POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)

The main sources of non occupational exposure to airborne PAHs are from combustion processes; these include motor vehicles, petroleum refineries, power plants using fossil fuels, coking plants, bitumen and asphalt production plants, aluminium refineries, iron and steel foundries, crop residue and forest management burning, bushfires, smoke from open fireplaces, environmental tobacco smoke and cooking food. Exposure also occurs through ingestion of PAH containing foods, raw food does not normally contain high levels of PAHs, but they are formed by roasting, baking, frying or processing.

Benzo[a]pyrene (BaP) is the best known and considered to be one of the most toxic of the PAHs. BaP rarely exists in the air on it's own but rather is associated with a large number of other PAHs present in both vapour phase and as particles. In some regulatory settings overseas, BaP is used as an indicator for this group of chemically diverse air pollutants.

Critical health endpoint
Individual PAHs. Such as benzo[a]pyrene and mixtures containing various PAHs have been determined to be carcinogenic to humans and animals. The site of tumour induction can be influenced by the route of exposure although tumours can form at other locations such as the lungs after dermal exposures

***Air Quality Guidelines for Europe*, *2nd edition* -WHO Regional Office for Europe, 2000 (WHO 2000)**

The aim of the WHO Air Quality Guidelines for Europe is to provide a basis for protecting public health from adverse effects of air pollution and for eliminating, or reducing to a minimum, those contaminants of air that are known or likely to be hazardous to human health and well being.

The critical endpoint for health risk evaluation is the well documented carcinogenicity of several PAHs (IARC 1983). BaP is by far the most intensively studied PAH in experimental animals. It produces tumours of many different tissues, depending on the species tested and the route of application. BaP is the only PAH that has been tested for carcinogenicity following inhalation, and it produced respiratory tract tumours (not lung tumours) in hamsters, the only species tested. Induction of lung tumours in rats and hamsters has also been documented for BaP and several other PAHs following direct application, such as intratracheal instillation into the pulmonary tissue.

The lung carcinogenicity of BaP can be enhanced by coexposure to other substances such as cigarette smoke, asbestos and probably also airborne particles. Several studies have shown that the benzene-soluble fraction, containing 4.to 7-ring PAHs of condensates from car exhausts, domestic coal-stove emissions and tobacco smoke, contains nearly all the carcinogenic potential of PAHs from these sources (PottandHeinrich, 1990).

Because several PAHs have been shown to be carcinogenic, and many more have been shown to be genotoxic in *in vitro* assays, a suitable indicator for the carcinogenic fraction of the large number of PAHs in ambient air is desirable. The most appropriate indicator for the carcinogenic PAHs in air seems to be BaP concentrations, given present knowledge and the existing database. Assessment of risks to health of a given mixture of PAHs using this indicator approach would entail, first, measurement of the concentration of BaP in a given mixture present in a medium such as air. Then, assuming that the given mixture resembles that from coke ovens, the unit risk estimate is applied in tandem with the measured BaP air concentration to obtain the lifetime cancer risk at this exposure level.

The proportions of different PAHs detected in different emissions and workplaces sometimes differ widely from each other and from PAH profiles in ambient air. Nevertheless, the profiles of PAHs in ambient air do not seem to differ very much from one area to another, although large variations may be seen under special conditions. Furthermore, the carcinogenicity of PAH mixtures may be influenced by synergistic and antagonistic effects of other compounds emitted together with PAHs during incomplete combustion. It should also be recognised that in ambient air the carcinogenic 4 to 7-ring PAHs (representing the majority of PAHs) are preferentially attached to particles and only a minor fraction, depending on the temperature, exists as volatiles. A few studies indicate that the toxicokinetic properties of inhaled BaP attached to particles are different from those of pure BaP alone. Virtually nothing is known about other PAHs in this respect.

Attempts to derive relative potencies of individual PAHs (relative to BaP) have also been published, and the idea of summarising the contributions from each of the selected PAHs into a total BaP equivalent dose (assuming their carcinogenic effects to be additive) has emerged (Heinrich et al 1994a). There are doubts, however, about the scientific justification for these procedures.

WHO presented an excess lifetime cancer risk, expressed in terms of the BaP concentration and based on observations in coke oven workers exposed to mixtures of PAHs. It was emphasised that the composition of PAHs to which coke oven workers are exposed may not be similar to that in ambient air. The working group also considered some recent animal data but concluded that the occupational epidemiology data should serve as the bases for the risk estimate.

The WHO adopted the lung cancer risk estimate calculated by the US Environmental Protection Agency. The US EPA based its calculations on extensive studies of coke oven workers in Pennsylvania. The US EPA used a linearised multistage model.

The unit risk for BaP is estimated to be 8.7×10^{-5} $(ng/m^3)^{-1}$. The corresponding concentrations of BaP producing excess lifetime cancer risks of 1/10 000, 1/100 000 and 1/1 000 000 are 1.2, 0.12 and 0.012 ng/m^3 respectively.

International Programme on Chemical Safety (IPCS, 1998)– Environmental Health Criteria 202 , Selected Non-Heterocyclic Polycyclic Aromatic Hydrocarbons

Many individual PAH are carcinogenic to animals and may be carcinogenic to humans, and exposure to several PAH-containing mixtures has been shown to increase the incidence of cancer in human populations. There is concern that those PAH found to be carcinogenic in experimental animals are likely to be carcinogenic in humans. PAH produce tumours both at the site of contact and at distant sites. The carcinogenic potency of PAH may vary with the route of exposure. Various approaches to assessing the risk associated with exposure to PAH, singly and in mixtures, have been proposed. No one approach is endorsed in this monograph; however, the data requirements, assumptions, applicability, and other features of three quantitative risk assessment processes that have been validated to some degree are described.

Effects on humans

There is little information on human exposure to single, pure polycyclic aromatic hydrocarbons (PAH). That which is available includes reports of accidental exposure to naphthalene and some data from defined short-term studies of volunteers. All other reports are of exposure to mixtures of PAH, which also contained other potentially carcinogenic chemicals, in occupational and environmental situations.

Epidemiological studies have been conducted of workers exposed at coke ovens during coal coking and coal gasification, at asphalt works, foundries, and aluminium smelters, and to diesel exhaust. Increased lung tumour rates due to exposure to PAH have been found in coke-oven workers, asphalt workers, and workers in Söderberg potrooms of aluminium reduction plants.

Estimates of the risk associated with exposure to PAH and PAH mixtures are based on estimates of exposure and the results of epidemiological studies.

The highest relative risk was found for lung cancer in coke-oven workers, with a standardised mortality ratio of 1.95 (1.59-2.33) (Costantino et al., 1995). Analysis of the relative risks and the numbers of deaths from lung cancer resulted in the conclusion that 124 deaths occurred among these coke-oven workers over a period of 30 years that can be attributed to exposure to coal-tar pitch volatiles, 2.3% of the cohort. Earlier findings from this study were used by others to estimate a unit risk coefficient of 8.7×10^{-2} for exposure to BaP (lifetime risk of lung cancer from a working lifetime exposure to 1 $\mu g/m^3$ of BaP. However, that the reports on which this estimate is based gave relatively little information on exposure levels, no data on time trends in the level of exposure, and no data on BaP levels in the participating plants.

In a large case-control study, an increased risk for lung cancer was found with exposure in a Söderberg potroom, and a significant correlation was seen between the increased risk and the duration and concentration of exposure and latency. Adjustment for smoking did not alter the correlation (Armstrong et al., 1994).

Similar increases were detected in other cohort studies. Work in potrooms where Söderberg electrolytic cells were used was also associated with an increased risk for urinary bladder cancer (Spinelli et al., 1991; Tremblay et al., 1995). This risk may be due to exposure not only to PAH but also to aromatic amines, which have been detected in the potrooms (Tremblay et al., 1995).

Dose-response relationships were found in several studies. In aluminium plants, not only urinary bladder cancer but also asthma-like symptoms, lung function abnormalities, and chronic bronchitis have been observed. Other studies, however, especially those involving small cohorts, did not show increased rates for lung cancer among coke-oven workers.

Effects On Laboratory Animals

Benzo[a]pyrene has been tested in a range of species, including rats, guinea pigs, rabbits, marmosets, and rhesus monkeys. Tumours have been observed in all experiments with small animals, and the failure to induce neoplastic responses in large animals has been attributed to lack of information on the appropriate route or dose and the inability to observe the animals for a sufficient time (Osborne & Crosby, 1987). In studies with other PAHs, BaP was often used as a positive control and therefore administered at only one concentration.

BaP has been shown to be carcinogenic when given by a variety of routes, including diet, gavage, inhalation, intratracheal instillation, intraperitoneal, intravenous, subcutaneous, and intrapulmonary injection, dermal application, and transplacental administration.

In hamsters exposed to 9.5 or 46.5 mg/m^3 BaP by inhalation for 109 weeks, a dose-response relationship was seen with tumours in the nasal cavity, pharynx, larynx, and trachea. The fact that lung tumours were not detected could not be explained (Thyssen et al., 1981). Hamster lung tissue can activate BaP to carcinogenic derivatives (Dahl et al., 1985).

PAHs in complex mixtures

Using a PAH-rich mixture, with the benzo[a]pyrene content about 90 $\mu g/m^3$, the tumour incidence in rats exposed for 16 h/day on five days per week for 22 months with a subsequent eight-month exposure to clean air was 18%. The mortality rate was not increased in comparison with controls exposed to clean air. The lung tumour incidences in mice exposed to the same atmosphere for 10, 12, or 24 months were 86, 70, and 79%, respectively, with 3.5, 12.5, and 32% in concurrent controls. (Heinrich et al., 1986a,b).

Heinrich et al., (1994b) exposed rats by inhalation to 1.1 (groups 1 and 2) or 2.6 mg/m^3 (groups 3 and 4) of an aerosol of a PAH-rich hard coal-tar pitch condensate (containing 20 or 50 $\mu g/m^3$ BaP), for 17 h per day on five days per week for 10 (groups 1 and 3) and 20 months (groups 2 and 4) and then to clean air for 20 or 10 months. Increased mortality in treated rats was observed due to the development of large, multiple tumours in the lungs and not to toxic effects. The lung tumour rates were 4, 33, 39, and 97% in groups 1,2, 3, and 4, respectively. Most of the lung tumours observed were classified as squamous-cell carcinomas

Summary

The carcinogenicity of individual PAH and PAH-containing mixtures in experimental animals has been well studied. Virtually no data exist on the carcinogenicity of individual PAH in humans, although a limited database on the carcinogenicity of PAH-containing mixtures is available: these have been shown to increase the

incidence of cancer in exposed human populations. The finding that a number of individual PAH are carcinogenic to experimental animals indicates that they are potentially carcinogenic to humans. PAH can produce tumours both at the site of contact and distantly, and the carcinogenic potency of PAH may vary with the route of exposure.

IPCS did not carry out quantitative risk estimates for PAH, either individually or as mixtures.

European Commission.(2001) Polycyclic Aromatic Hydrocarbons (PAH) Position Paper (July 2001), Prepared by the Working Group On Polycyclic Aromatic Hydrocarbons

This paper developed a Limit Value for PAH compounds that is intended to control exposure to PAH compounds in ambient air and reduce the attendant risk of cancer to a low level which would be regarded as tolerable by regulators. In setting a Limit Value recommendations were based on data produced by epidemiological studies of the effects on humans of exposure to industrial mixtures that contain PAH compounds.

Though exposure to high concentrations of PAH compounds can produce a range of toxicological effects the effect of greatest significance, on exposure to low and realistic concentrations, is the production of lung cancer. Problems of confounding by cigarette smoking and difficulties of exposure assessment have made many epidemiological studies in this area difficult to interpret.

They note that in some studies, eg, of workers at coal gasification plants in the UK (Doll et al., 1965; Doll et al., 1972), despite high levels of exposure, the risk of lung cancer was only moderately increased: by a factor of about two.

Of the Unit Risk estimates shown in the epidemiology, two are similar: the US coke oven workers study (87×10^{-6}), the aluminium smelters study (90×10^{-6}). The RIVM "most appropriate" estimate of $100\times10^{-6.}$ is not an epidemiological study as such, but a best estimate produced by the RIVM as a contribution to a Dutch Criteria Document on PAH compounds. This review (RIVM 1989) examined a range of studies then available and recommended a Unit Risk estimate of 100×10^{-6}, expressed as above, as the most appropriate estimate that the authors could produce.

The Working Group recommend, nevertheless, that the Unit Risk estimate adopted by WHO Air Quality Guidelines for Europe (WHO 1987; WHO 2001) from the US coke oven workers study, ie, 87×10^{-6}, be taken as a starting point for developing a Limit Value. This study has been considered in detail by a number of authors and the Unit Risk estimate produced is towards the centre of the Unit Risk estimates produced by the range of epidemiological studies listed above.

The contribution made by BaP to the total carcinogenicity of the four mixtures (ambient air in London, ambient air in Middlesborough, air at an aluminium smelter and in coke-oven fumes) was similar. Other authors have produced other figures. Petry et al., (1996) estimated the relative contribution made by BaP in mixtures encountered in coke plants, aluminium plants, graphite, silicon carbide and metal

recycling plants and bitumen paving as between 27 and 67%. The Canadian risk assessment of PAH compounds reported that BaP contributed 70-100% of the total PAH-attributable carcinogenic activity in different localities in Canada (Meek et al., 1994). In Sweden equivalent figures of 50-58% were produced and it was estimated that fluoranthene contributed 21-26% of total carcinogenic activity (Larsen and Larsen, 1998). In the Italian risk assessment, the excess risk globally associated with the seven carcinogenic PAHs was estimated to be approximately 75% due to BaP (Menichini 1992). These estimates, which though similar are by no means identical, have persuaded us that BaP can be used as an indicator compound in developing a Limit Value for PAH compounds.

Member States have variously set guideline or mandatory values of between 0.1 and 1.3 ng BaP/m^3. Since the risk has been evaluated on a lifetime exposure basis these limits usually relate to a yearly average. A consideration of the health based evidence and acceptance that the upper limit of the additional lifetime risk should be less than 1×10^{-4} ($\sim1\times10^{-6}$/year is generally accepted as the maximal risk level), would suggest a common air quality standard for BaP of less than 1.0 ng/m^3, averaged over a yearly period. PM_{10} is the most appropriate measurement fraction because lung cancer associated with inhaled PAH compounds occurs both in the large airways and in the deep lung.

The Working Group concluded that on the balance of current evidence BaP can be used as a marker of the carcinogenic risk of airborne PAH compounds despite not necessarily being the most potent carcinogen present. Data exist from occupational health studies which can be used as the basis for estimating the risk to human health posed by ambient levels of PAH. The unit risk (lifetime exposure to a mixture represented by 1 ng/m^3 BaP), based on a number of occupational studies, is in the range $80–100\times10^{-6}$. Working on the WHO estimate of a unit risk of 87×10^{-6} the risk associated with standards of 0.01, 0.1 and 1.0 ng/m^3 would be 1×10^{-6}, 1×10^{-5} and 1×10^{-4} respectively. As a result of developing knowledge there may be increasing uncertainty as to the reliability of the unit risk estimate*s*.

Taking into account the best available scientific evidence, in order to reduce the risk of harmful effects on human health arising from exposure to ambient levels of PAH, the EU should regulate PAH air quality. Bearing in mind the current uncertainty (in emissions estimation, assessment of ambient air concentrations, population exposures, and in the use of unit risk factors derived from occupational epidemiology studies), together with the difficulty in reducing emissions from some sources the EU should adopt an air quality limit of between 0.5–1.0 ng BaP/m^3, annual mean, measured in the PM_{10} fraction and expressed at ambient conditions. This limit should be reviewed in the light of improved knowledge after 5 years.

United Kingdom Report on Polycyclic Aromatic Hydrocarbons , UK Expert Panel on Air Quality Standards (EPAQS 1999)

The Expert Panel report concentrated on lung cancer as the most relevant outcome for PAH exposure from the air hence the recommendation for a standard was based on the need to protect people form developing lung cancer. The recommendation is intended to reduce any risk to the population of the United Kingdom from exposure to

polycyclic aromatic hydrocarbons to one that the Panel believes would be so small as to be undetectable.

The Panel considered the epidemiological study by Armstrong et al (1994) of lung cancer deaths in men who had worked in an aluminium smelter in Canada was particularly relevant since it addressed the confounder of smoking. In this investigation exposure to BaP as a marker of PAH exposure (benzene soluble coal tar pitch volatiles) was estimated for workers in each type of job within the plant. The heaviest exposure occurred for workers in two parts of the process known as 'the pot room' and 'anode manufacture', where BaP concentrations were 20-40$\mu g/m^3$. After adjustment for confounding by cigarette smoking and age, a clear association was found between increased exposure to BaP and lung cancer deaths RR 2.23 (95% CI 1.46-3.39 at 100-199 $\mu g/m^3$–years of BaP.

The excess risks of lung cancer have been shown in the coke oven workers with the highest and most prolonged exposures. For example, in a British study of coal gasification workers in the 1960s (Doll et al*.,* 1965; Doll et al., 1972), workers with heavy exposure in the carbonising plants showed an excess risk of lung cancer, while workers with intermittent exposure or exposure elsewhere in the workplace had no comparable excess. Workers exposed to high concentrations had an approximately 80% increase in the risk of lung cancer over and above other workers. A more recent investigation of coke oven workers in the USA revealed a significant excess of deaths from respiratory cancer, with the greatest increase in risk again occurring in those workers with the highest exposure to coke oven emissions (Costantino et al*.,* 1995).

Epidemiological investigations of workers in aluminium refineries in Canada, USA, and Norway have shown significant excesses of deaths from lung cancer related to prolonged exposure to PAH fumes (Armstrong et al*.,* 1994, Ronneberg and Andersen, 1995, Gibbs, 1985).

There is clear evidence that PAH mixtures are carcinogenic in humans and several individual PAHs are carcinogenic in experimental animals. Increased risks of lung cancer, in particular, have been associated with increased concentrations of PAHs in the workplace.

For practical reasons a marker compound for the carcinogenic activity of the PAH mixture was considered. Results from a recent Canadian study by Farant and Gariepy (1998) provided detailed support for the use of BaP as a marker for total PAH levels in the industrial context of ambient air on an aluminium smelting plant.

Analysis undertaken by the Panel led to the conclusion that epidemiological studies that used BaP as a marker of PAH exposure formed suitable basis for recommending an environmental standard, to be expressed in terms of BaP concentrations.

The Panel accept that several PAH compounds found in ambient air are genotoxic carcinogens. It is widely held that such compounds cannot be characterised by a threshold, and that therefore no absolutely safe exposure level can be defined. Epidemiological studies have shown that long-term exposure to mixtures of PAH compounds is associated with an increased risk of lung cancer.

It was noted that cumulative exposure to 10-99 µg/m^3-years of a mixture of PAH compounds represented by BaP was associated with an approximately 50% increase in the risk of lung cancer (Armstrong et al 1994). This was regarded as the lowest level at which effects have been observed, equivalent to exposure to 0.25-2.5 µg/m^3 of BaP (as a marker) for 40 years (working lifetime). The lower end of this range was adopted as the starting point.

In applying as safety factor of 10 for moving from a lowest observed adverse effect level (LOAEL) to a no observed adverse effect level (NOAEL), because PAH compounds are genotoxic carcinogens for which no completely safe level of exposure can be identified.10. In extrapolating from a working life (40 years, 5 days per week, 8 hours per day) to an entire life a factor of 10 was applied. Similarly a factor of 10 was applied to take account of the range of sensitivity to carcinogens likely to exist in the general population

A composite safety factor of 1000 was applied to the starting figure of 0.25µg/m^3 to derive a standard of 0.25 ng/m^3 for BaP.

The Panel was of the opinion that long-term exposure is more important than short duration exposure and as such recommended that the averaging time for the standard should be 1 year.

Government of Canada, Health and Welfare Canada, Environment Canada: Priority Substances List Assessment Report, Polycyclic Aromatic Hydrocarbons (PAHs) (1994)

Human Studies

The Report states up front that owing to the possible confounding by concomitant exposure to other substances that may have contributed to observed effects (increased lung and skin tumour incidence), available epidemiological data are considered inadequate to assess the health risks (including carcinogenicity) of PAHs in humans.

In addition, the composition of mixtures to which these workers (principally those in coke production, roofing, oil refining, or coal gasification) are exposed may vary considerably from those in the general environment.

The five PAHs considered principally in the assessment of potential risks to human health (benzo[a]pyrene (BaP), benzo[b]fluoranthene (BbF), benzo[j] fluoranthene (BjF), benzo[k]fluoranthene (BkF), and indeno[1,2,3-cd]pyrene (IND))are classified in Group II ("Probably Carcinogenic to Humans")

Experimental Animal Studies

The carcinogenic effects of exposure to PAHs by inhalation have been examined in only a few limited identified studies, all of which were restricted to BaP (Thyssen et al*.,* 1981; Laskin et al., 1970); moreover, in two of the investigations, animals were concomitantly exposed to other compounds (Heinrich et al., 1986b; Laskin et al., 1970). In the study by Heinrich et al. (1986b), the incidence of lung tumours was increased in rats exposed to combustion gases of a coal furnace for an average of 16 hours/day, 5 days/week over a maximum of 22 months. The incidence of respiratory

tract tumours was also increased in rats that inhaled 10 ppm (103 mg/m^3) BaP and the atmospheric irritant, sulphur dioxide ($S0_2$) (Laskin et al., 1970).

In a study by Thyssen et al. (1981), in Syrian golden hamsters exposed by inhalation to BaP for 96 weeks, the incidences of unspecified tumours of the respiratory tract (nasal cavity, larynx, and trachea) increased in incidence, at 9.5 and 45.6 mg/m^3. Lung tumours were not observed.

Deutsch-Wenzel *et al.* (1983), in which there were exposure-response relationships for epidermoid carcinomas and multiform sarcomas in Osborne-Mendel female rats administered BaP, BbF, IND, BkF, BjF, and ANT by pulmonary implantation.

Assessment

In order to calculate the exposure/carcinogenic potency indices (EPIs) for PAHs, two approaches have been adopted by the Canadians. One is based on the assumption that the carcinogenic potency of each of the components of a mixture of PAHs is equivalent to that of BaP on a weight basis; the other is based on calculation of relative carcinogenic potencies for several PAHs for which the data base is considered sufficient. Both of these approaches have considerable limitations, moreover, exposure from media other than air has not been taken into account.

For the BaP equipotency approach, the TD 0.05 (dose or concentration inducing a 5% increase in the relevant tumour) for inhaled BaP has been estimated based on multi-stage modelling of the respiratory tract tumours in Syrian golden hamsters in the study reported by Thyssen et al. (1981). The TD 0.05 for BaP estimated in this manner is 1.57 mg/m^3. Estimated interim EPIs for populations residing in the vicinity of aluminium smelters developed based on this likely conservative approach, and the total concentrations of the 17 to 28 PAHs at these locations 156 to 1690 ng/m^3 range from 1.0×10^{-4} to 1.1×10^{-3} (156 to 1690 ng/m^3÷1.57 mg/m^3). Therefore, based on this approach, the priority for analysis of options to reduce exposure solely on considerations of potential health effects would be high.

For the relative potency approach, carcinogenic potencies were estimated for the selected PAHs on the basis of multi-stage modelling of tumour incidence (epidermoid carcinomas) in rats exposed by lung implantation in the study by Deutsch-Wenzel et al. (1983) to each of the PAHs compared to that in the "solvent-vehicle"-exposed controls. Values were based on the dose that induced a TD 0.05 (5% increase in the incidence of relevant tumours). The potencies relative to that of BaP were computed by dividing the dose calculated to be associated with a 5% increase in tumours for BaP by those for each compound. The relative carcinogenic potency factors estimated on this basis were 0.06 for BbF, 0.05 for BjF, 0.04 for BkF, and 0.12 for IND (and 1 for BaP).

The values for total BaP equivalents/m^3 range from 2.72 to 48.98 ng/m^3 for cities near aluminium smelters using Horizontal or Vertical Stud Söderberg processes, 2.42 to 9.12 ng/m^3 for cities where wood stoves are commonly used, 0.13 to 2.25 ng/m^3 for urban cities, and 0.11 ng/m^3 for a rural area.

The EPIs have been calculated on the basis of the TD 0.05 for inhaled BaP estimated based on multistage modelling of the respiratory tract tumours in Syrian golden hamsters (Thyssen et al. (1981), and the BaP equivalents in ambient air at different types of sites in Canada for the five specified PAHs. For example, "interim" EPIs for the general population in Canada living near aluminium smelters that use the Horizontal or Vertical Söderberg process (the population that has the highest exposure to the selected PAHs) range from 1.7×10^{-6} to 3.1×10^{-5} (2.72 to 48.98 ng of BaP equivalent/m^3 ÷ 1 .57 mg of BaP/m^3).

Based primarily on the results of carcinogenicity bioassays in which PAHs have been administered to experimental animals by inhalation (benzo[a]pyrene only) and dermal application, and on supporting data, the Canadians concluded that " …the PAHs benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene may constitute a danger in Canada to human life or health".

US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, (ATSDR 1995) Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs)

Several epidemiological studies have shown increased mortality due to cancer has been associated with exposure to PAH-containing mixtures in humans exposed to coke oven emissions, roofing-tar emissions, and cigarette smoke. The cancers occur predominantly in the lungs and skin following inhalation and dermal exposure, respectively. It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens, and the potential interactions that could occur with other toxic substances in the mixtures. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene to cause cancer in humans. For these reasons, and also because of the lack of data on the effects of individual PAHs in humans, such information has been included in this profile on PAHs.

Human Studies

Only one study was located regarding respiratory effects in humans following inhalation exposure to PAHs, specifically, benzo[a]pyrene. The respiratory health of 667 workers in a rubber factory was investigated (Gupta et al. 1993). Statistically significant decrements in ventilation function occurred following prolonged exposure as assessed by duration of employment. Workers in the compounding section were the most affected, which was associated with the highest exposure to particulate matter and benzo[a]pyrene. These workers exhibited radiographic and other symptoms including bloody vomit, breathing problems, chest pains, chest irritation, throat irritation, and cough.

They could nor locate studies regarding cancer in humans following inhalation exposure to any of the 17 PAHs included in their profile. However, epidemiological studies have shown increased mortality due to lung cancer in humans exposed to coke oven emissions, roofing-tar emissions, and cigarette smoke. Each of these mixtures

contains potentially carcinogenic PAHs and other carcinogenic and potentially carcinogenic chemicals, It is thus impossible to evaluate the contribution of any individual PAH to the total carcinogenicity of these mixtures in humans because of the complexity of the mixtures and the presence of other carcinogens. The levels of individual or total PAHs were not quantified in any of these reports. Despite these limitations, reports of this nature provide qualitative evidence of the potential for mixtures containing PAHs such as benzo[a]pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, and dibenz[a,h]anthracene to cause cancer in humans.

Studies in Laboratory Animals
They considered that the chronic study of Thyssen et al. (1981) in Syrian Hamsters provides clear-cut evidence of a dose-response relationship between inhaled benzo[a]pyrene particles and respiratory tract tumourigenesis.

Schulte et al. (1993) found a significant increase in all lung tumours and a dose-dependent increase in malignant lung tumours for mice exposed to PAH-enriched exhausts containing 0.05 or 0.09 mg/m^3 benzo[a]pyrene.

Wolff et al. (1989). exposed groups of rats, nose-only, to an aerosol of benzo[a]pyrene at a single concentration 7.7 mg/m^3, 2 hours/day, 5 days/week, for 4 weeks. Nasal and left lung sections were examined histopathologically but no treatment-related lesions were noted in animals exposed to benzo[a]pyrene.

Assessment of Relevance to Public Health

Evidence exists to indicate that certain PAHs are carcinogenic in humans and animals. The evidence in humans comes primarily from occupational studies of workers who were exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (e.g., coal tar, coke oven emissions, soot, shale, and crude oil). The site of tumour induction is influenced by route of administration to laboratory animals: stomach tumours are observed following ingestion, lung tumours following inhalation, and skin tumours following dermal exposure, although tumours can form at other locations (lung tumours after dermal exposure).

They conclude by stating that evidence exists to indicate that mixtures of PAHs are carcinogenic in humans. The evidence in humans comes primarily from occupational studies of workers exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification. PAHs, however, have not been clearly identified as the causative agent. Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. Some ingestion of PAHs is likely because of swallowing of particles containing PAHs subsequent to mucociliary clearance of these particles from the lung.

A quantitative cancer risk estimate (ie cancer potency factor) has thus far been only developed for benzo[a]pyrene (EPA 1992). The cancer potency factor is 7.3 (4.5-11.7) per mg/kg/day, and is based on the geometric mean of risk estimates calculated from the oral dosing studies in mice (incidence of gastrointestinal

tumours)(Neal and Rigdon 1967) and rats (total number of tumours)(Brune et al 1981).

Californian Environmental Protection Agency (CEPA 1999) Office of Environmental Health Hazard Assessment (OEHHA) Air Toxics Hot Spots Program Risk Assessment Guidelines ,Part 11, Technical Support Document for Describing Available Cancer Potency Factors: benzo[*a*]pyrene

Human Studies

The predominant sources of airborne benzo[a]pyrene (BaP) are combustion processes. Thus, this compound rarely enters the environment alone but rather is associated with additional PAHs and other components frequently present in both vapour phase and particulate form. Available epidemiological information, therefore, is from persons exposed to mixtures such as tobacco smoke, diesel exhaust, air pollutants, synthetic fuels, or other similar materials. Several IARC publications have been dedicated to the analysis of cancer in processes which involve exposure to polynuclear aromatic compounds (PAHs) (IARC, 1983; 1987). The types of cancer reported are often consistent with the exposure pathway: scrotal cancer and lung cancer in chimney sweeps exposed to soot; skin cancer (including scrotal cancer) where shale oils are used; and lung cancer where airborne exposure of PAHs occurs, such as in iron and steel foundries

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Laboratory Animal Studies

Inhalation Exposures

Thyssen et al. (1981) inhalation study in male Syrian golden hamsters showed respiratory tract tumours which increased in a dose dependent manner. Lung tumours were absent.

Feeding Studies

Feeding BaP (50 to 250 ppm BaP for 4 to 6 months) to male and female CFW mice caused gastric tumours (papillomas and squamous cell carcinomas), pulmonary adenomas, and leukemia (Rigdon and Neal, 1966; 1969; Neal and Rigdon, 1967). The pulmonary adenomas, gastric tumours, and leukemia occurred independently of each other (Rigdon and Neal, 1969).

Summary

Because of the limited amount of data currently available for risk assessment of BaP, using a linearised multistage procedure (OEHHA, 1993), the inhalation unit risk of 1.1×10^{-3} $(\mu g/m^{3})^{-1}$ was based on respiratory tract tumours in hamsters (Thyssen et al., 1981), is used as a best value for inhalation exposures. For exposures to BaP by other routes, the potency of 11.5 $(mg/kg/day)^{-1}$ was based on gastric tract tumours in mice can be used (Neal and Rigdon, 1967).

Basis for Cancer Potency and Potency Equivalency Factors (PEFs) for BaP

A very large number of experiments have demonstrated that BaP causes tumours at several sites, by several routes of administration, in both sexes, and in several animal species. Many studies, however, are very limited in scope or in data reported and are not suitable for risk assessment (Zeise and Crouch, 1984).

OEHHA guidelines prescribe that risk assessment use the most sensitive sex, site, and species where a significant increase in cancer incidence is observed (CDHS, 1985). Since there is no adequate information regarding the carcinogenicity of BaP to humans from epidemiological studies, data from animal bioassays were extrapolated to estimate human cancer risk. Potency estimates were derived by OEHHA (1993).

Benzo[a]pyrene (BaP) was the index compound for relative potency and for Potency Equivalency Factors (PEF) for PAHs and derivatives. It has a cancer potency of 11.5 $(mg/kg/day)^{-1}$ and inhalation unit risk of 1.1×10^{-3} per $\mu g/m^3$. For the potency equivalency scheme, it was assigned a PEF of 1.

New Zealand Ambient Air Quality Guidelines, 2002 Update (2002)

New Zealand has noted the large number of reviews on adverse health effects from PAHs. They also state that there are no human data on the effects of acute or chronic exposures to BaP only. The epidemiological studies have reported increases in lung cancer in humans from exposure to coke oven and roof tar emissions and cigarette smoke, all of which contain a number of PAHs, including BaP.

Animal studies have reported respiratory tumours following inhalation exposure to BaP, and forestomach and lung tumours and leukaemia following oral exposure (USEPA 1998).

They state that a number of studies have shown that the benzene-soluble fraction of condensates from petrol and diesel vehicle exhaust, domestic coal stove emissions and tobacco smoke, containing 4-7 ring PAHs, account for nearly all the carcinogenic potential of PAHs from these sources (WHO 1996). They also note that the carcinogenic 4-7 ring compounds in ambient air are preferentially bound to particles, that only a minor fraction (depending on temperature) exists as volatiles, and that some studies indicate that the toxicokinetics of inhaled BaP attached to particles and pure BaP are different. WHO has determined an inhalation unit risk of 8.7×10^{-2} per $\mu g/m^3$ BaP, based on interpolation from risk estimates for PAHs in coke oven emissions. WHO has also determined an inhalation unit risk from studies of animals exposed to complex mixtures of PAHs of 2×10^{-5} per $\mu g/m^3$, BaP 10^{-5} per ng/m^3 (WHO, 1996).

The New Zealand authority considered that a criterion of 0.30 ng/m^3, annual average, for BaP (as an indicator of PAHs) PAHs (as Benzo(a)pyrene)is appropriate. The value was based on an acceptable risk to the community (lifetime risk of lung cancer) of between 1 in 10,000 and 1 in 100,000 and applying the WHO unit risk values, the calculated annual average guideline for BaP is in the range 1.2 to 0.12 ng/m^3 .

Summaries of Key Sudies

Human studies
Armstrong *et al.,* (1994) reported results of a case-cohort study of 338 lung cancer deaths in 1950-1988 and a random sample (sub-cohort) of 1,138 from among 16,297 men who had worked at least one year between 1950 and 1979 in manual jobs at a large aluminium production plant in Canada. In the past, certain workers were exposed to substantial quantities of coal tar pitch volatiles, a mixture known to include polynuclear (polycyclic) aromatic hydrocarbons, and thus suspected to be capable of causing lung cancer. PAH exposure was estimated (using BaP as a marker) for workers in each type of job within the plant. The heaviest exposure occurred for workers in two parts of the plant known as 'the Söderberg pot room' and 'Prebake process carbon plant or anode preparation area'. The Söderberg potroom workers may have been exposed to 0.15 to 3.5 mg/m^3 of benzene soluble material (estimated BaP levels of 2 to 35$\mu g/m^3$) and the Prebake workers exposed to 0.2 to 1.2 mg/m^3 of benzene soluble material (estimated BaP levels of 0.1 to 10.2$\mu g/m^3$).

After they controlled for the effects of smoking, the authors found that rate ratios rose with cumulative exposure to coal tar pitch volatiles measured as benzene-soluble material to 2.25 (95% confidence interval (CI) 1.50-3.38) at 10-19 mg/m^3-years benzene-soluble matter, but did not rise further at higher exposures. Similar effect was noted with estimated BaP levels, 2.23 (CI 1.46-3.39) at 100-199 $\mu g/m^3$ -years. The data were compatible with a linear relation with benzene-soluble matter (rate ratio (RR) = 1+0.031 mg/m^3-years benzene-soluble matter). This model predicts a rate ratio of 1.25, and lifelong excess risk of 2.2%, after 40 years exposure at the current hygiene standard (0.2 mg/m^3). A curved relation (RR = 1+0.098 mg/m^3-years benzene-soluble matter 0.7) fitted somewhat better. Under this model, the predicted risks after this exposure are higher: 1.42 and 3.8%. The data are compatible with both additive and multiplicative models for the combined effect of smoking and coal tar pitch volatiles.

Costantino et al., (1995) reported a significantly increased risk for lung cancer (SMR, 1.95 with 95% CI of 1.59-2.33) was found among a cohort of over 5000 workers who were heavily exposed at coke ovens in coke plants and were followed-up for over 30 years. The authors concluded that 124 deaths from lung cancer occurred among these coke-oven workers that could be attributed to exposure to coal-tar pitch volatiles, 2.3% of the cohort. Although no data were available on smoking habits, the observed effect is not likely to be due to smoking since unexposed steel workers in a comparison group were assumed to have similar smoking habits. In addition, a high correlation was seen between the risk for respiratory cancer and the concentration and duration of exposure. The authors noted however, that the rates of respiratory cancer decreased during the follow-up period, suggesting that implementation of emission controls and occupational exposure limits has been beneficial.

The respiratory health of 667 workers in a rubber factory was investigated (Gupta et al. 1993). Respiratory health was evaluated and examined for correlations to length of employment at the factory. In addition, total suspended particulate matter and benzo[a]pyrene concentrations were monitored in various parts of the factory and examined for possible correlation with the respiratory health of the workers in the

same area of the factory. Statistically significant decrements in ventilation function occurred following prolonged exposure as assessed by duration of employment. When different sections of the factory were considered, workers in the compounding section were the most affected, which was associated with the highest exposure to particulate matter and benzo[a]pyrene. Workers in the compounding section exhibited radiographic abnormalities including patch opacities, prominent bronchiovascular markings, and pleural effusions. Other symptoms included bloody vomit, breathing problems, chest pains, chest irritation, throat irritation, and cough. Workers in other areas of the plant exposed to lower levels of particulate matter and benzo[a]pyrene were similarly affected although to a lesser degree and in fewer numbers. No attempt was made to separate the effects of exposure to benzo[a]pyrene and particulate matter, or to identify possible simultaneous exposure to other toxic chemicals.

Laboratory Animal Studies

Male Syrian golden hamsters (24/group) were exposed by inhalation to 0, 2.2, 9.5 or 46.5 mg BaP/m^3 in a sodium chloride aerosol (Thyssen et al., 1981). (Greater than 99% of the particles had diameters between 0.2 and 0.5 μm.) For the first 10 weeks of the study, the hamsters were exposed to BaP daily for 4.5 hours/day; thereafter, daily for 3 hours/day. Animals dying within the first year of the study were replaced; the effective number of hamsters in the control, low-, mid- and high-dose groups was 27, 27, 26 and 25, respectively. (The total time of treatment, although over 60 weeks, was not stated.) During the first 10 weeks, animals in the 3 dose groups reportedly lost weight. After week 10, however, the body weights in all groups were similar until week 60 when the body weights of hamsters in the high-dose group decreased and the mortality increased significantly. The incidence of respiratory tract tumours (including tumours of the nasal cavity, larynx and trachea) in the control, low-, mid- and high-dose groups was 0/27, 0/27, 9/26 and 13/25, respectively; the incidences of upper digestive tract tumours (including tumours of the pharynx, oesophagus and forestomach) were 0/27, 0/27, 7/26 and 14/25, respectively. Trend analysis for incidences of both respiratory tract tumours and upper gastrointestinal tract tumours showed a statistically significant tendency for the proportion of animals with either tumour type to increase steadily with increased dose (Knauf and Rice, 1992).

Groups of 40 Fischer-344/Crl rats/sex were exposed nose-only to an aerosol of benzo[a]pyrene (7.7 mg/m^3) 2 hours/day, 5 days/week, for 4 weeks (Wolff et al. 1989). Nasal and left lung sections were examined histopathologically. No treatment-related lesions were noted in the lungs or nasal cavities of the animals exposed to benzo[a]pyrene. Although this was a well-conducted inhalation toxicity study, it is not appropriate for use in risk assessment because only one concentration was studied (thereby precluding the assessment of a dose-response relationship); no adverse treatment-related effects were observed; and the only parts of the respiratory tract examined histopathologically were the lungs and nose.

In a PAH-rich emission mixture prepared by burning tar pitch with coal, the benzo[a]pyrene content was about 90 μg/m^3, two to three times higher than the concentration measured in old coal plants. The tumour incidence in rats exposed for 16 h/day on five days per week for 22 months with a subsequent eight-month exposure to clean air was 18%; the mortality rate was not increased in comparison with controls exposed to clean air. The lung tumour incidences in mice exposed to the

same atmosphere for 10, 12, or 24 months were 86, 70, and 79%, respectively, with 3.5, 12.5, and 32% in concurrent controls. An additive or even potentiating carcinogenic effect with other respiratory-tract carcinogens was demonstrated. In contrast to a group exposed concurrently to diesel exhaust, the coal-tar pitch did not cause particle overload in the lung or impair lung clearance (Heinrich et al., 1986a,b).

Heinrich et al., (1994b) exposed Female Wistar rats were by inhalation to 1.1 (groups 1 and 2) or 2.6 mg/m^3 (groups 3 and 4) of an aerosol of a PAH-rich hard coal-tar pitch condensate containing 20 or 50 µg/m^3 benzo[a]pyrene (among other PAHs), for 17 h per day on five days per week for 10 (groups 1 and 3) and 20 months (groups 2 and 4) and then to clean air for 20 or 10 months. The aerosol contained benz[a]anthracene and chrysene at concentrations similar to that of benzo [a]pyrene. Increased mortality was observed due to the development of large, multiple tumours in the lungs and not to toxic effects. The lung tumour rates were 4, 33, 39, and 97% in groups 1,2, 3, and 4, respectively. Other groups exposed simultaneously to 2 or 6 mg/m^3 carbon black, which might serve as a PAH carrier, showed an additional increase in tumour rates, 89 and 72% in comparison with 39% in group 3. A group exposed only to carbon black had a tumour rate of 18%. The authors therefore concluded that there was a more than additive carcinogenic effect after 10 months of exposure. A 'PAH depot' effect may be involved, in which the residence time of the PAH is prolonged due to attachment to the inert carbon black particles, with an extended period elution of adsorbed PAH. Furthermore, the irritating, inflammatory, and cell proliferation effects of carbon black enhance the probability of genotoxic effects in the lungs (Heinrich, 1989; Heinrich et al., 1994a). Most of the lung tumours observed after exposure to tar-pitch aerosol with or without carbon black were classified as squamous-cell carcinomas (Deutsch-Wenzel et al., 1983) in conducted a study in rats with the broadest range of PAHs. Anthanthrene (ANT), BaP, benzo[e]pyrene (BeP), BbF, BjF, BkF, benzo[ghi]perylene (BghiP), or IND dissolved in residue-free acetone and a mixture of 1:1 beeswax and trioctanoin were implanted into the left lung of groups of 38 three-month-old, inbred Osborne-Mendel female rats. The rats were observed until their natural deaths, which occurred up to 32 months following implantation. At the site of implantation, a granulomatous inflammatory response was observed. In some animals, keratinised epidermoid carcinomas invading the extrapulmonary chest wall were observed; other tumours of this type metastasised predominantly into local and distant lymph nodes, heart, uterus, ovaries, adrenal glands, and kidneys. In a small number of animals, there were multiform sarcomas. On the basis of histological and statistical analysis, there was evidence of an exposure-response relationship for increases in tumour incidence for BaP, BbF, IND, BkF BjF, and ANT. The incidence of epidermoid carcinomas and multiform sarcomas of the lung at the highest dose for all compounds administered were: control, 0/0; BbF at 1.0 mg, 13/35 (37.1%); BeP at 5.0 mg, 1/35 (2.9%); BjF at 5.0 mg, 18/35 (51.4%); BkF at 4.15 mg, 12/27 (44.4%); IND at 4.15 mg, 21/35 (60%); ANT at 0.83 mg, 19/35 (54.3%); BghiP at 4.15 mg, 4/34 (11.8%); BaP at 1.0 mg, 33/35 (94.3%).

Feeding of pelletised chow containing BaP (50 to 250 ppm BaP for 4 to 6 months) to male and female CFW mice caused gastric tumours (papillomas and squamous cell carcinomas), pulmonary adenomas, and leukemia (Rigdon and Neal, 1966; 1969; Neal and Rigdon, 1967). The pulmonary adenomas, gastric tumours, and leukemia occurred independently of each other (Rigdon and Neal, 1969). The overall data strongly suggest a positive carcinogenic effect since there were no gastric tumours in

289 control mice while 178 out of 454 mice fed various levels of BaP had gastric tumours (Neal and Rigdon, 1967).

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