

# Polycyclic Aromatic Hydrocarbons and Fatal Ischemic Heart Disease

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**Background:** Several toxicologic and epidemiologic studies have produced evidence that occupational exposure to polycyclic aromatic hydrocarbons (PAH) is a risk factor for ischemic heart disease (IHD). However, a clear exposure–response relation has not been demonstrated.

**Methods:** We studied a relation between exposure to PAH and mortality from IHD (418 cases) in a cohort of 12,367 male asphalt workers from Denmark, Finland, France, Germany, Israel, The Netherlands and Norway. The earliest follow up (country-specific) started in 1953 and the latest ended in 2000, averaging 17 years. Exposures to benzo(a)pyrene were assessed quantitatively using measurement-driven exposure models. Exposure to coal tar was assessed in a semiquantitative manner on the basis of information supplied by company representatives. We carried out sensitivity analyses to assess potential confounding by tobacco smoking.

**Results:** Both cumulative and average exposure indices for benzo(a)pyrene were positively associated with mortality from IHD. The

highest relative risk for fatal IHD was observed for average benzo(a)pyrene exposures of 273 ng/m<sup>3</sup> or higher, for which the relative risk was 1.64 (95% confidence interval = 1.13–2.38). Similar results were obtained for coal tar exposure. Sensitivity analysis indicated that even in a realistic scenario of confounding by smoking, we would observe approximately 20% to 40% excess risk in IHD in the highest PAH-exposure categories.

**Conclusions:** Our results lend support to the hypothesis that occupational PAH exposure causes fatal IHD and demonstrate a consistent exposure–response relation for this association.

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**E**levated risk of mortality from ischemic heart disease has been associated with employment in jobs that entail exposure to polycyclic aromatic hydrocarbons (PAH) such as aluminum smelting,<sup>1,2</sup> chimney sweeping,<sup>3–5</sup> waste incineration,<sup>6</sup> motor vehicle operators,<sup>7</sup> bakers,<sup>7</sup> and tar distillation.<sup>8</sup>

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Diesel exhaust, rich in PAH, has also been associated with increased risk of cerebrovascular disease and arteriosclerosis.<sup>9</sup> In a study of asphalt workers, who are exposed to PAH,<sup>10,11</sup> a statistically nonsignificant increase in mortality from ischemic heart disease was observed,<sup>12</sup> but these results have remained controversial.<sup>13</sup> Norwegian asphalt paving workers (more than 25 years since first employment, included as part of the population described in this article) tended to be at an elevated risk of mortality from cardiovascular diseases compared with the general population (27 deaths: standardized mortality ratio = 1.5, 95% confidence interval [CI] = 1.0–2.2).<sup>14</sup> Tobacco smoke, rich in PAH, has long been established as a risk factor for ischemic heart disease, and it is plausible that this group of chemicals contributes to the chronic effects of tobacco smoke on the cardiovascular system.<sup>15</sup> In support of these findings in humans, animal experiments demonstrated that exposure to PAH can adversely affect the blood pressure and heart rate<sup>16</sup> and promote the development of atherosclerosis.<sup>17</sup>

There is mounting epidemiologic and toxicologic evidence that environmental PAH exposure, including occupational exposure, is a risk factor for ischemic heart disease. Nonetheless, quantitative exposure–response relations, important for inference of causality,<sup>18</sup> have not yet been demonstrated. Consequently, we explored the exposure–response relation between PAH exposure and cardiovascular mortality in a large cohort of European asphalt workers<sup>19,20</sup> who are exposed to low levels of PAH from bitumen and coal tar<sup>10</sup> and for whom we have previously developed an exposure matrix with modeled quantitative-exposure estimates for benzo(a)pyrene.<sup>21</sup>

## METHODS

### Study Population

Persons included in the historical cohort were first employed between 1913 and 1999 in 217 companies applying and mixing asphalt in Denmark, Finland, France, Germany, Israel, The Netherlands, and Norway. The requirement for the inclusion of a company in the study was the availability of a complete retrospective employee roster during the enrollment period. Once a company had been selected for the study, efforts were made to enroll all manual workers. Personal identifiers and employment histories of workers were abstracted from company records. The minimal duration of employment for inclusion in the cohort was one work season as reported by companies in a questionnaire that described production characteristics (see subsequently). The inclusion criterion was applied because short-term workers may differ in their occupational and nonoccupational risk factors from long-term employees.<sup>22</sup> Occupational histories were coded on the basis of information from personnel records according to classifications of jobs constructed for the study. A “job” in

this classification scheme represented the primary activity of a worker in a given time period (eg, asphalt paving), but does not reflect specific tasks performed. In the current analysis, we included 12,367 men who appeared to have been exclusively employed in asphalt paving. A detailed description of the cohort can be found elsewhere. Previous analyses of the cohort did not indicate associations of exposure to PAH with mortality from all causes and cancers.<sup>19,23</sup>

### Mortality Follow Up

A follow up for mortality was conducted in all participating countries, including data on primary causes of death. Data on contributing or underlying causes of death were not available. Subjects were followed beyond the period of employment in companies studied. The earliest follow up started in 1953, and the latest ended in 2000. Average ( $\pm$ SD) duration of follow up was 17 years ( $\pm$  9 years). These figures were similar for all countries. Cohort members accumulated 193,889 person-years of observations. The proportion of loss to follow up was 0.25%; an additional 0.39% of the cohort members emigrated during the follow up.

Causes of death were coded according to the International Classification of Diseases, 9th Revision (ICD-9). Mortality from diseases of circulatory system was identified by ICD-9 codes 390 to 459, and mortality from ischemic heart disease was restricted to ICD-9 codes 410 to 414.

### Exposure Assessment

We estimated exposures to coal tar, the main occupational source of PAH in the cohort, and benzo(a)pyrene, a marker for 4–6 ring PAH, which may arise from sources other than coal tar.<sup>21</sup> Exposures were reconstructed by using information about changes in asphalt paving technology in each company over time, the modeled relation between production characteristics and exposure levels, and job histories.<sup>21</sup>

We gathered information about companies enrolled in the study through a company questionnaire that ascertained temporal changes in production characteristics and work organization. These included average time spent using a given paving method (eg, mastic laying, hot mix paving). The questionnaire was administered to knowledgeable company representatives, and reviewed for inconsistencies and errors.

Quantitative estimates of exposure to benzo(a)pyrene were obtained for paving operations on the basis of previously available personal exposure measurements from workers in the asphalt industry (but not necessarily from cohort members), which were assembled into a single database for the study.<sup>24</sup> The contextual information coded for each exposure measurement included production characteristics within a job (using a classification similar to that used in the company questionnaire), repeated measurements within a worker, and country. We constructed<sup>11,25</sup> and validated<sup>26</sup> mixed-effects exposure assessment models, with production

characteristics as fixed effects and repeated measurements on the same worker as random effects, to predict quantitative exposures to benzo(a)pyrene among asphalt paving workers. Use of coal tar was the strongest determinant of exposure to benzo(a)pyrene; time period, mastic laying, repaving, surface dressing, and oil gravel paving were also important predictors.

In addition to being one of the predictors of exposure to benzo(a)pyrene, the information from company questionnaires on use of coal tar-containing materials was the basis of semiquantitative exposure assessment for coal tar. We assumed that all coal tar-containing materials had similar concentrations of coal tar and that exposure intensity was directly proportional to the frequency of use of coal tar-containing materials.

All predicted exposure levels in the exposure matrix<sup>21</sup> were standardized to an 8-hour work shift using information on average work shift duration reported in the company questionnaires. The exposure matrix was time period- and company-specific.

Diesel exhaust exposure was assessed on the basis of the proportion of time that diesel engines were used by paving crews. Exposures to total organic fume and vapor were modeled in a manner similar to benzo(a)pyrene, but is not presented here in details because there is not a strong *a priori* hypothesis as to why they would cause cardiovascular diseases, and because estimates of exposures to benzo(a)pyrene and total organic matter were strongly correlated.<sup>21</sup>

For all subjects, we estimated cumulative exposure (product of exposure duration and intensity integrated over work history) and average exposure over the work history (ratio of cumulative exposure and duration of exposure). The estimates of duration of exposure were corrected for differences in duration of working season between companies and countries. For each exposure index, unexposed subjects (when available) formed a separate reference category, and exposed subjects were divided into quintiles, each including approximately one fifth of the deaths from ischemic heart disease.

## Exposure–Response Analyses

Relative risks (RRs) and associated 95% CIs were estimated using Poisson regression.<sup>27</sup> All Poisson regression models included an exposure index for each agent of interest (benzo(a)pyrene or coal tar), age ( $\leq 39$ , 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70+ years), calendar period of exit from cohort (pre-1974, 1975–1979, 1980–1984, 1985–1989, 1990 and later), total duration of employment (<1, 1–4, 5–9, 10–14, 15–19, 20+ years) and country using the category at the lowest exposure as the reference. Duration of employment was included to partially control for the healthy worker effect; it was not equal to the duration of exposure because of seasonal nature of work that was considered in estimation of duration of exposure. Linear trends in log(RR) were estimated assuming constant differences between expo-

sure categories. Only the *P* values for these tests are reported. Poisson regression analyses were carried out in Stata 6.0 (Stata Corp., College Station, TX). Person-years were allocated in SAS 6.12 (SAS Institute, Cary, NC) using a computer program developed at the International Agency for Research on Cancer. In allocating person-years, exposure variables (cumulative and average) were treated as time-dependent because they changed throughout each individual's working history.

## Confounding by Tobacco Smoking

We adjusted RR for possible confounding for smoking using an approach suggested by Axelson.<sup>28</sup> Tobacco smoking contributes to the mortality from ischemic heart disease in relation to the strength of its association with the disease and the prevalence in the population. We considered 3 categories of smokers: never smokers (ns), former smokers (fs), and current smokers (cs), and expressed the total mortality from ischemic heart disease in the population ( $M_{\text{tot}}$ ) as

$$M_{\text{tot}} = M_{\text{ns}} P_{\text{ns}} + M_{\text{fs}} RR_{\text{fs}} P_{\text{fs}} + M_{\text{cs}} RR_{\text{cs}} P_{\text{cs}},$$

where RR indicates relative risk and *P* prevalence of smoking.

The RR for smoking ( $RR_{\text{smk}}$ ) in the total population is

$$RR_{\text{smk}} = M_{\text{tot}}/M_{\text{ns}} = P_{\text{ns}} + RR_{\text{fs}} P_{\text{fs}} + RR_{\text{cs}} P_{\text{cs}},$$

and the smoking-adjusted relative risk for the exposure of interest ( $aRR_{\text{exp}}$ ) is

$$aRR_{\text{exp}} = RR_{\text{exp}}/RR_{\text{smk}},$$

where  $RR_{\text{exp}}$  is the unadjusted RR for the exposure.

We assumed that  $RR_{\text{fs}} = 1.2$  and  $RR_{\text{cs}} = 2$  on the basis of the literature.<sup>29,30</sup> Based on data from the Dutch subcohort,<sup>31</sup> we assumed that the following distributions of smoking habits are plausible for the whole cohort: among the nonexposed, 40% never smokers, 30% former smokers, and 30% current smokers; and among the highest exposed, 20% never smokers, 30% former smokers, and 50% current smokers.

## RESULTS

During follow up, there were 660 deaths from cardiovascular diseases among asphalt paving workers, of which 418 were the result of ischemic heart disease. Both cumulative and average exposure indices for benzo(a)pyrene were positively associated with mortality from ischemic heart disease (Table 1). The highest relative risk for fatal ischemic heart disease was observed with average benzo(a)pyrene exposures of 273 ng/m<sup>3</sup> or higher (RR = 1.64; 95% CI = 1.13–2.38). The highest cumulative benzo(a)pyrene exposure category (>2013 ng years/m<sup>3</sup>) was associated with a similarly elevated excess of risk for fatal ischemic heart disease (1.58; 0.98–2.55). Adjustment for total duration of employment did not influence these results. Similar trends were

**TABLE 1.** Exposure to Polycyclic Aromatic Hydrocarbons and Mortality From Cardiovascular Diseases in the Cohort of Asphalt Paving Workers Using Relative Risks in Poisson Regression Models Adjusted for Country, Calendar Period, Age, and Duration of Employment

Agent and Exposure Metric	Exposure Group	Diseases of the Circulatory System		Ischemic Heart Disease	
		Deaths	RR (95% CI)	Deaths	RR (95% CI)
Coal tar Cumulative exposure (Dimensionless unit-years)	Nonexposed*	393	1.00	240	1.00
	0–0.29	67	1.04 (0.75–1.43)	37	1.00 (0.66–1.52)
	0.30–0.73	59	1.41 (0.99–2.00)	36	1.29 (0.82–2.01)
	0.74–1.41	50	1.41 (0.96–2.08)	35	1.45 (0.90–2.32)
	1.42–2.09	44	1.36 (0.89–2.08)	32	1.41 (0.84–2.36)
	2.10+	47	1.31 (0.86–1.99)	38	1.48 (0.90–2.44)
	<i>P</i> for trend		0.11		0.07
Average exposure (Dimensionless units)	Nonexposed*	393	1.00	240	1.00
	0–0.12	55	1.02 (0.72–1.44)	29	1.01 (0.65–1.57)
	0.13–0.25	59	1.11 (0.71–1.72)	43	1.09 (0.64–1.85)
	0.67–0.33	55	2.01 (1.29–3.14)	36	1.80 (1.04–3.10)
	0.34–0.99	42	1.35 (0.84–2.18)	33	1.47 (0.84–2.58)
	1.00+	56	1.85 (1.17–2.91)	37	1.64 (0.94–2.84)
	<i>P</i> for trend		<0.001		0.04
Benzo(a)pyrene Cumulative exposure (ng/m <sup>3</sup> -years)	0–189*	137	1.00	83	1.00
	189–501	145	1.08 (0.85–1.38)	83	0.99 (0.72–1.36)
	502–931	118	1.06 (0.80–1.42)	84	1.22 (0.86–1.74)
	932–2012	132	1.24 (0.89–1.71)	83	1.24 (0.82–1.85)
	2013+	128	1.42 (0.96–2.09)	85	1.58 (0.98–2.55)
	<i>P</i> for trend		0.09		0.06
	Average exposure (ng/m <sup>3</sup> )	0–68*	128	1.00	83
68–105		142	1.30 (1.01–1.67)	83	1.13 (0.82–1.55)
106–146		143	1.55 (1.18–2.05)	83	1.33 (0.94–1.90)
147–272		139	1.45 (1.09–1.93)	86	1.20 (0.84–1.71)
273+		108	1.58 (1.16–2.15)	83	1.64 (1.13–2.38)
<i>P</i> for trend			<0.001		0.02

\*Reference category.

observed for all cardiovascular diseases, although dose–response was evident only for ischemic heart disease (Table 1), and not for hypertension (ICD-9 code 401–405; 9 deaths), cerebrovascular diseases (ICD-9 code 430–438; 116 deaths), or other diseases of the heart (ICD-9 code 415.0, 415.2–429) (data not shown). Among deaths from cardiovascular diseases, we had sufficient power to examine exposure–response trends only for ischemic heart disease. Trends in RR were similar between PAH exposure indices and coal tar exposure indices, except that trends for benzo(a)pyrene were more monotonic. Diesel exhaust exposure index showed little variability among pavers and was not associated with risk of cardiovascular diseases (data not shown).

If we assume that RR for ischemic heart disease in the highest PAH-exposed group is in the order of 1.6, then our adjustment for possible confounding by smoking yields a RR

of 1.39 under our assumptions about distribution of smoking habits. The RR remains elevated (1.24) even if we assume an extreme distribution of smoking in the highest exposed group: 0% never smokers, 30% former smokers, and 70% current smokers. The RR also remains elevated (1.21) if we substitute into the original calculation considerably higher values of  $RR_{fs} = 2$  and  $RR_{cs} = 5$ , assuming stronger-than-expected effect of smoking (and possibly other associated lifestyle risk factors) on ischemic heart disease.

## DISCUSSION

We observed approximately 60% increase in risk of mortality from ischemic heart disease between the highest and the lowest PAH-exposure groups, demonstrating a clear exposure–response relation. Risk of fatal ischemic heart disease was also positively associated with coal tar exposure.



These associations can result from exposure to causal agents within the cohort, biases in exposure assessment, confounding by occupational exposures<sup>32,33</sup> and lifestyle factors,<sup>15</sup> and chance.

The plausibility of our findings is supported by toxicologic studies<sup>16,17,34,35</sup> and epidemiologic investigations in other PAH-exposed occupations.<sup>1-9</sup> This evidence lends support to the hypothesis that the mechanisms involved in the development of atherosclerotic plaques may parallel those relevant to carcinogenesis, including mutations induced by PAH and other carcinogens.<sup>34</sup> It has been observed that atherosclerotic plaques tend to be monoclonal, suggesting that they may arise as a result of mutations.<sup>34,35</sup> However, it should be noted that mosaic phenotypes in arteries could produce monoclonal atherosclerotic plaques resulting from injury without the intermediate step of a somatic mutation.<sup>35</sup>

Because we lacked complete occupational histories, it is possible that some cohort members were occupationally exposed to factors outside of the asphalt industry (such as PAH emitted during aluminum smelting<sup>1,2</sup> or carbon monoxide<sup>36</sup>) that contributed to deterioration of the subjects' cardiovascular health. If these exposures were correlated with exposures incurred during employment in the asphalt industry, our estimates of PAH-attributable risk could be confounded. This issue can be resolved only by collecting full occupational histories, including information on jobs outside the paving industry in a nested case-referent design. Such data were available on the Danish cohort, which has data from its pension fund covering the whole occupational history of its members. An analysis of this subset of workers does not indicate an elevated prevalence of employment in PAH-exposed occupations outside of the asphalt industry (data not shown).

We compensated for lack of data on individual smoking habits by conducting a sensitivity analysis, which indicated that differences in smoking status are an unlikely explanation for the observed exposure-response relations. Other lifestyle (eg, diet, physical activity) and personal (eg, blood pressure) risk factors were not considered, but we assume that, taken alone, their potential confounding influence on the observed trends in relative risks would be weaker than that of tobacco smoking. Even if additive effects of these risk factors were acting to confound our findings, we do not expect this effect to exceed that of a rather extreme assumption, which we tested, about greater-than-expected effect of smoking on ischemic heart disease. In addition, there is no reason why lifestyle and personal characteristics would be associated with occupational PAH exposure within the cohort. Nonetheless, we cannot exclude the possibility of bias in our risk estimates as a result of differential distribution of personal and lifestyle risk factors among different exposure groups.

Misclassification of exposure might have arisen during exposure assessment within the studied companies. For ex-

ample, we assumed that the use of all coal tar-containing products resulted in the same exposures to benzo(a)pyrene. We know from analysis of measurements gathered in the asphalt industry in France<sup>25</sup> that this assumption is flawed, but we could not obtain more detailed data on the past use of coal tar across the cohort. Exposure to diesel exhaust, a plausible risk factor for ischemic heart disease<sup>9</sup> and a source of PAH exposure, was assessed with too much uncertainty to draw reliable inferences. In addition, all pavers in the study were exposed to diesel exhaust either from passing traffic or from diesel-powered paving machines, resulting in limited variation in diesel exhaust exposure estimates. We were also not able to fully validate information that was gathered in company questionnaires, creating the possibility that not all cohort members were correctly classified with respect to determinants of exposure that were used in quantitative assessment of exposure to benzo(a)pyrene. Despite this possible error in exposure assessment, exposure models were considered to be reasonably valid and precise for the purposes of this epidemiologic study.<sup>26</sup>

Occupational histories could have also been extracted with errors for the cohort members, resulting in biases of unpredictable direction and magnitude. We attempted to mitigate this problem by selecting companies into the study that had precise personnel records<sup>37</sup> and limiting current analyses to those subjects who were employed only in paving, one of the most clearly identifiable group in the study.

Notwithstanding these limitations, exposures were assessed without consideration of vital status of a cohort member at the termination of the follow up. Therefore, we expect exposure misclassification to be nondifferential, yielding attenuated risk estimates (at least in the highest exposure categories) rather than positively biased risk estimates.<sup>38</sup> Bias in risk resulting from heterogeneity of measurement error in group-based exposure assessment<sup>39</sup> and categorization of continuous exposure variables<sup>40</sup> in occupational cohorts could arise when misclassification of assessed exposures is nondifferential, but such effects are small and are unlikely to affect the direction of observed associations. Our argument for the causal nature of the observed association is strengthened by the fact that similar trends were observed with using different, although not completely independent, measures (benzo(a)pyrene vs coal tar) and indices (cumulative vs average) of exposure to PAH.

Exposures that arise during asphalt paving include fine particles that are the focus of environmental air pollution studies. Mean exposure levels to respirable particulate mass (50% cut point of 2.5  $\mu\text{m}$  in diameter) on the order of 0.11 to 0.35  $\text{mg}/\text{m}^3$  have been reported among asphalt road pavers.<sup>41</sup> Average exposure levels to total particulates, 76% to 98% of which consist of fine particles,<sup>42</sup> have been reported to be approximately 0.3 to 14.2  $\text{mg}/\text{m}^3$  in asphalt operations.<sup>10</sup> Fine particles have been associated with increased mortality and

morbidity resulting from ischemic heart disease in vulnerable populations,<sup>43–45</sup> as well as with acute changes in cardiovascular system (eg, alterations of heart rate variability, increased cardiac arrhythmias, hypercoagulability of the blood).<sup>43</sup> However, the contribution of fine particles per se to development of ischemic heart disease is unclear. A contribution of exposure to fine particles, as present in bitumen fume, to development of ischemic heart disease remains a plausible hypothesis and an area of future research.<sup>46</sup> Furthermore, oxidative stress has been suggested as one of the mechanisms in development of atherosclerotic plaques,<sup>46</sup> and there appear to be plausible mechanisms by which oxidative stress can arise through either the interaction of inhaled fine particles with inflammatory leukocytes (probably mediated by particle-bound transition metals)<sup>46</sup> or exposure to PAH<sup>47</sup> in air pollution.

At present, exposure to PAH is a reasonable explanation for persistent endothelial damage leading to atherosclerosis and eventually heart disease. However, it is also true that we know more about potential mechanisms involving PAH (including mutations and other mechanisms similar to those taking place in carcinogenesis) than about those related to fine particles. Furthermore, our results cannot separate effects of fine particles from those of PAH, because 4–6 ring PAH has to be particle-bound to enter respiratory tract.<sup>11,21</sup>

Although we were not able to control for all possible sources of confounding and bias, our results lend support to the hypothesis that occupational PAH exposure causes ischemic heart disease. We have demonstrated consistent relations between quantitative levels of long-term exposure to PAH and risk of dying from ischemic heart disease. These findings suggest that public health policy aimed at reduction of risk of ischemic heart disease resulting from air pollution (either of occupational or environmental origin) should also consider PAH content of emissions.

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