	0	-	-
Acenaphthylene	-	0.001	0.001	0.01	-	-	-
Anthanthrene	0.320	-	-	-	-	-	0.28
Anthracene	-	0.01	0.01	0.01	-	-	-
Benz[a]anthracene	0.145	0.1	0.1	0.1	0.1	0.1	0.014
Benzo[a]pyrene	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Benzo[b]fluoranthene	0.141	0.1	0.1	0.1	0.1	0.1	0.11
Benzo[e]pyrene	0.004	-	0.01	-	-	-	0
Benzo[ghi]perylene	0.022	0.01	0.01	0.01	-	-	0.012
Benzo[j]fluoranthene	0.1	-	-	-	-	0.1	0.045
Benzo[k]fl uoranthene	0.061	0.1	0.1	0.1	0.01	0.1	0.037
Chrysene	0.0044	0.01	0.01	0.01	0.001	0.1	0.026
Coronene	-	-	0.001	-	-	-	-
Cyclopenta[cd]pyrene	0.023	-	0.1	-	-	0.1	0.012
Dibenzo[a,e]pyrene	-	-	-	-	-	1	-
Dibenz[a,c]anthracene	-	0.1	-	-	-	-	-
Dibenz[a,h]anthracene	1.11	5	1	1	1	1	0.89
Dibenzo[a,l]pyrene	-	-	-	-	-	100	100
Dibenzo[e]fluoranthene	-	-	-	-	-	-	1
Dibenzo[a,h]pyrene	-	-	-	-	-	0.1	1.2
Dibenzo[a,i]pyrene	-	-	-	-	-	1	-
Fluoranthene	-	0.001	0.001	0.01	-	-	-
Fluorene	-	0.001	0.001	0	-	-	-
Indeno[l,2,3-cd]pyrene	0.232	0.1	0.1	0.1	0.1	0.1	0.067
Naphthalene	-	0.001	0.001	-	-	-	-
Perylene	-	-	0.001	-	-	-	-
Phenanthrene	-	0.001	0.001	0	-	-	0.0006
Pyrene	0.81	0.001	0.001	0.001	-	-	0

[1] Krewski *et al*. 1989; [2] Nisbet and LaGoy 1992; [3] Malcom and Dobson 1994; [4] Kalberlah *et al.* 1995; [5] EPA 1990; [6] McClure and Schoeny 1995; [7] Muller *et al*. 1998, 1995, and 1998 . Source IPCS, 1998[70].
-, not determined.

H3 Classification of PAH

Single PAH

Compound	IARC classification[a]			EPA classification[b]	EU classification[c]	Classification in the Netherlands[d]
	Degree of evidence of carcinogenicity					
	Human	Animal	Overall			
Acenaphtalene	-	-	-	D	-	-
Acenaphtylene	-	-	-	D	-	-
Anthanthrene	ND	L	3	-	-	-
Anthracene	ND	I	3	D	-	-
Benz[a]anthracene	ND	S	2A	B2	2	+
Benzo[b]fluoranthene	ND	S	2B	B2	2	+
Benzo[j]fluoranthene	ND	S	2B	B2	2	+
Benzo[k]fluoranthene	ND	S	2B	B2	2	+
Benzo[ghi]fluoranthene	ND	I	3	-	-	-
Benzo[a]fluorene	ND	I	3	-	-	-
Benzo[b]fluorene	ND	I	3	-	-	-
Benzo[ghi]perylene	ND	I	3	D	-	-
Benzo[c]phenanthrene	ND	I	3	-	-	-
Benzo[a]pyrene	ND	S	2A	B2	2; mut cat 2	+
Benzo[e]pyrene	ND	I	3	C	2	+
Chrysene	ND	L	3	B2	2; mut cat 3	-
Coronene	ND	I	3	-	-	-
Cyclopenta[cd]pyrene	ND	L	3	B2	-	-
Dibenz[a,h]anthracene	ND	S	2A	B2	2	+
Dibenzo[a,e]pyrene	ND	S	2B	B2	-	-
Dibenzo[a,h]pyrene	ND	S	2B	B2	-	+
Dibenzo[a,i]pyrene	ND	S	2B	B2	-	+
Dibenzo[a,l]pyrene	ND	S	2B	B2	-	-
Dibenzo[e,l]pyrene	-	-	-	D	-	-
Dibenzo[a,e]fluoranthene	ND	L	3	B2	-	-
Dibenzo[a,h]fluoranthene	-	-	-	B2	-	-
Dibenzo[a,i]fluoranthene	-	-	-	B2	-	-
Dibenzo[a,l]fluoranthene	-	-	-	B2	-	-
Fluoranthene	ND	I	3	D	-	-
Fluorene	ND	I	3	D	-	-
Indeno[1,2,3-cd]pyrene	ND	S	2B	B2	-	+
5-Methylchrysene	ND	S	2B	-	-	+
1-Methylphenanthrene	ND	I	3	-	-	-
Naphtalene	-	-	-	D/C	3	-
Perylene	ND	I	3	-	-	-
Phenanthrene	ND	I	3	D	-	-
Pyrene	ND	I	3	D	-	-
Triphenylene	ND	I	3	-	-	-

[a] Based on IARC Monographs[57,62]; ND, no adequate data; I, inadequate evidence; L, limited evidence; S, sufficient evidence; Group 1, the compound is carcinogenic to human; Group 2A, the compound is probably carcinogenic to humans; Group 2B, the compound is possibly carcinogenic to humans; Group 3, the compound is not classifiable as to its carcinogenicity to humans.

[b] Classification according to the US EPA[127]: B. Substance probably carcinogenic to humans; B1: Substance having limited epidemiological evidence; B2: Substance having enough evidence based on experiments on animals but insufficient epidemiological evidence; C. Substance with only limited evidence by experiments on animals and possibly carcinogenic to humans; D. Not classifiable as to human carcinogenicity.

[c] Annex I EU Directive no. 67/548/EEG; category 2, this compound should be regarded as carcinogenic to humans; category 3, this compound is a suspected human carcinogen (see also http://ecb.jrc.it/).

[d] Ministry of Social Affairs and Employment, the Netherlands; official list of carcinogenic substances and processes, 2004 (Staatscourant 28 december 2004, nr. 251/pag.26 [in Dutch]; the list includes category 1 and 2 carcinogens obtained from the EU Directive 67/548/EEG, or from DECOS.

- = not evaluated.

PAH mixtures from coal derived sources

CAS no.	EINECS no.	Substance name	EU classification[a]
8001-58-9		Creosote	Carc. Cat. 2
8007-45-2		Tar, coal	Carc. Cat. 1
8030-30-6		Naphtha	Carc. Cat. 2
65996-79-4	266-013-0	Solvent naphtha (coal)	Carc. Cat. 2
65996-82-9	266-016-7	Tar oils, coal	Carc. Cat. 2
65996-83-0	266-017-2	Extracts, coal tar oil alk.	Carc. Cat. 2
65996-84-1	266-018-8	Tar bases, coal, crude	Carc. Cat. 2
65996-85-2	266-019-3	Tar acids, coal, crude	Carc. Cat. 2
65996-86-3	266-020-9	Extract oils (coal), tar base	Carc. Cat. 2
65996-87-4	266-021-4	Extract residues (coal), tar oil alk.	Carc. Cat. 2
65996-88-5	266-023-5	Benzol forerunnings (coal)	Carc. Cat. 2
65996-89-6	266-024-0	Tar, coal, high-temp.	Carc. Cat. 1
65996-90-9	266-025-6	Tar, coal, low-temp.	Carc. Cat. 1
65996-91-0	266-026-1	Distillates (coal tar), upper	Carc. Cat. 2
65996-92-1	266-027-7	Distillates (coal tar)	Carc. Cat. 2
65996-93-2	266-028-2	Pitch, coal tar, high-temp.	Carc. Cat. 2
68187-57-5	269-109-0	Pitch, coal tar-petroleum	Carc. Cat. 2
68937-63-3	273-077-3	Extract oils (coal), tar base, collidine fraction	Carc. Cat. 2
68990-61-4	273-615-7	Tar, coal, high-temp., high-solids	Carc. Cat. 2
73665-18-6	277-567-8	Extract residues (coal), tar oil alk., naphthalene distn. residues	Carc. Cat. 2
84650-02-2	283-482-7	Distillates (coal tar), benzole fraction	Carc. Cat. 2
84650-03-3	283-483-2	Distillates (coal tar), light oils	Carc. Cat. 2
84650-04-4	283-484-8	Distillates (coal tar), naphthalene oils	Carc. Cat. 2
84989-09-3	284-898-1	Distillates (coal tar), naphthalene oils, naphthalene-low	Carc. Cat. 2
84989-10-6	284-899-7	Distillates (coal tar), upper, fluorene-free	Carc. Cat. 2
84989-11-7	284-900-0	Distillates (coal tar), upper, fluorene-rich	Carc. Cat. 2
84989-12-8	284-901-6	Extract oils (coal), acidic, tar-base free	Carc. Cat. 2
85536-17-0	287-498-5	Solvent naphtha (coal), light	Carc. Cat. 2
85536-19-2	287-500-4	Solvent naphtha (coal), coumarone-styrene contg.	Carc. Cat. 2

85536-20-5	287-502-5	Solvent naphtha (coal), xylene-styrene cut	Carc. Cat. 2
90640-86-1	292-607-4	Distillates (coal tar), heavy oils	Carc. Cat. 2
90640-87-2	292-609-5	Distillates (coal tar), light oils, acid exts.	Carc. Cat. 2
90640-88-3	292-610-0	Distillates (coal tar), light oils, alk. exts.	Carc. Cat. 2
90640-89-4	292-611-6	Distillates (coal tar), naphthalene oils, alk. exts.	Carc. Cat. 2
90640-90-7	292-612-1	Distillates (coal tar), naphthalene oils, naphthalene-free, alk. exts.	Carc. Cat. 2
90641-02-4	292-625-2	Extract residues (coal), light oil alk., distn. overheads	Carc. Cat. 2
90641-03-5	292-626-8	Extract residues (coal), light oil alk., indene naphtha fraction	Carc. Cat. 2
90641-06-8	292-629-4	Extract residues (coal), tar oil alk., carbonated, limed	Carc. Cat. 2
90641-12-6	292-636-2	Naphtha (coal), distn. residues	Carc. Cat. 2
90669-57-1	292-651-4	Pitch, coal tar, low-temp.	Carc. Cat. 2
90669-58-2	292-653-5	Pitch, coal tar, low-temp., heat-treated	Carc. Cat. 2
90669-59-3	292-654-0	Pitch, coal tar, low-temp., oxidized	Carc. Cat. 2
90989-38-1	292-694-9	Aromatic hydrocarbons, C-8	Carc. Cat. 2
90989-41-6	292-697-5	Aromatic hydrocarbons, C6-10, C8-rich	Carc. Cat. 2
91082-50-7	293-764-1	Tar, coal, storage residues	Carc. Cat. 2
91082-52-9	293-766-2	Tar bases, coal, lutidine fraction	Carc. Cat. 2
91082-53-0	293-767-8	Tar bases, coal, toluidine fraction	Carc. Cat. 2
91697-23-3	294-285-0	Extract residues (coal), brown	Carc. Cat. 2
91995-20-9	295-281-1	Aromatic hydrocarbons, C8-9, hydrocarbon resin polymn. by-product	Carc. Cat. 2
91995-31-2	295-292-1	Distillates (petroleum), alkene-alkyne manuf. pyrolysis oil, mixed with high-temp. coal tar, indene fraction	Carc. Cat. 2
91995-35-6	295-295-8	Distillates (coal), coal tar-residual pyrolysis oils, naphthalene oils	Carc. Cat. 2
91995-42-5	295-304-5	Distillates (coal tar), heavy oils, pyrene fraction	Carc. Cat. 2
91995-48-1	295-309-2	Distillates (coal tar), naphthalene oils, acid exts.	Carc. Cat. 2
91995-49-2	295-310-8	Distillates (coal tar), naphthalene oil crystn. mother liquor	Carc. Cat. 2
91995-51-6	295-312-9	Distillates (coal tar), pitch, heavy oils	Carc. Cat. 2
91995-52-7	295-313-4	Distillates (coal tar), pitch, pyrene fraction	Carc. Cat. 2
91995-61-8	295-323-9	Extract residues (coal), benzole fraction alk., acid ext.	Carc. Cat. 2
91995-66-3	295-329-1	Extract oils (coal), coal tar-residual pyrolysis oils, naphthalene oil, redistillate	Carc. Cat. 2
92045-71-1	295-454-1	Paraffin waxes (coal), brown-coal high-temp. tar	Carc. Cat. 2
92045-72-2	295-455-7	Paraffin waxes (coal), brown-coal high-temp. tar, hydrotreated	Carc. Cat. 2
92061-92-2	295-505-8	Residues (coal tar), anthracene oil distn.	Carc. Cat. 2
92061-93-3	295-506-3	Residues (coal tar), creosote oil distn.	Carc. Cat. 2
92061-94-4	295-507-9	Residues (coal tar), pitch distn.	Carc. Cat. 2
92062-20-9	295-535-1	Tar, coal, high-temp., distn. and storage residues	Carc. Cat. 2
92062-22-1	295-536-7	Tar acids, brown-coal gasification	Carc. Cat. 2
92062-27-6	295-541-4	Tar bases, coal, aniline fraction	Carc. Cat. 2
92062-28-7	295-543-5	Tar bases, coal, collidine fraction	Carc. Cat. 2
92062-33-4	295-548-2	Tar bases, coal, picoline fraction	Carc. Cat. 2
92062-34-5	295-549-8	Waste solids, coal-tar pitch coking	Carc. Cat. 2
92062-36-7	295-551-9	Aromatic hydrocarbons, C9-12, benzene distn.	Carc. Cat. 2
93821-38-6	298-725-2	Extract residues (coal), benzole fraction acid	Carc. Cat. 2
94114-13-3	302-650-3	Pitch, coal tar, high-temp., secondary	Carc. Cat. 2
94114-29-1	302-662-9	Tar acids, brown-coal, C2-alkylphenol fraction	Carc. Cat. 2

94114-40-6	302-674-4	Tar oils, brown-coal	Carc. Cat. 2
97675-87-1	307-661-7	Hydrocarbons, C17-30, hydrotreated solvent-deasphalted atm. distn. residue, distn. lights	Carc. Cat. 2
97722-06-0	307-755-8	Hydrocarbons, C17-40, hydrotreated solvent-deasphalted distn. residue, vacuum distn. lights	Carc. Cat. 2
97926-76-6	308-296-6	Paraffin waxes (coal), brown-coal high-temp. tar, carbon-treated	Carc. Cat. 2
97926-77-7	308-297-1	Paraffin waxes (coal), brown-coal high-temp tar, clay-treated	Carc. Cat. 2
97926-78-8	308-298-7	Paraffin waxes (coal), brown-coal high-temp tar, silicic acid-treated	Carc. Cat. 2
100684-51-3	309-726-5	Tar, coal, high-temp., residues	Carc. Cat. 2
101316-49-8	309-855-7	Distillates (coal tar), pitch	Carc. Cat. 2
101316-62-5	309-867-2	Extract residues (coal), light oil alk., acid ext., indene fraction	Carc. Cat. 2
101316-63-6	309-868-8	Extract residues (coal tar), benzole fraction alk., acid ext.	Carc. Cat. 2
101316-83-0	309-885-0	Tar, brown-coal	Carc. Cat. 1
101316-84-1	309-886-6	Tar, brown-coal, low-temp.	Carc. Cat. 1
101316-85-2	309-887-1	Tar, coal, low-temp., distn. residues	Carc. Cat. 2
101316-86-3	309-888-7	Tar acids, brown-coal, crude	Carc. Cat. 2
101316-87-4	309-889-2	Tar oils, coal, low-temp.	Carc. Cat. 2
101794-74-5	309-956-6	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polyethylene-polypropylene pyrolysis-derived	Carc. Cat. 2
101794-75-6	309-957-1	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polyethylene pyrolysis-derived	Carc. Cat. 2
101794-76-7	309-958-7	Aromatic hydrocarbons, C20-28, polycyclic, mixed coal-tar pitch-polystyrene pyrolysis-derived	Carc. Cat. 2
101794-90-5	309-971-8	Distillates (coal tar), light oils, neutral fraction	Carc. Cat. 2
101794-91-6	309-972-3	Distillates (coal tar), naphthalene oils, indole-methylnaphthalene fraction	Carc. Cat. 2
101896-26-8	309-984-9	Distillates (coal tar), benzole fraction, BTX-rich	Carc. Cat. 2
101896-27-9	309-985-4	Distillates (coal tar), naphthalene oils, methylnaphthalene fraction	Carc. Cat. 2
121575-60-8	310-162-7	Pitch, coal tar, high-temp., heat-treated	Carc. Cat. 2
121620-46-0	310-165-3	Distillates (coal tar), benzole fraction, distn. residues	Carc. Cat. 2
122070-79-5	310-170-0	Extract oils (coal), coal tar residual pyrolysis oils, naphthalene oils	Carc. Cat. 2
122070-80-8	310-171-6	Extract oils (coal), coal tar residual pyrolysis oils, naphthalene oil, distn. residues	Carc. Cat. 2
122384-78-5	310-191-5	Extract residues (coal), low temp. coal tar alk.	Carc. Cat. 2

[a] Annex I EU Directive no. 67/548/EEG; category 1, substances known to be carcinogenic to man; category 2, this compound should be regarded as carcinogenic to humans (see also http://ecb.jrc.it/).

Annex I

Epidemiological data on carcinogenesis

Note: The complete references of the studies evaluated in annex I1 to I4 are listed at the end of annex I

I1 Summary of cohort-based studies used in the meta-analysis by Armstrong *et al*. (2003, 2004)[5,6]: lung cancer mortality and morbidity

study design and population information	exposure information	mortality / morbidity rates	RR at 100 μg/m^3 BaP years	Ref.
Coke ovens				
Cohort; 1 Norwegian coke plant; follow-up period 1962-1993; n = 888		Standardized incidence ratio (SIR): 0.82 (7 observed, 8.5 expected), 95% CI: 0.33-1.70. Not adjusted for smoking habits.	>1000 (95% CI: 0.01->1000), non-significant risk. Exposure data obtained by proxy.	[16]
Cohort; one French coke plant; follow-up periode 1963-1987; n = 536	Reference, national population of France. Workers were classified by job group.	Standardized mortality ratio (SMR) for all workers: 2.38 (25 observed), p<0.001. Adjusted for smoking habits.	Risk for lung cancer by job group: 1.00 (95% CI: 0.68-1.46), non-significant risk. Exposure data obtained from other sources.	[18]
Cohort; 17 plants; 30 year follow-up; n total = 15,818.	For exposure classes: 1) topside full-time (3.15 mg/m^3 BSM), 2) topside part-time (1.99 mg/m^3 BSM), 3) side of the oven (0.88 mg/m^3 BSM).	Relative risk (RR) of cancer death all workers by weighted exposure index (mg/m^3 BSM-mo): 0 mg/m^3: 1.00 (203/10,497) 1-49: 1.24 (34/1,576), 95% CI: 0.85-1.81 50-199: 1.56 (43/1,062), 95% CI: 1.13-2.27 200-349: 1.95 (56/976), 95% CI: 1.48-2.79 350-499: 2.02 (39/682), 95% CI: 1.55-3.19 500-649: 2.69 (27/348), 95% CI: 1.98-4.57 ≥ 650: 3.13 (56/677), 95% CI: 2.43-4.56. Not adjusted for smoking habits.	1.15 (95% CI: 1.10-1.21), significantly increased risk.	[21]

Cohort; 1 plant; 30 years follow-up, average employment, 18.6 years; n total = 538.		Standardized mortality ratio (SMR): 1.90 (19/538), 95% CI: 1.14-2.96, was not significant compared to control (SMR 1.70, 95% CI: 1.02-2.65). Not adjusted for smoking habits.	1.41 (95% CI: 1.07-1.79), significantly increased risk. Exposure data obtained from other sources.	[30]
Cohort of 6,767 workers was divided in two sub-cohorts: 1) follow-up 1966-1978, n = 1,617, 2) follow-up 1967-1980, n = 1,158	Reference, national population of UK. Cumulative exposure.	Standardized mortality ratio (SMR): - cohort: 1.17 (167 observed), $p<0.01$ - sub-cohort 1: 0.94 (34 observed) - sub-cohort 2: 1.05 (32 observed) Not adjusted for smoking habits. No clear relation with duration of expsure.	Sub-cohort 1: 1.36 (95% CI: 1.04-1.79), non-significant increase. Sub-cohort 2 : 1.19 (95% CI: 0.77-1.85), risk significantly increased. Exposure data obtained by proxy.	[43]
Cohort; several plants; average duration of employment: 16.3 years for oven workers, 23 years for all workers.	Three groups by job title: 1) oven workers, 2) by-product workers, and 3) maintenance.	Observed versus expected deaths according to occupational exposure: Oven workers: 14 versus 10; Never employed as oven workers: 7 versus 13; By-product workers: 4 versus 6; Never employed as by-porduct workers: 17 versus 17. Not adjusted for smoking habits.	0.94 (95% CI: 0.64-1.39), non-significant risk. Exposure data obtained from other sources.	[71]
Cohort; 11 plants; maximum duration of exposure 34 years; n = 2.178.	Job categories.	Standardized mortality rate (SMR) was significantly increased for gas company workers only: 1.28 (15 observed, 11.72 expected). Data were not adjusted for smoking habits.	1.13 (95% CI: 0.85-1.45). Exposure data obtained from other sources.	[78]
Cohort; three plants in the Netherlands; follow-up 1945-1984; n = 5,639.	Job categories. Reference national population of the Netherlands.	Standardized mortality ratio (SMR): 1.29 (62 observed), 95% CI: 0.99-1.66. Data not adjusted for smoking habits.	1.19 (95% CI: 0.97-1.45), non-significant increase. Exposure data obtained from other sources.	[88]
Nested case-control; 1 large iron-stell complex; 10 or more years employed; n total = 196,993 active and retired employees.	Several occupational groups. 610 Cases of lung cancer and 959 controls interviewed.	Lung cancer morbidity (odd ratios) by cumulative total BaP ($\mu g/m^3$ years) exposure: < 0.84 $\mu g/m^3$: 1.1 (72/114), 95% CI: 0.8-1.17 0.85-1.96: 1.6 (117/116), 95% CI: 1.2-2.3 1.97-3.2: 1.6 (96/115), 95% CI: 1.1-2.3 >30: 1.8 (105/117), 95% CI: 1.2-2.5 Adjusted for birth year and smoking habits.	1.33 (95% CI: 1.14-1.56), significantly increased risk.	[97,98]
Coal gas production				
Cohort; 1 gas plant; at least 10 years of employment; n total = 4,908	Three subcohorts: gas furnace workers (I, high exposure), workers in other parts of the plant (II), and white collar workes (III, no exposure). Average BaP concentration of 28 $\mu g/m^3$ (0.9-89 $\mu g/m^3$) (Manz et al, 1983).	Standardized mortality ratio (SMR): (I): 7.28 (83/789), 95% CI: 5.79-9.03 (II): 2.21 (106/3,401), 95% CI: 1.81-2.28 (III): - (7.18): served as standard. Not adjusted for smoking habits.	1.15 (95% CI: 1.12-1.19), significantly increased risk.	[9]

Cohort; 8 gas boards; 8 and 12 year follow-up; original boards: n total = 11,499; additional boards: n total = 4,687	Four exposure classes by job (A (high), B, C1, C2 (minimal or no exposure)). Average: 3 µg/m^3 BaP for all classes (Law65).	Annual death rate per 1,000 men: $A_{12\ yr}$: 3.82 (99/2,499), $p \leq 0.001$ $A_{8\ yr}$: 2.72 (23/1,176) $B_{8\ yr}$: 3.50 (40/1,430), $p \leq 0.01$ $C_{1\ 12\ yr}$: 1.59 (11/579) $C_{2\ 8\ yr}$: 1.08 (16/2,081) Standard all men in England and Wales: 2.13 (12 yr) and 2.03 (8 yr). Not adjusted for smoking habits.	*8 yr survey*: 4.01 (95% CI: 1.16-13.87) *12 yr survey*: 5.82 (95% CI : 1.06-32.00) For both surveys, risk was significantly increased.	24
Cohort; Swedish gas plant; follow-up period 1966-1986; n total = 295.	Reference, local mortality in occupational active men. Average 2.4 µg/m^3 BaP.	Lung cancer mortality by job group: In coke oven department (n=66): no lung cancer. mean length of exposure was 11.9 years. Data not adjusted for smoking habits.	0.00 (95% CI: 0.00-66.56), non-significant URR.	37
Aluminum production				
Case-cohort; 1 plant; employment of at least 1 year; n total = 16,297	From the cohort a subcohort was at random selected of 1,138 men. Several groups by selected jobs. Cumulative exposure to BSM en BaP measured.	Lung cancer mortality (rate ratios) by cumulative exposure (BaP in µg/m^3 years): <10 µg/m^3: 1.0 10-99: 1.48 (95%CI: 1.09-2.00) 100-199: 2.23 (95%CI: 1.46-3.39) 200-299: 2.10 (95%CI: 1.40-3.15) ≥ 300: 1.87 (95%CI: 1.05-3.33) Adjusted for smoking habits.	1.22 (95% CI: 1.09-1.37), risk significantly increased.	7
Cohort; 1 prebake-type aluminium reduction plant; 30 years of follow-up; n total = 2,103	Job-exposure categories, and all workers in one group.	Standardized mortality rates (SMR): All workers: 1.17 (35 observed, 29.8 expected). Not adjusted for smoking habits.	0.19 (95% CI: 0.00->1000), non-significant URR. Exposure data obtained from other sources.	61
Cohort; 1 aluminum reduction plant; employment for at least I year, follow-up period 26 years; n total = 2,133 men		Standardized mortality rates (SMR): 0.63 (95% CI: 0.38-0.98), 19 observed deaths. Not adjusted for smoking habits.	1.11 (95% CI: 0.46-2.66), non-significant URR. Exposure data obtained from other sources.	62
Cohort; 11 plants in France, both prebake and Soderberg processes; follow-up period 1950-1976; n total = 6,455, total of 11,671 person years	Reference, national French population.	Standardized mortality ratio (SMR): 1.14 (37 observed), 95% CI: 0.85-1.48. No correlation with duration of exposure or latency. Not adjusted for smoking habits.	0.69 (95% CI : 0.31-1.54), non-significant URR. Exposure data obtained from other sources.	65
Cohort; 14 American reduction plants with Soderberg and prebake processes; follow-up period 1946-1977; n total = 22,010	Reference, general population of the USA.	Standardized mortality ratio (SMR): All workers, 0.96 (272 observed). Some correlation with duration of exposure and latency. No information on smoking habits.	Soderberg: 1.85 (95% CI: 0.53-6.53) Prebake: 0.06 (95% CI: 0.00-9.58) Exposure data obtained from other sources.	74
Cohort; Norwegian aluminium plants; follow-up period 1953-1996; n total = 11,103 men, total of 272,554 person years	Reference, national Norwegian population. Cumulative exposure of BaP.	There was no association between cumulative exposure to BaP and lung cancer mortality. No data on smoking habits presented.	0.99 (95% CI: 0.79-1.22), not statistically significant.	75

Cohort; 1 Canadian Soderberg plant; follow-up period 1954-1985; n total = 4,213, total of 60,590 person years	Reference, regional rates. Cumulative exposure of coal tar pitch volatiles, measured as BSM: low, <0.2 mg/m^3; medium, 0.2-1.0 mg/m^3; high, > 1 mg/m^3.	Standardized mortality ratio (SMR): 0.93 (32 observed), 95% CI: 0.68-1.25, no change in lung cancer risk. Standardized incidence ratio (SIR): 0.97, no association with BSM exposure. Some information on smoking habits.	1.31 (95% CI: 0.72-2.39), not statistically significant increase in URR. Exposure data obtained by proxy.	87
Carbon electrode production				
Cohort; 1 carbon (graphite) electrode production plant; employment of at least 1 year, follow-up > 40 years; n total = 1,006 males	Reference Italian population.	Standardized mortality rates (SMR): 0.77 (95% CI: 0.53-1.08), 34 death cases observed and 44.2 expected. Not adjusted for smoking habits.	0.18 (95% CI: 0.01-5.61), non-significant URR. Exposure data obtained from other sources.	25
Cohort; 7 Chinese factories; follow-up period 1971-1985; n total = 6,635 male caron workers, total of 95,847 person years	Results reported by 4 BaP exposure levels.	Standardized mortality ratio (SMR): All workers: 2.16, $p<0.01$ All workers, moderately exposed: 1.52, $p>0.05$ All workers, highly exposed: 4.30, $p<0.01$ Non-smokers, moderately exp: 3.00, $p<0.01$ Non-smokers, highly exp: 5.34, $p<0.01$.	53.07 (95% CI: 3.44-819), statistically significant increase.	53
Nested case-control; carbon electrode production plant (plant A); 11 year period; n total = 1,302 workers	BaP concentrations: mean area samples (n=19), 1.90 μg/m^3 (0.34-12.00); mean personal samples (n=16), 2.7 μg/m^3 (0.59-6.2).	Cancer morbidity (standardized incidence ratio): 0.79 (7 observed, 8.82 expected), 95% CI: 0.32-1.63. Adjusted for smoking habits.	2.82 (95% CI: 0.20-40.59),	64
Nested case-control; carbon electrode production plant (plant B); 28 year period; n total = 1,115 workers	BaP concentrations: mean area samples (n=10), 0.46 μg/m^3 (0.18-0.74); mean personal samples (n=7), 0.17 μg/m^3 (0.015-0.57).	Cancer mortality (standardized mortality ratio): 1.18 (13 observed, 11.05 expected), 95% CI: 0.63-2.01. Not adjusted for smoking habits.	0.00 (95% CI: 0.00->1000), non-significant URR	64
Asphalt and tar destillation workers				
Cohort; workers joining union; > 9 years of employment; n total = 5,939 aspaht roofers and waterproofers	BaP inhaled at various roofing occupations per 7-hr working day and by mask: all roofing occupations, 16.7 g BaP (range: not detected – 135.0).	Mortality ratios by attained time since joining union: 9-19 yrs: 0.92 (22 observed, 23.93 expected) 20-29 yrs: 1.52 (66 observed, 43.45 expected) 30-39 yrs: 1.50 (21 observed, 14.02 expected) > 40 yrs: 2.47 (12 observed, 4.85 expected).	5.63 (95% CI: 0.89-35.53), non-significant increase in risk. Not adjusted for smoking habits.	38
Cohort; 679 Danish mastic asphalt workers; follow-up period 1959-1985	Reference, general Danish population. BaP measurements. Primary exposure was bitumen.	Standardized mortality ratio (SMR): 2.9 (25 observed), 95% CI: 1.88-4.29, significant increase. Not adjusted for smoking habits.	189.59 (95% CI: 22.19->1000), statistically significant increase in URR	41

Cohort; asphalt industry; follow-up period 1970-1980; n total = 1,320 unskilled workers	Reference, unskilled workers (n = 43,024) in Denmark.	Standardized mortality ratio (SMR): 1.52, 95% CI: 0.76-2.71. Non-significant increase in respiratory cancer mortality. No information on smoking habits and length of employment.	35.76 (95% CI: 0.13->1000), non-significant increase. Exposure data obtained from other sources.	[40]
Retrospective cohort; local companies; follow-up average 27.8 years; no. of tar distillery workers = 907, no. of roofers = 866.		Standardized mortality ratios (SMR): All workers: 1.23 (87 observed, 70.3 expected), 95% CI: 0.99-1.53 Tar distillery: 1.18 (48 observed, 0.40 expected), 95% CI: 0.87-1.57 Roofers: 1.31 (39 observed, 0.29 expected), 95% CI: 0.93-1.79. Not adjusted for smoking habits.	Roofers: 15.23 (95% CI: 0.50-347), non-significant increase in risk. Tar distillery: 5.32 (95% CI: 0.25-89.38), non-significant increase in risk. Exposure data obtained from other sources.	[89]
Cohort; four tar destillation plants; follow-up > 17 years; n total = 259		Standardized mortality ratio (SMR): 1.60 (12 observed, 7.5 expected), $p>0.05$. Not adjusted for smoking habits.	>1000 (95% CI: 0.04->1000), non-significant increase in risk. Exposure data obtained from other sources.	[56]
Chimney sweeps				
Cohort; follow-up cancer incidence, 1958-1987; follow-up cancer mortality, 1951-1990; no. of chimney sweep is 5,542		Standard Incidence Rate (SIR): - Period 1982-1987: 1.78 (15 observed, 8.5 expected), 95% CI: 0.99-2.93; - Period 1958-1987: 2.09 (50 observed, 23.9 expected), 95% CI: 1.55-2.76). Standard Mortality Rate (SMR): - Period 1983-1990: 1.12 (11 observed, 9.8 expected), 95% CI: 0.56-2.01; - Period 1951-1990: 2.06 (53 observed, 25.8 expected), 95% CI: 1.54-2.69. Not adjusted for smoking habits.	Mortality : 9.88 (95% CI: 0.60-162), non-significant increase. Exposure data obtained from other sources.	[28]
Cohort; mean exposure time of death cases was 30 years; n = 713 Danish chimney sweeps		Mortality ratio: 3.13 (5 Observed, 1.6 expected), $p<0.05$. Not adjusted for smoking habits.	44.63 (95% CI: 1.02-752), risk significantly increased. Exposure data obtained from other sources.	[39]
Thermoelectric power				
Cohort; 1 thermoelectric power plant; follow-up > 25 years; n = 270		Mortality ratio: 1.77 (5 observed, 2.83 expected). Not adjusted for smoking habits.	>1000 (95% CI: 0.00->1000), non-signifiacnt URR. Exposure data obtained from other sources.	[17]
Cohort; 2 traditional electric power plants; follow-up 20 years; n = 406	Also data on exposure duration presented.	Standardized mortality ratio (SMR): 1.71 (9 observed, 5.26 expected), 95% CI: 0.89-2.99. Not adjusted for smoking habits.	0.02 (95% CI: 0.00->1000), non-signifiacnt URR. Exposure data obtained from other sources.	[29]
Retrospective cohort; 2 power plants; foolow-up 16 years; n = 1,307	Reference, standard Italian population.	Standardized mortality ratio (SMR): 1.30 (3 observed, 2.31 expected), 95% CI: 0.26-3.79. Not adjusted for smoking habits.	>1000 (95% CI: 0.00->1000), non-signifiacnt URR. Exposure data obtained from other sources.	[69]

Carbon black production			
Cohort; 4 carbon black producing companies; 60 year observation period; n total = 54,784 person years.	Standardized mortality ratio (SMR): 0.84 (34 observed, 40.8 expected), 95% CI: 0.58-1.14. Not adjusted for smoking habits.	0.00 (95% CI: 0.00->1000), non-signifiacnt URR. Exposure data obtained from other sources.	[73]
Cohort; five UK carbon black manufactories; investigation period 1951-1996; n = 1,147	Standardized mortality ratio (SMR): 1.73 (61 observed, 35.3 expected), 95% CI: 1.32-2.22), $p<0.001$. Not adjusted for smoking habits.	>1000 (95% CI: 0.00->1000), non-significant and very imprecisely estimate of URR. Exposure data obtained by proxy.	[86]

SMR: standardized mortality ratio (no. of cases observed/no. of cases expected).
SIR: Standardized incidence ratio.
CI: confidence interval.

I2 Summary of cohort-based studies on PAH exposure evaluated by IPCS[44], but not included in the meta-analyses of Armstrong *et al*. (2003, 2004)

study design and population information	exposure information	mortality / morbidity rates	outcome and notes	ref.
Coal gas production				
Cohort; 1 plant in Germany; follow-up 1953-1980; no. in cohort 724; controls: n= 3,792 (same plant, not coke-oven), n= 681 (office and administra-tion), and local population (Hamburg).	Median of 8 measurements: - total dust: max. 264 mg/m^3; - BaP: 28 $\mu g/m^3$ (max. 89 $\mu g/m^3$). Some information on smoking habits.	Standardized mortality ratio (SMR) for lung cancer: 3.53 (68 death cases), $p<0.01$. SMR for urinary system: 4.35. No other data given by IPCS.	No correlation with duration of exposure; 88% of workers were less than 10 year exposed.	[59]
Aluminum production				
Cohort; 3 aluminium reduction plants in Canada (Söderberg prebake); follow-up 1950/1951-1977; in cohort I, 5,406 men; in cohort II, 485 men. Local and regional population in the provence of Quebec served as controls.	Occupations were classified as: A, no tar exposure; B, some tar exposure (degree 25%); C, definite tar exposure (degree 100%). Tar refers to the condensated pitch volatiles. No informa-tion on smoking habits.	Standardized mortality ratios in cohort I, never *versus* ever exposed: - lung cancer: 1.02 (30 obs, 29.6 exp) *versus* 1.43 (101 obs, 70.7 exp), $p<0.05$; - bladder cancer: 0.28 (1 obs, 3 exp) *versus* 1.61 (12 obs, 7.5 exp). SMR in cohort II, never *versus* ever exposed: - lung cancer: 2.31 (3 obs, 1.3 exp) *versus* 1.53 (9 obs, 5.9 exp)	Significant increase in lung cancer risk in cohort I. Correlation found with duration of exposure and latency. Number of deaths in cohort II is small.	[32,33]
Cohort; one Norwegian aluminium smelter (Söderberg prebake); follow-up 1953-1991; a total of 1,137 workers, of which 694 were substantially exposed to coal tar pitch volatiles (CTPVs); reference General Noregian population.	Some information on smoking habits.	Standardized incidence ratios for by exposure to CTPVs (> 3 yrs of exposure), n=694: - lung cancer: 1.27 (4 obs, χ^2 0.33) - bladder cancer: 2.38 (4 obs, χ^2 1.57).	Increased risk for lung and bladder cancer.	[76]

Carbon electrodes				
Population-based cohort; employees from Union Carbide Cooporation's carbon based electrode (11 plants); follow-up 1974-1983; 2,219 white males; reference US white male population.	Substantial exposure to pitch, coal tar pitch volatiles, silica, chlorine and asbestos possible.	Standardized mortality ratios: - cancer in respiratory tract: 0.85 (29 obs, 34.3 exp; 95% CI, 0.57-1.21) - cancer in urinary tract: too few cases.		90
Asphalt and tar destillation workers				
cohort; Swedish construction industry; follow-up 1971-1979 to 1985 (average follow-up, 11.5 years); no. of road paving asphalt workers, 2,572; no. of roofers, 704; reference, national Swedish population.	No data on exposure presented.	Standardized mortality ratios: -road paving: lung cancer, 1.10 (7 cases); stomach cancer, 2.01 (5 cases) - roofers: lung cancer, 2.79 (3 cases); stomach cancer, 2.30 (1 case) Standardized incidence ratios: - road paving: lung cancer, 1.24 (8 cases); stomach cancer, 2.07 (6 cases) - roofers: lung cancer, 3.62 (4 cases); stomsch cancer, 1.98 (1 case).	Not significantly increased risks. Follow-up period is too short.	27
Follow-up 1962-1972; number of workers 76; reference national German population and 449 from rubber industry.	PAH: 29 μg/m^3, BaP: 4 μg/m^3; some information on smoking habits.	Number of deaths 4.		80
Creosate impregnation				
Cohort; follow-up period in Sweden 1958-1985, and in Norway 1953-1987; 346 Swedish and 576 Norwegian impregnators, total of 922 subjects; reference group, national Swedish and Norwegian population.	Creosates consist of hundreds of compounds, the main being naphthalene and alkyl homologues. The degree of exposure at the plants was unknown.	Standardized incidence ratio: - Lung cancer: 0.79 (13 observed; 95% CI, 0.42-1.35) - Bladder cancer: 1.11 (10 observed; 95% CI, 0.53-2.04).	Substantial exposure to substances other than PAH possible.	47
Foundries				
Nested case-referent study; male union members, USA, working in iron and/or steel foundries; death reported between 1971-1975; no. of death certificates, 2,990 (2,651 white males; 339 black males); reference general population.	Not given.	Proportional mortality ratio for cancer in traches, bronchus and lung: - white males: 1.44 (224 obs, 155.17 exp), $p<0.01$. - black males: 1.76 (39 obs, 22.1o exp), $p<0.01$.		26
Cohort; Steel foundry, Canada; 439 steel foundry workers and 1,103 non foundry workers; urban population around Toronto served as reference.	BaP: 0.049-0.152 μg/m^3. Coal-tar pitch volatiles: 0.19-0.43 mg/m^3. Respirable dust: 0.69-2.65 mg/m^3.	Standardized mortality ratios for lung cancer: - foundry workers: 2.50 (21 obs, 8.4 exp), p<0.01; - non-foundry workers: 0.66 (11 obs, 16.58 exp).	Correlation with duration of exposure; no correlation between latency and exposure concentration.	34

Cohort and nested case-control study; ferrochromium and stainless steel production plant in France; follow-up 1952-1982; 2,269 foundry workers; reference general population of France.	Not given.	Standardized mortality ratios for cancer in trachea, bronchus and lung: - exposed workers: 2.04 (11 obs, 5.40 exp; 95% CI, 1.02-3.64) - non-exposed workers: 0.32 (1 obs, 3.15 exp; 95% CI, 0.01-1.77).	No clear correlation with duration of exposure and latency.	62
Historical cohort in a stainless steel plant in France; follow-up 1968-1984; in cohort 4,227 workers, in subcohort 477 steel foundry workers; reference general population of France.	Primary exposures include PAH, chrome, nickel, silica and heat.	Standardized mortality ratio for lung cancer: - all workers: 1.32 (39 obs, 29.6 exp; 95% CI, 0.94-1.80) - steel foundry: 2.29 (11 obs, 4.8 exp; 95% CI, 1.14-4.09).		63
Cohort: steel foundry workers in the UK; follow-up 1946-1985; no. in cohort 10,491; reference general population of England and Wales.	Not given. Categories by occupation.	Standardized mortality ratio for lung cancer 1.47 (441 obs, 299.2 exp), $p<0.001$.		84
Cohort; six ferrosilicon and ferromangese plants in Norway, using Söderberg electrodes; follow-up 1953-1982; 6,494 employees; reference total male Norwegian population.	Exposure to PAH (3-49 $\mu g/m^3$) is estimated to be less than in coke plants or aluminium industry. Also sub-stantial co-exposure with (manganese) dust and asbestos.	Standardized incidence ratios: - lung cancer: 0.99 (77 obs, 77.7 exp; 95% CI, 0.78-1.24) - bladder cancer: 0.89 (34 obs, 38.3 exp; 95% CI, 0.62-1.24) - all cancer: 0.94 (634 obs, 674.1 exp; 95% CI, 0.87-1.02).		48
Cohort; Iron and steel foundries in Denmark, including nonferrous foundries; average follow-up 10.7 years (period 1967/69-1980, 1972/74-1980); 5,579 foundry workers; three reference populations used: total Danish population, economically active workers and (un)skilled manual workers.	Job-exposure categories used.	Standardized mortality ratios: - lung cancer: 1.17 (74 obs, control economically active pop.) - urogenital cancer: 1.32 (36 obs, economically active poop.).	Non-significantly increased risk. Misclassification possible.	82
Retrospective cohort study; 1 gray iron foundry in Michigan, USA; follow-up 1950-1984; 8,147 male and 627 female workers; reference US general population.	Not given.	Standardized mortality ratios: *White men*: - Trachea, bronchus and lung cancer: 1.23 (72 obs, 58.8 exp; 95% CI, 0.96-1.54) - Bladder cancer: 0.98 (5 obs, 5.1 exp; 95% CI, 0.32-2.29). *Nonwhite men*: - Trachea, bronchus and lung cancer: 1.32 (67 obs, 50.8 exp; 95% CI, 1.02-1.67) - Bladder cancer: 1.02 (3 obs, 3 exp; 95% CI, 0.20-2.97).	Smoking may be responsible for lung cancer.	4

Nickel and Copper Smelter and Refinery				
Retrospective cohort; Copper Cliff Copper Refinery (CCCR), Ontario, Canada; follow-up > 15 years; subcohort, no. of workers not reported; reference regional population in Ontario.	Laboratory fume generation experiments showed high concentrations of PAH (asphalt > tar > mastic); no information on smoking habits.	Standardized mortality lung cancer ratios: - all exposures: 1.37 (50 obs, 36.5 exp; 95 % CI, 1.02-1.81) - > 5 yr exposure: 1.54 (39 obs, 25.3 exp; 95% CI, 1.10-2.11).	The authors conclude that the significantly elevated lung cancer mortality observed at CCCR was probably due to PAH. The effects of the PAH may have been enhanced by interaction with sulfur-dioxide or particulates.	[94]

SMR: standardized mortality ratio (no. of cases observed/no. of cases expected).
SIR: Standardized incidence ratio.
CI: confidence interval.

I3 Summary of cohort-based studies *not* included by Armstrong *et al.* (2003, 2004) and IPCS (1998)

study design and population information	exposure information	mortality / morbidity rates	outcome and notes	ref.
Coal gas production / coke oven				
Rertospective cohort; two coke oven plants in France; follow-up 1963-1982; 534 male workers; reference French male population.	Three exposure categories according to job task: - on the ovens; - near the ovens; - intermittent on ovens.	Standardizes mortality ratio for workers exposed for > 5 years: - lung cancer: 2.78 (7 observed), not significant; - upper respiratory and alimentary tract: 0.00 (0 observed).	Risk for lung cancer in coke oven workers was increased, although not significant.	[10]
Retrospective cohort; 2 coke plants in the United Kingdom; follow-up 1954-1965; 610 coke oven workers; reference general population.	Not given.	Standardized mortality ratios: - lung cancer: 0.82 (8 obs, 9.75 exp) - bladder & Kidney cancer: 2.52 (3 obs, 1.19 exp).	Possible under-ascertainment of deaths.	[22]
Cohort; 19 coke oven plants in China; follow-up 1971-1982; 21,995 workers; reference workers from a primary rolling mill (steel company).	Exposure categorized by job title.	Standardized risk ratio for lung cancer: - all workers: 2.55 (95% CI, 2.13-3.08)- - top of coke oven: 8.59 (13 obs, 0.52 exp), $p<0.01$ - side of coke oven: 4.91 (15 obs, 3.05 exp), $p<0.01$	Significantly increased risk for lung cancer.	[95]
Cohort; 6 coal gas plants in China; follow-up 1971-1981; 3,107 workers; reference workers from a primary rolling mill (steel company).	No information.	Standardized lung cancer risk ratio for those who worked in the gas departments of the plants: - 3.66 (95% CI, 2.36-5.43). Also an excess risk of cancers in digestive tract.	Significantly increased risk for lung cancer.	[95]

Carbon electrode production				
Cohort; one large Swedish graphite electrode plant ; follow-up 1969-1989, average exposure time 10.8 years; 901 workers; reference regional population.	BaP measured at five occasions between 1974 and 1987. Information on smoking habits were obtained by questionnaire.	Standardized mortality ratio: - lung cancer: 1.68 (2 obs, 1.19 exp; 95% CI, 0.2-6.07) - bladder cancer: 8.33 (1 obs, 0.12 exp; 95% CI, 0.21-46.37).	The number of observed cases was too low for definite conclusion. The cohort will be under continued surveillance.	[36]
Iron and steel foundries				
Historical cohort; 37 local German iron foundries; follow-up 1951-1993; 17,708 foundry workers; reference German general population.	Employment and occupational histories were collected.	2,896 death certificates obtained. SMR by cancer site: - Trachea, bronchus, lung: 1.64 (322 obs, 253.2 exp; 95% CI, 1.24-2.23) - Larynx: 1.73 (20 obs, 14.3 exp; 95% CI, 0.86-5.50) - bladder cancer: 1.05 (23 obs, 27.2 exp; 95% CI, 0.53-3.09) - Liver cancer: 3.22 (28 obs, 12.4 exp; 95% CI, 1.50-8.45).	Increased risk for lung and liver cancer. Workers are exposed to a mixture of potential carcinogens, such as PAH and nitrosamines.	[1]
Cohort; 1 gray iron foundry, USA; follow-up 1938-1967; 2,861 workers; reference general US male population.	No information.	Standardized mortality for respiratory cancer: - ever employed: 29 obs, 23.1 exp - employed > 5 yrs: 12 obs, 9.4 exp - employed > 5 yrs before 1938: 8 obs, 4 exp.	Increased risk for respiratory cancer.	[23]
Cohort; 20 foundries from the Finnish Foundry Project; follow-up 1950-1973; 3,876 male workers; reference general Finnish male population.	Classification by foundry.	Lung cancer mortality among those exposed for 5 or more years: - iron foundries: 10 obs, 3.7 exp - steel foundries: 0 obs, 1.5 exp - nonferrous foundries: 1 obs, 0.7 exp. - all foundries: 10 obs, 4.8 exp. Confidence intervals not given.	Higher risk for lung cancer in iron workers.	[49]
Cohort; 58 Danish steel and iron foundries; follow-up 1967-1985; 3,377 foundry workers; refrence general Danish population.	Foundry workers include moulders, oven workers, casters, crane operators and shake out. Substantial exposure to PAH, silica dust and metallic fumes.	Standardized mortality ratio: - lung cancer: 1.21 (85 obs, 70.22 exp; 95% CI, 0.98-1.50) - bladder cancer: 1.14 (32 obs, 28.01 exp; 95% CI, 0.81-1.61).	Risk for lung cancer moderately increased. No latency period.	[83]
Historical prospective cohort; 9 steel foundries in England and 1 in Scotland; follow-up 1946-1990; 10,438 male production workers; reference general population of England and Wales.	Classification of occupation. Data on smoking habits were not available.	Standardized mortality ratio: - lung cancer: 1.46 (551 obs, 378.3 exp; 95% CI, 1.34-1.58), p<0.001 - bladder cancer: 1.07 (37 obs, 34.5 exp; 95% CI, 0.76-1.48) - stomach cancer: 1.34 (124 obs, 92.5 exp; 95% CI, 1.11-1.60), p<0.01.	Limited evidence of an excess of lung cancer risk. See also Sor01 for continuation.	[85]

Retrospective follow-up;one iron foundry plant in Ohio, USA; follow-up period 1970-1987; 5,540 male workers; reference general US or Cuyahoga County population.	No information.	Standardized mortality ratio: - lung cancer: 1.21 (72 obs, 95% CI, 0.94-1.52) - stomach cancer: 1.13 (7 obs, 95% CI, 0.45-2.32) - prostate cancer: 1.55 (15 obs, 95% CI, 0.87-2.56)	Nonsignificant excess of lung and prostate cancer.	77
Carbon black production				
Cohort; five carbon black producing factories in the United Kingdom; follow-up 1947-1980; 1,422 male workers; reference regional male population.	Exposure to carbon black dust and PAH.	Standardized mortality ratio: - lung cancer: 1.52 (25 obs, 16.5 exp) - bladder cancer: 2.50 (3 obs, 1.2 exp).	Increase is statistically non-significant. No trend in lung cancer with duration of exposure. Survival bias possible.	42
Retrospective cohort; 2 carbon black plants in China; follow-up period not given; 5,122 workers; reference workers from a primary rolling mill (steel company).	Air pitch concentration at work sites as high as 40 mg/m^3.	Standardized risk ratio for lung cancer: - 2.60 (24 obs; 95% CI, 1.79-3.60).	Significantly increased risk for lung cancer.	95

SMR: standardized mortality ratio (no. of cases observed/no. of cases expected).
SIR: Standardized incidence ratio.
CI: confidence interval.

I4 Summary of case-control studies on occupational PAH exposure by cancer type

study design and population information	exposure information	odds ratios	outcome and notes	ref.
Lung cancer				
Two case-control studies pooled; East and West Germany; 3,498 cases and 3,541 controls obtained from general population.	PAH exposure was evaluated on the basis of job and industry codes, written job descriptions and job specific questionnaires. Information obtained from various industries.	Odds ratio for lung cancer risk by cumulative exposure to PAH (μg/m^3 BaP-yrs): - >0-20: 1.15 (80 cases, 56 controls; 95% CI, 0.77-1.71) - > 20: 2.09 (101 cases, 38 controls; 95% CI, 1.36-3.22). OR was adjusted fro smoking and asbestos exposure. Weighting factors were given for probability and frequency of exposure.	Elevated lung cancer risk.	15

Nested case-referent mortality study on foundry workers; no. of death certificates examined 2,990: no. of death cases 113, no. of referents 249.	No PAH exposure measurements. Only 65% of the workers older than 65 were traced.	Proportional mortality ratio: -white males: 1.44 (224 obs, 155.17 exp), $p<0.01$ - black males: 1.76 (39 obs, 22.10 exp), $p<0.01$ Lung cancer odds ratio by age in iron foundries: - age 42-64: 2.36, $p<0.05$ - age ≥ 65: 1.19 Lung cancer odds ratio by age in steel foundries: - age 42-64: 1.25 - age ≥ 65: 1.09		26
Population-based case-control study in Norwegian municipality, in the neighbourhood of an iron and steel plant; 52 cases and 156 controls.	Information on occupational history obtained by questionnaires and interviews.	Odds ratio of lung cancer to PAH exposure: 2.9 (18 cases, 18 controls; 95% CI, 1.2-6.7). Adjusted for smoking habits.	Significantly increased risk. Authors cannot exclude combined exposure with asbestos or dust.	35
Nested case-referent study; carbon electrode manufactory in France;	Measurement of airborne PAH exposure in plants. Plant A is a incidence study, Plant B is a mortality study.	Odds ratios for lung cancer: *Plant A:* - 1-10 yrs: 2.90 (2 cases, 5 ref; 95% CI, 0.18-46.61) - 11-20 yrs: 2.91 (2 cases, 5 ref; 95% CI, 0.19-45.78) - > 21 yrs: 4.07 (2 cases, 3 ref; 95% CI, 0.32-51.00). Trend test (P), 0.27. *Plant B:* - 1-10 yrs: 0.38 (3 cases, 12 ref; 95% CI, 0.07-2.16) - 11-20 yrs: 0.88 (2 cases, 4 ref; 95% CI, 0.12-6.38) - > 21 yrs: 0.32 (1 case, 5 ref; 95% CI 0.02-4.29). Trend test (P), 0.50.	No relationship with duration of exposure. No statistically significant increases in risk.	64
Nested case-control mortality study; stainless steel production workers in France; recording period 1952-1982; no. in cohort 2,269.	No PAH exposure measurements. Smoking habits were recoreded and found to be similar between the exposed and non-exposed groups.	In cohort 12 cases of lung cancer death. These were matched with 58 controls (selected from cohort). Odds ratios for workers exposed to PAH: 4.51 (95% CI, 1.28-15.94), statistically significant.	Statistically significant increased ncreased risk.	62
Nested case-cohort; 13 iron foundries; no. of workers in cohort 3.425; controls selected from cohort.	Exposure estimation by job history and duration. Four PAH exposure classes: 1) heavy, 2) some exposure, 3) low exposure and 4) miscellaneous or undefined. Smoking habits were recoreded.	In cohort, 51 cases of lung cancer death. Proportional lung cancer mortality: 1.44 (51 obs, 35.3 exp), $p<0.05$. Smoking was propably not a confounding factor in this study.	Statistically significant increased risk	92

Case-cohort; 1 aluminium plant; employment of at least 1 year; n total = 16,297	From the cohort a sub-cohort was at random selected of 1,138 men. Several groups by selected jobs. Cumulative exposure to BSM en BaP measured.	Lung cancer mortality (rate ratios) by cumulative exposure (BaP in µg/m^3 years); <10 µg/m^3: 1.0 10-99: 1.48 (95%CI: 1.09-2.00) 100-199: 2.23 (95%CI: 1.46-3.39) 200-299: 2.10 (95%CI: 1.40-3.15) ≥ 300: 1.87 (95%CI: 1.05-3.33) Adjusted for smoking habits.	Statistically significant increased risk by increasing cumulative exposure to BaP and BSM.	[7]
Hospital-based case-control study; 194 lung cancer cases, 194 hospital control and 194 population controls.	Expected level of exposure estimated by questionnaire on job tasks. Smoking habits were recorded.	Lung cancer incident cases by occupational exposure to PAH, expressed as smoking adjusted odds ratio: - category 0-3 (low): 1.0 (95% CI, -) - category >3-15: 1.0 (95% CI, 0.52-1.88) - category >15-40: 0.7 (95% CI, 0.31-1.66) - category >40 (very high): 1.4 (95% CI, 0.48-4.20). Smoking-adjusted OR for smelter and foundry workers: 4.8 (95% CI, 1.15-20.16).	Risk increased with duration of exposure and with latency.	[46]
Population-based case control study; China; 965 female lung cancer incidence cases, 959 controls selected from general population.	Categorization by occupation and exposure to substance.	Odds ratio of lung cancer cases for foundry workers: 1.5 (based on 39 cases, 25 controls; 95% CI, 0.9-2.6). Odds ratio for lung cancer cases for coke oven emissions: 1.5 (51 cases, 32 controls; 95% CI, 0.9-2.5). Adjusted for smoking, study area, age and education.	Increased risk, not statistically significant.	[96]
Case-control; Italy; no. of death cases 756; no. of controls 756 (general population of the provence of Trieste)	Smoking habits and possible asbestos exposure were recorded.	Relative risk to lung cancer death: - gas workers: 1.43 (7 cases, 6 controls; 95% CI, 0.45-4.47); - smelting/foundry workers: 3.69 (9 cases, 4 controls; 95% CI, 0.99-13.7). Data are adjusted for smoking.	Increased risk for smelting/foundry workers, not significant.	[13]
Case control; coke oven plant; no. of workers in study 3,530.	No exposure measurements. No relation made with possible PAH exposure.	Standardized mortality ratio (SMR) for bronchial, lung and tracheal cancer (men employed five or more years): Coke oven: 3.55 (27 obs, 7.6 exp), $p<0.05$.	Statistically significant increased risk.	[55,70]
Population-based case-cohort in the Netherlands; follow-up period 4.3 yrs; from a randomly selected subcohort (1,688), 524 lung cancer cases were available.	Information based on self administered questionnaires.	Rate ratios by PAH exposure: - 0 (no exp.): 1.0 - 1 tertile (low): 0.53 (10 cases; 95% CI, 0.13-2.14) - 2 tertile: 0.83 (12 cases; 95% CI, 0.32-2.20) - 3 tertile (high): 0.28 (12 cases; 95% CI, 0.09-0.89). test for trend χ^2 (P value): 9.05 ($p<0.01$).	No significant association between cumulative propability exposure to PAH and lung cancer risk.	[54]

Population-based case-control study in Missouri, USA; 294 lifetime non-smoking cases (all women) cases, 1,021 controls (all women).	Exposure by occupation.	Odds ratio by occupation: - iron/steel plant: 0.6 (2 cases, 10 controls; 95% CI, 0.1-2.7).	Risk not significantly increased.	14
Population-based case-control study; Montreal erea, Canada; 3,730 cancer patients, 533 controls.	PAH exposure by occupation. Different types of cancer evaluated. Data adjusted for age, smoking habits and combined exposure with other substances.	Odds ratios by BaP exposure: - low: 0.9 (160/322, 95% CI, 0.7-1.2) - high: 1.0 (75/137, 95% CI, 0.7-1.4) Odds ratios by coal exposure: - low: 1.1 (63/112, 95% CI, 0.8-1.6) - high: 1.0 (28/51, 95% CI, 0.6-1.8).	Slightly increased risk, not significant.	66
Case-control study in Pennsylvenia, USA; steel industry; 335 cases of lung cancer death, 332 matched controls.	Information on job title, possible exposure, smoking habits etc. obtained by interviews and death certificates.	Odds ratio for lung cancer by job category: - coke worker: 1.2 (2 cases, 2 controls; 95% CI, 0.2-6.9) - foundry worker, mold maker: 7.1 (6 cases, 1 control; 95% CI 1.2-42.3).	Possible exposure to a mixture of substances, including PAH. Number of cases and controls is small.	11
Hospital-based case control study; Japan; 144 cases, 676 matched controls.	Information on occupation, job history and personal lifestyle factors obtained by a self-administered questionnaire.	Relative risk by industry: - steel manufacturing: 0.92 (26 cases, 110 controls; 95% CI, 0.54-1.56). Adjusted for smoking habits.	Relative risk not increased. No clear definition on jobs within steel manufactury given.	99
Population-based case-control study; Utah, USA; a large coke oven with a steel plant in a county with a population of approximately 130,000. Total number of lung cancer cases not reported.	Clustering of cancers near point source of air polluation.	Relative risk for lung cancer by distence of point source: - 1 mile: 0 (0 obs, 0 exp; 95% CI, -) - 2 miles: 1.41 (5 obs, 3.5 exp; 95% CI, 0.47-4.20) - 5 miles: 1.18 (30 obs, 25.4 exp; 95%CI, 0.89-1.57) - 10 miles: 1.03 (71 obs, 69.8 exp; 95% CI, 0.82-1.26).	Concerns exposure of general population. No data presented on occupational exposure in the coke oven.	55
Bladder cancer				
Population-based case-control; area of Toronto, Canada; no. of histologically verified cases 826; no. of matched controls 792, randomly selected from population.	No exposure measurements. No relation made with possible PAH exposure.	Odds ratios for bladder cancer cases (employed 8-28 years in the past): - aluminium melting industry: 2.61 (95% CI, 0.7-12.5); - tar, asphalt exposure: 3.11 (95% CI, 1.19-9.68)	Significant increased risk for tar and asphalt exposure. Combined exposure with other carcinogenic substances than PAH cannot be excluded.	72
Nested case-control; aluminium production workers; original population >16,000; subcohort of 3,138.	Cumulative exposure to BaP en BSM measured.	Bladder cancer morbidity expressed as rate ratios by cumulative exposure to BaP ($\mu g/m^3$-yr) and adjusted for smoking habits: < 10: 1.00 (95% CI, -) 10-99: 1.97 (95% CI, 1.10-3.51) 100-199: 6.24 (95% CI, 3.00-12.97) 200-299: 6.66 (95% CI, 3.42-12.99) ≥ 300: 4.36 (95% CI, 2.10-9.17)	Authors cannot exclude combined-exposure with aromatic amines, such as 2-naphtyl-amine and 4-amino-biphenyl. These are known bladder carcinogens.	91,93

Population-based case-referent study; certain boroughs in London, United Kingdom; for each case, two controls were included.	No exposure measurements. No relation made with possible PAH exposure.	Of the 1,080 death certificates with cause of death bladder cancer, 11 cases were gas workers (relative risk, 1.4 (*versus* all other cancers) and 0.8 (*versus* all other causes, including cancer)). These data were not statistically significant at a CI of 95%.	Increased risk compared to all cancer cases, not significant.	[8]
Population-based case-control study; 417 (332 men and 85 women) cases of bladder cancer, 877 (685 men and 192 women) controls (never exposed).	No exposure measurement. Substance exposure obtained by questionnaire.	Odds ratio for men exposed to coal tar and pitch (a total of 92 cases and 160 controls): - ever exposed: 1.08 (95% CI, 0.78-1.49) - < 10 yrs exposed: 1.10 (95% CI, 0.76-1.60) - > 10 yrs exposed : 1.04 (95% CI, 0.64-1.68). Odds ratio was adjusted for age, smoking, religion and education.	No statistically significant increased risk. Authors point out the possiblility of a relation between bladder cancer and aromatic amines, although they could not find a positive relation.	[79]
Hospital-based case-control study consisting of 531 male and 144 female matched pairs; Germany.	No exposure measurement. Substance exposure obtained by questionnaire. No relation with PAH exposure made.	Odds ratios for bladder cancer associated to certain exposure or occupation category among male subjects: - coal tar: 1.4 (49 cases, 35 controls; 95% CI, 0.9-2.3) - aluminium: 1.3 (32 cases, 25 controls; 95% CI, 0.8-2.2) - gas worker: 6.0 (6 cases, 1 control; 95% CI, 0.9-38.5).	increased risk, not statistically significant.	[52]
Hospital-based case-control study in France; 658 male cases of bladder cancer and 658 male controls.	PAH exposure determined by reviewing job descriptions.	Estimated odds ratio for bladder cancer and cumulative exposure to PAH (ng/m^3-yr): - unexposed: 1.0 (95% CI, -) - <100: 1.7 (95% CI, 1.2-2.4) - 100-499: 0.8 (95% CI, 0.5-1.3) - 500-14,999: 1.3 (95% CI, 0.8-2.0) - >15,000: 1.8 (95% CI, 0.8-3.9) Adjusted on matching variables, cumulative smoking, coffee consumption after having excluded subjects possibly exposed to aromatic amines.	Non statistically significant increased risk.	[19]
Population-based case-control study in Italy; 121 male cases and 342 male controls, matched by age.	Occupational PAH-exposure was evaluated by means of job exposure matrix.	Odds ratios for bladder cancer and PAH exposure: - no PAH exposure : 1.00 (21 cases, 92 controls; 95% CI, -) - possible PAH exposure: 1.01 (8 cases, 32 controls ; 95% CI : 0.40-2.50) - definite PAH exposure: 2.53 (3 cases, 5 controls; 95% CI, 0.56-11.5) Data were adjusted for smoking and aromatic amine exposure.	Increased risk, not statistically significant.	[12]

Population-based case-control study in Norwegian municipality, in the neighbourhood of an iron and steel plant; 52 cases and 156 controls.	Information on occupational history obtained by questionnaires and interviews.	Odds ratio for bladder cancer to PAH exposure: - ≤ 1 yr exposed: 1.0 (59 cases, 165 controls; 95% CI, -) - > 1 yr exposed: 0.5 (3 cases, 19 controls; 95% CI, 0.1-1.9). Not adjusted for smoking habits.	No association found between bladder cancer and occupational PAH exposure at iron, steel and coke plant.	35
Nested case-control study in Illinois, USA; one large steel manufacturing plant; 16 cases, 74 controls.	Some information on smoking habits.	Odds ratio for bladder cancer by job title: - heater: 21.1 (3 cases; 95% CI, 2.2-205.8), $p<0.01$ - laborar: 0.9 (4 cases, 95% CI, 0.3-2.8). Adjusted for age, not for smoking habits.	Limitation of the study is the relatively small number of cases. Heaters could be exposed to a number of substances, especially PAH.	57
Population-based case-control study; Montreal erea, Canada; 3,730 cancer patients, 533 controls.	PAH exposure by occupation. Different types of cancer evaluated. Data adjusted for age, smoking habits and combined exposure with other substances and exposure with aromatic amines.	Odds ratios by BaP exposure: - low: 1.2 (91/380, 95% CI, 0.9-1.5) - high: 0.5 (20/175, 95% CI, 0.3-0.8) Odds ratios by coal exposure: - low: 0.8 (28/154, 95% CI, 0.6-1.3) - high: 0.6 (8/67, 95% CI, 0.3-1.2).	No increased risk.	66
Renal cancer				
Retrespective case-control study; Montreal area, Canada; 164 cases and 161 matched controls.	No PAH exposure measurements. Information by questionnaire; smoking habits and occupation were recorded.	Odds ratio for renal cancer and exposure to: - coal burning at work: 2.54 (17 cases, 7 controls; 95% CI, 0.96-6.99), $p<0.05$; - coal tar or pitch: 9.29 (9 cases, 1 control; 95% CI, 1.16-74.20), $p<0.02$.	Statistically significant increased risk due to exposure to coal tar or pitch. Low response rate.	81
Hospital-based case-control study; Denmark; 96 cases and 294 hospital controls	No PAH exposure measurements. Information by questionnaire. Smoking habits and occupation were recorded.	Relative risks, adjusted for smoking: - coke-coal exposure: 4.0 (8 cases, 7 controls; 95% CI, 1.2-13.6); - asphalt, tar exposure: 5.5 (9 cases, 6 controls; 95% CI, 1.6-19.6).	Statistically significant increased risk, possibly as a result of icreased exposure to PAH. Because estimates are based on small numbers, chance cannot be excluded.	45
Population-based case-referent study; Finland; 408 eligible cases and 819 referents.	Job and exposure history on occupational PAH obtained by questionnaire.	Odds ratios for PAH exposure: - men and woman: 1.10 (7 cases; 95% CI, 0.39-3.09); - men only: 1.21 (7 cases, 95% CI: 0.43-3.45). Adjusted for obesity, smoking and coffee consumption.	Increased risk, not statistically significant.	67

Population-based multicenter case-control study in Germany; 935 incident cases and 4,298 matched-controls.	Occupational exposure to substances was assessed by job history.	Odds ratios by PAH exposure (males only, Job task-exposure matrix approach): - medium: 0.9 (80 cases; 95% CI, 0.7-1.2) - high: 0.8 (67 cases; 95%CI, 0.6-1.0). Data adjusted for age, study centre and smoking habits.	Slightly increased risk, not statistically significant.	[68]
Population-based case-control study; Montreal erea, Canada; 3,730 cancer patients, 533 controls.	PAH exposure by occupation. Different types of cancer evaluated. Data adjusted for age, smoking habits and combined exposure with other substances.	Odds ratios by BaP exposure: - low: 0.7 (21/505, 95% CI, 0.4-1.1) - high: 0.8 (10/207, 95% CI, 0.4-1.5) Odds ratios by coal exposure: - low: 1.0 (11/190, 95% CI, 0.5-1.9) - high: 0.9 (4/77, 95% CI, 0.3-2.6).	No increased risk.	[66]
International multicenter population-based case-control study; Australia, Denmark, Germany, Sweden and the United States; 1,732 incident renal-cell cancer cases and 2,309 controls.	Information on job history and exposure, and life style factors obtained by interviews.	Relative risk for industries (men only): - blast furnaces and coke ovens: 1.7 (57 cases, 40 controls; 95% CI, 1.1-2.7) - iron or steel industry: 1.6 (113 cases, 87 controls; 95% CI, 1.2-2.2). Data adjusted for age, smoking habits, body-mass index, education and study center.	Significant positive association between renal-cell cancer and industry.	[58]
Population-based case control study in Minneapolis, USA; 495 cases of renal cell carcinoma and 697 controls.	Information on occupation, substance exposure and lifestyle factors by interviews.	Odds ratio for petroleum, tar, and pitch products: - males: 1.6 (95% CI, 0.9-2.7) - females: 4.6 (95% CI, 0.4-51.0).	Odds ratios by occupation did not reveal an association with renal cell cancer. Exposure to tar and pitch products was associated with a significant raised risk level.	[60]
Skin cancer				
Case-referent study; Poland; 376 cases, 2 control group I (general population), 752, control group II (hospital), 752.	Estimation on occupational PAH exposure by questionnaire. No information on smoking habits.	Odds ratio by exposure product: - tar: 1.09 (28 cases, 56 controls I), 1.00 (28 cases, 61 controls II); - pitch: 0.93 (15 cases, 35 controls I), 0.86 (15 cases, 38 controls II); - coke: 1.29 (32 cases, 54 controls I), 0.99 (32 cases, 70 controls II). No 95% confidence intervals given.	No significant increase in skin cancer risk.	[50,51]
Population-based case-referent study; Alberta, Canada; 180 cases of squamous cell carcinoma (SCC) and 226 cases of basal call carcinoma (BCC); 406 randomly matched controls.	Risk based on occupation.	Odds ratios: - tar, pitch (SCC): 0.9 (27 cases; 95% CI, 0.5-1.7) - tar,pitch (BCC): 1.2 (32 cases; 95% CI, 0.7-2.1).	No clear association between occupation and skin cancer.	[31]

Population-based case-control study; Montreal erea, Canada; 3,730 cancer patients, 533 controls.	PAH exposure by occupation. Different types of cancer evaluated. Data adjusted for age, smoking habits and combined exposure with other substances.	Odds ratios for melanomas by BaP exposure: - low: 0.4 (6/498, 95% CI, 0.2-0.9) - high: 1.0 (5/207, 95% CI, 0.4-2.4) Odds ratios by coal exposure: - low: 0.4 (2/191, 95% CI, 0.1-1.8) - high: 0.0 (0/81, 95% CI, 0.0-1.3).	No increased risk.	66
Laryngeal cancer				
Nested case-referent study; carbon electrode manufactory in France; for each case, three referents were chosen from the cohort.	Measurement of airborne PAH exposure in plants. Plant A is an incidence study, Plant B is a mortality study.	Odds ratios for cancer in pharynx, larynx and buccal cavity: *Plant A:* - 1-10 yrs: 2.27 (3 cases, 7 ref; 95% CI, 0.31-14.99) - 11-20 yrs: 1.63 (2 cases, 7 ref; 95% CI, 0.18-14.34) - > 21 yrs: 3.85 (3 cases, 4 ref; 95% CI, 0.44-33.64). Trend test (P), 0.27. *Plant B:* - 1-10 yrs: 0.00 (0 cases, 6 ref) - 11-20 yrs: 1.74 (2 cases, 2 ref; 95% CI, 0.24-12.95) - > 21 yrs: 0.36 (2 cases, 9 ref; 95% CI 0.04-3.42). Trend test (P), 0.50.	No relationship with duration of exposure. No statistically significant increases in risk.	64
Hospital-based case-control study in Germany; 100 prevalent male cases and 100 matched-controls.	Occupational exposure evaluated by questionnaire.	Odds ratios by coal tar/bitumen exposure: 0.6 (95% CI, 0.2-1.9). Data adjusted for age, smoking, alcohol consumption and corresponding confidence limits.	No increased risk. Findings were based on small numbers of cases and controls.	2
Pancreatic cancer				
Hospital-based case-control study; eastern part of Spain; 164 cases, 238 controls.	Occupational exposure evaluated by industrial hygienists and by using the Finnish job-exposure matrix.	Odds ratios by substance exposure: - BaP (>0.01 μg/m^3): 3.10 (6 cases, 4 controls; 95% CI, 0.73-13.2) - PAH (>0.35 μg/m^3): 0.78 (2 cases, 3 controls; 95% CI, 0.12-5.18). Adjusted for sex, age, hospital, consumption of alcohol and tobacco.	No significant increased in risk.	3
Stomach cancer				
Population-based case-control study; USA; 41,957 death cases (white and black men and women), two controls for each case	Occupational PAH exposure estimated by questionnaire.	Odds ratio of stomach cancer in white men by intensity of exposure: - low: 1.0 (4,047 cases; 95% CI, 0.95-1.04) - medium: 1.08 (1,983 cases; 95% CI, 1.02-1.15); - high: 1.0 (616 cases, 95% CI, 0.90-1.10).	No significantly increased risk.	20

Population-based case-control study; Montreal erea, Canada; 3,730 cancer patients, 533 controls.	PAH exposure by occupation. Different types of cancer evaluated. Data adjusted for age, smoking habits and combined exposure with other substances.	Odds ratios by BaP exposure: - low: 0.8 (36/486, 95% CI, 0.6-1.2) - high: 1.4 (23/192, 95% CI, 0.9-2.2) Odds ratios by coal exposure: - low: 1.1 (17/180, 95% CI, 0.7-1.9) - high: 1.5 (9/73, 95% CI, 0.8-3.1).	No increased risk.	[66]

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Annex **J**

Animal data on carcinogenesis

J1 Number of carcinogenic animal studies on single PAH (reproduced from IPCS, 1998)[70]

PAH	Weight of evidence	Species	Oral			dermal			s.c./i.m.			i.p./i.p.			inh./tr.			other		
			+	-	+/-	+	-	+/-	+	-	+/-	+	-	+/-	+	-	+/-	+	-	+/-
Acenaphthene	Questionable	Mouse					1	1												
Acenaphthylene	No studies																			
Anthanthrene	Positive	Mouse				2	6			1					1				1	
Anthracene	Negative	Mouse					6	1		1			1							
		Rat	2						1	2				1		1				
		Rabbit																	1	
Benz[a]anthracene	Positive	Mouse	2		1	7	4		4	2			2					1		
		Rat		1			1			2			1						1	
		Hamster					2											1		
Benzo[b]fluoranthene	Positive	Mouse				7			1			1								
		Rot													1					
		Hamster														1				
Benzo[j]fluoranthene	Positive	Mouse				3		1				1								
		Rat													1					
Benzo[ghi]fluoranthene	(Negative)	Mouse					2													
Benzo[k]fluoranthene	Positive	Mouse				1	2	1	1					1						
		Rat													1					
Benzo[a]fluorene	(Questionable)	Mouse					1	1		1										
Benzo[ghi]perylene	Negative	Mouse					8			2										
		Rat														1				

Benzo[c]phenanthrene	(Positive)	Mouse				2		2		1	1														
		Rat									1														
Benzo[a]pyrene	Positive	Mouse	5			26			6			3			1			2						
		Rat	2						1			1			9			3						
		Hamster	1			1	1	1							11	1	1							
		Dog																1						
		Cattle								1														
		Pig								2														
		Monkey							1	1	1				1									
Benzo[e]pyrene	Questionable	Mouse				2	1	5						1										
		Rat														1				1				
Chrysene	Positive	Mouse				11	9	1	3	3	1	1	2	1										
		Rat							1	2					1									
Coronene	Questionable	Mouse					1	1																
Cyclopenta[cd]pyrene	Positive	Mouse				4		1				1												
		Rat																						1
Dibenz[a,h]anthracene	Positive	Mouse	1		1	6			8			1												
		Rat							2		1				1									1
		Hamster					1								1		1							
		Monkey																						1
Dibenzo[a,e]pyrene	Positive	Mouse				3			2															1
		Rat																						
Dibenzo[a,h]pyrene	Positive	Mouse				6			2			1												
		Rat																						
Dibenzo[a,i]pyrene	Positive	Mouse				7			4			1												
		Rat																						1
		Hamster							2						2									
		Monkey																						1
Dibenzo[a,l]pyrene	Positive	Mouse				7			1															
		Rat																						2
Fluoranthene	(Positive)	Mouse					6			2		3												
Fluorene	Negative	Mouse					3			1			1											
		Rat		2																				
Indeno[l,2,3-cd]pyrene	Positive	Mouse				2	1	2	1				1											
		Rat													1									
5-Methylchrysene	Positive	Mouse				13			1		1	1	1											
		Rat																						1
1-Methylphenanthrene	(Negative)	Mouse					1																	
Naphthalene	(Questionable)	Mouse					1	2									2			1				
		Rat	1							1	1		1											
Perylene	(Negative)	Mouse					2																	
Phenanthrene	(Questionable)	Mouse				1	3	3		3			1											
		Rat		1												1								
Pyrene	(Questionable)	Mouse				1	7	3		1			1											
		Hamster														1								
Triphenylene	(Negative)	Mouse					2																	

+, positive outcome; -, negative outcome, +/- questionable outcome. Parentheses, limited number of studies. s.c., subcutaneous; i.m., intramuscular; i.p., intraperitoneal; i.v., intraveneous; inh., inhalation; tr., intratracheal. Other: *e.g.,* intramammary injecton, bladder implant, bronchial implant.

J2 Exposure by inhalation

Table J.2 Adapted from IPCS 1998 (Table 90, page 399 - 471: Carcinogenicity of polycylic aromatic hydrocarbons in experimental animals)[70].

Purity	Species, strain	Sex	No./ sex/ group	Route of dosage administration	duration at death/ sacrifice	Incidence and type of tumour	Result Stat./ Val.	References adapted from IPCS 1998
Benzo[a]pyrene								
	Hamster, Syrian golden	m	10	Inhalation; 4.5 h/ day, 5 days/week, 9.8 mg/m^3 for 16 weeks or 44.8 mg/ m3 for 10 weeks	Life	No tumours	n no/ld	Thyssen *et al*. (1980)
	Hamster, Syrian golden	m	24	Inhalation; 2.2, 9.5, or 46.5 mg/ m^3, 4.5 h/day in the first 10 weeks, thereafter 3 h/day, 109 weeks	109 weeks	Dose-dependent tumours in nasal cavity, pharynx, larynx, and trachea; also in oesophagus and forestomach (papillomas, polyps, squamous-cell carcinomas); no lung tumours; larynx most affected with 0, 31 and, 52% incidence; control: no tumours	p no/val	Thyssen *et al*. (1981)
Naphthalene								
98-99%	Mouse, A/J	f	30	Inhalation; 0.05 and 0.15 mg/l, 6 h/ day, 5 days/week, 6 months	6 months	29 and 30% with pulmonary tumours; control: 21% (increase in treatment groups not significant)	q yes/val	Adkins *et al*. (1986)
> 99%	Mouse, B6C3F1	m/f	75 (150)	Inhalation; 0.053 and 0.16 mg/litre, 6 h/day, 5 days/ week, 103 weeks	103 weeks	Significantly increased pulmonary alveolar and bronchiolar adenomas in females; no cararacts	q yes/val	Abdo *et al*. (1992); National Toxicology Program (1992b)
>99% pure	Rat, Fischer 344/N	m/f	49	inhalation; 0, 50, 150, and 300 mg/ m^3 (= 0,10, 30 and 60 ppm), 6 h/day, 5 days/week for 105 weeks	105 weeks	Significantly increased incidence of respiratory epithelial adenomas and olfactory epithelial neuroblastomas in males and females	p yes/val	Abdo *et al*. (2001); National Toxicology Program (2000)

Result: p(ositive), n(egative), q(uestionable); Stat, statistical evaluation: yes or no; Val, validity: val, valid; ld, limited design; lc, limited documentation; ls, limited survival; ln, limited number of animals; m, male; f, female.

J3 Intratracheal and intrapulmonary installation

Table J.3 Adapted from IPCS 1998 (Table 90, page 399 - 471: Carcinogenicity of polycylic aromatic hydrocarbons in experimental animals)[70].

Purity	Species, strain	Sex	No./ sex/ group	Route of dosage administration	duration at death/ sacrifice	Incidence and type of tumour	Result Stat./ Val.	References adapted from IPCS 1998
Acenaphthene								
99.4%	Rat Osborne-Mendel	f	35	Intrapulm.; 0.65 and 3.4 mg/kg, 1x	102/88 weeks	1/35 and 19/35 with lung tumours; control: no tumours	p yes/val	Deutsch-Wenzel *et al*. (1983)
Anthracene								
	Rat, Osborne/ Mendel	f	60	Intrapulm.; 0.5 mg/animal,	1x/year	No lung tumours; control: no tumours	n no/d	Stanton *et al*. (1972)
Benz[a]anthracene								
	Hamster Syrian golden	m	47 or 33	Intratracheal; 0.5 or 3 mg/animal per week 30 or 15 weeks	≤ 110 weeks	No tracheal tumours; control: no tumours	n yes/val	Sellakumar & Shubik (1974)
Benzo[b]fluoranthene								
99.5%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.1, 03 and 1 mg/animal, 1x	110/113/ 112 weeks	0/35, 1/35, and 9/35 pulmonary carcinomas; 1/ 35, 2/35, and 4/35 pleomorphic sarcomas; control: no tumours	p yes/val	Deutsch Wenzel *et al*. (1983)
	Hamster, Syrian golden	m	47	Intratracheael; 0.5 and 0.5 mg/ animal per week, 30 weeks	≤ 110 weeks	0/47 and 1/47 tracheal tumours; control: no tumours	n yes/val	Sellakumar & Shubik (1974)
Benzo[j]fluoranthene								
99.9%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.8, 4, and 20 mg/kg, 1x	110/117/89 weeks	1/35, 3/35 and 18/35 pulmonary carcinomas; control: no tumours	p yes/val	Deutsch-Wenzel *et al*. (1983)
Benzo[k]fluoranthene								
99.5%	Rat, Osborne/ Mendel	f	27-35	Intrapulm.; 0.65, 3.4, and 17 mg/ kg, 1x	114/95/98 weeks	0/35, 3/31 and 12/27 pulmonary carcinomas; control: no tumours	p yes/val	Deutsch-Wenzel (1983)
Benzo[ghi]perylene								
98.5%	Rat, Osborne/ Mendel	f	34-35	Intrapulm.; 0.65, 3.4, and 17 mg/ kg, 1x	109/114/ 106 weeks	0/35, 1/35 and 4/34 pulmonary carcinomas effect of impurity suggested; control: no tumours	n yes/val	Deutsch-Wenzel *et al*. (1983)

Benzo[a]pyrene

99%	Mouse, NMRI	f	19-22	Intratracheal; 0.05 and 0.15 mg/animal, 20x		27 and 42% with carcinomas in the respiratory tract; control: 9%	p na/val	Pott *et al*. (1978)
	Rat, Wistar	f	13-17	Intratracheal; 0.5, 1, or 2 mg/animal in infusion; 1x/2 weeks; 18x	Life	7, 65, and 92% with lung tumours; control: no tumours	p yes/val	Davis *et al*. (1975)
	Rat, Wistar	m/f	15/15	Intratracheal; 1 mg/animal, 1x/week, 15x	Life (mean, 491/540 days)	3/13 (m) and 3/14 (f) with malignant lung tumours (mean: 22.2%); vehicle control: 0%	p no/val	Ishinishi *et al*. (1976)
	Rat, Wistar	f	36-40	Intratracheal; 1 mg/animal; 20x		19% with lung tumours; control: no tumours	p no/val	Pott *et al*. (1987)
	Rat, Sprague- Dawley	m/f	20/20	Intratracheal; 7 mg/kg, every 14 days, 22x (total dose: 154 mg/kg)	≤ 781 days	19/20 m and 18/20 l with lung tumours; vehicle control: 0%	p no/val	Steinhoff *et al*. (1991)
99.1%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.1, 0.3, or 1 mg/animal, 1x	111/77/54 weeks	4/35, 21/35 and 33/35 pulmonary carcinomas; 6/35, 2/35 and 0/35 pleomorphic sarcomas; control: no tumours	p yes/val	Deutsch-Wenzel *et al*. (1983)
	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.05, 0.1, or 0.2 mg/animal, 1x		11, 17, and 46% with tumours; control: no tumours	p yes/val	Grimmer *et al*. (1987)
99.6%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.03, 0.1, or 0.3 mg/animal, 1x	≤ 135 weeks	8.6, 31.4, and 77.1% tumour incidence; control: no tumours	p yes/val	Wenzel-Hartung *et al*. (1990)
	Rat, Fischer 344/ Du Crj	m	14-15	Intrapulm.; 50, 100, or 200 µg/animal	≤ 100 weeks	0/10, 3/10 and 4/9 lung tumours; control: no tumours	p no/val	Horikawa *et al*. (1991)
	Rat,		94	Intrabronchial pellet; approx. 3-5 mg/animal, 1x	approx. 5 months	Carcinoma incidence: 17%	p no/lc	Laskin *et al*. (1970)
Pure	Hamster, Syrian golden	m/f	30/30	Intratracheal; 3 mg/animal, 1x/wk, 15 week (mixed with inert dust of haematite [ferric oxide]	≤ 45/60 weeks	14/19 and 21/21 with tumours in respiratory tract; control: no tumours	p no/val	Saffiotti *et al*. (1968)
	Hamster, Syrian golden	m	30	Intratracheal; 3 mg/animal, 1x/week, 14 weeks	≤ 74 weeks	All with bronchioalveolar metaplasia; 5/19 squamous-cell carcinomas, 3/19 adenomas, 1/19 tracheal tumours	p no/val	Crocker *et al*. (1970)

Pure	Hamster, Syrian golden	m/f	30-50	Intratracheal; 0.25, 0.5, 1, or 2 mg/ animal, 1x/ week, 30 wks (mixed with inert dust of ferric oxide)	Life	Dose-related increase in respiratory tract tumours; control: no tumours	p no/val	Saffiotti *et al*. (1972)
Pure	Hamster, Syrian golden	m	30	Intratracheal; 0.0625, 0.125, 0.25, 0.5, and 1 mg/animal, 1x/ week, 52 weeks	78 weeks	Dose-related increase in respiratory tract tumours (3-26%); controls: no tumours	p no/val	Feron *et al*. (1973)
	Hamster, Syrian golden	m/f	25/25	Intratracheal; 0.9 mg/animal per week, 30 weeks	≤ 100 weeks	17% (8/46) tumours in respi-ratory tract; con-trol: no tumours	p no/val	Henry *et al*. (1975)
	Hamster, Syrian golden			Intratracheal; 0.3 or 0.9 mg/ani-mal, 1x/week, 20 weeks	≤ 2 years	17 and 68% with tumours	p no/lc	Pott *et al*. (1978)
	Hamster, Syrian golden	m	29	Intratracheal; 0.125, 0.25, 0.5, or 1 mg/animal, 1x/week, life	Life	31, 83, 66, and 31% tumours in respiratory tract; control; no tumours	p no/val	Ketkar *et al*. (1979)
	Hamster, Syrian golden	m	30	Intratracheal; 5, 20 or 40 µg/ani-mal, every 2 weeks, life	Life	4/28, 5/27 and 7/28 with meta plasia in respiratory tract, malignant neo-plasm and 1 adenoma in high-dose group; con-trols: 1/29 or 3/30	q no/val	Kunstler (1983)
	Hamster,		97	Intrabronchial pellets; 3-5 mg		63/97 with lung cancers	p no/val	Laskin *et al*. (1970)
	Hamster, Syrian golden			Tracheal insuf-flation; approx. 0.83 mg/animal, 3x/week, 1 year		Tracheal papillomas and carcinomas	p no/lc	Mohr (1971)
	Hamster, Syrian golden			Bronchial implants	150 days	> 90% with focal cancers	p no/lc	Benfield & Ham-mond (1992)
	Monkey, *Galago crassust*	m/f	4/2	Intratracheal; 3-15 mg, 1x/week (with ferric oxide), up to 69 weeks	67-69 weeks	Bronchioalveolar meta-plasia; 2/3 squamous car-cinomas arising from bronchus	p no/val	Crocker *et al*. (1970)
Benzo[e]pyrene								
99.7%	Rat, Osborne/ Mendel	f	30-35	Intrapulm.; 0.8, 4.2, or 20 mg/kg, 1x	117/111/ 104 weeks	1 pulmonary sarcoma at 4.2 mg/kg; 1 squamous-cell carcinoma at 20 mg/ kg; no tumours in con-trols	n yes/val	Deutsch-Wenzel *et al*. (1983)

Recrystallized	Rat, Fischer 344	f	20	Tracheal pellet; 1 mg, 1x	28 months	No tumours	n yes/val	Topping *et al*. (1981)
Chrysene								
99.6%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 1 and 3 mg/animal, 1 × weeks	≤ 135	14.3% and 28.6% tumour incidence; control: no tumours	p no/val	Wenzel-Hartung *et al*. (1990)
Dibenz[a,h]anthracene								
99.3%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.1 mg/animal, 1x	≤ 123 weeks	57.1% tumour incidence; control: no tumours	p no/val	Wenzel-Hartung *et al*. (1990)
	Hamster, Syrian golden	m	46	Intratracheal; 0.05 and 0.25 mg/animal, 1x/ week, 30 weeks	≤ 110 weeks	0/46 and 0/46 respiratory tract tumours; control: no tumours	q yes/val	Sellakumar & Shubik (1974)
	Hamster, Syrian golden			Intratracheal; 10.3 and 0.9 mg/ animal, 1x/week, 20 weeks	≤ 2 years	55 and 65% with tumours	p no/val	Pott *et al*. (1978)
Dibenzo[a,i]pyrene								
99%	Hamster, Syrian	m	4/34	Intratracheal; 0.5 and 2 mg/animal, weekly, 24 and 4 weeks, respectively	≤ 110 weeks	Tumours (i) 6/44 (trachea), 37/44 (bronchi), 2/ 34(trachea); (ii) 1/34 (larynx), 13/34 (bronchi); control: no tumours	p yes/val	Sellakumar & Shubik (1974)
	Hamster, Syrian golden	m/f	24/24	Intratracheal; 0.5 and 1 mg/animal, 1 x/week, 17 and 12 weeks, resp.		65 and 75% respiratory tumours (bronchi, trachea); shortest latency: 8 weeks	p no/ld	Stenback & Sellakumar (1974)
Indeno[1,2,3-cd]pyrene								
99.4%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 0.16, 0.83 and 4.15 mg/animal, 1x	116/109/ 92 weeks	3/35, 8/35 and 21/35 with lung tumours; control: no tumours	p yes/val	Deutsch-Wenzel *et al*. (1983)
Phenanthrene								
99.9%	Rat, Osborne/ Mendel	f	35	Intrapulm.; 1, 3 and 10 mg/animal, 1x	≤ 135 weeks	No tumours; control: no tumours	n no/val	Wenzel-Hartung *et al*. (1990)
Pyrene								
> 99%	Hamster, Syrian golden	m	48	Intratracheal; 3 mg/animal, 1x/ week, 30 weeks	≤ 110 weeks	1/48 tumours of the trachea, 2/48 malignant lymphomas; control: 0/ 82 and 2/82	n yes/val	Sellakumar & Shubik (1974)

Result: p(ositive), n(egative), q(uestionable); Stat, statistical evaluation: yes or no; Val, validity: val, valid; ld, limited design; lc, limited documentation; ls, limited survival; ln, limited number of animals; intrapulm., intrapulmonary injection; m, male; f, female; DMSO, dimethylsulfoxide.

J4 Oral exposure

Table J.4 Adapted from IPCS 1998 (Table 90, page 399 - 471: Carcinogenicity of polycylic aromatic hydrocarbons in experimental animals)[70].

Purity	Species, strain	Sex	No./ sex/ group	Route of dosage administration	duration at death/ sacrifice	Incidence and type of tumour	Result Stat./ Val.	References adapted from IPCS 1998
Anthracene								
	Rat		31	Oral; 6 mg/animal/day, 7x/(diet) week	33 months	22/31 alive after 1 year; no tumours after 33 months	n no/lc	Schmahl & Reuter, cited by Gerarde (1960)
Highly purified	Rat, BD I/ BD III		28	Oral; 5-15 mg/animal/day, (diet) 6x/week, 78 weeks	700 days	2/28 malignant tumours,	n no/ld	Schmähl (1955)
Benz[a]anthracene								
	Mouse, C57/BL		8-19	Oral; 0.5 mg/animal, 1x, 8x or 16 × (highest dose), ≤ 2 months	16 months	0/13, 1/19 and 1/8 with papillomas; no carcinomas observed; control: 0/12	q yes/ln	Bock & King (1959)
	Mouse, B6AF1/J, newborn	m	20 or 40	Oral; 1.5 mg/animal, 3x/wk, 5 weeks	≤ 547-600 days	100% hepatomas and 95% pulmonary adenomas; solvent only: 10% hepatomas and 35% pulmonary adenomas	p no/val	Klein (1963)
	Mouse, B6AF1/J, newborn	m	20	Oral; 1.5 mg/animal, 1x/day, 2 days	568 days	80% hepatomas and 85% lung adenomas (inadequately reported)	p no/val	Klein (1963)
	Rat, Sprague- Dawley	f	10	Oral; 200 mg/rat, 1x	60 days	No tumours in treated animals; control: 8/164 after 310 days	n no/ln, lc	Huggins & Yang (1962)
Benzo[a]pyrene								
	Mouse, A/ HeJ	f	15	Oral; 3 mg/animal in sesame oil, 2x	30 weeks	Increased pulmonary tumours (16.6); control: 0.3	p yes/val	Wattenberg & Leong (1970)
	Mouse, A/J	f	15	Oral; 2 mg/animal, 3x, every2 weeks	26 weeks	15/15 with forestomach tumours and 15/15 with pulmonary adenomas; no control	p yes/val	Sparnins *et al*. (1986)
	Mouse, CFW	m/f	25-73	Oral (diet); 0.004-1 mg/animal per day, < 110-165 days	140-200 days	Dose-dependent gastric tumours (0-90%); control: no tumours	p no/val	Neal & Rigdon (1967)

	Mouse, CFW	m/f	9-26	Oral (diet); 1-20 mg/animal/day, < 1-30 days	150-300 days	Dose-dependent gastric tumours (0-100%); control: no tumours	p no/val	Neal & Rigdon, (1967)
	Mouse, White Swiss	m/f	60-175	Oral (diet); 0.25 and 1 mg/g food, < 34 weeks	≤ 34 weeks	33 and 61 % with stomach tumours; 53 and 20% with lung tumours; controls: 1 and 21%	p no/val	Rigdon & Neal (1966)
	Rat, Sprague- Dawley	f	9	Oral; 100 mg/kg, 1x	60 days	8/9 with mammary tumours; control: 8/164 in 310 days	p no/ln, lc	Huggins & Yang (1962)
	Rat LEW/ Mai	f	20	Oral; 625 mg/animal, 1x/week, 8x; 50 mg/animal, 1 ×	90 weeks	67-77% with mammary tumours; control: 30%	p yes/val	McCormick *et al*. (1981)
	Hamster, Syrian golden	m/f	13	Oral (diet); 2.5 mg/animal, 4 days/week, < 14 months	≤ 14 months	9/13 with forestomach cancer; 2/13 with papillomas	p no/val	Chu & Malmgren (1965)
Dibenz[a,h]anthracene								
	Mouse Swiss	m		Oral; 1.5 mg/animal in PEG-400, 1 x; initiation experiment	30 weeks	21 % forestomach papillomas; promotor only: 14%	q no/lc	Berenblum & Haran (1955)
	Mouse DBA/2	m/f	21/21 control: 25/10	Drinking water; 0.8 mg/day/animal in olive oil, 8-9 months	8-9 months	14/14 m and 13/13 f with pul-monary aden.; 14/14 m and 10/13 f with alveologenic carc; control: 1 mouse with tumour	p no/val	Snell & Stewart (1962)
Fluorene								
Highly purified	Rat, Buffalo	f	20	Oral (diet); 0.05% diet; 4.3 mg/rat per day = 796 mg/rat (total intake over 6 months	10.7 months	2/11 carcinomas (renal pelvis, ureter); control: 4/16 with carcinomas	q no/ld	Morris *et al*. (1960)
	Rat, Buffalo	f	18	Oral (diet); 0.05% diet; 4.6 mg/rat per day = 2553 mg/rat (total intake) over 18 months	≤ 20.1 months	7/18 tumours; control: 4/18 or15/18 tumours	q no/val	Morris *et al*. (1960)
Naphthalene								
	Rat, BDI/ BDI II inbred		28	Oral (diet); 10-20 mg/animal, 6x/ week, 70 weeks	Life	No tumours	n no/ld	Schmahl (1955)
Phenanthrene								
	Rat, Sprague- Dawley	f	10	Oral; 200 mg/rat, 1x; experiment on mammary tumours	60 days	No tumours at 60 days; controls: 8/164 after 310 days	n no/ln, lc	Huggins & Yang (1962)

Result: p(ositive), n(egative), q(uestionable); Stat, statistical evaluation: yes or no; Val, validity: val, valid; ld, limited design; lc, limited documentation; ls, limited survival; ln, limited number of animals; m, male; f, female.

J5 Dermal exposure

Table J.5 Adapted from IPCS 1998 (Table 90, page 399 - 471: Carcinogenicity of polycylic aromatic hydrocarbons in experimental animals)[70].

Purity	Species, strain	Sex	No./ sex/ group	Route of dosage administration	duration at death/ sacrifice	Incidence and type of tumour	Result Stat./ Val.	References adapted from IPCS 1998
Acenaphthene								
	Mouse		100	Dermal; dissolved in 90% benzene	9 months	No tumours observed	n no/lc	Kennaway (1924)
'Pure'	Mouse, white	m	85	Dermal; 3 drops, 1x/ week of approx. 300 solution, 1 year; initiation experiment	≤1 year	After 12 months 5/85 survived with a total of 2 tumours; 0.4 tumour/ animal; promotor only: 0.08 tumour/animal	q no/ls	Graffi *et al*. (1953)
	Mouse		30	Dermal; 0.3% in benzene, 2 x/week, life	Life	1/30 lung adenoma	n no/ld	Badger *et al*. (1940)
Recrystallized	Mouse, Ha/lcR/ Mil	f	20	Dermal; 0.05 or 0.1%, 3 x/week, 12 months	15 months	0/20 with tumours	n no/val	Hoffmann & Wynder (1966)
Recrystallized	Mouse, Swiss Ha/ lcR/Mil	f	30	Dermal; 25 µg/animal, 10 × over20 days; initiation experiment	6 months	2/25 papillomas; promotor only: 526	n no/val	Hoffmann & Wynder (1966)
'Rigourously purified'	Mouse, lcR/Ha	f	13	Dermal; 0.25 mg/animal, 4 x; initiation experiment	65 weeks	2/13 papillomas; promotor only: 520 papillomas; control acetone: 0/ 20 papillomas	n no/val	Van Duuren *et al*. (1968)
Recrystallized	Mouse, Swiss	f	30	Dermal; 43 µg/animal, 2 x/week, 75 weeks	< 100	1/30 with skin carcinoma; control: 2/30 with carcinomas	n no/val	Lijinsky & Garcia (1972)
98.65%	Mouse, Swiss	f	40	Dermal; 109 µg/animal, 2 x/week, 30 weeks	70 weeks	47% skin-tumour-bearing animals; solvent control: 0%	p no/val	Cavalieri *et al*. (1977)
TLC- purified)	Mouse, CD-1	f	30	Dermal; 0.69 mg/animal, 1x; initiation experiment	35 weeks	18% with papillomas; promoter only: 3%	p no/val	Scribner (1973)
> 99%	Mouse, Sencar	f	27	Dermal; 221 µg/animal, 1x; initiation experiment	26 weeks	11 % papillomas; solvent only: 9%	n yes/val	Cavalieri *et al*. (1989)
Anthracene								
	Mouse		2x100	Dermal; 40% suspension/solution	5 months	0/100, 1/100 tumours	n no/lc	Kennaway (1924)

	Mouse		44	Dermal; 5%, 3x/week	< 11 months	No skin tumours	n no/lc	Miescher (1942)
	Mouse, 'S'		20	Dermal; 1.5 mg/animal, 2x/day; 3 days/week; total: 20 x; initiation experiment	21 weeks	3/17 with tumours; promotor only: 4/19	n yes/val	Salaman & Roe (1956)
	Mouse, Swiss Millerton	f	5	Dermal; 10% solution, 3x/week, life	< 20 months	No skin tumours	n no/ln, ld	Wynder & Hoffmann (1959a)
TLC- purified	Mouse, CD-1	f	30	Dermal; 1.8 mg/animal, 1x; initiation experiment	35 weeks	14% with papillomas; promoter only: 3%	q no/val	Scribner (1973)
	Mouse, Skh:hairless 1, outbred	m/f	24	Dermal; 4 µg, 1 x/day, 5 days/week, 38 weeks, then 2 h/day UV	38 weeks	No increased tumour frequency compared with controls	n yes/val	Forbes *et al*. (1976)
	Mouse, Swiss albino (Ha/lcR)	f	20	Dermal; 100 µg/animal, 10x on alternate days; initiation experiment	24 weeks	15% with tumours; solvent: 10%	n yes/val	LaVoie *et al*. (1983a)
Benz[a]anthracene								
Purified	Mouse		30	Dermal; 0.3% in benzene, 2x/week,life	≤ 584 days	1/30 epitheliomas	n no/ld	Barry *et al*. (1935)
'Pure'	Mouse, white	m	75	Dermal; 3 drops, 1x/week of 0.5% solution, 1 year; initiation experiment	≤ 1 year	After 12 months 9/75 survived with a total of 18 tumours; 2 tumours/animal; promotor only: 0.08 tumour/animal	p no/val	Graffi *et al*. (1953)
Recystallized	Mouse, albino	f	30	Dermal; 66 µg/animal, 2x/week, 20 weeks	13-15.5 months	No tumours; solvent only: no tumours	n no/val	Miller & Miller (1963)
	Mouse, C3H		20	Dermal; 0.5% solution, 2x/week, 638 days	638 days	No tumours; control: no tumours	n no/val	Stevenson & von Haam (1965)
Recrystallized	Mouse, C3H+e		30-50	Dermal; 0.0001-0,5 mg/animal in n-dodecane or 0. 1 mg/animal in toluene, 3x/week, 50 weeks	≤ 88 weeks	Dose-dependent increase in malignant tumours; solvent control: no tumours	p yes/val	Bingham & Falk (1969)
Recrystallized	Mouse, Swiss Millerton ICR/Ha	f	20	Dermal; 1 mg/animal, 1x; initiation experiment	58-60 weeks control: 0	10/20 with papillomas; promotor only: 1/20; solventn 0%	p no/val	Van Duuren *et al*. (1970)
TLC purified	Mouse, CD-1	f	30	Dermal; 0.5 mg/animal, 1x; initiation experiment	35 weeks	62% with papillomas; promotor only: 3%	p no/val	Scribner (1973)
> 99%	Mouse, Swiss	f	40	Dermal; 90 µg/animal, 2x/week, 30 weeks	70 weeks	2.6% skin-tumour bearing animals; solvent control: 0%	n no/val	Cavalieri *et al*. (1977)

> 99%	Mouse, CD-1	f	30	Dermal; 0.46 mg/animal, 1x; initiation experiment	26 weeks	57% with papillomas; promotor only: 6%	p no/val	Slaga *et al*. (1978)
	Mouse, CD-1	f	30	Dermal; 0.1 and 0.57 mg/animal, 1x; initiation experiment	27 weeks	14% and 36% ($p < 0.05$) with tumours; solvent control: 7%	p yes/val	Levin *et al*. (1984)
	Mouse, CD-1	f	30	Dermal; 0.23 and 0.57 mg/animal, 1x; initiation experiment	27 week	17% and 38% papillomas; solvent control: 4%	p yes/val	Weyand *et al*. (1990); Wood *et al*. (1980)
	Rat, Donryu	m	25	Dermal; saturated solution in acetone, dropped at 2x/wk to cover 2 cm2, 5 months	≤ 18 months	No tumours	n no/ld	Tawfic (1965)
Chromatography control	Hamster Syrian golden	m/f	50	Dermal ; 8 drops of a 0.5% solution, 2x/week, 10 weeks	≤ 85/61 weeks	No tumours	n no/ln, ld	Shubik *et al*. (1960)
	Hamster, Syrian golden	m 26	5 or	Dermal (buccal pouch); 20 mmol/litre solution, painting 2x/wk, 5 or 20 wks	≤ 44 weeks	No tumours; control: no tumours	n no/val	Solt *et al*. (1987)
Benzo[b]fluoranthene								
	Mouse, Swiss Millerton	f	20	Dermal; 0.01, 0.1 and 0.5%, 3x/week, life	≤ 14,12, and 8 months	0.01%: 5% papillomas after 14 mo; 0.1%: 65% papillomas and 85% carcinomas after 12 mo; 0,5%: 100% carcinomas after 5 mo	p no/ld	Wynder & Hoffmann (1959b)
	Mouse, Swiss ICR/Ha	f	20	Dermal; 1 mg, 1x; initiation experiment	63 weeks	18/20 papillomas, 5/20 carcino-mas; promotor only: 5/20, 1/20	p no/val	Van Duuren *et al*. (1966)
> 96%	Mouse, NMRI	f	40	Dermal; 3.4, 5.6, 9.2 µg/animal, 2x/week, life	≤ 2 years	5/15/540% with local tumours; control: no tumours	p yes/val	Habs *et al*. (1980)
	Mouse, CD-1			Dermal; 10-100 µg/animal; initiation experiment	20 weeks	Dose-related skin tumour incidence	p yes/val	LaVoie *et al*. (1982b)
> 99%	Mouse, Cr1:CD1 (ICR)BR	f	20	Dermal; 4 and 10 nmol/animal, 10x every other day; initiation experiment	34 weeks	45 and 95% tumour incidence; solvent control: 5%	p yes/val	Amin *et al*. (1985a)
	Mouse, CD-1	f	20	Dermal; 0.025 and 0.1 mg/animal, 10x every other day; initiation experiment	24 weeks	100 and 100% tumour incidence; solvent control: 10%	p yes/val	Weyand *et al*. (1990)
	Mouse, Cr1:CD1 (ICR)BR	f	20	Dermal; 3 and 10 µg/animal, 10x; initiation experiment	34 weeks	65 and 100% with tumours; solvent control: 15%	p yes/val	Amin *et al*. (1991a)

Benzo[j]fluoranthene								
Highly purified	Mouse, Swiss	f	20	Dermal; 0.1 and 0.5%, 3x/week, life	≤ 9 and 7 months	100%/95% with skin carcinomas	p no/ld	Wynder & Hoffmann (1959b)
96%	Mouse, NMRI	f	40	Dermal; 3.4, 5.6, 9.2 µg/animal, 2x/week, life	≤ 2 years	3, 3, and 5% with local tumours; controls: 0%	q yes/val	Habs *et al*. (1980)
> 99%	Mouse, Cr1:CD1 (ICR)BR	f	20	Dermal; 3, 10, 100 µg, 10x over 20 days; initiation experiment	24 weeks	30, 55, and 95% with tumours (papillomas/ keratinizing lesions); 1 malignant lymphoma	p yes/val	LaVoie *et al*. (1982b)
	Mouse, CD-1	f	20	Dermal; 25, 75 µg, 10x over 20 days; initiation experiment	24 weeks	70 and 90% with papillomas; vehicle control: 10%	p yes/val	Rice *et al*. (1987)
Benzo[ghi]fluoranthene								
Highly purified	Mouse, Swiss	f	20	Dermal; 0.1 and 0.5%, 3x/week, life	≤ 13 months	No skin tumours	n no/ld	Wynder & Hoffmann (1959b)
	Mouse, Swiss ICR/Ha	f	20	Dermal; 1 mg, 1x; initiation experiment		4/20 papillomas, no carcinomas; promotor only: 5/20, 1/20	n no/val	Van Duuren *et al*. (1966)
Benzo[k]fluoranthene								
Highly purified	Mouse, Swiss	f	20	Dermal; 0.1 and 0.5%, 3x/week, life	≤ 13 months	0/20 and 2/20 skin papillomas	q no/ld	Wynder & Hoffmann (1959b)
	Mouse, NMRI	f	25	Dermal; 1 mg/animal (total dose) in 50 aliquots	2 years	No skin tumours; spontaneous tumours: 10%	n na/val	Mohr (1969)
> 96%	Mouse, NMRI	f	40	Dermal; 3.4, 5.6, 9.2 µg/animal, 2x/week, life	≤ 2 years	3, 0 and 0% with local tumours; control: no tumours	n yes/val	Habs *et al*. (1980)
> 99%	Mouse, Cr1:CD1 (ICR)BR	f	20	Dermal; 3, 10, 100 µg, 10x over20 days; initiation experiment	24 weeks	5, 25, and 75% with tumours (papillomas/ keratinizing lesions)	p yea/val	LaVoie *et al*. (1982b)
Benzo[a]fluorene								
	Mouse, stock'		20	Dermal; 0.3%, 2x/ week, life	≤ 20 months	No skin tumours; 4/20 lung adenoma; 1/20 sebaceous adenoma	q no/ld	Badger *et al*. (1942)
> 99.5%	Mouse, Swiss Ha/ ICR	f	20	Dermal; 100 µg, 10x over 20 days; initiation experiment	24 weeks	2/20 skin tumours; control: 1/20	n yes/val	LaVoie *et al*. (1981c)
Benzo[b]fluorene								
99.5%	Mouse, Swiss Ha/ ICR	f	20	Dermal; 100 µg, 10x over 20 days; initiation experiment	24 weeks	4/20 skin tumours; control: 1/20	q yes/val	LaVoie *et al*. (1981c)

Benzo[ghi]perylene								
	Mouse, Swiss	f	50	Dermal; 0.38% solution in benzene, 3x/week, life		2/50 with skin tumours; control: 1/59 skin carcinomas	n no/val	Lijinsky & Saffiotti (1965)
Chromatography purified	Mouse, Swiss Ha/I CR/Mil	f	20	Dermal; 0.05% and 0.1 %, 3x/week, 12 months	15 months	1/20 and 0/20 skin papillomas; solvent control: no tumours	n no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss Ha/ICR/Mil	f	30	Dermal; 25 µg/animal, 10x over 28 days; initiation experiment	6 months	2/30 papillomas; control: 2/30 0/20	n no/val	Hoffmann & Wynder (1966)
	Mouse, NMRI	f	50	Dermal; 20 µg, 2 mg and 4 mg/ animal, 2x/week, 25 weeks	≤ 22.5 months	3/50, 6/50, and 4/50 with tumours; vehicle control: 7/50	n no/val	Muller (1968)
	Mouse, NMRI	f	50	Dermal; 1 and 2 mg/animal, 1x; initiation experiment	≤ 22.5 months	5/50 and 4/50 with tumours; vehicle control: 7/50	n no/val	Muller (1968)
Rigourously purified	Mouse, Swiss	f	20	Dermal; 0.8 mg/animal, 1x; initiation experiment	12-13 months	3/20 papillomas, 1/20 squamous-cell carcinoma; vehicle control: 1/20 with2 papillomas	n no/val	Van Duuren *et al*. (1970)
Highly purified	Mouse, ICR/Ha	f	50	Dermal; 5.5 and 16.5 µg/animal, 3x/week, 33 weeks	33 weeks	No tumours	n no/lc	Goldschmidt *et al*. (1973)
	Mouse, Swiss ICR/Ha	f	50	Dermal; 21 µg/animal, 3x/week, 52 weeks	52 weeks	No skin tumours; solvent control: no tumours	n no/val	Van Duuren & Goldschmidt (1976)
Benzo[c]phenanthrene								
	Mouse,		20	Dermal; not specified	< 676 days	7 epitheliomas, 5 papillomas	p no/ld	Barry *et al*. (1935)
	Mouse,		40	Dermal; 0.3%, 2x/week, < 19 months	≤ 19 months	1 papilloma, 4 squamous cell	q no/ld	Badger *et al*. (1940)
	Mouse, C3H		20	Dermal; 0.5% solution, 2x/week, 638 days	638 days	3 carcinomas, 2 sarcomas; control: no tumours	q no/val	Stevenson & von Haam (1965)
	Mouse, CD-1	f	30	Dermal; 91 and 457 µg, 1x; initiation experiment	21 weeks	5/30 and 11/30 papillomas; control: no tumours	p	Levin *et al*. (1980)
Benzo[a]pyrene								
	Mouse, Swiss	f	20-30	Dermal; 0.001, 0.005, and 0.01%, 3x/week, life	21, 14, and 11 months	3 and 43%, 63 and 73%, and951% and 95% with skin carcinomas/papillomas	p no/ld	Wynder & Hoffmann (1959a)

	Mouse, Swiss Millerton	f	20	Dermal; 0.01, 0.05 and 0.5%, 3x/week, life	≤ 12, 6, and 6 months	85, 95, and 75% with skin carcinomas	p no/ld	Wynder & Hoffmann (1959b)
Recrystallized	Mouse, Swiss Ha/ICR/Mil	f	20	Dermal; 0.05 and 0.1%, 3x/week, 12 months	15 months	17/20 and 19/20 skin tumours; solvent control: no tumours	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss Ha/ICR/Mil	f	30	Dermal; 25 µg/animal, 1/x over 28 days; initiation experiment	6 months	24/30 papillomas; promotor only: 2/30	p no/val	Hoffmann & Wynder (1966)
	Mouse, NMRI	f	50	Dermal; 20 and 200 µg/animal, 2x/week, 25 weeks	22.5 months	50/50 and 50/50 with skin tumours; vehicle control: 7/50	p no/val	Muller (1968)
	Mouse, C3H/He		20-30	Dermal; (a) 0.00002% in n-dodecane/decalin; (b) 0.02% in decalin, 3x/week, 50 weeks		(a) 21% malignant tumours; (b) 50% tumours (three orders of magnitude difference in dose)	p yes/val	Bingham & Falk (1969)
	Mouse, Swiss Ha/ICR/Mil	f	30	Dermal; 5 µg/animal, 10x, 20 days; initiation experiment	24 weeks	19/29 tumour-bearing animals, 67 skin tumours; control: 1/30	p no/val	Hoffmann *et al*. (1972)
	Mouse, Swiss ICR	f	20	Dermal; 0.05 and 0.1 mg/animal; 60x	6 months	13 and 18 with skin tumours; no solvent control	p no/val	Masuda & Kagawa (1972)
	Mouse, Swiss Ha/ICR/Mil	f	20	Dermal; 5 µg/animal, 3x/week, 72 weeks	≤ 72 weeks	13/20 with 22 skin tumours; 4/20 with 4 carcinomas; solvent control: no tumours	p no/val	Hecht *et al*. (1974)
	Mouse, Swiss ICR/Ha	f	50	Dermal; 5 µg/animal, 3x/week, life	440 days	16 animals with 26 tumours; control: no tumours	p no/val	Van Duuren & Goldschmidt (1976)
	Mouse, Swiss Ha/ICR	f	20	Dermal; 5 and 10 µg/animal, 3x/week, 62 weeks	62 weeks	Low dose: 10/20 with 19 skin tumours, 7/20 with 8 carcinomas; high dose: 18/20 with 70 skin tumours, 14/20 with 16 carcinomas; solvent control: no tumours	p yes/val	Hecht *et al*. (1976b)
99.9%	Mouse, Swiss	f	40	Dermal; 100 µg/animal, 2x/week, 30 weeks	70 weeks	79% skin-tumour bearing ani-mals; solvent control: no tumours	p no/val	Cavalieri *et al*. (1977)
	Mouse, NMRI	f	40	Dermal; 1.7, 2.8, 4.6 µg/animal, 2x/week, life	2 years	24, 69 and, 61 % with local tumours (high rate of systemic tumours); control: no tumours	p yes/val	Habs *et al*. (1980)
> 99.5%	Mouse, Swiss Ha/ICR	f	20	Dermal; 30 µg/animal, 10x on alternate days; initiation experiment	24 weeks	93% with tumours; vehicle control: no tumours	p no/val	LaVoie *et al*. (1981b)

	Mouse, Cr1:CD1 (ICR)BR	f	20	Dermal; 3 µg, 10x over 20 days; initiation experiment	24 weeks	85% with tumours (papillomas/ keratinizing lesions)	p yes/val	LaVoie *et al*. (1982b)
> 96%	Mouse, NMRI	f	20	Dermal; 2 and 4 µg/ animal, 2x/week, life	648 and528 days (mean)	45% (10% papillomas/ 35% carcinomas) and 85% (0%/85%) with skin tumours; control: no tumours	p yes/val	Habs *et al*. (1984)
99.5%	Mouse, CH3/HeJ	m	50	Dermal; 12.5 µg/animal, 2x/week, 99 weeks	≤ 99 weeks	94% with malignant skin tumors; solvent control: no tumours; untreated control: no tumours	p no/val	Warshawsky & Barkley (1987)
	Mouse, Sencar	f	24	Dermal; 0.8 µmol/ mouse, 1x; initiation experiment	24 weeks	Enhanced incidence of skin papillomas (80-92%)	p no/val	Cavalieri *et al*. (1988b)
	Mouse, Swiss	m	12	Dermal; 1.2 mg/animal, 6 days/wk, 19 weeks	27 weeks	Multiple tumours; squamous-cell carcinomas	p no/ln	Shubik & Della Porta (1957)
> 99%	Mouse, CD-1	f	20	Dermal; 2.5 µg/animal, 10x over 20 days; initiation experiment	24 weeks	89% tumours, 5.5 skin tumours/animal; control: 5%	p yes/val	Rice *et al*. (1988b)
	Mouse, CD-1	f	25	Dermal; 2.5 µg/animal, 10x over 20 days; initiation experiment	23 weeks	96% tumours, 3.4 skin tumours/ animal; control: no tumours	p yes/val	Rice *et al*. (1990)
Chromatography purified	Mouse, Sencar	f	23-24	Dermal; 8.4, 25.2 and 75.7 µg/ animal, 1x; initiation experiment	15 weeks	10/23, 17/24 and 21/23 with tumours; control: no tumours	p yes/val	Cavalieri *et al*. (1991)
	Mouse, Sencar	f	24	Dermal; 1, 5 and 25 µg/ animal, 1 x; initiation experiment	27 weeks	1/24, 10/24 and 22/24 with tumours; control: no tumours	p yes/val	Cavalieri *et al*. (1991)
	Mouse, Sencar	f	24	Dermal; 25 µg/animal, 1x; initiation experiment without promotion	27 weeks	1/24 with tumours	p yes/val	Cavalieri *et al*. (1991)
HPLC control	Mouse, ICR/Harlan	f	43-50	Dermal; 16, 32, or 64 µg/animal, 1x/week, 29 weeks	≤ 35 weeks	1, 1.5 and 7.5 tumours/ animal after 35 weeks	p no/val	Albert *et al*. (1991a)
	Mouse, Balb/c	m	20	Dermal; 100 µg/animal, 2x/week, 3 weeks-5 months		Tumours from 15 weeks onwards	p no/val	Andrews *et al*. (1991)
Chromatography control	Hamster, Syrian golden	m/f	15/15	Dermal; 4 drops of a 0.8% solution in mineral oil, 1x/week, 8 weeks including a 30-week interval	≤ 99/68 weeks	m:1 small nodular melanotic lesion, 2 malignant lymphomas; f: no tumours	q no/ln, ld	Shubik *et al*. (1960)
Chromatography control	Hamster, Syrian golden	m/f	5/5	Dermal; 6 drops of 0.01% solution in acetone, 2x/week, 40 weeks	≤ 70 weeks	No skin tumours	n no/ln, ld	Shubik *et al*. (1960)

	Hamster, Syrian golden	m	5 or28	Dermal (buccal pouch); 20 mmol/litre solution, painting 2x/week, 5 or 20 weeks	≤ 44 weeks	10% buccal pouch carcinomas after 40 week; control: no tumours	p no/val	Solt *et al*. (1987)
Benzo[e]pyrene								
	Mouse, Swiss Millerton	f	20	Dermal; 0.1%, 3x/ week, life	13 months	2/20 papillomas, 3/20 carcinomas	q no/ld	Wynder & Hoffmann (1959a)
	Mouse, Swiss ICR/Ha	f	20	Dermal; 1 mg, 1x; initiation experiment	64 weeks	2/20 with papillomas; pure substance: no tumours	q no/val	Van Duuren *et al*. (1968)
TLC purified	Mouse, CD-1	f	20	Dermal; 2.5 mg/animal, 1x; initiation experiment	35 weeks	85% with papillomas; promotor only: 3%	p no/val	Scribner (1973)
Highly purified	Mouse, ICR/Ha	f	50	Dermal; 15 µg/animal, 3x/week, 368 days	368 days	No tumours observed; control: no tumours	n no/val	Van Duuren & Goldschmidt (1976)
> 99%	Mouse, CD-1	f	30	Dermal; 100 µg/animal, 2x/week, 30 weeks	30-40 weeks	At 30 wks: 68% papillomas, at 40 weeks: 24% carcinomas	p no/val	Slaga *et al*. (1979)
	Mouse, CD-1	f	30	Dermal; 100 and 252 µg/animal, 1 x; initiation experiment	30-40 weeks	High dose: at 30 weeks, 19% papillomas; at 40 weeks, no carcinomas; vehicle control: at 30 weeks, 14% papillomas	q no/val	Slaga *et al*. (1979)
99%	Mouse, CD-1	f	30	Dermal; 0.25, 0.63, or 1.5 mg/ animal, 1x; initiation experiment	26 weeks	15, 11, or 140% with papillomas; vehicle control: 7% papillomas	q no/val	Buening *et al*. (1980)
> 95%	Mouse, Sencar	f	30	Dermal; 0.5 mg/animal, 1 x; initiation experiment	15 weeks	17% with papillomas; vehicle control: 10%	q no/val	Slaga *et al*. (1980, 1981)
Chrysene								
	Mouse		100	Dermal; 1% in 90% benzene	≤ 11 months	No tumours	n no/ld, lc	Kennaway (1924)
Purified	Mouse			Dermal; 7.5% in liquid paraffin or oleic acid, 5x/week, 78 or 50 weeks	78 or 50 weeks	6 or 18 benign, 1 or 9 malignant tumours	q no/lc	Bottomley & Twort (1934)
Doubtful purity	Mouse		100 20	Dermal; (a) 0.3% in benzene or (b) 0.3% ln mouse fat, 2 x/week, life	≤ 704 days	(a) 1/100 papilloma and 1/100 epithelioma, (b) no tumours	n no/ld	Barry *et al*. (1935)
'Synthesized'	Mouse		20	Dermal; 0.3% (pure), 2x/week, 440 days	440 days	No tumours	n no/lc, ld	Barry *et al*. (1935)
	Mouse		50 100	Dermal; (a) 0.3% in benzene, (b) 7.5% in oleic acid, 2x/week, life	≤ 797 days	(a) 2/50 papillomas, (b) no tumours	n no/lc, ld	Barry *et al*. (1935)

'Pure'	Mouse		50	Dermal; in benzene, 2x/week, 276 days	≤ 276 days	After 276 days at 11/50 survivors, no tumours	n no/lc, ld	Schurch & Winterstein (1935)
	Mouse, CF1	m/f	10/10	Dermal; 40 µg/animal, 2x/week, 31 weeks	31 weeks	1/15 carcinomas	n no/ld	Riegel *et al*. (1951)
	Mouse, Swiss	f	20	Dermal; 1%, 3x/week, life	≤ 12 months	9/20 papillomas, 8/20 carcinomas; no solvent control	p no/ld	Wynder & Hoffmann (1959a)
	Mouse, Swiss ICR/Ha	f	20	Dermal; 1 mg, 1x; initiation experiment	63 weeks	16/20 papillomas, 2/20 carcino-mas; promotor only: 5/20, 1/20	p no/val	Van Duuren *et al*. (1966)
TLC purified	Mouse, CD-1	f	30	Dermal; 1 mg/animal, 1x; initiation experiment	35 weeks	73% with papillomas; promotor only: 3%	p no/val	Scribner(1973)
	Mouse, C3H	m	20	Dermal; 75 µg/animal in decalin, 2x/week, 82 weeks	82 weeks	1/12 papillomas; solvent control: 2/13 papillomas	n no/ld	Horton & Christian (1974)
	Mouse, C3H	m	20	Dermal; 75 µg/animal in decalin/ dodecane 50/50, 2x/week, 82 weeks; co-carcinogenicity experiment	82 weeks	5/19 papillomas; 12/19 carcinomas; solvent control: 2/13 papillomas	p no/val	Horton & Christian (1974)
> 99.9%	Mouse, Swiss Ha/ ICR/Mil	f	20	Dermal; 0.1 mg/animal/day, 110x; initiation experiment	22 weeks	11/18 papillomas/carcinomas; chrysene only: 4/11 after 72 weeks; solvent control: no tumours	p no/val	Hecht *et al*. (1974)
	Mouse, CD-1	f	30	Dermal; 0.09, 0.29 and 0.91 mg/ animal, 1x; initiation experiment	26 weeks	25, 43 and 52% papillomas; promotor only: 7%	p no/val	Levin *et al*. (1978)
95%	Mouse, CD-1	f	30	Dermal; 0.46 mg/animal, 2x; initiation experiment	26 weeks	21/30 papillomas; promotor only: 1/30	p no/val	Wood *et al*. (1979)
98%	Mouse, CD-1	f	30	Dermal; 0.57 mg/animal, 1x; initiation experiment	27 weeks	80% papillomas; promotor only: 4%	p yes/val	Wood *et al*. (1980)
> 95%	Mouse, Sencar	f	30	Dermal; 0.46 mg/animal, 1x; initiation experiment	15 weeks	21/29 papillomas; promotor only: 3/30	p no/val	Slaga *et al*. (1980, 1981)
	Mouse, CD-1	f	30	Dermal; 0.09 and 0.274 mg/animal, 1 x; initiation experiment	26 weeks	43, 43% (or 39%) with skin pa-pillomas; vehicle control: 100%	p yes/val	Chang *et al*. (1983)
> 99%	Mouse, CD-1	f	20	Dermal; 3.4, 11.4 and 34 µg/ animal, 10x over 20 days; initiation experiment	24 weeks	25, 90 and 95% with tumours; 0.5, 3, and 4.5 skin tumours/ animal; control: 20%	p yes/val	Rice *et al*. (1988b)
	Mouse, CD-1	f	20	Dermal; 7.5 µg/animal, 1x; initiation experiment	21 weeks	10% with skin tumours; solvent control: 10%	n yes/val	Amin *et al*. (1990)

	Mouse, Sencar	m/f	16/16	Dermal; 365 µg/animal, 1x; initiation experiment	≤ 100 weeks	No skin tumours; solvent control: no tumours	n no/val	Bhatt & Coombs (1990)
Coronene								
> 96%	Mouse, NMRI	f	40	Dermal; 5 or 15 µg/animal, 4x/week, 104 weeks	≤ 104 weeks	Low dose: 1/39, high dose: 2/40 local tumours at application site; vehicle control: no tumours	n yes/val	Habs *et al*. (1980)
TLC control	Mouse, Swiss ICR/Ha	f	20	Dermal; 0.1 mg, 5x; initiation experiment	65 weeks	6/20 papillomas; promotor only: 5/20; coronene only: no tumours	q no/val	Van Duuren *et al*. (1968)
Cyclopenta[cd]pyrene								
> 96%	Mouse, NMRI	f	40	Dermal; 1.7, 6.8 and 27.2 µg/ animal, 2x/ week, 112 weeks	112 weeks	Low dose: no tumours; high dose: 2/38 skin carcinomas, 1/38 sarcomas; control: no tumours	q yes/val	Habs *et al*. (1980)
> 98%	Mouse, CD-1	f	30	Dermal; 23, 91, 226, 566 µg/ animal, 1x; initiation experiment	27 weeks	10, 21, 30, and 37% papillomas; promotor only: 4%	p yes/val	Wood *et al*. (1980)
> 99.9%	Mouse, Swiss	f	30	Dermal; 45, 136 and 407 µg/ animal, 2x/ week, 30 weeks	57 weeks	Low dose: 17; med. dose: 11; high dose: 7 skin tumours; control: no tumours	p no/val	Cavalieri *et al*. (1981b)
> 99.9%	Mouse, CD-1	f	30	Dermal; 4.5, 14 and 41 µg/animal, every other day, 20 days; initiation experiment	44 weeks	Low dose: 1/30; med. dose: 9/29; high dose: 6/29 papillomas; promotor only: 3/29	p no/val	Cavalieri *et al*. (1981b)
	Mouse, Sencar	f	30	Dermal; 10, 100 and 200 µg/ animal, 1x; initiation experiment	26 weeks	Low dose: 11 %; med. dose: 39%; high dose: 57% papillomas; promotor only: 10%	p no/val	Raveh *et al*. (1982)
Dibenz[a,h]anthracene								
	Mouse, Swiss Millerton	f	20	Dermal; 0.001, 0.01, and 0.1%, 3x/week, life	≤ 21, 13 or 9 months	0.001%: 30% papillomas, 30% carcinomas; 0.01%:95/90% papilloma/carcinoma; 0.1%: 90%/75% papilloma/ carcinoma	p no/ld	Wynder & Hoffmann (1959a)
	Mouse, Swiss albino DBA/2Jax	m	< 50	Dermal; 0.02 and 0.16 µg/animal, 1x; initiation experiment	32 weeks	33 and 38% with skin tumours; acetone control: 13%	p yes/val	Klein (1960)
Chromatograph recrystallized	Mouse, Swiss	f	20	Dermal; 38 µg/animal, 2x/wk, 44 weeks	≤ 60 weeks	80% with skin tumours; vehicle control: 4%	p no/val	Lijinsky *et al*. (1965)

	Mouse, IF/Bcr	m/f	30/30	Dermal; m: 0.3% solution (= 1.5 mg/animal), 1x/wk, 18 weeks; f: 0.5% (= 1 mg/ animal), 8x, every 2 weeks	≤ 29/22 weeks	m: 26% with papillomas after 20 wks, 100% after 29 weeks; f: 100% with breast tumours after 22 wks	p no/val	Johnson (1968)
> 99%	Mouse, NMRI	f	50	Dermal; 1 drop, 3x/ week, 112 weeks; total doses: 37.8, 125, and 378 µg/animal	112 weeks	6%, 8% and 32% with skin tumours; controls: 2-4%	p no/val	Platt *et al*. (1990)
> 99%	Mouse, NMRI	f	16	Dermal; 83.5 and 167 µg/animal, 1x; initiation experiment	24 weeks	38 and 93% with skin tumours; vehicle control: no tumours	p no/val	Platt *et al*. (1990)
Chromatography control	Hamster, Syrian golden	m/f	5/5 weeks	Dermal; 8 drops of a 0.2% solution, 2x/ week, 10 weeks	≤ 75	No tumours	n no/ln, ld	Shubik *et al*. (1960)
Dibenzo[a,e]pyrene								
Recrystallized	Mouse, Swiss albino Ha/ ICR/Mil	f	40/20	Dermal; 0.05 and 0.1% solution, 3x/week, 12 months	15 months	16/40, 9/20 with papillomas and 9/40, 6/20 with epitheliomas; solvent control: no	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss albino Ha/ ICR/Mil	f	28	Dermal; 25 µg/animal, 10x over 20 days; initiation experiment	6 months	10/28 papillomas; promotor only: 2/30	p no/val	Hoffmann & Wynder (1966)
> 99%	Mouse, Sencar	f	21	Dermal; 242 µg/animal, 1x; initiation experiment	26 weeks	240% papillomas; solvent control: 9%	p yes/val	Cavalieri *et al*. (1989)
Dibenzo[a,h]pyrene								
	Mouse		74	Dermal; 1 drop of a 0.15% solution alternate days, 55 or 86 times	4.5 months	50% with skin tumours	p no/lc	Kleinenberg (1939)
Recystallized	Mouse, Swiss albino Ha/ ICR/Mil	f	20	Dermal; 0.05 and 0.1% solution, 3x/week, 12 months	11,15 months	16/20,15/20 with papillomas and 13/20, 15/20 with epitheliomas; solvent control: no tumours	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss albino Ha/ ICR/Mil	f	29	Dermal; 25 µg/animal, 10x over 20 days; initiation experiment	6 months	21/29 papillomas; promotor only: 2/30	p no/val	Hoffmann & Wynder (1966)
96.6%	Mouse, Swiss	f	40	Dermal; 120 µg/animal, 2x/week, 30 weeks	70 weeks	90% tumour incidence; solvent control: no tumours	p no/val	Cavalieri *et al*. (1977)
Pure	Mouse, CD-1	f	30	Dermal; 15.1, 60.5 and 181.4 µg/animal, 1x; initiation experiment	17 weeks	55, 79, and 72% with skin tumours; controls: 0-10%	p yes/val	Chang *et al*. (1982)
> 99%	Mouse, Sencar	f	24	Dermal; 242 µg/animal, 1x; initiation experiment	26 weeks	75% papillomas; solvent control: 9%	p yes/val	Cavalieri *et al*. (1989)

Dibenzo[a,i]pyrene								
	Mouse, XVII	m	23	Dermal; 1 drop of a saturated solution, 2x/week	7 months	21/23 papillomas and 8/23 epitheliomas; solvent control: no tumours (14 months)	p no/val	Lacassagne *et al*. (1958)
	Mouse, Swiss Millerton	f	20/10	Dermal; 0.01 and 0.1 %, 3x/week, 16 and 13 months	≤ 16 and13 months	0.01%: 10% papillomas, no carcinomas; 0.1%: 50% papillomas, 10% carcinomas	p no/ld	Wynder & Hoffmann (1959a)
Recrystallized	Mouse, Swiss albino Ha/ICR/Mil	f	20	Dermal; 0.05 and 0.1 % solution, 3x/week, 12 months	15 months	16/40, 16/20 with papillomas and 13/20, 15/20 with epitheliomas; solvent control: no tumours	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss albino Ha/ICR/Mil	f	30	Dermal; 25 µg/animal, 10x over 20 days; initiation experiment	6 months	12/30 papillomas; promotor only: 2/30	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss albino Ha/ICR	f	20	Dermal; 100 and 500 µg/animal, 1x; initiation experiment	22 weeks	40 and 80% with tumours; vehicle control: no tumours	p no/val	Hecht *et al*. (1981)
Pure	Mouse, CD-1	f	30	Dermal; 15.1, 60.5 and 181.4 µg/ animal, 1x; initiation experiment	17 weeks	28, 67, and 70% with skin tumours; controls: 0-10%	p yes/val	Chang *et al*. (1982)
> 99%	Mouse, Sencar	f	24	Dermal; 242 µg/animal, 1x; initiation experiment	26 weeks	63% papillomas; solvent control: 95%	p yes/val	Cavalieri *et al*. (1989)
Dibenzo[a,l]pyrene								
Recrystallized	Mouse, Swiss albino Ha/ICR/Mil	f	20	Dermal; 0.05 and 0.1% solution, 3x/week, 12 months	11, 14 months	17/20, 18/20 with papillomas and 17/20, 18/20 with epitheliomas; solvent control: no tumours	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss albino Ha/ICR/Mil		30	Dermal; 25 µg/animal, 10x over 20 days; initiation experiment	6 months	18/30 papillomas; 1/30 epitheliomas; promotor only: 2/30	p no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss ICR	f	19-21	Dermal; 55, 200, 240, 350 and 700 µg/animal given in 55, 40, 24, 7 and 7 applications	6 months	20, 19, 21, 19 and 16 with skin tumours; no solvent control group	p no/val	Masuda & Kagawa (1972)
> 99%	Mouse, Sencar	f	24	Dermal; 242 µg/animal, 1x; initiation experiment	26 weeks	92% papillomas; solvent control: 9%	p yes/val	Cavalieri *et al*. (1989)
Pure, 161-162°C)	Mouse, Sencar	f	24	Dermal; 10, 30 and 90 µg/animal, 1x; initiation experiment	15 weeks	23/24, 22/24 and 24/24 with tumours; control: no tumours	p yes/val	Cavalieri *et al*. (1991)
Pure	Mouse, Sencar	f	24	Dermal; 1.2, 6 and 30 µg/animal, 1x; initiation experiment	7 weeks	22/24, 20/24 and 20/24 with tumours; 2 control: no tumours	p yes/val	Cavalieri *et al*. (1991)

Chomatography purified	Mouse, Sencar	f	24	Dermal; 30 µg/animal, 1x; initiation experiment without promotion	27 weeks	7/24 with tumours	p yes/val	Cavalieri *et al*. (1991)
Fluoranthene								
	Mouse,		2x10	Dermal; 0.3% in benzene, 2x/week, life	≤ 501 days	No tumours	n no/ld	Barry *et al*. (1935)
	Mouse, Swiss Millerton	f	20	Dermal; 0.1 % solution, 3x/week, life	17 months	No papillomas or carcinomas	n no/ld	Wynder & Hoffmann (1959a)
	Mouse, Swiss Ha/ ICR/Mil	f	20	Dermal; 1%, 3x/week, 12 months	15 months	At 12 months 0/20 tumours; no vehicle control	n no/val	Hoffmann *et al*. (1972)
99.9%	Mouse, Swiss Ha/ ICR/Mil	f	30	Dermal; 0.1 mg/animal, 10x over 20 days; initiation experiment	24 weeks	1/29 skin tumours; solvent control: 1/30	n no/val	Hoffmann *et al*. (1972)
Recrystallized	Mouse, C3H	m	15	Dermal; 250 µg/animal in decalin, 2x/ week, 82 weeks	82 week	No papillomas or carcinomas; solvent control: 2/13 papillomas	n no/val	Horton & Christian (1974)
Purified, 107-109°C	Mouse, Swiss ICR/Ha	f	50	Dermal; 40 µg/animal, 3x/week, life	440 days	No tumours observed; controls: no tumours	n no/val	Van Duuren & Goldschmidt (1976)
Fluorene								
	Mouse		100	Dermal; dissolved in 90% benzene	9 months	No tumours	n no/ld, lc	Kennaway (1924)
	Mouse, CF1	m/f	10/10	Dermal; 60 µg/animal, 2x/week, 31 weeks	31 weeks	No skin tumours	n	Riegel *et al*.
'Pure'	Mouse, white	m	100	Dermal; 3 drops, 1x/ week of ≈ 3% solution, 1 year; initiation experiment	≤ 1 year	After 9 months 10/100 survived, no tumours; promotor only: 0.08 tumour/animal	n no/val	Graffi *et al*. (1953)
Indeno[1,2,3-cd]pyrene								
Recrystallized	Mouse, Swiss Ha/ ICR/Mil	f	30	Dermal; 25 µg/animal, 10x over 20 days; initiation experiment	6 months	5/30 papillomas; promotor: 2/30	q no/val	Hoffmann & Wynder (1966)
	Mouse, Swiss albino Ha/ ICR/Mil	f	20	Dermal; 0.05 and 0.1 % solution, 3x/week, 12 months	15 months	Dioxane solvent: no tumours; acetone solvent: dose-related tumour increase	q no/val	Hoffmann & Wynder (1966)
> 96%	Mouse, NMRI	f	40	Dermal; 3.4, 5.6, 9.2 µg/animal, 2x/week, life	≤ 2 years	3, 0, 0% with local tumours; control: no tumours	n yes/val	Habs *et al*. (1980)
	Mouse, Crl:CD1 (ICR)BR	f	25	Dermal; 100 µg/animal, 10x over 20 days; initiaton experiment	25 weeks	90% with skin tumours; vehicle control: < 5%	p yes/val	Rice *et al*. (1986)

> 99%	Mouse, CD-1	f	25	Dermal; 110 µg/animal, 10x over 20 days; initiation experiment	23 weeks	72% tumours, 2.1 skin tumours/animal; control: no tumours	p yes/val	Rice *et al*. (1990)
5-Methylcholanthrene								
> 99.9%	Mouse, Swiss Ha/ ICR/Mil	f	20	Dermal; 0.1 mg/animal, 3x/week, 35 weeks	35 weeks (solvent control: 72 weeks)	20/20 with 85 skin tumours by 25 week; 20/20 with 99 tumours and 12/20 with 37 carcinomas by 35 wks; solvent control: no tumours	p no/val	Hecht *et al*. (1974)
	Mouse, Swiss Ha/ ICR/Mil	f	20	Dermal; 10, 30 and 100 µg, 10x over 20 days; initiation experiment	24 weeks	Low dose: 20/20 mice with110 skin tum; med dose: 20/20 with 160 skin tumours; high dose: 17/18 with 96 skin tumours; solvent control: no tumours	p no/val	Hecht *et al*. (1974)
	Mouse, Swiss Ha/ ICR	f	20	Dermal; 5 and 10 µg/ animal, 3x/week, 62 weeks	62 weeks	Low dose: 9/20 with 22 skin tum, 6/20 with 7 carcinomas; high dose: 15/20 with 38 tumours, 10/20 with12 carcinomas; solvent control: no tumours	p yes/val	Hecht *et al*. (1976a)
Highly purified	Mouse, Swiss Ha/ ICR	f	20	Dermal; 1 and 3 µg, 10x over 20 days; initiation experiment	24 weeks	Low dose: 2/20 mice with 2 skin tumours; high dose: 20/20 with 45 skin tumours (1 carcinoma); solvent control: no tumours	p yes/val	Hecht *et al*. (1976a)
> 99.9%	Mouse, Swiss Ha/ ICR/Mil	f	8x20	Dermal; 3 and 10 µg, 10 × over 20 days; initiation experiment	24 weeks	Low dose: 55-95% of mice with skin tumours; high dose: 80-90%; solvent control: no tumours	p yes/val	Hecht *et al*. (1978)
> 99.9%	Mouse, Swiss Ha/ IC outbred	f	20	Dermal; 1 and 3 µg, 10x over 20 days; initiation experiment	24 weeks	Low dose: 75% of mice with skin tumours; high dose: 85%	p no/val	Hecht *et al*. (1979)
	Mouse, Swiss CD-1	f	20	Dermal; 1 or × or 3 µg/ animal, 10x over 20 days; initiation experiment	21 weeks	55, 75, and 90% with skin tumours; solvent control: 5%	p yes/val	Amin *et al*. (1981)
HPLC purified	Mouse, CD-1	f	20	Dermal; 8 and 24 µg/ animal, 1x; initiation experiment	26 weeks	80 and 90% tumour-bearing animals; solvent control: 10%	p yes/val	Hecht *et al*. (1985)
	Mouse, CD-1	f	20	Dermal; 8 µg/animal, 1x; initiation experiment	21 weeks	65% with skin tumours; solvent control: 5%	p yes/val	Amin *et al*. (1985b)
	Mouse, CD-1	f	20	Dermal; 24.2 µg/animal, 1x; initiation experiment	26 weeks	90% with tumours; 5.2 tumours/ animal; solvent control: 10%/0.1	p no/val	El-Bayoumy *et al*. (1986)

> 99%	Mouse, CD-1	f	20	Dermal; 3.6, 12.1 and 36 µg/ animal, 10x over 20 days; initiation experiment	24 weeks	100, 100 and 100% with tumours; 9.2, 10.7 and 9.4 tum/animal; solvent control: 20%	p yes/val	Rice *et al*. (1988b)
	Mouse, CD-1	f	20	Dermal; 8 µg/animal, 1x;initiation experiment	21 weeks	85% with skin tumours; solvent control: 10%	p yes/val	Amin *et al*. (1990)
	Mouse, CD-1	f	20	Dermal; 8 µg/animal, 1x; initiation experiment	26 weeks	65% with skin tumours; solvent control: 10%	p yes/val	Amin *et al*. (1992)
1-Methylphenanthrene								
>99.5%	Mouse, Swiss Ha/ ICR	f	20	Dermal; 100 µg, 10x over 20 days; initiaton experiment	24 weeks	No tumours; vehicle control: no tumours	n no/val	LaVoie *et al*. (1981b)
Naphthalene								
	Mouse			Dermal; several times/ wk, < 11 months	≤ 11 months	No skin tumours	n no/lc	Kennaway (1930)
Highly purified	Mouse, SW inbred		25; control: 21	Dermal; 0.5% in benzene, 6x/week for 3 weeks, then 2x/wk for life	Life	4/25 with lymphatic leukaemia; 1/25 lymphosarcoma of thymus; 4/25 with benign tumours; with sarcomas; 1/21 with lung benzene only: 2/21 adenoma	q no/lc, ln	Knake (1956)
	Mouse, ICR/Ha	f	30	Dermal; 0.25 mg/animal + 3 µg benzo[a]pyrene, 3x/wk, 78 weeks; co-carcinogenicity test	78 weeks	5/30 lymphomas; inhibitory effect on skin tumours; naphthalene only: no skin tumours	q no/val	Schmeltz *et al*. (1978)
Perylene								
Recrystalized	Mouse, Swiss ICR/Ha	f	20	Dermal; 0.8 mg/animal, 1x; initiation experiment	58-60 weeks	3/20 papillomas; promotor only: 1/20 with papillomas; pure substance only: no tumours	n no/val	Van Duuren *et al*. (1970)
Recrystallized	Mouse, C3H	m	20	Dermal; 75 µg/animal in decalin, 2x/week, 82 weeks	82 weeks	No skin tumours; solvent control: 2/13 papillomas	n no/val	Horton & Christian (1974)
Phenanthrene								
	Mouse		100	Dermal; dissolved in 90% benzene	9 months	No tumours	n no/ld, lc	Kennaway (1924)
'Pure'	Mouse, white	m	100	Dermal; 3 drops, 1x/ week of ≈ 3% solution, 1 year; initiation experiment	≤ 1 year	After 12 months 6/100 survived with a total of 1 tumour; 0.16 tumour/ animal; promotor only: 0.08 tumour/animal	n no/val	Graft *et al*. (1953)
	Mouse, 'S'		20	Dermal; 54 mg/animal, 3x/wk, total: 10x; initiation experiment	24 weeks	5/20 survivors with 12 papillomas; promotor only: 4/19 survivors/4 papillomas	q yes/val	Salaman & Roe (1956)

High purity	Mouse, 'stock albino'	m/f	10/10	Dermal; 0.3 mg, 4x on days 0, 2, 6 and 8; initiation experiment	24 weeks	4/19 papillomas; solvent control: 2/20	q yes/val	Roe (1962)
TLC purified	Mouse, CD-1	f	30	Dermal; 1.8 mg/animal, 1x; initiation experiment	35 weeks	40% with papillomas; promotor only: 3%	p no/val	Scribner (1973)
> 98%	Mouse, CD-1	f	30	Dermal; 1.8 mg/animal, 1x; initiation experiment	36 weeks	5/30 papillomas; solvent control: 2/30	q no/val	Wood *et al*. (1979)
	Mouse, Swiss Ha/ ICR	f	20	Dermal; 100 µg, 10x over 20 days; initiation experiment	24 weeks	No skin tumours observed; vehicle control: no tumours	n no/val	LaVoie *et al*. (1981b)
Pyrene								
	Mouse		2x20	Dermal; 1% in benzene, 2x/week, life	≤ 717 days	1/20 and 1/20 papillomas	n no/ld	Barry *et al*. (1935)
	Mouse		40	Dermal; 0.3% in benzene, 2x/ week, < 680 days	≤ 680 days	No skin lesions	n no/ld	Badger *et al*. (1940)
'Pure'	Mouse, white	m	150	Dermal; 3 drops, 1x/ week of a 0.3% solution, 1 year; initiation experiment	≤ 1 year	After 6 months 18/150 survived with a total of 1 tumour; 0.06 tumour/ animal; promotor only: 0.08 tumour/animal	n no/val	Graffi *et al*. (1953)
	Mouse, 'S'		20	Dermal; 25 mg/animal, 3x/week; total:10x; initiation experiment	24 weeks	6/20 mice with 9 papillomas; promotor only: 4/19 mice with 4 papillomas	q yes/val	Salaman & Roe (1956)
	Mouse, Swiss Millerton	f	5	Dermal; 10%, 3 x/ week, life	≤18 months	No skin tumours	n no/ld, ln	Wynder & Hoffmann (1959a)
TLC purified	Mouse, CD-1	f	30	Dermal; 2 mg/animal, 1x; initiation experiment	35 weeks	17% with papillomas; promotor only: 3%	q no/val	Scribner (1973)
High purity	Mouse, C3H	m	20	Dermal; 250 µg/animal in decalin, 2x/ week, 82 weeks	82 weeks	3/13 papillomas; solvent control: 2/13	q no/val	Horton & Christian (1974)
Recrystallized	Mouse, Swiss ICR/Ha	f	50	Dermal; 12 or 40 µg/ animal, 3 x/week, 368 or 440 days	≤ 440 days	No skin tumours observed; control: no tumours	n no/val	Van Duuren & Goldschmidt (1976)
High purity	Mouse, Swiss ICR/Ha	f	50	Dermal; 4 and 12 µg/ animal + 5 µg benzo[a]pyrene, 3x/ week, 33 weeks; cocarcinogenicity test	33 weeks	High dose: 13/50 papillomas, 5/50 carcinomas; benzo[a]-pyrene only: 6/50 papillomas; pyrene only: no tumours	n no/val	Goldschmidt *et al*. (1973)

Recrystallized	Mouse, Swiss ICR/Ha	f	50	Dermal; 4, 12 and 40 µg/animal + 5 µg benzo[a]pyrene, 3x/ week, 368/368 /440 days; co-carcinogenicity test	368 or 440 days	12/26/35 mice with papillomas, 6/20/26 with squamous cell carcinomas; positive control: 15, 11 tum; solvent control: no tum	p no/val	Van Duuren & Goldschmidt (1976)
> 98%	Mouse, CD-1	f	30	Dermal; 20.2 and 80.9 µg/animal, 1x; initiation experiment	27 weeks	14 and 10% with tumours; vehicle control: 10%	n yes/val	Wood *et al*. (1980)
Triphenylene								
	Mouse		10	Dermal; 0.3% in benzene, 2x/ week, life	≤ 548 days	No skin lesions	n no/ln, ld	Barry *et al*. (1935)
Recrystallized	Mouse, C3H	m	20	Dermal; 250 µg/animal in decalin, 2x/ week, 82 weeks	82 weeks	No skin tumours; solvent control: 2/13 papillomas	n no/val	Horton & Christian (1974)

Result: p(ositive), n(egative), q(uestionable); Stat, statistical evaluation: yes or no; Val, validity: val, valid; ld, limited design; lc, limited documentation; ls, limited survival; ln, limited number of animals; intrapulm., intrapulmonary injection; i.p., intraperitoneal injection; s.c., subcutaneous injection; i.m., intramuscular injection; m, male; f, female; TLC, thin-layer chromatography; DMSO, dimethylsulfoxide; HPLC, high-performance liquid chromatography; DMBA, 7,12-dimethylbenz[a]anthracene

J6 Subcutaneous injection

Table J.6 Adapted from IPCS 1998 (Table 90, page 399 - 471: Carcinogenicity of polycylic aromatic hydrocarbons in experimental animals)[70].

Purity	Species, strain	Sex	No./ sex/ group	Route of dosage administration	duration at death/ sacrifice	Incidence and type of tumour	Result Stat./ Val.	References adapted from IPCS 1998
Acenaphthene								
	Mouse, XVII	m/f	27	s.c.; 0.6 mg/animal, 1x/ month, 3 months		No local sarcomas observed	n no/ln, ld	Lacassagne *et al*. (1958)
Anthracene								
	Mouse, C57BI	m/f	40-50	s.c.; 5 mg/animal in tricaprylin; 1x	≤ 22-28 months	0/26 sarcomas after 5 months	n yes/ld	Steiner (1955)
Highly purified	Rat		10	s.c.; 1 mg/animal, 1x/ week, 103 weeks	< 103 weeks	No subcutaneous sarcomas	n no/ln	Boyland & Burrows (1935)
	Rat, Wistar		5	s.c.; 5 mg/animal, 6-7x	10 months	No tumours observed	n no/ln	Pollia (1941)
Highly purified	Rat, BD I/BD III		10	s.c.; 20 mg/animal, 1x/ week, 33 weeks	≤ 29 months	5/9 tumours (fibromas) at site injection	p no/ln, ld	Druckrey & Schmahl (1955)
Benz[a]anthracene								
Spectrometer	Mouse, C57BI control	m/f	50	s.c.; 5 mg/animal in tricaprylin; 1x	≤ 22 months	8/46 sarcomas after 4 months; solvent control: 3/280	p no/val	Stainer & Falk (1951)
	Mouse, C57BI	m/f	40-50	s.c.; 0.05, 0.2, 1, 5, or 10 mg/animal in tricaprylin; 1x	≤ 22-28 months	5/44,11/45,15/44, 20/36 and 5/16 sarcomas	p yes/ld	Steiner & Edgcomb (1952); Steiner (1955)
Recrystallized	Mouse, albino	f	30	s.c.; 0.94 mg/animal, 1x	≤ 15 months	No sarcomas; solvent control: no tumours	n no/val	Miller & Miller (1963)
	Mouse C3H		20	s.c.; 5 mg in tricaprylin, 1x	638 days	No tumours; control: no tumours	n no/val	Stevenson & von Haam (1965)
	Mouse, C57BL	m/f	10/10	s.c.; 1 mg/animal, 1x/ week, 10 weeks	60-80 weeks	8/10 m and 6/10 f with sarcomas; control: 0/20 m and 0/20 f	p no/val	Boyland & Sims (1967)

	Mouse, Swiss newborn	m/f	87	s.c.; 0.2 mg/animal in polyethylene glycol on days 0, 1 and 2 after birth	70-75 weeks	70 weeks: 15/15 m and 2/18 f with liver tumours, 4/15 m and10/ 18 f with lung tumours; corrected control data: 4/22 m and 1/23 f with liver tumours and 3/22 m and 1/23 f with lung tumours	p no/val	Grover *et al*. (1975)
Recrystal-lized	Rat, Holtzman	m	20	s.c.; 1.88 mg/animal, 1x	≥ 4 months	No sarcomas; solvent control: no tumours	n no/val	Miller & Miller (1963)
Benzo[b]fluoranthene								
	Mouse, XVII nc/ Z	m/f	16/14	s.c.; 0.6mg/animal, 1x/ month, 3 months	approx. 200 days	8/16 m and 10/14 f with local sarcoma	p no/ld	Lacassa-gne *et al*. (1963a)
Benzo[k]fluoranthene								
> 99%	Mouse XVII nc/ Z	m/f	16/14	s.c.; 0.6 mg/animal, 1x/ month, 3 months	≈ 200 days	8/16 m and 5/14 f with local sarcomas	p no/ld	Lacassa-gne *et al*. (1963a)
Benzo[a]fluorene								
> 99.5%	Mouse, stock'		10	s.c.; 5 mg/animal, at intervals of a few weeks, life	≤ 23 months	1/10 lung adenoma; no sarcomas	n no/ln, ld	Badger *et al*. (1942)
Benzo[ghi]perylene								
	Mouse, NMRI	f	50	s.c.; 0.83 and 16.7 mg/ animal, 1 x/2 weeks, 6 months	≤ 22.5 months	5/50 and 4/40 with tumours; control:4/50	n no/val	Muller (1968)
	Mouse, NMRI	f	20	s.c.; 0.1, 1 and 10 mg/ animal, 1x/2 weeks, 20 weeks	≤ 22 months	No skin/subcutaneous tumours; other tumours same as control	n no/val	Muller (1968)
Benzo[c]phenan-threne								
	Mouse		10	s.c.; 5 mg at intervals of several weeks, life	< 15 months	No injection-site tumours	n no/ln, ld	Badger *et al*. (1940)
	Mouse C3H		20	s.c.; 5 mg in tricaprylin, 1x	638 days	3 sarcomas; controls: no tumours	q no/val	Stevenson & von Hearn (1965)
	Rat,		6	s.c.; 5 mg/animal; sev-eral repeated doses	approx. 18 months	1/6 sarcoma at injection site	q no/ln, ld	Badger *et al*. (1940)
Benzo[a]pyrene								
HPLC con-trol	Mouse, C57BI	m/f	40-50	s.c.; 0.09 mg/animal in tricaprylin; 1x	≤ 22-28 months	16/21 sarcomas after 5 months	p yes/ld	Steiner (1955)
	Mouse, XVII	m/f	14/16	s.c.; 0.6 mg/animal, 1x/ month, 3 months	129/160 days (av. latency)	13/14 m and 8/16 f with local sarcomas	p no/ld	Lacassa-gne *et al*. (1958)
	Mouse, XVII nc/ Z	m/f	154/162	s.c.; 0.6 mg/animal, 1x/ month, 3 months	≈ 110/150 days	154/154 m and 112/162 f with local sarcomas	p no/ld	Lacassa-gne *et al*. (1963a)

	Mouse, NMRI		20	s.c.; 0.1, 1 and 10 mg/ animal, 1 x/2 weeks, 20 weeks	17, 7, 6 months	All animals with sarcomas at injection site	p no/val	Muller (1968)
	Mouse, NMR1	f	90	s.c.; 25, 50, 100, 200 and 400 µg/animal, 1x	16 months	25, 50, 55, 75 and 65% with tumours; solvent control: < 5%	p no/val	Pott *et al*. (1973)
	Mouse, newborn	m/f	31-38	s.c.; 0.01 and 0.1 mg/ animal, 1x	30 weeks	16 and 64% with lung tumours; control: 13% with lung tumours	p no/val	Rippe & Pott (1989)
99%	Rat, Wistar	f	50	s.c.; 33, 100, 900, and 2700µg/animal, 1x	16 months	10, 15, 70 and 75% with tumours; solvent only: < 5%	p no/val	Pott *et al*. (1973)
Pure	Monkeys (a) *S. oedipus*; (b) *S. fusciocolli*	m/f m/f	1/1 1/1	s.c.; 10 mg/animal, 1x (co-administration with 10 mg DMBA at other site)	(a) ≥18 months, (b) ≤ 5 weeks	(a) 1/2 with local tumours (b) death within 5 weeks	q no/ln	Noyes (1969)
	Monkey, *Galago crassus*			s.c.; 1 × (not specified)		Fibrosarcomas	p no/lc	Adamson & Sieber (1983)
	Monkey, Old world		17	s.c.; 30-90 mg/kg, multiple administration (not specified)	≤ 18 years	No tumours observed; survival: 9/17	n no/lc	Adamson & Sieber (1983)
Chrysene								
Purified	Mouse		50	s.c.; 2 mg/animal, 1x	≤ 35 weeks	No tumours	n no/lc	Bottomley & Twort (1934)
	Mouse, Jackson A		30	s.c.; 10 mg/animal, 2x (4-month interval)	15 months	No tumours	n no/ld	Shear & Leiter (1941)
Spectrometer control	Mouse, C57BI	m/f	50	s.c.; 5 mg/animal in tricaprylin; 1x	≤ 22 months	4/39 sarcomas after 4 months; solvent control: 3/280	p no/val	Steiner & Falk (1951)
	Mouse, C57BI	m/f	40-50	s.c.; 5 mg/animal in tricaprylin; 1x	22-28 months	5/22 sarcomas after 5 months	p yes/ld	Steiner (1955)
	Mouse, C57BI	m	20	s.c.; 1 mg/animal in arachis oil, 1 x/week, 10 weeks	60-80 weeks	2/20 injection site tumours; control: no tumours	p no/val	Boyland & Sims (1967)
	Mouse, Swiss newborn	m/f	104	s.c.; 0.1 mg/animal in polyethylene glycol on days1,2 and 3 after birth	70-75 weeks	70 weeks: 13/27m liver, 1/27 m and 1/21 f lung tumours; vehicle control: 9/30 m liver, 3/30 in and 1/15 f lung tumours	q no/val	Grover *et al*. (1975)
	Mouse,		10	s.c.; 1 mg, weekly; later 2 mg at longer intervals	350 days	No tumours; control: no tumours	n no/ln, ld	Barry & Cook (1934)
> 98%	Rat		10	s.c.; 2 mg/animal, weekly; later 6 mg at longer intervals	≤ 626 days	4/10 tumours; control: 2/10 sarcomas	p no/ln, ld	Barry & Cook (1934)

Purified	Rat		10	s.c. ; 1 mg/animal, weekly, 103 weeks	< 103 weeks	No tumours	n no/ln, ld	Boyland & Burrows (1935)
	Rat, Wistar		5	s.c.; 5 mg/animal, 7-9x	10 months	No tumours	n no/ln	Pollia (1941)
Dibenz[a,h]anthracene								
	Mouse		10	s.c./i.p.; 0.2 mg/animal, 2x/week, 50 weeks alternating	Life	3/10 with subcutaneous sarcomas	p no/ln, ld	Boyland & Burrow, (1935)
Spectrometer control	Mouse, C57BI	m/f	50	s.c.; 0.02 mg/animal in tricaprylin; 1x	≤ 22 months	28/48 sarcomas after 4 months solvent control: 3/280	p no/val	Steiner & Falk (1951)
	Mouse, C57BI	m/f	40-50	s.c.; 0.02, 0.04 mg/animal in tricaprylin; 1x	≤ 22-28 months	7/21 and 6/18 sarcomas after 6 and 5 months	p yes/ld	Steiner (1955)
	Mouse, C57BL	m/f	20/19	s.c.; 1 mg/animal, 1x/week, 10 weeks	60-80 weeks	20/20 m and 17/19 f with sarcomas; control: no sarcomas	p no/val	Boyland & Sims (1967)
	Mouse, NMRI	f	60	s.c.; 10, 30, 90, 270 and 810 µg/animal, 1x	16 months	40, 35, 65, 75, and 90% with tumours	p no/val	Pott *et al*. (1973)
	Mouse, B6, D2	m/f	30 (60)	s.c.; 0.15 and 0.3 mg/animal, 1x	12 months	B6 mice: 16/30 and 14/30; D2 mice: 1/30 and 0/30 with fibrosarcomas	p no/val	Kouri *et al*. (1983)
> 99%	Mouse, NMRI	f	47-50	s.c.; 10, 30, 86 µg/animal, 1 ×	112 weeks	52, 46, and 63% with fibrosarcomas; controls: 2-6%	p no/val	Platt *et al*. (1990)
> 99%	Mouse, NMRI newborn	m/f	40-50	s.c.; 11.1 and 111 µg/animal on day 2, 1x	40 weeks	12/35 with pulmonary tumours; controls: 2/33 and 4/41	p no/val	Platt *et al*. (1990)
	Rat		2x10	s.c.; 2 mg/animal, weekly; later 6 mg at longer intervals	approx. 200 days	1/10 and 7/10 with tumours; control: 2/10	q no/ln, ld	Barry & Cook (1934)
	Rat		10-18 (6 exp.)	s.c./i.p.; 1 mg/animal, 2x/week, 50 weeks alternating	Life	3-6/10 and 9/18 with subcutaneous sarcomas	p no/ln, ld	Boyland & Burrows (1935)
	Rat, Wistar		5	s.c.; 5 mg/animal, 4-8x	10 months	2 with tumours after 8-9 months	p no/ln	Pollia (1941)
Dibenzo[a,e]pyrene								
> 99%	Mouse, XVII nc/Z	m/f	21/14	s.c.; 0.6 mg/animal, 1x/month, 3 ×	≤ 142 days m or 126 days f	18/21 m and 14/14 f local sarcomas; no vehicle control	p no/val	Lacassagne *et al*. (1963b)
	Mouse	m/f	12/15	s.c.; 0.6 mg/animal, 1x	≤ 196 days m or 220 days f	10/12 m and 10/15 f local sarcomas; no vehicle control	p no/val	Lacassagne *et al*. (1963b)

Dibenzo[a,h]pyrene								
> 99%	Mouse, XVII	m/f	35/10	s.c.; 0.6 mg/animal, 1x/ month, 3 months (average latency)	≥ 111/128 days	34/35 mand 1/10 f with local sarcomas	p no/ld	Lacassagne *et al*. (1958)
	Mouse, CD-1	f	31	s.c.; 0.2 mg/animal, 1x; initiation experiment	27 weeks	26/28 with tumours; solvent control: 2/32	p no/val	Sardella *et al*. (1981)
Dibenzo[a,i]pyrene								
> 99%	Mouse, XVII	m/f	17/18	s.c.; 0.6 mg/animal, 1x/ month, months	3> 75/82 days (average latency)	17/17 m and 16/18(f) with local sarcomas	p no/ld	Lacassagne *et al*. (1958)
	Mouse, XVII/ C57BI hybrids	m/f	8/8	s.c.; 2 mg/animal, 1x	2-3 months	100, 100% with skin tumours; average latency: 74 days	p no/ln, ld	Waravdekar & Ranadive (1958)
	Mouse, C57BL/6	m		s.c.; 0.5 mg/animal, 1x	4-5 weeks	100% fibrosarcomas; malignant cells identifiable after 4-5 weeks	p no/ld	Homburger *et al*. (1962)
	Mouse, CD-1	f	50	s.c.; 0.1 mg/animal, 1x	75 weeks	40/41 with tumours; solvent control: no tumours	p no/val	Sardella *et al*. (1981)
> 99%	Hamster, Syrian	m	6-10	s.c.; 0.25, 0.5, 1 and 2 mg/ animal, 1x	9-14 weeks (average latency)	55, 90, 100, and 100% with fibrosarcomas; vehicle control: 0%	p no/val	Wodinsky *et al*. (1964)
	Hamster, Syrian	m/f	139/157	s.c.; 1 mg/animal, 1x	11 weeks (average latency)	99/100% with fibrosarcomas	p no/val	Wodinsky *et al*. (1964)
Dibenzo[a,l]pyrene								
Chomatography purified	Mouse, XVII nc/ ZE	m/f	12/12	s.c.; 0.6 mg/animal, 1x/ month, 2 months (some animals, 3rd injection after 2 months)	≤ 7 months	All animals with local sarcomas (mean latent period: 120 days); control: no tumours	p no/val	Lacassagne *et al*. (1968a)
Fluoranthene								
Purified, 107-109°C	Mouse, Jackson A	m/f	7/7	s.c.; 10 mg/animal, 5x	19 months	No tumours	n no/ld, ln	Shear (1938)
	Mouse, XVII nc/ Z	m/f	10/10	s.c.; 0.6 mg/animal, 1x/ month, 3x		No sarcomas	n no/ld, ln	Buu-Hoi (1964)
Fluorene								
'Pure'	Mouse, Jackson A	m	10	s.c.; 10 mg/animal, 7x over 16 months	19 months	No tumours	n no/ln, ld	Shear (1938)
Indeno[1,2,3-cd]pyrene								
> 99%	Mouse, XVII nc/ Z	m/f	14/14	s.c.; 0.6 mg/animal, 1x/ mth, 3 months	Average, 265 days m, 145 days f	Sarcomas: 10/14 m and 1/14 f	p no/val	Lacassagne *et al*. (1963a)

5-Methylcholanthrene								
> 99%	Mouse, Swiss/ C3H	m/m	20/2x10	s.c.; 2 mg/animal in tri-caprylin, 1x	6 months	Swiss mice: no local tumours; 16/20 mice died; C3H mice: 7/10 or 3/10 local sarcomas	q no/ld	Dunlap & Warren (1943)
Highly purified	Mouse, C57BL	m	25	s.c.; 50 µg/animal in tri-octanoin, 1 x/2 weeks, 20 weeks	32 weeks	22/25 mice with 24 fib-rosarco-mas; vehicle control: no tumours	p no/val	Hecht *et al*. (1976b)
Naphthalene								
> 99%	Rat, BDI/ BDI II inbred		10	s.c.; 20 mg/animal, 1x/ week, 40 weeks	Life	No tumours	n no/ln	Schmahl (1955)
Crude, 90%	Rat, white'		38	s.c.; 0.5 g/kg, 2x/ month, 3.5 months	Life	5 malignant tumours (4/ 38 Imphosarcomas, 1/ 38 uterine sarcoma); 1 benign tumour; vehicle control: 1/38 lympho-sarcoma and 1 benign tumour	q no/val	Knake (1956)
Phenanthrene								
> 98%	Mouse, C57BI	m/f	40-50	s.c.; 5 mg/animal in tri-caprylin; 1x	22-28 months	No sarcomas after 8 months	n yes/ld	Steiner (1955)
	Mouse, 'stock albino'	m/f	10/10	s.c.; 0.3 mg, 5x on days 0, 2, 4, 6 and 8; initia-tion experiment	24 weeks	3/17 papillomas; sol-vent control: 2/20	n yes/val	Roe (1962)
	Mouse, ‘stock albino' newborn	m/f	57	s.c.; 40 µg/animal; 1x administered to neona-tal mice	≤ 62 weeks	3/49 lung adenomas; control: 8/34 and 5/38	n yes/val	Grant & Roe (1963)
Pyrene								
Crystals	Mouse, Jackson A	m/f	30	s.c.; 10 mg/animal, 2 × at 4- month interval	≤ 18 months	No malignant tumours	n no/ld	Shear & Leiter (1941)

Result: p(ositive), n(egative), q(uestionable); Stat, statistical evaluation: yes or no; Val, validity: val, valid; ld, limited design; lc, limited documentation; ls, limited survival; ln, limited number of animals; s.c., subcutaneous injection; m, male; f, female; TLC, thin-layer chromatography; DMSO, dimethylsulfoxide; HPLC, high-performance liquid chromatography; DMBA, 7,12-dimethylbenz[a]anthracene.

J7 Intraperitoneal injection

Table J.7 Adapted from IPCS 1998 (Table 90, page 399 - 471: Carcinogenicity of polycylic aromatic hydrocarbons in experimental animals)[70].

Purity	Species, strain	Sex	No./ sex/ group	Route of Dosage admin.	duration at death/ sacrifice	Incidence and type of tumour	Result Stat./ Val.	References adapted from IPCS 1998
Anthracene								
	Mouse, Swiss	m	5	i.p.; 1000 mg/kg, 1x	≤ 5 months	No effects observed	n no/ln	Shubik & Della Porta (1957)
Highly purified	Rat, BD I/ BD III		10	i.p.; 20 mg/animal, 1x/week,	> 2 years 33 weeks	1/10 spindle-cell sarcoma	q no/ld	Schmahl (1955)
Benz[a]anthracene								
Recrystallized	Mouse, Swiss Webster BLU:Ha(ICR) newborn	m/f	140	i.p.; 9.1, 18.2, and 36.4µg/animal on days 1, 8, and 15 after birth	26 weeks	10/47 m and 4/38 f with pulmonary tumours; solvent control: 7/43 and 2/24	n no/val	Wislocki *et al*. (1979)
Benzo[b]fluoranthene								
	Mouse, CD-1 newborn	m/f	15/17	i.p.; 126 µg/animal in DMSO on days 1,8, and 15 after birth (total dose)	≤ 52 weeks	53% hapatic, 18% lung tumours; control: 6% hepatic tumours, no lung tumours	p yes/val	LaVoie *et al*. (1987)
Benzo[j]fluoranthene								
99%	Mouse, CD-1 newborn	m/f	21/18	i.p.; 278 µg/animal in DMSO on days 1, 8, and 15 after birth (total dose)	≤ 52 weeks	81% males and 22% females with liver and lung tumours; control: 6%:0%	p yes/val	LaVoie *et al*. (1987)
Benzo[k]fluoranthene								
> 99%	Mouse, CD-1 newborn	m/f	16/18	i.p.; 530 µg/animal in DMSO on days 1, 8, and 15 after birth (total dose)	≤ 52 weeks	19% males and 17% females with tumours; control: 6%:0% liver and lung tumours	q yes/val	LaVoie *et al*. (1987)
Benzo[a]pyrene								
> 99%	Mouse, CD-1 newborn	m/f	17/14	i.p.; 278 µg/animal in DMSO on days 1, 8, and 15 after birth (total dose)	≤ 52 weeks	76% hepatic and 64% lung tumours; control: 6% hepatic tumours, no lung tumours	p yes/val	LaVoie *et al*. (1987)
	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	28/27	i.p.; 59.5 µg/animal on days1, 8, and 15 after birth (total dose)	26 weeks	46 m, 70, f with lung tumours; vehicle control: 14 m, 7 f	p yes/val	Busby *et al*. (1989)

99%	Rat, Wistar	f	37	i.p.; 5 mg/animal; 1x; in bees' wax/tricaprylin 25/75 (a) or saline (b)	2 years	(a) 89% abdominal tumours (mesotheliomas, sarcomas); (b) 50%; vehicle controls: (a) 70%; (b) 3%	p no/val	Roller *et al*. (1992)
Benzo[e]pyrene								
99%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	30/30	i.p.; 0.1, 0.2, 0.4, or 0.2, 0.4, 0.8 mg on days 1, 8, and 15 of life	62-66 weeks	21/35 (m), 0/35 (f) or 12/30 (m), 0/30 (f) with hepatic tumours; controls: 11/53 (m), 0/24 (f)	q no/val	Buening *et al*. (1980)
Chrysene								
Purified	Mouse		50	i.p.; 2 mg/animal, 1 ×	≤ 45 weeks	No tumours	n no/lc	Bottomley & Twort (1934)
TLC control	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	100	i.p.; total dose 0.32 mg/animal in DMSO on days 1, 8 and 15 after birth	38-42 weeks	5/24 m and 2/11 f pulmonary tum; 6/24 m liver tum; 1/24 m lymphosarcoma; control: 2/21 m and 7/38 1 lung tumours	q yes/val	Buening *et al*. (1979)
Repurified, 256°C	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	80	i.p.; 0.045, 0.09 and 0.18 mg/animal in DMSO on days 1, 8 and 15 after birth	39-41 weeks	Males: 4/27 lung and 6/27 liver tum; females; 1/11 lung and 0/11 liver tum; vehicle control: no tum	p yes/val	Chang *et al*. (1983)
> 98%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	20-29	i.p.; 6.3 and 210 µg/animal (total dose) in 3 aliquots on day 1, 8, and 15 after birth	26 weeks	7/10% and 15/0% m/f with lung tumours; vehicle control: 14/7% m/f	n yes/val	Busby *et al*. (1989)
Cyclopenta[cd]pyrene								
> 99%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	8-14	i.p.; 0.35, 0.7, 1.05, 1.4, and 1.75 mg/animal (total dose) in 3 aliquots on day 1, 8, and 15 after birth	26 weeks	62, 60, 56, 70, 86, 93%, 77, 100, and 89, 100% m/f with lung tumours; vehicle control: 8, 8%	p yes/val	Busby *et al*. (1988)
Dibenz[a,h]anthracene								
	Mouse		10	s.c./i.p.; 0.2 mg/animal, 2x/week, 50 weeks alternating	Life	3/10 with subcutaneous sarcomas	p no/ln, ld	Boyland & Burrow, (1935)
	Rat		10-18 (6 exp.)	s.c./i.p.; 1 mg/animal, 2x/week, 50 weeks alternating	Life	3-6/10 and 9/18 with subcutaneous sarcomas	p no/ln, ld	Boyland & Burrows (1935)

Dibenzo[a,h]pyrene								
> 99%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	40	i.p.; 3.8, 7.6 and 15.1 µg on days 1, 8 and 15 of life	49-54 weeks	97% with pulmonary and 44% with hepatic tumours; control: pulmonary tumours 27%, no hepatic tumours	p yes/val	Chang *et al*. (1982)
Dibenzo[a,i]pyrene								
> 99%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	40	i.p.; 3.8, 7.6 and 15.1 µg on day 1, 8, and 15 of life	49-54 weeks	97% with pulmonary and 54% with hepatic tum; control: pulmonary tum 27%, no hepatic tumours	p yes/val	Chang *et al*. (1982)
Fluoranthene								
99%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn	m/f	20-31	i.p.; 0.7 and 3,5 mg/animal (total dose) in 3 aliquots on days 1, 8 and 15 after birth	24 weeks	23, 15, and 74, 38% m/f with lung tumours; vehicle control: 4,14%	p yes/val	Busby *et al*. (1984)
> 99.5%	Mouse, CD-1 newborn	m/f	22/30	i.p.; 0.7 and 3.5 mg/animal (total dose) in 3 aliquots on days 1, 8, and 15 after birth	52 weeks	43, 35, and 65, 86% with lung tum; 64, 0% and 100, 7% with hepatic tumours; vehicle only: 17, 12% (lung) and 17, 6% (liver)	p yes/val	La Voie *et al*. (1994)
Fluorene								
'Pure'	Mouse, Swiss	m	5	i.p.; 1000 mg/kg, 1x	≤ 5 months	No effects	n no/ld, ln	Shubik & Della Porta (1957)
Indeno[1,2,3-cd]pyrene								
> 99%	Mouse, CD-1 newborn	m/f	11/9	i.p.; 580 µg/animal in DMSO on days 1, 8 and after birth (total dose)	≤ 52 weeks	9% hepatic or 0% lung tumours; controls: 6%/0%	n yes/val	LaVoie *et al*. (1987)
5-Methylcholanthrene								
HPLC purified	Mouse, ICR/Ha newborn	m/f	35/48	i.p.; 1.9 µg/animal on day 1; 3.9 µg on day 8; 7.8 µg on day 15	Weaned after 3 weeks; sacrificed after 35 weeks	20/21% with pulmonary tumours; 23/12% with hepatic tumours; solvent control: 4/7% and 2/2%	p yes/val	Hecht *et al*. (1985)
Naphthalene								
Crude, 90%	Rat, BDI/BDI II inbred		10	i.p.; 20 mg/animal, 1x/week, 40 weeks	Life	No tumours	n no/ln	Schmahl (1955)

Phenanthrene								
> 98%	Mouse, Swiss-Webster BLU:Ha (ICR) newborn		100	i.p.; 35, 70 and 140 µg/animal in DMSO on days 1, 8 and 15 after birth	38-42 weeks	6/35 pulmonary adenomas; DMSO only: 9/59	n yes/val	Beuning *et al*. (1979)
Pyrene								
Recrystallized, HPLC	Mouse, Swiss-Webster BLU:Ha (lCR) newborn	m/f	23-28	i.p.; 86.1 and 1750 µg/animal (total dose) in 3 aliquots on days 1, 8 and 15 after birth	26 weeks	17, 4, and 7, 12% m/f with lung tumours; vehicle control: 14, 7% m/f	n no/val	Busby *et al*. (1989)

Result: p(ositive), n(egative), q(uestionable); Stat, statistical evaluation: yes or no; Val, validity: val, valid; ld, limited design; lc, limited documentation; ls, limited survival; ln, limited number of animals; intrapulm., intrapulmonary injection; i.p., intraperitoneal injection; s.c., subcutaneous injection; i.m., intramuscular injection; m, male; f, female; TLC, thin-layer chromatography; DMSO, dimethylsulfoxide; HPLC, high-performance liquid chromatography; DMBA, 7,12-dimethylbenz[a]anthracene.

J8 Summary on the carcinogenic effects of individual PAH given by ATSDR (1995)[128]

PAH	Summary of results
Benzo[ghi]perylene	There are no reports on the carcinogenicity of benzo[g,h,I]perylene administered by inhalation. The compound is a weak pulmonary carcinogen in rats after intrapulmonary administration. No skin tumours (upon skin painting) or injection site tumours (upon subcutaneous injection) were observed.
Fluoranthene	There are no reports on the carcinogenicity of fluoranthene administered by inhalation. Other studies, which involved skin painting or intraperitoneal injection, indicated that the compound has virtually no activity as a complete carcinogen.
Fluorene	There are no reports on carcinogenicity of fluorene administered by inhalation. In other studies, which involved skin painting or subcutaneous injection, the compound was found to be inactive as a carcinogen.
Naphthalene	In several inhalation studies, naphthalene gave rise to alveolar and bronchiolar carcinomas in mice. The chemical was not carcinogenic in rats after intraperitoneal injection, and it did not induce skin tumours in mice when topically applied. Naphthalene appeared to reduce the formation of skin tumours in mice by benzo(a)pyrene, when the two chemicals were applied together.
Phenanthrene	There are no reports on the carcinogenicity of phenanthrene administered by inhalation. This compound has been studied in skin carcinogenesis experiments. It is not a complete carcinogen. Its initiating activity seems to be dependent on the mouse strain used. Also, subcutaneous administration did not result in a treatment-related increase in tumour incidence.
Pyrene	Intratracheal instillation of pyrene with Fe_2O_3 particles did not result in respiratory tumours in hamsters. Intraperitoneal injection of this compound in newborn mice induced a small but significant increase in liver carcinomas, but only in the mid-dose group. Pyrene was tested in skin painting experiments as a complete carcinogen or as an initiator of skin tumours in mice, but the results were negative. The compound did not induce tumours upon subcutaneous injection. However, co-administration of pyrene enhanced the BaP-induced tumorigenicity on mouse skin.
Benz[a]anthracene	There are no reports on carcinogenicity of benz[a]anthracene administered by inhalation. The compound produced tumours in mice after oral administration, and in various mouse strains upon intraperitoneal, intravenous, subcutaneous or intramuscular injection. Benz[a]anthracene is a well-documented skin carcinogen. Subcutaneous injection resulted in injection site sarcomas.
Benzo[a]pyrene	Benzo[a]pyrene is known to produce lung tumors when administered by inhalation. It is generally more effective when adsorbed onto a respirable particulate matter. Rats developed squamous cell carcinomas in the lung when exposed to benzo[a]pyrene. The tumour incidence was increased when the animals were subsequently exposed to SO_2. Hamsters developed tumours in the upper respiratory tract and in the upper digestive tract when exposed to BaP adsorbed onto NaCl particles. The occurrence of the latter type of tumours is probably the result of clearance from the respiratory tract and subsequent ingestion of the chemical. Intratracheal administration of BaP induced tumours in rats and hamsters. Orally administered BaP was carcinogenic in various mouse strains. Intraperitoneal injection caused tumours in rats and mice. BaP is by far the most extensively studied skin carcinogen in mice, rats, rabbits and guinea pigs. It also produces tumors when given subcutaneously.
Benzo[b]fluoranthene	There are no reports on carcinogenicity of benzo[b]fluoranthene administered by inhalation. Lung implantation produced tumors in rats, and intraperitoneal exposure was tumorigenic in newborn mice. The compound is a well-documented initiator of skin tumors. Subcutaneous injection resulted in injection site sarcomas.
Benzo[k]fluoranthene	There are no reports on carcinogenicity of benzo[k]fluoranthene administered by inhalation. Lung implantation produced tumors in rats, and initiation/promotion studies in mice showed increased tumor incidence. Intraperitoneal exposure was weakly or not tumorigenic in newborn mice.

Chrysene	There are no reports on carcinogenicity of chrysene administered by inhalation. The compound causes hepatic and lung tumors in mice, after intraperitoneal administration of newborns, and skin tumors after topical application. Chrysene is an initiator of skin carcinogenesis.
Dibenz[a,h]anthracene	There are no reports on carcinogenicity of dibenz[a,h]anthracene administered by inhalation. The compound induced lung adenomas in mice after pulmonary administration, while intratracheal administration induced squamous cell carcinomas. Oral exposure yields tumors in various mouse strains. Dibenz[a,h]anthracene is a well-known skin carcinogen, inducing papillomas and sarcomas. Subcutaneous injection resulted in injection site sarcomas.
Indeno[1,2,3-cd]pyrene	There are no reports on carcinogenicity of this compound administered by inhalation. The compound caused keratinized epidermoid carcinomas in rats when implanted in the lung, in wax pellets. It induced skin tumors when applied in acetone on mouse skin in a complete carcinogenicity assay. Subcutaneous injection resulted in injection site sarcomas.
Combinations of PAH	Dermal application of two carcinogenic PAH, *e.g.,* benzo[a]pyrene and cyclopente-no[cd]pyrene, has been observed to result in more-than-additive effects with respect to skin tumor incidence. Noncarcinogenic PAH may either reduce (*e.g.*, naphthalene) or enhance (*e.g.*, pyrene) the carcinogenic action of benzo[a]pyrene. It is assumed that two opposite effects on metabolizing enzymes, *viz* induction and competitive binding, which may each be dependent on the relative concentrations of the PAH, will determine the net amount of the ultimate carcinogenic metabolite formed. Therefore, additive, synergistic and inhibitory effects may be observed. Experiments have also been carried out with a larger number of PAH, which were mixed in weight ratios occurring in ambient air or in different emissions. The general outcome of these studies indicated an additive effect on tumor incidence, which could be explained by assuming that the two opposite influences on the metabolic enzymes are equally effective.

Annex **K**

Cancer risk values based on animals studies

Introduction

Malignant tumours as well as benign tumours that are suspected of possibly transforming into malignant tumours relevant to humans are taken into account. The carcinogenic activity per unit air concentration is calculated as*

$$I_{concentration} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times (\text{exposure hours per day}/24) \times (\text{exposure days per week}/7)}$$

To estimate the additional risk of cancer in humans under lifespan conditions it is assumed that no differences exists between experimental animals and humans with respect to kinetics, mechanism of tumour induction, target susceptibility, etcetera.

The committee assumes, furthermore, that the standard human being lives 75 years and weighs 70 kg. Exposure is taken as life-long 24 hours per day, 7 days per week, 52 weeks per year. Per day the standard person is assumed to inhale 18 m^3 of air. For humans exposed in the workplace, the committee assumes that workers are exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years. They are expected to inhale 10 m^3 of air during the 8-hour working day.

* I is estimated tumour incidence; I_e and I_c are tumour incidences in exposed and control animals, respectively; C is the daily dose (mg/kg bw); X_{po} and X_{pe} are exposure and experimental period, respectively; L is the standard lifespan for the animal species in question (L rats is assumed to be 1,000 days; L mice is assumed to be 750 days).

The HBC-OCRV is calculated from the carcinogenic activity for lifespan exposure per unit air concentration ($I_{concentration}$) by adjusting for the differences in exposure duration and breathing rate between lifelong and occupational exposure. Starting from the carcinogenic activity per unit air concentration, $I_{concentration}$, the expression is:

$$HBC\text{-}OCRV = \frac{I_{concentration} \times 40\ years \times 48\ weeks \times 5\ days \times 8\ hours \times (10\ m^3/8\ hr)}{75\ years \times 52\ weeks \times 7\ days \times 24\ hours \times (18\ m^3/24\ hr)}$$

$$HBC\text{-}OCRV = I_{concentration} \times 0.195$$

Schulte *et al.* 1993[119]

animal species	experimental design	findings	comments
Newborn female NMRI/BR mice (n=40/group)	Coal tar pitch volatile; 0, 50 or 90 µg BaP/m^3; 16 h/d, 5 d/w for 44 weeks. Volatiles were produced by pyrolizing preheated (80°C) coal tar pitch in nitrogen atmosphere at 750-800°C. After that the volatiles were diluted with fresh air and led into the exposure chamber.	No. of animals with lung tumours (adenomas, adenocarcinomas, squamous cell carcinomas, and adeno-squamous carcinomas): - control: 5/40 - 50 µg BaP/m^3: 40/40 (p<0.001) - 90 µg BaP/m^3: 40/40 (p<0.001)	Exposure started one day after birth; experimental period relatively short; tumours at other sites in the body not examined.

Calculation of carcinogenic activity and HBC-OCRV

The lowest exposure concentration at which the number of tumour bearing animals was statistically significantly increased was at 50 µg BaP/m^3. Though lung adenomas are benign of origin, they can transform in malignant adenocarcinomas. Therefore, the committee included adenoma bearing animals in calculating a HBC-OCRV.

$$I_{concentration} = \frac{(40/40) - (5/40)}{50 \times (308/750) \times (308/750) \times (16/24) \times (5/7)}$$

$$I_{concentration} = 0.218\ [mg/m^3]^{-1}$$

$$HBC\text{-}OCRV = I_{concentration} \times 0.195 = 0.218 \times 0.195 = 0.0425\ [mg/m^3]^{-1}$$

Based on the HBC-OCRV of 0.0425 per μg BaP/m^3 the additional lifetime cancer risk for BaP en PAH amounts to:

- 4 x 10^{-3} for 40 years of occupational exposure to 94.0 ng BaP/m^3
- 4 x 10^{-5} for 40 years of occupational exposure to 0.9 ng BaP/m^3.

Heinrich *et al*. 1994[54]

animal species	experimental design	findings	comments
Female Wistar rats (n=72/group)	Coal tar/pitch condensation aerosols, free of carbon black carrier particles; cumulative exposure 0, 71, 142, 158 and 321 mg BaP/m^3-hours; total experimental period was 30 months, of which the first 10 (20 μg BaP/m^3) or 20 (46 μg BaP/m^3) months were exposure to coal tar. Animals were exposed 17 hours/day for 5 days/week.	Increased incidence of lung tumours with increasing cumulative exposure: 0 mg BaP/m^3-hrs: 0.0% 71 mg BaP/m^3-hrs: 4.2% 142 mg BaP/m^3-hrs: 33.3% 158 mg BaP/m^3-hrs: 38.9% 321 mg BaP/m^3-hrs: 97.2%. Authors stated that "most of the tumours were benign and malignant keratinizing squamous cell tumours. Furthermore, some broncho-alveolar adenomas and adenocarcinomas were found. No exposure-related tumours were found in organs other than the lung". More details were not presented in the paper.	The authors fitted a multistage model to the experimental data by the maximum likelihood method, and the goodness-of-fit was tested by the chi-squared statistic. A chi-squared value of 0.5 was obtained with a *p*-value of 0.78. This indicates no significant deviation of the data from the model. Authors calculated lifetime unit lung cancer risk (EPA, linearized multistage model): 2 per 100 000 with 1 ng BaP/m^3.

Calculation of carcinogenic activity and HBC-OCRV

Assuming the lowest cumulative concentration (71 mg BaP/m^3-hrs) significantly increased the number of tumour bearing animals compared to control, an HBC-OCRV can be calculated from data of this exposure group. In this group, animals were exposed to 20 g BaP/m^3 for 10 months (305 days), followed by a period of 20 months (610 days) with filtered clean air. The lung tumour risk was 4.2% (3/72) compared to 0% in controls (0/72).

$$I_{concentration} = \frac{(3/72) - (0/72)}{20 \times (305/1000) \times (915/1000) \times (17/24) \times (5/7)}$$

$$I_{concentration} = 0.015\ [mg/m^3]^{-1}$$

$$HBC\text{-}OCRV = I_{concentration} \times 0.195 = 0.015 \times 0.195 = 0.003\ [mg/m^3]^{-1}$$

Based on the HBC-OCRV of 0.003 per μg BaP/m^3 the additional lifetime cancer risk for BaP en PAH amounts to:

- 4 x 10^{-3} for 40 years of occupational exposure to 1330 ng BaP/m^3
- 4 x 10^{-5} for 40 years of occupational exposure to 13 ng BaP/m^3.

More likely, however, is that not in the lowest exposure group, but in the second lowest exposure group (142 mg BaP/m^3-hrs) the number of tumour bearing animals was statistically increased. Animals in this exposure group were exposed to 20 μg BaP/m^3 for 20 months (610 days), followed by a period of 10 months (305 days) with filtered clean air. The lung tumour rate was 33.3% (24/72) compared to 0% in controls (0/72).

$$I_{concentration} = \frac{(24/72) - (0/72)}{20 \times (610/1000) \times (915/1000) \times (17/24) \times (5/7)}$$

$$I_{concentration} = 0.059\ [mg/m^3]^{-1}$$

$$HBC\text{-}OCRV = I_{concentration} \times 0.195 = 0.059 \times 0.195 = 0.012\ [mg/m^3]^{-1}$$

Based on the HBC-OCRV of 0.012 per μg BaP/m^3 the additional lifetime cancer risk for BaP en PAH amounts to:

- 4 x 10^{-3} for 40 years of occupational exposure to 333 ng BaP/m^3
- 4 x 10^{-5} for 40 years of occupational exposure to 3 ng BaP/m^3.

From the animal data, the authors themselves estimated a lifetime unit cancer risk of 0.02 per μg BaP/m^3 (continuous exposure). Using this value as starting point, a HBC-OCRV for the occupational situation would be 0.02 x 0.195 = 0.0039 [μg/m^3]$^{-1}$.

Based on the HBC-OCRV of 0.0039 per μg BaP/m^3 the additional lifetime cancer risk for BaP en PAH amounts to:

- 4 x 10^{-3} for 40 years of occupational exposure to 1026 ng BaP/m^3
- 4 x 10^{-5} for 40 years of occupational exposure to 10 ng BaP/m^3.

Annex **L**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBC-OCRV	Health-based calculated – occupational cancer risk value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at which inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration [in German]
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion (v/v)10^{-9}

ppm	parts per million (v/v)10^{-6}
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit
tgg	tijd gewogen gemiddelde (English: time weighed average)
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test

GSH	glutathione
HliA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration
MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RliA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	Relative Risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography

IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

BaP	Benzo[a]pyrene
BSM	Benzene Soluble Matter
PAH	Polycyclic Aromatic Hydrocarbons

Annex **M**

DECOS documents

Aanpassing van grenswaarden bij flexibele werktijden	2001/06OSH
Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
Azobisisobutyronitril	2002/01OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10WGD
n-, iso-, sec-, tert-Butylacetaten	2001/03OSH
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chlorotrimethylilane	2001/05OSH
Chromium and its inorganic compounds	1998/01WGD
Chromium VI and its compounds	2001/01OSH

Cresols	1998/15WGD
Copper sulphate	1999/01OSH
1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dibromoethane	1999/07OSH
1,2-Dichloroethane	1997/01WGD
Diethylsulphate	1999/08OSH
Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
Endotoxins	1998/03WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene oxide	2001/11OSH
Ethylene thiourea	1999/03OSH
Formaldehyde	2003/02OSH
Formamide and dimethylformamide	1995/08WGD
Glutaraldehyde	2005/05OSH
Halothane	2002/14OSH
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Hydrogen cyanide, sodium cyanide, and potassium cyanide	2002/15OSH
Isopropyl acetate	1997/04WGD
Lactate esters	2001/04OSH
Lindane	2001/07OSH
Man made mineral fibers	1995/02WGD
Manganese and its compounds	2001/02OSH
2-Methylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
Nitrogen dioxide	2004/01OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD

Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH
1- and 2-Propanol	1994/24
Propylene oxide	1997/02WGD
Quartz	1998/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Styrene	2001/08OSH
Sulphur dioxide	2003/08OSH
Tetrachloroethylene (PER)	2003/01OSH
Tin and inorganic tin compounds	2005/06OSH
Toluene	2001/09OSH
1,1,1-Trichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD
Urethane (ethyl carbamate)	2000/12OSH
Vinylbromide	1999/15OSH
Wheat and other cereal flour dusts	2004/02OSH
Wood dust	1998/13WGD
Xylene	2001/10OSH