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# Cancer risk following exposure to polycyclic aromatic hydrocarbons (PAHs): a meta-analysis

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# Cancer risk following exposure to polycyclic aromatic hydrocarbons (PAHs): a meta-analysis

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We carried out a review and meta-analysis of published reports of occupational epidemiological studies quantitatively informative to the PAH-cancer (lung and bladder) relationship. On average over 39 included cohorts, the estimated unit relative risk (URR) at 100 mg/m 3 years BaP was 1.20 (95%CI: 1.11, 1.29) for lung cancer , and was not sensitive to particular studies or analytic method. However, the URR varied by industry. The estimated mean in coke ovens, gasworks, and aluminium production works were similar (1.15-1.17). Average URRs in other industries were higher but imprecisely estimated, with those for asphalt (17.5; CI:4.21-72.78) and chimney sweeps (16.2; CI: 1.64-160.7) significantly higher than the above three. There was no statistically significant variation of URRs within industry, or in relation to study design (including whether adjusted for smoking), or source of exposure information. Limited information on total dust exposure did not suggest that dust exposure was an important confounder or modified the effect. For bladder cancer (n=27), the average URR was 1.33 (95%CI: 1.17, 1.51), with no statistically significant variation by industry or other putative determinants. However, numbers of cases were small in most studies, and results were highly dependent on two large studies of aluminium production workers.

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# EXECUTIVE SUMMARY

*Background:* Airborne PAHs have long been known to cause cancer in animals and have been widely classified as known human carcinogens. We carried out a review of published reports of occupational epidemiological studies quantitatively informative to this relationship, and a meta-analysis to identify the average and determinants of lung and bladder cancer risk per unit exposure.

*Methods:* Relevant peer reviewed reports published up to early 2001 were identified systematically using bibliographic databases. We excluded cohorts exposed occupationally to known or suspected carcinogens other than PAH that may have lead to substantial risks (eg foundries, diesel exhaust-exposed, rubber) were excluded. From each study that met the inclusion criteria (n=39), unit relative risk (URR: relative risk at 100 $\mu g/m^3$ BaP years cumulative exposure) was estimated by loglinear Poisson regression from published tables of risk against estimated cumulative exposure. For slightly more than half the studies, this required published data to be supplemented by estimated concentrations and sometimes duration of exposure. This exposure estimation was based on a review of published exposure data carried out by an industrial hygienist. Distribution and determinants of URRs were investigated using standard meta-analytic methods.

*Results:* On average, URR was 1.20 (95%CI: 1.11, 1.29) for lung cancer , and was not sensitive to particular studies or analytic method. However, the URR varied by industry. The average in coke ovens, coal gasification and aluminium production works were similar (1.17,1.15,1.16 respectively). Average URRs in other industries were higher but imprecisely estimated, with those for asphalt and chimney sweeps significantly higher than the above three. There was no statistically significant variation of URRs within industry, or in relation to study design (including whether adjusted for smoking), or source of exposure information. Limited information on total dust exposure did not suggest that dust exposure was an important confounder or modified the effect.

For bladder cancer, the average URR was 1.33 (95%CI: 1.17, 1.51), with no statistically significant variation by industry or other putative determinants. However, numbers of cases was small in most studies, and results were highly dependent on two large studies of aluminium production workers.

*Discussion:* Biases in the included studies could bias this meta-analytic synthesis, in particular if consistent across studies in one industry. However, URRs for coke oven, coal gasification, and aluminium production workers were rather consistent. The larger URRs in other industries, in particular asphalt and chimney sweeping, could not be due to chance. It is possible that they may be affected by biases, in particular relating to problems of exposure estimation, but for asphalt evidence is from more than one study, some of which included investigator-reported exposure estimates.

There was no evidence against a single URR for bladder cancer across all industries, but little evidence to positively support this either, with only aluminium smelters showing strongly positive associations. The average URR was slightly higher than for lung cancer but more imprecisely estimated.

# 1 INTRODUCTION

Airborne PAHs, which are emitted when organic matter is burned, are ubiquitous in the occupational and general environment. It has long been known that several PAHs can produce cancers in experimental animals, and epidemiological studies of exposed workers, especially in coke-ovens and aluminium smelters, have shown clear excesses of lung cancer, and highly suggestive excesses of bladder cancer (IARC 1984; IARC 1985; IARC 1987; Boffetta, Jourenkova et al. 1997; Negri and La Vecchia 2001). The animal experiments have included some using airborne exposure, and have been of mixtures and individual compounds, including in particular benzo(a)pyrene (BaP). Although the existence of a cancer risk is beyond reasonable doubt, there is considerable uncertainty as to the exposure-response relationship, and hence as to the risks posed at today's levels in the workplace and general environment. Information on this relationship is clearly important to inform the setting of occupational and environmental standards.

Estimating exposure-response relationships by extrapolation from animal studies is possible (USEPA 1984; Collins, Brown et al. 1991), but the limitation of this approach, in particular species differences, makes sole reliance on it problematic. A large study of coke-oven workers carried out since the 1960's in the USA (Lloyd 1971, Costantino et al 1995) has been used to estimate risk per unit residential exposure for the USEPA (Nisbet and LaGoy 1992) and the WHO (WHO 1987). However, these two estimates differ widely, and many new studies provide information that has not yet been systematically used to quantitatively assess risk.

The fact that PAHs comprise a mixture, several components of which are animal carcinogens, adds to the complexity of the task. One issue is whether a single index of exposure, such as benzo(a)pyrene (BaP) or total benzene or cyclohexane soluble matter (BSM or CSM) is adequate to determine risk. If such an index is used, risk per unit exposure may differ between studies (and unstudied exposures) because of differences in the ratio of this index to the total carcinogenic potential of the mixture. It is possible that such variation, if present, can be adequately described by classifying exposures in broad categories (for example by source). However, this remains untested.

We report here a review and meta-analysis that aimed to use all relevant published evidence from epidemiological studies to obtain an estimate or estimates of the relationship of PAH exposure with lung and bladder cancer, and to identify sources of variation in this relationship.

# 2 METHODS

## 2.1 LITERATURE SEARCH

We sought to include all published, peer reviewed epidemiological studies potentially informative on the PAH–cancer exposure response relationship. The following inclusion and exclusion criteria were employed:

### *Cancer site*

Only studies reporting on *lung* or *bladder* cancer were included. In a review of cancers associated with PAH exposure, Boffetta, Jourenkova et al. 1997 concluded that while some evidence exists for cancer of the larynx, kidney, colon and oesophagus, the evidence is not as conclusive as for lung and bladder. An increase in skin cancer was observed in some studies, but tended to be limited to settings entailing substantial dermal exposure. The restriction to lung and bladder cancer was designed to retain focus on the magnitude of the exposure-response relationship, rather than on whether a causal relationship exists.

### *Types of study:*

Only epidemiological studies of occupational exposure by inhalation were included. Most studies of non-occupational PAH exposure would in any case have been excluded on other criteria (in particular the likelihood of PAH not being the predominant carcinogen).

- Biomarker studies were excluded.
- We made no attempt to access studies published only in the grey literature, although such literature as informed published studies further (e.g. fuller research reports of studies) was sought.
- We excluded studies reporting only proportional cancer analyses.
- Language of publication was restricted to English, for practicality.
- Non-primary research papers (e.g. reviews) were excluded, but such papers were obtained for background information.

### *Exposures:*

- To reduce potential for confounded results, we excluded studies of workplaces in which PAH was considered unlikely to be the predominant lung or bladder carcinogen (i.e. other risks from carcinogenic co-exposures were likely to be substantial). Workplaces excluded by this rule included those in the rubber industry, those involving exposure to diesel exhaust, and foundries. We also excluded studies of steel works on this basis (co-exposure to silica), unless they included separate analyses specifically of coke oven workers.
- We excluded studies for which estimating a quantitative measure of exposure to PAH would be likely to lead to substantial misclassification of exposure. This rule lead us to exclude hospital- and population-based case-control and registry studies.

### *Duplication*

To avoid double counting of information from the same workforce reported in several papers (often from later studies updating earlier ones) we included only the last reported results.

## 2.2 LITERATURE SEARCH STRATEGY

The search strategy was conducted in three stages:

### *First stage*

Electronic searches were made using the online databases MEDLINE and EMBASE to identify papers relating to epidemiological studies of PAH exposure or PAH associated industries (see search terms in appendix A) and neoplasms. This produced 744 references, with publication dates between

1965 - January 2001 (MEDLINE) and between 1980 and February 2001 (EMBASE). Searches using OLDMEDLINE (papers published between 1958 and 1965), NIOSH and Cancerlit databases identified a further 5 studies. Abstracts and bibliographical information from these studies were imported into a reference manager, Endnote. After exclusion of studies with fields that contained the following terms: hospital based, population based, proportionate cancer, molecular, polymorphism, adduct, reviews, PMR, PCMR, bioassay, assay, biomarker, animal, metabolite, 521 studies remained.

#### *Second stage. First screen on titles and abstracts*

Of the 521 studies, 338 could be excluded using the above rules by reading titles and abstracts. To the remaining 183 papers we added a further 31 studies identified from reference lists of reviews or included studies, giving a total of 214 papers.

#### *Third stage: Second screen on further criteria and on full papers*

From the full text of the 214 papers, we excluded a further 178, leaving 36 fully meeting our criteria.

#### *Extraction of information*

From each included study we systematically extracted general descriptive information, information on potential modifiers of risk associated with PAH, and information from which we estimated unit relative risk increments (see next two sub-sections). Extraction forms were designed to enable standardised extraction of epidemiological information from published studies.

### 2.3 EXPOSURE ESTIMATION

We distinguished studies according to whether the authors reported:

(a) exposures to PAH indexed as benzo(a)pyrene (N=11).

(b) exposures to PAH indexed by a proxy which we could convert to BaP: Benzene soluble matter (BSM), total PAH, carbon black (N=5).

(c) no measures of exposure (N=20)

For two of the first group, cancer risks were tabulated by total PAH, but the reports gave conversion ratios to BaP:

- Romundstad 2000 (aluminium smelter): Ratio used 50 µg BaP/mg total PAH
- Hansen 1989 (roofers): Ratio used 21.86 µg BaP/mg total PAH (or BaP 0.02% of asphalt condensate)

We converted exposures in the second group to BaP by using a conversion ratio as follows:

(a) BSM:

- Spinelli 1991 (soderberg auminium smelter): Ratio used: 8 µg BaP/mg BSM (Armstrong 1994);
- Costantino 1995, Hurley 1983 (coke ovens): Ratio used: 7.1 µg BaP/mg BSM (WHO 1987);

(b) Total PAH:

- Bye 1998 ( Coke oven): Ratio derived from Romundstad 2000, but corrected for Coke oven Vs aluminium smelter ratios of BaP/BSM: 50X7.1/8=44 µg BaP/mg total PAH

(c) Carbon black manufacture:

- Sorahan 2001. Ratio used: 4.8 mg BaP/Kg carbon black (Van Tongeren 2001 – private communication, IARC 1996).

For the group with no exposure measures, with the collaboration of industrialhygienists, we estimated concentration of exposure to PAH for each workgroup for which risk estimates were presented. These estimates drew on the estimates published in the same industries in studies in groups 1 and 2 (Appendix B1), and on a literature review of hygiene surveys of similar workplaces (Appendix B2).

Particularly valuable were a review by Lindstedt and Sollenberg 1982 and the most relevant IARC monograph (IARC 1984). From these sources we derived a job-exposure matrix indicating estimated mean concentrations of exposure to PAH (as BaP) in job groups for which relative risks were published (Appendix B3). Synthesis of data on exposure was by judgement rather than formal statistical summaries of reported concentrations, to allow for data in a wide variety of forms ("hot-spot" measurements, personal and stationary samples, different sampling and analytical technique, very similar and roughly similar workplaces). To reduce bias due to this somewhat subjective process, this was carried out blind with respect to the relative risks found in the epidemiological studies.

- **Scale.** To simplify the task of making estimates for the JEM we made these on the scale: 50,20,10,5,2,1,0.5,0.2, <=0.1, unless there was clear information to lead us to place values between adjacent scale values. (Note for =0.1, we used 0.05)
- **Uncertainty**. We sought to estimate mean exposure in groups of jobs correct to within two points of our scale (i.e. a factor of five), with 95% confidence. Where we did not believe this possible (N=2), we set these studies aside (Ronneberg et al 1988, Martin et al 2000)
- **Time period.** For all included studies, the overwhelming majority of exposure in the likely etiologically relevant period (i.e. with ten or more years latency) occurred before 1970. We thus sought to estimate exposure for this period. In principal we were prepared to separate periods before this if we found clear evidence for changes in exposure, but in practice this never happened. Thus we made just one exposure estimate for each job group.

Most estimates were drawn from the matrix presented in table 1. A full list of exposure estimates made is given in Appendix B3.

### 2.3.1 Cumulative exposure.

Where risk estimates in categories 1 (BaP measures) and 2 (Proxy measures) were in groups according to cumulative exposure (eg 0, 0.1-9.9,10-99.9,100-199.9,200-) the only further information required was the mean cumulative exposure in each group. For closed groups (0.1-9.9,10-99.9,100-99.9 example above) we took the midpoint of the interval (5,55,150). For upper groups (200- example above) we estimated the mean from the observed distribution over groups by maximum likelihood, under the assumption that the distribution of non-zero cumulative exposures followed a lognormal distribution.

A similar procedure was followed for tables of risk by duration of exposure, except that an upper limit of 40 years was assumed if no upper limit was given for the highest group. Mean durations were then multiplied by the estimated concentration to obtain mean cumulative exposures for each period.

For other studies (for example where risk estimates were by job group, regardless of duration of exposure) estimates of duration of exposure were made using what information was available. In the absence of other information, twenty years was assumed, being a round number representing the average found in studies for which duration was reported.

### 2.3.2 Dust Exposure

At the inception of this study, we had not planned to seek information on potentially confounding exposures beyond those commented on by the authors. However, there has recently been a sharp increase in interest in the hypothesis that inhaled dust carries a risk of lung cancer regardless of composition. We therefore sought to add what information we could find on total dust exposure. Since very few of the publications reported such estimates, we relied entirely on supplementary data and the judgement of the hygienists on the research team for this. We were aware that this could only be a very rough assessment, so chose a simple scale: LOW (<1 $mg/m^3$); MODERATE (1-5 $mg/m^3$); HIGH (5-10 $mg/m^3$); VERY HIGH (10-25 $mg/m^3$), and broad job groups or, in some cases, entire industries. Assessments are listed in the final column of table 1. A list of references on which this was based is included in Appendix B4.

## 2.4 STATISTICAL ANALYSIS

### 2.4.1 Estimation of unit relative risks (URRs)

A technical description of the estimation of URRs for cancer, and discussion of associated models is given in Appendix C. We present a summary here.

We anticipated that a major determinant of cancer risk due to PAH exposure would be level and duration of exposure. To standardise for these two determinants, and increase the usefulness of our summary, we estimated from published results of each study increments in relative risk per unit cumulative exposure (Smith and Sharp 1985; Smith 1988) to BaP ($\mu g/m^3$ year). Working a normal working year in which the mean shift concentration is 1 $\mu g/m^3$ is defined to comprise 1 $\mu g/m^3$ year cumulative exposure.

For this purpose we fitted two different models for the dependence of relative risk on cumulative exposure:

(a) Loglinear relative risk model: $RR = \exp(b_{loglin} x)$

(b) Linear relative risk model: $RR = 1 + b_{lin} x$

where x is cumulative exposure in $\mu g/m^3$ years; and the b is the slope of the exposure-response relationship. (For both models, RR=1 if x=0.) Thus relative risk represents the risk of lung cancer at a specified exposure (x) relative to that at zero exposure. For example RR=1.30 at x=100 $\mu g/m^3$ BaP years exposure implies that at this exposure, lung cancer risk is 1.3 times that of an unexposed person – a 30% excess.

We used both these models because each has advantages and disadvantages over the other. In summary, the linear model fits the data and most proposed biological mechanisms better (Greenland 1987), but the loglinear model is more reliable in investigating heterogeneity and patterns of URRs over cohorts. Following Greenland (1987) we present main results for the loglinear model for its better statistical properties, but note also those from the linear model.

Estimates of slopes b were made by each method from each study from published tables of risk (usually SMRs or internal RRs) by cumulative exposure, duration of exposure, job group or single group for SMRs. Technical description of this is given in Appendix C. For the thirteen cohorts for which only one SMR was published, these estimates depended on assuming that at zero exposure that cohort would have experienced the same rates as those of the general population (allowing for age and calendar time). For the remainder, rates at zero exposure were inferred from the cohort itself (i.e. exposure-response curves were not constrained to SMR=1 at zero exposure).

To make results more easily interpretable, rather than reporting the slopes b we report results as relative risks predicted by the models at 100 $\mu g/m^3$ BaP years, which is close to the mean of the maximum exposures in included studies. 100 $\mu g/m^3$ BaP years corresponds to a concentration of 2.5 $\mu g/m^3$ BaP over 40 years. We refer to these as unit relative risks (URRs)

### 2.4.2 Selection of exposure contrasts for estimation of URRs

We referred above to URRs being estimated for **studies**. This was a simplification, for two reasons:

(a) Some publications included separate presentation of risks for quite distinct cohorts. For example, Hurley (1983) presented results (risks by cumulative exposure) for coke-workers from two different companies with distinct exposure estimates (British Steel Corporation workers and National Smokeless Fuels Limited workers). In these cases we considered the two cohorts as separate, and included two separate URR estimates in our meta-analyses.

(b) For just over half cohorts more than one contrast of risk in differently exposed sub-groups was published, each allowing a URR estimate. For example, there were often tables of risk by duration of service (sometimes sub-divided by job-group) and by job group (eg coke-oven top-worker, side worker, and distillation products), as well as on overall SMR.

It would be inappropriate to include URRs estimated from different contrasts from the same cohort as if they were separate studies. Primary analyses used contrasts selected according to the following rules (in order of priority):

i. Internal comparisons were favoured over external (i.e. comparing two SMRs or RRs was preferred over comparing an SMR with an assumed RR of 1.0 at 0 exposure).

ii. Contrasts with high difference in cumulative exposure in highest Vs lowest exposure group were favoured over contrasts with lower difference (e.g. if RRs given for 0 Vs 1-40 years exposure, and for 0, 1-10,10-20,20-30,30-40 years, then the latter is used in preference)

iii. Mortality outcomes were preferred over morbidity outcomes for lung and the reverse for bladder.

iv. Confounder-controlled contrasts were preferred over uncontrolled (eg smoking -adjusted Vs unadjusted)

v. Estimation of URRs from k groups was preferred over estimation of URRs from less than k groups. (i.e. intermediate groups were retained).

vi. To maximise comparability in primary analyses, estimates without latency or lag restrictions were preferred over those with such restrictions.

Rules for assigning preferred contrasts were set up before cancer risks for each contrast were investigated (i.e. the assignation was carried out blind).

### 2.4.3 Meta-analysis

The distribution of URRs (essentially slopes b) from each cohort were summarised using standard meta-analytic methods (Sutton 2000). Broadly, these methods allow for variation in precision by which URRs are estimated in different studies, but allow also for possible variation between studies that is not due to imprecision in URR estimates ("random effects"). Thus to obtain an average URR weights were implicitly given to each study reflecting these two factors. Further, to identify cohort or exposure characteristics that explained variation in URRs (eg industry, source of exposure information) each was considered as a dependant variable in a meta-regression analysis (Thompson and Sharp 1999) (see table 4 or 6 for examples.)

For URRs estimated from the log-linear model, meta-analyses were carried out on the log scale, in view of their approximately lognormal sampling distribution.

# 3 RESULTS

## 3.1 LUNG CANCER

### 3.1.1 Study characteristics

Of the 34 publications included, five reported two distinct cohorts for which results were presented separately. Thus there were 39 cohorts from which we could estimate URRs and include in the meta-analyses. Characteristics of these 39 cohorts, are shown in table 2 (which also shows estimated URRs - see below). Summaries of selected quantitative study characteristics are given in table 3 and Table 4 in which studies are divided by qualitative characteristics (the table is also used to show URR in these groups, as described below). A full description of the included studies is included in Appendix D.

All were essentially cohort studies, but one (Armstrong 1994) used case-cohort sampling, and three used nested case-control samples from within the cohort. For thirteen of the cohorts only single SMRs were reported; for the remainder there were risk comparisons (contrasts) across two or more (maximum 7) exposure groups. Of these, the contrasts selected according to our criteria were by cumulative exposure (8), duration of exposure (12), and job group (6).

A remarkable feature was the large range of exposures. Table 2 lists the cumulative exposure in the highest exposure group in each study, which ranged across three orders of magnitude, from 0.75 to 805 $\mu g/m^3$ BaP years. This corresponds approximately to concentrations in air of 0.04 $\mu g/m^3$ to 40 $\mu g/m^3$. This large range was the predominant reason for the large range in precisions with which the URR was estimated.

### 3.1.2 Unit relative risks

Relative risks predicted at 100 $\mu g/m^3$ BaP years from the loglinear model are shown to the right of the cohort characteristics in table 2. They ranged from 0 to over 1000. There was also substantial variation in the precision with which these relative risks were estimated, with standard errors (log scale) ranging from 0.02 to over 1000. Most of the variation in precision was due to variation in the degree of exposure contrast in the studies. Many of the studies at the foot of the table (power and carbon black industries) have low exposures. This limits the range of exposures , which causes imprecision in estimated URRs, shown as wide confidence limits. (This can be understood by reference to fact that the URRs are essentially regression coefficients – a narrow range in the x variable leaves uncertainty in the slope of the line.) Some variation in precision was also due to variation in size of cohort populations and duration of follow-up, which is reflected in the number of cases.

For cohorts without any exposure groups with mean higher than 100 $\mu g/m^3$ BaP, the estimate of relative risk at this value (the URR) is an extrapolation, and this explains the extreme variation of URRs. To give an indication of the actual relative risks found in the cohorts, we also show for each cohort (table 2, last column) the relative risks for the group with the highest exposure in that cohort, as predicted by the (loglinear) model.

Twenty-eight (72%) of the URRs were above zero, with the lower confidence limit above one ($P<0.05$) in 14 of these. The mean (estimated by random effects meta-analysis), overall and in sub-groups, is shown in table 4. A graph of all results loses definition catastrophically in the more precise studies. Limiting the graph to studies with standard errors below 10 (Figure 1a) and 1 (Figure 1b) allows focus on the more precise and consequently influential cohorts.

The overall mean URR was 1.20 and significantly above zero ($p<0.001$). There was no one cohort dominating this estimate, and it was little changed on removal of less precise cohorts. However, there was significant heterogeneity of URRs across cohorts ($p<0.001$).

Meta-regression revealed that much of the heterogeneity was explained by variation in URRs across industries ($p=0.002$); although coke ovens, gasworks, and aluminium smelters, exposed to coal tar

volatiles at similar levels, had similar mean URRs. There was no significant heterogeneity of URRs within industry groups. We therefore examined variation in URRs according to other factors after allowing for the differences across industries by including industry in the meta-regression. After doing so, there was no difference more than could easily be explained by chance ($p>0.20$) when studies were grouped according to source of exposure information, exposure contrast, continent, or whether the outcome of studies was mortality or morbidity, study design, smoking adjustment, or exposure contrast (cumulative exposure, duration, etc). Neither did maximum exposure explain variation. The higher URRs in the three nested case-control studies ($p=0.02$) was related to that in the four smoking-adjusted studies ($p=0.05$), as two of the case-control studies also adjusted for smoking.

### 3.1.3 Publication bias

There was little evidence that the URR was related to its standard error or to number of cases ($p>0.20$), factors that might relate to publication. Further, neither Egger's test nor Begg's ($p>0.20$) gave evidence for publication bias (Sutton et al 2000). Applying a trim-and-fill analysis (designed to correct for publication bias, if any) made negligible difference to the mean.

### 3.1.4 Dust

Because our information on dust exposure was for each cohort, or sometimes for broad job group within studies (Table 1), we could not use conventional methods for controlling for confounding (stratification or inclusion of dust in multiple regression analyses). We adopted three ad-hoc approaches to use the data we had to shed what light we could on this issue:

We compared relative risks estimated at 100 µg/m3 BaP years in cohorts in which we had identified substantial dust exposure with those in which there was less. If generic dust were an important cause of lung cancer in these cohorts one would expect greater apparent risks per unit PAH (BaP) where it was accompanied by dust. Results are shown at the bottom of table 4. There was no association between estimated relative risk per unit PAH (BaP) exposure and dust exposure in the industry.. This give some reassurance that dust is not the predominant cause of the association seen in this cohort between PAH and lung cancer.

The above approach assumes that dust exposure is correlated with PAH exposure within studies, at least across the groups used for exposure-response estimation. In general, this appeared to be the case, but for aluminium production there was some important independence between dust exposure and PAH exposure in groups for which we had risk estimates. Specifically, Soderberg potrooms were estimated to have very high dust and PAH exposure, whereas prebake potrooms had only slightly lower dust exposure, but very much lower PAH level. This suggests that the above approach is of limited values for aluminium production, but it also gave us the opportunity to look directly to see whether the dust or the PAH exposure explained risk. Table 8 shows risks by duration of service in prebake and Soderberg potrooms in the two included studies which reported this. For neither cohort was there evidence of a trend in risk by duration of service in prebake potrooms. In Armstrong 1994 there was a significant trend by duration of service in Soderberg potrooms. Thus this pattern of results does not support the hypothesis that the association of PAH with lung cancer in the aluminium industry is due to dust.

Finally, we can reason informally from the comparisons of fitted maximum relative risks on Table 2 (last column). In particular, carbon black workers are assessed as having similar levels of dust exposure as coke oven workers, but much lower PAH exposure. In both industries we expect total dust exposure to be highly correlated with PAH exposure. If dust rather than PAH were the predominant carcinogen, we would expect maximum risk to be similar in the two industries. In fact, maximum risk is considerably higher on average in the coke oven workers. Indeed, it is unclear if there is any excess at all in the carbon black workers.

### 3.1.5 Sensitivity analysis

By investigating dependence of URRs on study characteristics ( section 3.1.2; Table 4) we have already implicitly examined sensitivity of results to these characteristics (study design, smoking

adjustment, exposure information, etc), and found little such sensitivity. Here we examine sensitivity of our results to some statistical modelling assumptions.

Repeating analyses using the linear model, we found very similar rankings of URRs (Spearman's correlation = 0.99); the mean estimated relative risk at 100 μg/m3 BaP years was similar (1.19, compared to 1.20; both highly significant); and the patterns of variation of risk across industries were broadly similar. Fitted relative risks at the maximum exposure found in each plant were also similar. However, there was some variation in URRs of individual cohorts, with those with lower exposures typically lower with the linear model, and those with higher exposures higher. For example, the mean URR for the asphalt industry was 17.50 with the exponential model, but 6.29 with the linear model; relative risks predicted at 10 $\mu g/m^3$ years, however (more typical for asphalt workers) were less different and reversed in order: 1.33 and 1.53 respectively.

We also repeated analyses using alternative criteria for choice of contrast:

- minimum standard error;
- as above, using internal comparisons instead of single SMRs whenever available.

In either case, the mean URR and the basic pattern of URRs between industry changed little, although estimates for individual studies changed, sometimes substantially.

Finally, we investigated dependence of our results on extrapolation of risks from very high exposures, by repeating analyses three times, excluding exposure groups with means more than 80 $\mu g/m^3$ BaP years (40 years at 2 $\mu g/m^3$), 40 $\mu g/m^3$ BaP years (1 $\mu g/m^3$), and 20 $\mu g/m^3$ BaP years (0.5 $\mu g/m^3$). For example Costantino et al (1994), who included 7 groups with means: 0.0, 14.8, 73.7, 162.4, 251.2, 339.9, 805.4, contributed only the first three groups to the first re-estimated URR (means $\leq$ 80), and the first two only to the second and third re-estimated URRs (means $\leq$40 and $\leq$20). Overall mean URRs and mean URRs for coke ovens, gasworks and aluminium smelters are given in Table 5. The mean URR increases substantially on removal of higher exposure groups. This is partly explained by the greater weight given by URRs from industries with lower exposures, which we have seen to have higher URRs. However, looking at the results for coke ovens, gasworks, and aluminium smelters only (last column), we see that even within these industries restricting analyses to groups with lower cumulative exposures led to higher mean URRs, suggestive of an exposure-response curve steeper at the origin than at higher exposures. However, for all these analyses except those excluding all exposures above 20 $\mu g/m^3$ BaP years, which was very imprecise, there was significant heterogeneity between studies. These results should therefore be interpreted with caution.

## 3.2 BLADDER CANCER

There were 27 cohorts for which risk estimates were published for bladder cancer (Table 6). Mean numbers of cases was much lower than for lung cancer ( 19 Vs 74), and a much higher proportion (16/27) were simple single-group SMRs. Some large cohorts reporting full lung cancer results reported only partial results for bladder cancer; often only a single group SMR was reported.

Nineteen (70%) unit relative risks were above one, though only one (Tremblay 1995) statistically significantly so. The mean URR was 1.33 (95%CI: 1.16,1.52), and this changed little on excluding less precise URRs (table 7). Neither a general test of heterogeneity ($p>0.20$), nor specific tests for variation in URRs over industries ($p=0.20$) or other potential modifiers ($p>0.20$) showed evidence for variation more than could be easily explained by chance (table 7).

The overall mean was strongly dependent on results for the aluminium production industry, in particular two large studies (Romundstad 2000 and especially Tremblay 1995). Although the URRs from other industries were statistically compatible with those for aluminium, there was little independent evidence for an association of bladder cancer with PAH in coke ovens or in other industries. However, small numbers of cases, especially for mortality studies, limited power.

As with lung cancer, there was no evidence for publication bias, nor did analysis with contrasts chosen by alternative criteria change overall patterns substantially. However, application of the linear

model led to rather different results – there was significant heterogeneity in URRs between studies and the overall mean was no longer statistically significant. We return to this in the discussion section.

# 4 DISCUSSION

## 4.1 LUNG CANCER

That our meta-analysis supports the conclusions of previous reviews that lung cancer is associated with PAH exposure is not surprising. The attention in this meta-analysis to quantification of this relationship is novel, though such estimates have been made in a selective review, and by several methods from the Costantino (1994) cohort. We compare our results with these in section 4.1.4.

Our results for coke ovens, gasworks, and aluminium production are relatively well-supported, though biases (4.1.1) should be considered. Our findings of higher URRs for other industries are more tentative, and need careful consideration of potential biases (4.1.1) and possible explanations (4.1.3).

### 4.1.1 Possible biases

Each of the studies included in this meta-analysis is subject to the usual range of biases in epidemiological studies, in particular confounding and information bias (exposure error).

Our first concern is potential confounding by smoking, which was uncontrolled in most studies. There are two reasons, however, that this seems unlikely to have caused major bias:

(a) Though only four studies controlled for smoking, two of these were large studies with substantial exposure allowing quite precise estimates of URRs. The mean URR in smoking-adjusted studies was statistically compatible with, but somewhat higher than that for the studies uncontrolled for smoking, and statistically significant in its own right.

(b) Several methodological papers (Axelson and Steenland 1988; Blair, Steenland et al. 1988; Siemiatycki, Wacholder et al. 1988) have explored the potential for confounding by smoking mathematically. One common conclusion was that where manual workers are compared with other manual workers, substantial confounding is unlikely because smoking rates are unlikely to differ much in exposed and unexposed.

Confounding by other occupational exposure is also possible, but we have limited potential for this by excluding cohorts in which PAH was judged unlikely to be the predominant carcinogen. An exception to this is total dust, because the hypothesis that dust may cause lung cancer regardless of composition has only recently gained credence (EC Scientific Committee for Toxicity, Ecotoxicity and the Environment http://europa.eu.int/comm/food/fs/sc/sct/out108_en.html), and because dust is a universal co-exposure of PAHs. The analyses that we were able to carry out addressing the possibility of confounding by dust gave no support to the hypothesis that dust played a major confounding role. However, these could not rule out confounding completely, because of the limited information on total dust exposure available to us, and the lack of control for this exposure in the published studies. Further evaluation of this will be possible when assessments are carried out of the "dust" hypothesis in its own right, which was not possible in this study.

Exposure is likely to have been inaccurately estimated in many studies, in particular those for which no exposure data was published in the report of the epidemiological study itself, so we made estimates. Random exposure error tends to bias exposure-response slopes towards the null value (Armstrong 1996). However, if our estimates were systematically too high or too low, exposure response slopes would be under- or over-estimated respectively. We included estimates if we believed them to be within five times the true exposure, so considerable margin for uncertainty remains. It is of some reassurance that the mean URR in those studies for which we estimated exposure was not much different from the mean URR in those studies with author-provided exposure information (Table 4). However, errors in exposure estimation might explain particularly high or low URRs in specific studies or industries. In those industries (tar distillation, chimney sweeping, power) with no studies reporting investigators own exposure estimates, interpretation should be particularly cautious.

### 4.1.2 Explanations for variation in URRs

URRs may vary between industries and cohorts for three reasons: (a) chance, (b) biases, or (c) because risk per unit BaP really varies. We have established that variation in URRs *between* industries cannot be explained by chance (in particular Coke ovens and Aluminium production Vs asphalt and chimney sweeping), but variation *within* industry can be, so it seems sensible to focus attention on explaining variation between industries. We have discussed biases and confounding above. Biases, in particular from inevitably inaccurate exposure estimation, could explain some variation. Confounding by other occupational exposures, perhaps dust, could also play a part.

There are two reasons that might account for true variation in URRs:

(a) *A factor which modifies the effect is present to varying degrees in different industries.* An example is smoking. Even if the exposed and unexposed groups in each cohort smoke to the same extent (so there is no confounding) a heavily smoking cohort might exhibit greater or lesser effect per unit occupational PAH than a lightly smoking cohort. Unfortunately, we did not have the information to address this. In the main, we can assume that our cohorts were mixed smokers and non-smokers, so the exposure-response relationships are most likely to predict risk well in similarly mixed groups. Other occupational exposures might also modify the effect per unit PAH, by promoting or inhibiting the action of PAH. Such a hypothesis is too general to evaluate without making it more specific. Finally we mention the possibility that *cumulative* exposure is not the right metric. If another metric – say early adult exposure, lagged exposure, or another time-weighted exposure – were the relevant one, modification would arise if the time pattern of exposure differed across cohorts. Information on timing of exposure was insufficiently available for us to evaluate such hypotheses, but we expect that timing of exposure would be in any case too similar across cohorts for very informative results to emerge. A few studies reported risk by lagged cumulative exposure, but these generally differed little from tables of risk by overall cumulative exposure.

(b) *The carcinogenic potency of the PAH mixture varies across industries*. It is known that many PAH aside from BaP are carcinogenic in animals (IARC 1985). BaP is used as an indicator of the total risk, not because it is the sole causal agent but in the hope that it is well-correlated with others. To the extent that the PAH mixtures in different industries have different relative concentrations of the various carcinogenic PAHs (their "profiles"), this could thus explain differences in risk per unit BaP. An approach that derives a risk metric by combining information on PAH profiles with information on relative carcinogenic potency from animal studies has been proposed (Krewski, Thorslund et al. 1989). For us to apply this to this meta-analysis, however, would require estimates of PAH profiles for each study, or at least each industry. We did not have such information, which is not readily available, for this study. However, PAH profiles are slowly being ascertained and some are published (some publications of profiles are listed in appendix B3), so this approach could probably be applied in the future.

Some specific studies with URRs quite different from the mean for their industry deserve specific mention.

- The two cohorts of gasworks workers studies by Doll (1972) have high URRs. The estimate of exposure for retort workers in these plants was 3 $\mu g/m^3$ BaP, heavily influenced by measurements reported in 1965 from mask samples. It may be that these were underestimates.
- The very high URR estimated from the study by Liu (1997) for carbon anode plant workers was based on exposure estimates reported by Liu, but just for one of seven plants, which may not have been representative.
- The low and precisely-estimated URR from the study of several Norwegian aluminium production plants (Romunstad 2000) has no obvious explanation. Exposure estimation was based on substantial hygiene data for most plants. The non-significance of the test for

heterogeneity in URRs among studies of aluminium production workers indicates that the absence of excess risk in this study could have been due to chance, but the result remains noteworthy.

### 4.1.3 Comparisons with other studies

The most directly comparable study is the brief report of,Gibbs 1997 who estimated lifetime risks of lung cancer per 100,000 from 50 years *continuous* exposure to 1 ng/m$^3$ BaP from nine studies, using a "linear no-threshold model". Eight of the nine studies were occupational (4 from coke ovens, 2 gasworks, one aluminium production, and one asphalt), and they or updates of them were included in our analysis. The ninth was a study of domestic exposure to "smoky coal" in China. To translate Gibbs' risk lifetime estimates from continuous exposure to relative risk estimates from occupational exposure we used the conversion factors used by Gibbs to do the reverse:

$$URR = 1 + \left[ ULR \cdot \left( \frac{1}{50} \right) \cdot \left( \frac{10}{23} \right) \cdot \left( \frac{230}{365} \right) \cdot \left( \frac{1}{0.09} \right) \right] = 1 + \left[ ULR \cdot 0.61 \right]$$

where ULR is the lifetime risk per ng/m$^3$ continuous (23 m$^3$ /day Vs 10 occupational) exposure (365 days Vs 230 occupational - our assumption) over 50 years, assuming a 9% lifetime risk. Gibbs' finding of ULRs: 0.3,4.2,4.4,5.8,6.6,7.2,7.8,9.5 translates to URRs: 1.02,1.26,1.27,1.35,1.40,1.44,1.48,1.58 – somewhat higher on average than the estimates in this study, but not grossly different.

It is also possible to compare our meta-analytic estimates with those that have been published from the cohort reported by Costantino (1995):

- The USEPA (1984), cited by WHO (1987,2000) estimated a lifetime risk from *continuous* exposure per ng/m$^3$ BaP of 8.7/100,000, using the linearised multistage model. Following the translation we used for Gibbs' study, this corresponds to a URR (relative risk from 100 µg/m3 BaP years) of about 1.53.
- Moolgavkar, Luebeck et al. 1998 estimated a unit absolute risk from continuous 1 µg/m3 BSM of 15/100,000 using the two-stage clonal expansion model. Roughly re-expressing this as above gives URR=1.13.

The second of these alternative estimates of URR is very similar to our estimate from Costantino (1994) using the exponential model (Table 2: URR=1.15). Our estimate from Costantino (1994) using the linear relative risk model was 1.31.

Our findings of a larger URR in the asphalt industry than in coke-ovens or aluminium smelters was tentative. Recent publication of a very large European study of mortality in the asphalt industry (Boffetta, Burstyn et al. 2001) will add importantly to information on this question. The study was not published in time for formal inclusion in this meta-analysis. It found an association of lung cancer with exposure to bitumen fumes in some but not other analyses. Estimates of exposure to PAH as BaP were made, allowing as far as possible for knowledge of the extent to which coal tar was used as an additive, time trends in exposure levels and type of asphalt paving. In the asphalt industry, PAH exposure originates from bitumen, coal tar (banned in Western Europe) and diesel exhaust. Contribution of diesel exhaust to PAH exposure was not incorporated into quantitative PAH exposure metric, because available data did not permit the investigators to identify groups of asphalt pavers within the cohort with different diesel exhaust exposure. The report includes a table (8.9.4) of lung cancer rate ratios in relation to cumulative exposure to PAH (as BaP), from which it was possible to estimate a URR in the method standard for this meta-analysis. The estimate (44.9; 95% CI: 25.0,64.8) places it similar to the other asphalt worker studies included in this review, adding support to the hypothesis that risk per unit BaP is higher in this industry than in coke ovens or aluminium production. However, analysis of risk by quantitative estimate of PAH exposure was possible only for workers only employed in paving (including mastic paving); it may be that other groups in the study (eg roofers) showed different patterns.

### 4.1.4 Interpretation for risk assessment

We have used a benchmark of 100 μg/m$^3$ years exposure to provide a scale for presenting the URR, but risk predictions at other exposures (x) can be made using the formulae:

$$URR_{cum.exp=x} = [URR_{cum.exp=100}]^{(x/100)}$$

For example, relative risk consequent on exposure to 1 μg/m$^3$ for 40 years (40 μg/m$^3$ years) according to the mean estimate for coke ovens is $1.17^{(40/100)}$=1.06. (At these moderate-low relative risks, log-linear interpolation is close to linear interpolation.) Risk estimates calculated this way for a range of URRs and exposure concentrations are given in Table 9.

*Model choice.* We adopted the log-linear model because it was amenable to statistical evaluation – p-values for heterogeneity are unreliable when meta-analysis was conducted on $URR_{lin}$. However, there is evidence (Appendix C) that the linear model fits the data and arguments on mechanism better. As we noted in the "Sensitivity analyses" section of the Results, risk prediction made from the two differ little if applied within the range of exposures from which they were estimated. Thus for simplicity we work with the loglinear model. This is not ideal. The development of methods to allow better synthesis of linear relative risk models would be useful. Other more elaborate models (eg two-stage, multistage) are possible with much more information on timing of exposure than was available from published studies (effectively original individual data).

Our URRs for coke ovens, gasworks, aluminium production, and the overall mean, are driven by risks observed at levels around 100 μg/m$^3$ BaP years. Risks estimates are at their most secure at exposure not too far from this (say 20-500 μg/m$^3$ BaP years). estimating risks for much lower levels inevitably requires model assumptions. We have emphasised the log-linear model, and noted that estimates are similar for the linear model (this includes low exposures). Models with very different assumptions about increments at low exposures (eg threshold models) could predict very different risks at these levels. The sensitivity analysis (Table 5) investigating dependence of results on high exposures is suggestive of an exposure-response curve steeper at lower exposure than at higher.

*Overall or industry-specific means?* The URRs overall had significant and substantial heterogeneity – there was evidence that risk per unit BaP varied across cohorts. The mean in the presence of this heterogeneity is a rather artificial one, reflecting those industries and cohorts that happen to have been studied. Within industries there was no significant heterogeneity, so that the industry-specific means could be interpreted as representative of each industry. These considerations favour use of industry-specific means. Means for coke ovens, gas works, and aluminium production are consistent and relatively precisely estimated. The combined mean URR for these industries was 1.17 (95%CI:1.12,1.22), and might reasonably be used for all these industries. However, means for other industries are rather imprecise. Risk assessment for these industries will inevitably be very uncertain, whether the imprecise industry-specific mean or the overall mean was used.

*Attributable burden of disease* The number of cancers caused by occupational exposure to PAH depends on three factors beyond the exposure-response relationship: (a) the number of persons exposed; (b) the levels at which they are exposed, and (c) the background rate of lung cancer, on which relative risks will act. A comprehensive assessment is beyond the scope of this report, but we have made an estimate of cases that would be caused in UK coke oven workers, by PAH exposures continuing at current levels, ignoring probably higher past exposures. There are currently about a thousand coke oven workers in the UK, with mean exposure about 1.5 μg/m$^3$ BaP (John Unwin, personal communication). General population lifetime risk of lung cancer in UK males, using 1997 rates, is 8% (Office of National Statistics 2000). Using the URR of 1.17 for coke ovens, one year's exposure will therefore lead eventually to a lifetime excess risk of $0.08X(1.17^{(1.5/100)}-1)=1.9X10^{-4}$, which among 1000 workers will lead to 0.2 cases. 40 years of such exposure would lead to 40X0.2=8 cases, almost all of whom will die from this cancer.

## 4.2 BLADDER CANCER

Results for bladder cancer were more uncertain than for lung cancer, due mainly to the much smaller number of cases in this rarer cancer. Although our results support a PAH-bladder cancer association,

there is less evidence for a PAH–bladder cancer causal association than there is for lung cancer. Only for the aluminium production industry was the evidence for an association strong. On the other hand the data from the other industries were weak rather than negative – and were compatible with a generic PAH risk of the same magnitude per unit BaP across all cohorts.

As we commented in the Introduction, previous reviews have similarly concluded that there is a much stronger weight of evidence that PAH causes lung than that it causes bladder cancer. One recent review (Negri and La Vecchia 2001) noted specifically that the evidence was confined to the aluminium production industry. Other co-exposures, in particular aromatic amines and nitro-PAH (Tremblay 1995) known to be present in small concentrations in aluminium potrooms, have been suggested as alternative causal agents. However, it is unclear why these would not also be present in other PAH-exposed workplaces.

If we do assume a causal association, the absence of significant heterogeneity between studies suggests focusing for quantitative risk estimation on the overall mean URR: 1.33. As for lung cancer, estimates of risk from exposures other than 100 $\mu g/m^3$ BaP years can be calculated from this. This mean URR is slightly larger than that for lung cancer (1.20). However background mortality due to bladder cancer is much lower than that that of lung cancer, so that number of lung cancer deaths attributable to PAH would be much higher than the number of attributable bladder cancer deaths. For example, using the same methods as for lung cancer the expected number of bladder cancers in 1000 coke oven workers following 40 years exposure at 1.5 $\mu g/m^3$ is 3.3 (Vs 8 lung cancers), with about one third expected to die of the cancer.

Most of the caveats discussed for the lung cancer results apply also to bladder cancer. One is stronger: application of the linear model leads to quite different results We have noted that p-values are unreliable for the linear model, so this observation should be taken as a note of caution rather than an invalidation of the loglinear results.

## 4.3 METHODOLOGICAL ISSUES

Compared to their widespread use in clinical trials, meta-analyses are relatively new to occupational epidemiology, and even more rare in investigations of exposure-response relationships. In entering this poorly charted territory, this study threw up several methodological challenges for which we found ad-hoc solutions. It might be useful to future similar meta-analyses for us to draw attention to the principle ones:

(a) We needed to choose one contrast from each study from which to estimate an exposure-response relationship. To be objective, we chose a simple choice algorithm and explored sensitivity of results to it, but it may be that this could be improved on.

(b) We needed to estimate mean exposure in upper exposure groups for which only a lower limit is published.

(c) A priori considerations and data in the meta-analysis studies suggested use of linear rather than log-linear models, but estimates of URRs from linear models proved intractable in meta-analysis, so we worked with loglinear models. It would be preferable not to have to compromise. One possibility would be to apply a random effects linear relative risk model to semi-aggregated data (see below), but such models have not to our knowledge been discussed in the statistical literature, nor can they be fitted with standard software.

(d) We proceeded in this meta-analysis to estimate first a single effect measure (URR) from each study, then analyse these using standard meta-analytic methods. However, it appears to us that once "semi-aggregated" data has been assembled for cases, exposures, and relative risks in *each exposure-group* in each study (eg Appendix E), it would be possible to use methods developed more multi-level data (multi-level models) more generally.

## 4.4 CONCLUSIONS

(a) **On average, relative risk predicted for lung cancer at 100 mg/m$^3$ BaP years (URR) was 1.20 (95%CI:1.11-1.29), but this varied significantly across industries. Coke ovens (1.17; CI:1.12-1.22), gasworks (1.15; CI:1.11-1.20), and aluminium production (1.16; CI:1.05-1.28) were slightly lower than the mean, and asphalt (17.50; CI:4.21-72.78) and chimney sweeping (16.2; CI:1.64-160.7) were much higher but imprecisely estimated.**

(b) These results are subject to several uncertainties, the most important being due to uncertainty in past exposures.

(c) Difference between industries may be due to artifacts, or to real differences in risk associated with one unit BaP in different industries.

(d) Within coke ovens, gasworks, and aluminium smelters, there is no evidence against BaP being an adequate indicator of lung cancer risk from PAHs. In other industries this is less certain.

(e) Linear models fitted better than loglinear though they gave a similar mean URR. We worked with the loglinear model because of its better statistical properties, but this compromise is not ideal.

(f) There was also an association of PAH with bladder cancer (mean URR=1.33; 95%CI: 1.16-1.52, no significant heterogeneity), but this finding was less robust than that for lung cancer, being largely dependent on two studies of aluminium production workers. Bladder cancer is also much less common than lung cancer, especially as a cause of death, so lung cancer is reasonably considered as the lead risk.

(g) The URR represents risk at fairly common exposures historically, but high for today. Risks at other exposures can be estimated from URRs under (loglinear) model assumptions: eg at 1µg/m3 BaP for 40 years, cumulative exposure is 40 µg/m$^3$ BaP years, and the average lung cancer risk is 1.20(40/100)=1.076.

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# TABLES AND FIGURES

**Table 1: Main supplementary exposure estimates (BaP; total dust).**

| Industry | Job group | | BaP(ug/m$^3$) | Dust* |
|---|---|---|---|---|
| Coke ovens | Top | | 20 | H |
| | Side | | 10 | M |
| | Other | | 0.5 | M |
| | Typical mean | | 10 | H/M |
| Coal gas production | Retorts | | 3 | M |
| | By-products | | 0.5 | L |
| | Typical mean | | | M/L |
| Aluminium smelting | Soderberg potroom | | 15 | VH |
| | Prebake potroom | | 0.05 | H |
| | Carbon plant | | 2 | H |
| | Typical mean | Sod | 3 | H |
| | Typical mean | Pre | 0.5 | H/M |
| Carbon anode plants | - | | 1 | H |
| Asphalt | - | | 0.5 | M |
| Tar distillation | - | | 0.5 | M |
| Chimney sweep | - | | 1 | VH |
| Thermo-electric Power | - | | 0.05 | L |
| Carbon black | - | | 0.05 | H |

*Dust classification: LOW (<1 mg/m$^3$); MODERATE (1-5 mg/m$^3$); HIGH (5-10 mg/m$^3$); VERY HIGH (10-25 mg/m$^3$)

## Table 2 Cohort characteristics and unit relative risk estimates: Lung cancer

| Cohort Characteristics | | | | | | | | | | | RR at 100 µg/m$^3$ BaP years | | | | RR at |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author-year | Industry | Country | design | author exposure inform. | Contrast | Outcome | Smok adj | n of cases | n of exp. gps | max exp | estimate | (95%CI) | | standard error | max exp. |
| Bye et85 | coke_ovens | Norway | cohort | Proxy | cum. exp. | Morb | N | 7 | 4 | 10.0 | >1000 | 0.01 | >1000 | 11.43 | 6.10 |
| Chau, 93 | coke_ovens | France | cohort | None | job group | Mort | Y | 24 | 5 | 294.4 | 1.00 | 0.68 | 1.46 | 0.20 | 0.99 |
| Costan95 | coke_ovens | USA&Canada | cohort | Proxy | cum. exp. | Mort | N | 458 | 7 | 805.4 | 1.15 | 1.10 | 1.21 | 0.02 | 3.18 |
| Franco93 | coke_ovens | Italy | cohort | None | single SMR | Mort | N | 19 | 1 | 186.0 | 1.41 | 1.07 | 1.79 | 0.17 | 1.90 |
| Hurley83 | coke_ovens | UK | cohort | Proxy | cum. exp. | Mort | N | 182 | 4 | 252.9 | 1.36 | 1.04 | 1.79 | 0.14 | 2.19 |
| Hurley83 | coke_ovens | UK | cohort | Proxy | cum. exp. | Mort | N | 59 | 4 | 262.9 | 1.19 | 0.77 | 1.85 | 0.22 | 1.60 |
| Reid a56 | coke_ovens | UK | cohort | None | job group | Mort | N | 21 | 3 | 400.0 | 0.94 | 0.64 | 1.39 | 0.20 | 0.79 |
| Sakabe75 | coke_ovens | Japan | cohort | None | single SMR | Mort | N | 15 | 1 | 200.0 | 1.13 | 0.85 | 1.45 | 0.18 | 1.28 |
| Swaen,91 | coke_ovens | Holland | cohort | None | job group | Mort | N | 273 | 3 | 200.0 | 1.19 | 0.97 | 1.45 | 0.10 | 1.41 |
| Xu et 96 | coke_ovens | China | nested_cc | BaP | duration | Morb | Y | 194 | 3 | 453.8 | 1.33 | 1.14 | 1.56 | 0.08 | 3.65 |
| Berger92 | gasworks | Germany | cohort | BaP | single SMR | Mort | N | 78 | 1 | 747.6 | 1.15 | 1.12 | 1.19 | 0.02 | 2.88 |
| Doll e72 | gasworks | UK | cohort | None | job group | Mort | N | 79 | 3 | 60.0 | 4.01 | 1.16 | 13.87 | 0.63 | 2.30 |
| Doll e72 | gasworks | UK | cohort | None | job group | Mort | N | 110 | 2 | 60.0 | 5.82 | 1.06 | 32.00 | 0.87 | 2.88 |
| Gustav90 | gasworks | Sweden | cohort | BaP | single SMR | Mort | N | 0 | 1 | 28.7 | 0.00 | 0.00 | 66.56 | 1450 | 0.00 |
| Armstr94 | aluminium | Canada | case-coh | BaP | cum. exp. | Mort | Y | 338 | 5 | 413.1 | 1.22 | 1.09 | 1.37 | 0.06 | 2.30 |
| Milham79 | aluminium | USA | cohort | None | duration | Mort | N | 35 | 6 | 99.2 | 0.19 | 0.00 | >1000 | 6.15 | 0.19 |
| Moulin00 | aluminium | France | cohort | None | duration | Mort | N | 19 | 5 | 200.0 | 1.11 | 0.46 | 2.66 | 0.45 | 1.23 |
| Mur, J87 | aluminium | France | cohort | None | duration | Mort | N | 17 | 3 | 248.2 | 0.69 | 0.31 | 1.54 | 0.41 | 0.40 |
| Rocket83 | aluminium | USA | cohort | None | duration | Mort | N | 64 | 5 | 116.1 | 1.85 | 0.53 | 6.53 | 0.64 | 2.05 |
| Rocket83 | aluminium | USA | cohort | None | duration | Mort | N | 133 | 5 | 15.4 | 0.06 | 0.00 | 9.58 | 2.59 | 0.65 |
| Romund00 | aluminium | Norway | cohort | BaP | cum. exp. | Morb | N | 189 | 4 | 222.4 | 0.99 | 0.79 | 1.22 | 0.11 | 0.97 |
| Spinel91 | aluminium | Canada | cohort | Proxy | cum. exp. | Morb | N | 37 | 5 | 251.1 | 1.31 | 0.72 | 2.39 | 0.30 | 1.99 |
| Donato00 | carbon | Italy | cohort | None | duration | Mort | N | 34 | 3 | 36.4 | 0.18 | 0.01 | 5.61 | 1.75 | 0.54 |
| Liu97 | carbon | China | cohort | BaP | job group | Mort | N | 50 | 4 | 17.3 | 53.07 | 3.44 | 819 | 1.40 | 1.99 |
| Moulin89 | carbon | France | nested_cc | BaP | duration | Morb | Y | 7 | 4 | 94.9 | 2.82 | 0.20 | 40.59 | 1.36 | 2.67 |
| Moulin89 | carbon | France | nested_cc | BaP | duration | Mort | N | 13 | 4 | 5.8 | 0.00 | 0.00 | >1000 | 24.21 | 0.41 |
| Hammon76 | asphalt | USA | cohort | BaP | duration | Mort | N | 121 | 4 | 66.8 | 5.63 | 0.89 | 35.53 | 0.94 | 3.17 |
| Hansen91 | asphalt | Denmark | cohort | BaP | single SMR | Mort | N | 25 | 1 | 20.3 | 189.59 | 22.19 | >1000 | 1.35 | 2.90 |
| Swaen,97 | asphalt | Holland | cohort | None | single SMR | Mort | N | 39 | 1 | 10.0 | 15.23 | 0.50 | 347 | 2.19 | 1.31 |
| Hansen89 | tar_distil. | Denmark | cohort | None | single SMR | Mort | N | 16 | 1 | 10.0 | 35.76 | 0.13 | >1000 | 3.42 | 1.43 |
| Maclar87 | tar_distil. | UK | cohort | None | single SMR | Mort | N | 12 | 1 | 6.0 | >1000 | 0.04 | >1000 | 6.58 | 1.60 |
| Swaen,97 | tar_distil. | Holland | cohort | None | single SMR | Mort | N | 48 | 1 | 10.0 | 5.32 | 0.25 | 89.38 | 1.97 | 1.18 |
| Evanof93 | chim_sweep | Sweden | cohort | None | duration | Mort | N | 53 | 4 | 40.0 | 9.88 | 0.60 | 162 | 1.43 | 2.50 |
| Hansen83 | chim_sweep | Denmark | cohort | None | single SMR | Mort | N | 5 | 1 | 30.0 | 44.63 | 1.02 | 752 | 2.04 | 3.13 |
| Cammar86 | power | Italy | cohort | None | single SMR | Mort | N | 5 | 1 | 1.0 | >1000 | 0.00 | >1000 | 61.16 | 1.77 |
| Forast89 | power | Italy | cohort | None | duration | Mort | N | 8 | 3 | 1.5 | 0.02 | 0.00 | >1000 | 110.37 | 0.94 |
| Petrel89 | power | Italy | cohort | None | single SMR | Mort | N | 6 | 1 | 1.0 | >1000 | 0.00 | >1000 | 55.83 | 1.36 |
| Robers96 | carbon_bla | USA | cohort | None | single SMR | Mort | N | 34 | 1 | 1.0 | 0.00 | 0.00 | >1000 | 23.45 | 0.84 |
| Soraha01 | carbon_bla | UK | cohort | Proxy | cum. exp. | Mort | N | 64 | 4 | 0.8 | >1000 | 0.00 | >1000 | 58.15 | 1.48 |

**Table 3: Summaries of cohort characteristics (lung cancer)**

| Variable | n of studies with information | mean | min | max |
|---|---|---|---|---|
| Year: | | | | |
| of publication | 39 | 1988 | 1956 | 2001 |
| of first exposure | 28 | 1923 | 1893 | 1964 |
| of last exposure | 4 | 1981 | 1968 | 1989 |
| of start of follow up | 39 | 1958 | 1935 | 1987 |
| of end of follow-up | 39 | 1983 | 1954 | 1996 |
| Duration (years) | | | | |
| of follow-up (maximum) | 39 | 25.3 | 5 | 59 |
| of latency (maximum) | 28 | 53.8 | 24 | 87 |
| Number | | | | |
| of lung cancer cases | 39 | 74.2 | 0 | 458 |
| of exposure groups | 39 | 3.1 | 1 (13 studies) | 7 |
| Cumulative exposure in highest exposure group ($ug/m^3$ years) | 39 | 154.9 | 0.75 | 805.4 |

**Table 4 Distribution and determinants of unit relative risks for lung cancer**

| Group | n of studies | mean URR*(95%CI) | Significance tests** |
|---|---|---|---|
| All | 39 | 1.20( 1.11,1.29) | p(het)=0.007 |
| Studies with SE<10 | 31 | 1.20( 1.11,1.30) | p(het)=0.002 |
| Studies with SE<1 | 19 | 1.18( 1.12,1.23) | p(het)=0.19 |
| | | | |
| By Industry | | | p=0.002 |
| - coke_ovens | 10 | 1.17(1.12, 1.22 ) | |
| gasworks | 4 | 1.15(1.11, 1.20 ) | |
| aluminium | 8 | 1.16(1.05, 1.28 ) | |
| [above 3 combined | 22 | 1.17(1.12, 1.22) | p(het)>0.20] |
| carbon | 4 | 4.30(0.81, 22.79) | |
| asphalt | 3 | 17.50(4.21, 72.78) | |
| tar_distillery | 3 | 12.28(0.48, 314.4) | |
| chimney_sweep | 2 | 16.24(1.64, 160.7) | |
| power | 3 | >1000(0 , >1000) | |
| carbon_black | 2 | 0 (0 , >1000) | |
| | | | |
| By exposure information from authors* | | | p>0.20 |
| BaP | 10 | 1.29( 1.11, 1.49) | |
| Proxy | 6 | 1.16( 1.11, 1.21) | |
| None | 23 | 1.17( 1.03, 1.33) | |
| | | | |
| By contrast* | | | p>0.20 |
| cum. exp. | 8 | 1.16(1.11, 1.22) | |
| duration | 12 | 1.27(1.10, 1.48) | |
| job group | 6 | 1.16(0.99, 1.36) | |
| single SMR | 13 | 1.20(0.95, 1.51) | |
| | | | |
| By study design* | | | p=0.10 |
| cohort | 36 | 1.16(1.11, 1.21) | |
| nested cc | 3 | 1.33(1.14, 1.55) | |
| | | | |
| By smoking adjustment* | | | p=0.05 |
| N | 35 | 1.16(1.11, 1.21) | |
| Y | 4 | 1.31(1.16, 1.48) | |
| | | | |
| By continent* | | | p>0.20 |
| Asia | 3 | 1.30(1.13, 1.50) | |
| Europe | 28 | 1.13(1.02, 1.26) | |
| N.America | 8 | 1.16(1.11, 1.22) | |
| | | | |
| By outcome | | | p>0.20 |
| Mortal | 34 | 1.17(1.12, 1.22) | |
| Morbid | 5 | 1.21(1.06, 1.38) | |
| | | | |
| By dust exposure for industry | | | p=0.12 |
| low | 3 | >1000(0,>1000) | |
| moderate | 10 | 1.16(1.11,1.21) | |
| high | 24 | 1.17(1.13,1.22) | |
| very high | 2 | 16.24(1.64,14.8) | |

* URR: Unit relative risk (RR at 100 µg/m3 BaP years). Adjusted for differences across industries by including industry indicator in a meta-regression. Means are scaled to show fitted values for coke ovens, though ratios would apply to any industry.

** Generally, the Wald test for significance of variation in mean URRs across the groups indicated; "p(het)" indicates the test for heterogeneity across all studies.

## Table 5 Investigating the dependence of Mean URR on high exposures

| Excluding groups with exposures: | All studies | | | Coke, gas, aluminium | | |
|---|---|---|---|---|---|---|
| | N* | URR(95%CI) | p(het) | N* | URR(95%CI) | p(het) |
| No exclusions | 39 | 1.20(1.11,1.29) | <0.001 | 22 | 1.17(1.12, 1.22) | >0.20 |
| >80 ug/$m^3$ | 34 | 3.46(2.03,5.90) | <0.001 | 17 | 1.88(1.22,2.91) | 0.02 |
| >40 ug/$m^3$ | 30 | 6.49(1.99,21.12) | <0.001 | 14 | 2.42(0.56,10.40) | 0.01 |
| >20 ug/$m^3$ | 21 | 4.54(1.26,16.30) | >0.20 | 7 | 1.87(0.24,14.22) | >0.20 |

* remaining number of studies from which URRs could be estimated
p(het): test for heterogeneity between URRs.

## Table 6 Cohort characteristics and unit relative risk estimates bladder cancer

| Cohort Characteristics | | | | | | | | | | | Unit Relative Risk Increment | | | | RR at |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author-year | Industry | Country | design | author exposure inform. | Contrast | Outcome | Smok adj | n of cases | n of exp. gps | max exp | estimate | (95%CI) | | standard error | max exp. |
| Bye et85 | coke_ovens | Norway | cohort | Proxy | cum. exp. | Morb | N | 5 | 4 | 10.0 | 0.00 | 0.00 | >1000 | 107.38 | 0.01 |
| Chau, 93 | coke_ovens | France | cohort | None | single SMR | Mort | N | 1 | 1 | 97.4 | 0.69 | 0.01 | 4.04 | 1.76 | 0.70 |
| Costan95 | coke_ovens | USA&Canada | cohort | Proxy | single SMR | Mort | N | 16 | 1 | 217.0 | 1.06 | 0.82 | 1.33 | 0.20 | 1.14 |
| Hurley83 | coke_ovens | UK | cohort | Proxy | single SMR | Mort | N | 8 | 1 | 143.8 | 0.91 | 0.51 | 1.47 | 0.42 | 0.88 |
| Hurley83 | coke_ovens | UK | cohort | Proxy | single SMR | Mort | N | 16 | 1 | 143.8 | 1.08 | 0.73 | 1.51 | 0.30 | 1.11 |
| Swaen,91 | coke_ovens | Holland | cohort | None | job group | Mort | N | 38 | 3 | 200.0 | 1.02 | 0.50 | 2.07 | 0.36 | 1.04 |
| Doll e72 | gasworks | UK | cohort | None | job group | Mort | N | 5 | 3 | 60.0 | 8.23 | 0.01 | >1000 | 3.22 | 3.54 |
| Doll e72 | gasworks | UK | cohort | None | job group | Mort | N | 11 | 2 | 60.0 | 9.56 | 0.01 | >1000 | 3.59 | 3.88 |
| Milham79 | aluminium | USA | cohort | None | single SMR | Mort | N | 1 | 1 | 60.0 | 0.00 | 0.00 | 3.64 | 17.14 | 0.00 |
| Moulin00 | aluminium | France | cohort | None | duration | Mort | N | 7 | 5 | 200.0 | 1.66 | 0.32 | 8.59 | 0.84 | 2.75 |
| Rocket83 | aluminium | USA | cohort | None | job group | Mort | N | 19 | 3 | 100.0 | 2.46 | 0.33 | 18.06 | 1.02 | 2.46 |
| Romund00 | aluminium | Norway | cohort | BaP | cum. exp. | Morb | N | 130 | 4 | 222.4 | 1.19 | 0.88 | 1.61 | 0.16 | 1.47 |
| Spinel91 | aluminium | Canada | cohort | Proxy | cum. exp. | Morb | N | 16 | 4 | 131.7 | 4.47 | 0.94 | 21.26 | 0.80 | 7.19 |
| Trembl95 | aluminium | Canada | nested_cc | BaP | cum. exp. | Morb | Y | 138 | 5 | 413.1 | 1.48 | 1.24 | 1.76 | 0.09 | 5.04 |
| Donato00 | carbon | Italy | cohort | None | duration | Mort | N | 7 | 3 | 37.2 | 0.10 | 0.00 | >1000 | 4.78 | 0.43 |
| Moulin89 | carbon | France | cohort | BaP | single SMR | Mort | N | 3 | 1 | 2.0 | >1000 | 0.00 | >1000 | 48.30 | 1.94 |
| Moulin89 | carbon | France | cohort | BaP | single SMR | Morb | Y | 0 | 1 | 37.4 | 0.00 | 0.00 | 3.30 | 6081.8 | 0.00 |
| Hammon76 | asphalt | USA | cohort | BaP | single SMR | Mort | N | 15 | 1 | 28.6 | 3.94 | 0.52 | 22.65 | 1.55 | 1.48 |
| Hansen89 | asphalt | Denmark | cohort | BaP | single SMR | Morb | N | 5 | 1 | 20.3 | 8.66 | 0.03 | 563.1 | 3.78 | 1.55 |
| Swaen,97 | asphalt | Holland | cohort | None | single SMR | Mort | N | 3 | 1 | 10.0 | 3.94 | 0.00 | >1000 | 9.89 | 1.15 |
| Hansen89 | tar_distil. | Denmark | cohort | None | single SMR | Mort | N | 5 | 1 | 10.0 | >1000 | 0.74 | >1000 | 7.66 | 3.01 |
| Maclar87 | tar_distil. | UK | cohort | None | single SMR | Mort | N | 3 | 1 | 6.0 | >1000 | 0.08 | >1000 | 16.49 | 4.29 |
| Swaen,97 | tar_distil. | Holland | cohort | None | single SMR | Mort | N | 2 | 1 | 10.0 | 0.00 | 0.00 | 953.4 | 12.12 | 0.55 |
| Evanof93 | chim_sweep | Sweden | cohort | None | duration | Morb | N | 37 | 4 | 40.0 | 0.16 | 0.00 | 14.61 | 2.30 | 0.48 |
| Cammar86 | power | Italy | cohort | None | single SMR | Mort | N | 2 | 1 | 1.0 | >1000 | 0.00 | >1000 | 121.17 | 7.41 |
| Forast89 | power | Italy | cohort | None | single SMR | Mort | N | 2 | 1 | 1.0 | >1000 | 0.00 | >1000 | 121.17 | 1.74 |
| Soraha01 | carbon_bla | UK | cohort | Proxy | single SMR | Mort | N | 6 | 1 | 0.3 | >1000 | 0.00 | >1000 | 246.33 | 1.73 |

**Table 7 Distribution and determinants of unit relative risks for bladder cancer**

| Group | n of studies | mean URR* | (95%CI) | Significance tests* |
|---|---|---|---|---|
| All | 27 | 1.33 | (1.17, 1.51) | p(het)>0.2 |
| Studies with SE<10 | 18 | 1.33 | (1.17, 1.51) | p(het)>0.2 |
| Studies with SE<1 | 8 | 1.30 | (1.12, 1.51) | p(het)>0.2 |
| By Industry | | | | p=0.20 |
| coke_ovens | 6 | 1.04 | (0.79, 1.37) | |
| gasworks | 2 | 8.80 | (0.08, 967.68) | |
| aluminium | 6 | 1.42 | (1.23, 1.65) | |
| [above 3 combined | 14 | 1.32 | (1.16, 1.51) | p(het)>0.20] |
| carbon | 3 | 0.14 | (0.00, >1000) | |
| asphalt | 3 | 4.40 | (0.27, 70.67) | |
| tar_distillery | 3 | >1000 | (0.04, >1000) | |
| chimney_sweep | 1 | 0.16 | (0.00, 14.61) | |
| power | 2 | >1000 | (0.00, >1000) | |
| carbon_black | 1 | >1000 | (0.00, >1000) | |
| By exposure information from authors | | | | p>0.2 |
| BaP | 6 | 1.41 | (1.21, 1.64) | |
| Proxy | 6 | 1.10 | (0.82, 1.48) | |
| None | 15 | 1.18 | (0.65, 2.14) | |
| By contrast | | | | p>0.2 |
| cum. exp | 4 | 1.42 | (1.22, 1.65) | |
| duration | 3 | 1.18 | (0.26, 5.42) | |
| job group | 4 | 1.17 | (0.61, 2.27) | |
| single SMR | 16 | 1.06 | (0.79, 1.43) | |
| By study design | | | | p>0.2 |
| cohort | 26 | 1.15 | (0.95, 1.41) | |
| nested_cc | 1 | 1.48 | (1.24, 1.76) | |
| By smoking adjustment | | | | p>0.2 |
| unadjusted | 25 | 1.15 | (0.95, 1.37) | |
| adjusted | 2 | 1.48 | (1.24, 1.76) | |
| By continent | | | | p>0.2 |
| Europe | 21 | 1.13 | (0.89, 1.44) | |
| N.America | 6 | 1.42 | (1.22, 1.67) | |
| - | | | | |
| By outcome | | | | p>0.2 |
| Mortal | 20 | 1.09 | (0.83, 1.42) | |
| Morbid | 7 | 1.41 | (1.22, 1.64) | |

* URR: Unit relative risk (RR at 100 μg/m3 BaP years).
** Generally, the Wald test for significance of variation in mean URRs across the groups indicated; “p(het)” indicates the test for heterogeneity across all studies.

**Table 8 Special investigation of prebake aluminium potrooms to inform on potential confounding by dust.**

| Cohort/contrast | Group | Prebake potrooms | | Soderberg potrooms | |
|---|---|---|---|---|---|
| | | n. cases | RR* | n. cases | RR* |
| Armstr94 | <1yr | 88 | 1.00 | 88 | 1.00 |
| | 1-9yrs | 32 | 1.22(0.68-2.02) | 65 | 1.32(0.91-1.92) |
| | 10-19yrs | 70 | 1.15(0.55-2.42) | 35 | 1.37(0.87-2.16) |
| | 20+yrs | 7 | 1.25(0.40-3.89) | 74 | 2.00(1.38-2.90) |
| Rocket83 | <10yrs | 51 | 1.14(0.85,1.49) | 13 | 0.66(0.35,1.13) |
| | 10-15yrs | 6 | 0.60(0.22,1.34) | 10 | 1.40(0.67,2.57) |
| | 15-20yrs | 11 | 1.03(0.51,1.81) | 12 | 1.15(0.59,2.01) |
| | 20-25yrs | 10 | 1.41(0.68,2.60) | 2 | 0.32(0.04,1.16) |
| | 25+yrs | 9 | 0.73(0.33,1.38) | 5 | 2.06(0.66,4.81) |

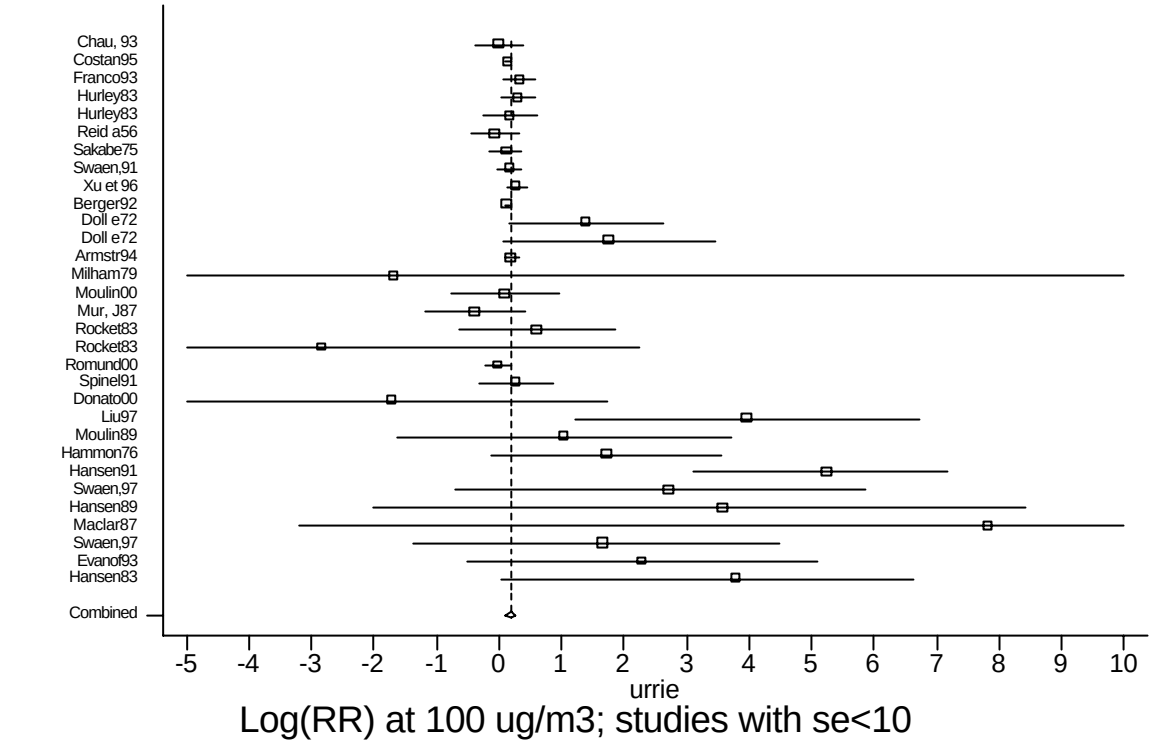
* RR; For Armstrong 1994: internally estimated rate ratio adjusting for smoking and years worked in Soderberg potrooms; for Rockette 1983: SMR.

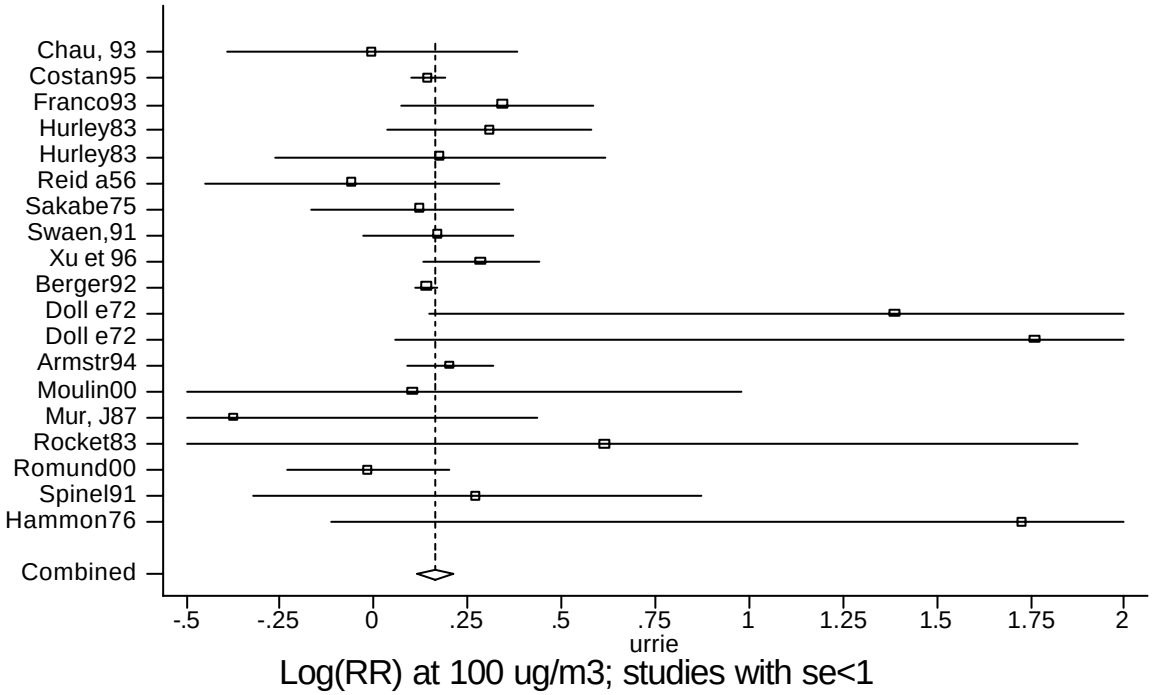
**Table 9. Relative risks for contracting cancer estimated to follow from 40 years occupational exposure**

| | Exposure to BaP in μg/m$^3$ for a working life of 40 years | | | |
|---|---|---|---|---|
| | 0.1 | 0.2 | 0.5 | 1 |
| Overall mean URR(1.20) | | | | |
| Lung cancer | 1.007 | 1.015 | 1.035 | 1.076 |
| Bladder cancer | 1.011 | 1.023 | 1.059 | 1.121 |
| Mean URR for Coke ovens, aluminium smelters, and gasworks (1.16) | | | | |
| Lung* cancer | 1.006 | 1.012 | 1.030 | 1.061 |
| Mean URR for asphalt (17.5) | | | | |
| Lung* cancer | 1.12 | 1.26 | 1.78 | 3.14 |

* no evidence for variation in bladder cancer risk across industries

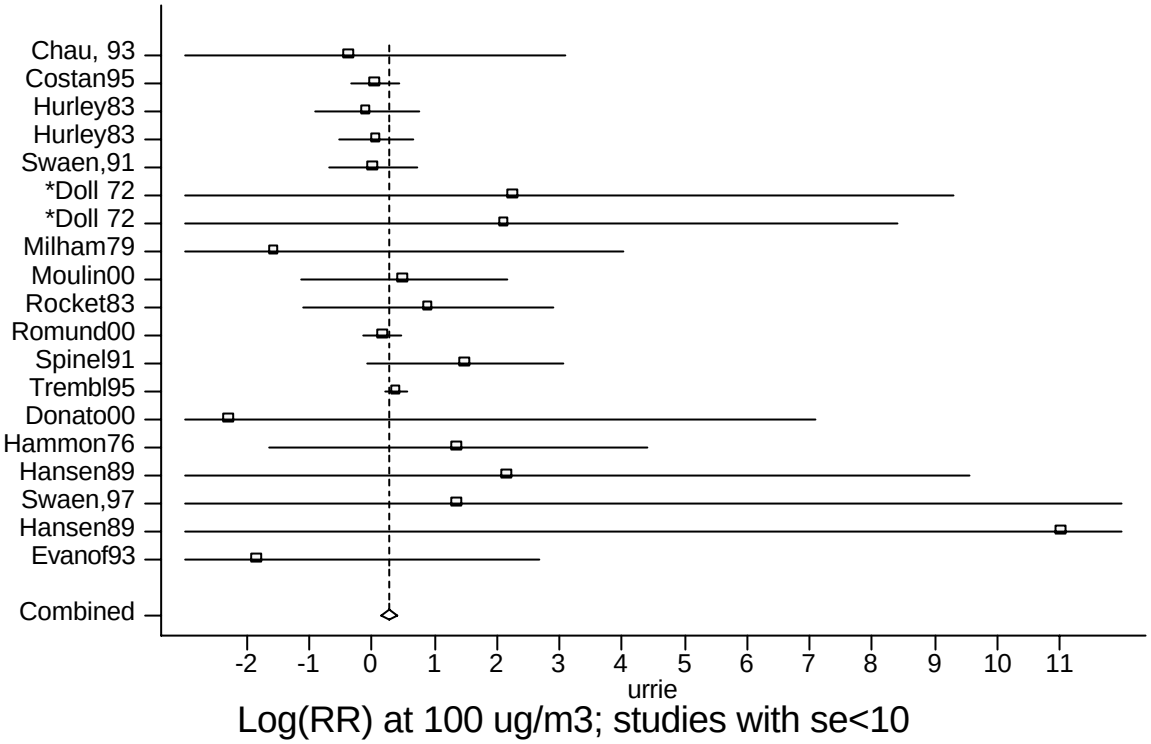
**Figure 1: Relative risk at 100 mg/m$^3$ years (URR) for lung cancer.**




Figures 1a and 1b show estimated URRs (squares) and 95% confidence intervals (lines) for each cohort. These are presented as (natural) logarithms, thus a log(RR) of 1 is equivalent to a RR of 2.3. Confidence intervals are truncated at the edges of the graph. Diamonds at the bottom of each show the overall mean and its CI. The top figure shows all studies with standard errors (SEs) below 10. To show the detail of more precise studies, the lower figure shows studies with SEs below 1. Very imprecise studies (SE >10) are not graphed.

**Figure 2: Relative risk at 100 µg/m$^3$ years (URR) for bladder cancer**



# APPENDICES

## Appendix A. Specific search terms used to identify studies.

| | Search terms for electronic databases | | |
|---|---|---|---|
| | Neoplasm (MESH term) | | |
| And | (epidemiolog* or occupational*) | Not | Molecular |
| | | Not | adduct* |
| And | Polycyclic aromatic hydrocarbon (MESH term) | Not | Polymorphism* |
| Or | Smoky coal | Not | Bioassay |
| Or | Unvented coal smoke | Not | Assay |
| Or | Carbon black* | Not | review* |
| Or | Carborundum | Not | PMR |
| Or | silicon carbide | Not | PCMR |
| Or | Bitumen | Not | Proportionate cancer |
| Or | Coal tar* | Not | Population based |
| Or | Creosote* | Not | hospital based |
| Or | Mineral oil* | Not | registry data |
| Or | shale oil* | Not | Biomarker* |
| Or | Soot* | Not | animal* |
| Or | Aluminium | Not | Metabolite* |
| Or | Anode baking | | |
| Or | Coke | | |
| Or | coal gasification | | |
| Or | Iron foundry | | |
| Or | Steel foundry | | |
| Or | Tar distillation | | |
| Or | Roofers | | |
| Or | asphalt workers | | |
| Or | Carbon electrode* | | |
| Or | graphite electrode* | | |
| Or | Chimney sweeps | | |
| Or | Calcium carbide production | | |
| Or | Wood treatment | | |
| Or | gas worker* | | |

***Mesh terms:***

Mesh headings were used in searches of electronic databases, in order to broaden the scope of the search. These headings are mapped to the following terms:

Polycyclic Aromatic Hydrocarbon

used for

- Arene
- Aromatic Hydrocarbon,Polycyclic
- Hydrocarbon,Polycyclic Aromatic
- Pah
- Polyaromatic Hydrocarbon
- Polycyclic Hydrocarbons, Aromatic
- Polycyclic Aromatic Hydrocarbon

Polycyclic Aromatic Hydrocarbon (7680)
[Associated Terms]

- Benz[A]Anthracene (645)
- Benz[A]Anthracene Derivative (81)
- Benzo[A]Pyrene (6232)
- Benzo[A]Pyrene Derivative (376)
- Benzo[E]Pyrene (195)
- Benzo[Ghi]Perylene (111)
- Benzo[K]Fluoranthene (149)
- Chrysene (479)
- Chrysene Derivative (143)
- Dibenz[A,C]Anthracene (60)
- Dibenz[A,H]Anthracene (237)
- Dibenzo[A,L]Pyrene (30)
- 7,12 Dimethylbenz[A]Anthracene (2486)
- Dimethylbenz[A]Anthracene (1635)
- Fluoranthene (663)
- 3 Methylcholanthrene (4312)
- Naphthacene Derivative (25)
- Perylene (213)
- Polycyclic Aromatic Hydrocarbon Derivative (957)
- Pyrene (1263)
- Pyrene Derivative (357)

BLADDER CANCER

- Urinary Bladder Cancer
- Urine Bladder Cancer
- Vesical Cancer

LUNG CANCER

- Bronchus Cancer
- Cancer,Lung
- Pulmonary Cancer
- Schneeberg Disease

CANCER

- Cancer Morphology
- Cancer Pattern
- Primary Cancer

**Appendix B1: Summary of information on PAH exposure (as BaP) in published epidemiological studies.**

| Industry | Cohort | Sub-groups (if any) | | | | Mean | Comment |
|---|---|---|---|---|---|---|---|
| Coke ovens | | top | side | other | | | |
| | Constantino 95 | 22.4 | 6.2 | | | 3.5 | total includes about 60% zero exp. |
| | Hurley 1983 | 14.3 | 6.4 | 3.5 | | 7.2 | |
| | Berger 1992 | | | | | 28 | |
| | Bye 1998 | | | | | 0.07 | includes many unexposed |
| | Gustavsonn 1990 | | | | | 2.4 | |
| | Xu 1996 | 50? | 15? | 5? | | 16.5 | some guessing from JEM supplied by Xu |
| Aluminium smelters | | potroom-sod | potroom-prebake | Carbon plant | other | | |
| | Armstrong 1994 | 15 | 0.03 | 1 | | 2.3 | |
| | Spinelli 1991 | | | | | 2.2 | |
| | Romunstad2000 | 3 to 20 | 0 to 5 | 1 to 10 | | 3.5 | |
| carbon plant | | "high" | "med" | "low" | "none" | | |
| | Moulin 1989 | | | | | 2.2 | 16+4 4 hr personal samples from 2 plants: Hot spots? |
| | Liu 1997 | 1.2 | 0.3 | 0.1 | 0 | 0.8 | |
| Asphalt | | | | | | | |
| | Hansen 1989&91 | | | | | 1 | |
| | Hammond 1976 | | | | | 17 | Probably mostly CTP |

Note: this information was used only to inform exposure estimates for studies for which none were provided (Appendix B3); exposure-response relationships for the studies referenced on this table were estimated directly from published tables of risk by exposure (typically cumulative exposure).

## Appendix B2: Review of PAH exposure information pertaining to studies for which this was not provided by the authors

(John Unwin)

Units are in μg/$m^3$ unless stated.

### A: Studies for which a conversion from a proxy measures of exposure was sought.

**Study: Ronneberg et al 1988**
Subject: Exposure to oil mist in cable manufacturing (1916 - 1983).
Unable to find any data on this subject. Suggest exposures are < 0.1 or less due to the low aerosol exposures involved, low temperatures for volatilisation of BaP and the use of refined oils after 1972.

**Study : Spinelli 2001.**
LSH to use own BaP/BSM conversion ratio.

Study: Sorahan T et al - 2001

Subject: Proportion of BaP in Carbon Black (1947 - 1996).
Source: IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 2, Carbon Blacks, Mineral Oils and Some Nitroarines, Vol 33, IARC,Lyon, France, April 1984, p45.
Results:
(1) in toluene extracts of 5 furnace blacks 0.55, 1.64, 1.5, 5.06 and 3.15 μg/mg. Mean value = 2.38 μg/mg (Taylor et al 1980). Typical exposures from Sorahan range from 0.5 - 30 mg/$m^{-3}$ equivalent to 1.19 - 71.4.
((2) in benzene extracts of furnace blacks 2 - 40 μg/mg (as total benzopyrenes)).
3) Gabor et al (1969) ( in the criteria for a recommended standard Occupational exposure to carbon black. US Department of health, Education and Welfare. N IOSH, September 1978) described the respiratory system of workers who produced furnace, thermal, or channel blacks in Rumania. The 6 hour concentrations of 3,4-benzp yrene were 260 - 510 during thermal black production. During furnace black production, 6 hour concentration was 52.
Analysis of thermal black for BaP revealed 345 μγ/γ. Furnace black contained 68 μγ/γ. No PAHs were detected in channel black.

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### B: Studies for which no exposure information was not provided by the authors

**Study: Moulin J J et al 2000**
Subject: Exposure in various tasks during Al smelting (1910 - 1994).
Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification , Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
One estimate in workshops/pot room/electrode manufacture/LEV operations/pot lining/maintenance.
i) Soderberg: 36.0 - 38.0 .
(Adamiak-Zie mba J A et al (1977) The evaluation of exposure to harmful substances emitted in the process of the production of aluminium using selfbaking anodes (Pol). Med. Pr., 28, 481-489).
ii) Prebake potroom: 0.03 - 0.1
(Shuler P J and and Bierbaum P J (1974), Environmental surveys of aluminium reduction plants (HEW/NIOSH) Publ. no 74-101) Cincinatti, OH, National Institute for Occupational Safety and Health (USA).
iia) Pre bake potroom 0.02-0.05
(Bjorseth et al. (1978) Polycyc ic aromatic hydrocarbons in the work atmosphere. I. Determination in an aluminium reduction plant. Scand. J. Work Environ. Health, 4, 212-223, (Norway).

(PAH profile data given in IARC)

Source: Holliday M and Engelhardt F R. Occupational health aspects of exposure to coal tar pitch volatiles (CTPV) in Ontario. CA: Ontario. Ministry of Labour
Ottawa, 1983.
Results:
i) Soderberg 0.6 - 56 (8 - 23 mg/m3 CTPV).
ii) Prebake - zero.

Source: Angerer et al. Occupational exposure to polycyclic aromatic hydrocarbons in a graphite electrode producing plant: biological monitoring of 1-hydroxypyrene and monohydroxy lated metabolites of phenanthrene. Int Arch Occup Environ Health (1997) 69:323-331.
Results:
(i) Baking (n=6) mean = 1.06 (range 0.22 - 1.96),
(ii) Impregnation (n=2) mean 0.44 (range 0.07 - 0.8),
(3) Graphitisation (n=4) mean 0.11 (range 0.01 - 0.33).

Source: Tjoe Ny E et al. The relationship between polycyclic aromatic hydrocarbons in air and urine of workers in a Soderberg potroom. Am Ind Hyg Assoc J. 54(6):277 - 284 (1993).
Results: means of 2.7, 14 and 48 for people continuously employed in potroom.

**Study:Mur J M et al 1987**.
Subject: Al production 1910 - 1976.
Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification , Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results: Three estimates in pot rooms.
i) Soder berg: pot operator during pot processing 17.9 - 29.4 (ref Konstantinov 1971 USSR).
Soderberg potroom: 0.02 - 53.0 (ref Shuler and Bierbaum 1974, USA).
Soderberg potroom: 3.4, 116.3, 53.7 (ref Bjorseth et al 1978, Norway).
ii) Prebake potroom: 0.03 - 0.1 (ref Shuler and Bierbaum 1974, USA).
Prebake potroom 0.02-0.05 (ref Bjorseth et al 1978, Norway).
Prebake potroom not detected (ref Konstantino v 1971 USSR).
iii) Soderberg and prebake together ?

Source:Bjorseth A et al. Polycyclic aromatic hydrocarbons in the work atmosphere. Determination of area-specific concentrations and job-specific exposure in a vertical pin Soderberg aluminium plant . Scand J Work Environ Health, (1981), 7, 223-232.
i) PAH profile given.

Source:In Lindstedt G and Sollenberg J. Polycyclic aromatic hydrocarbons in the occupational environment. With special reference to benzo(a)pyrene measurements in Swedish industry. Scand J Work Environ Health, 8 , 1-19.
i) prebake potrooms:0.01 - 0.2 (1966 197 USSR)
ii) Soderberg potrooms: 1.8 - 51 (1968 - 1978 Sweden)

Source: Tremblay and Armstrong . American Journal of of Industrial Medicine 27:335 - 348 (1995).
Results:
i) Soderber g potroom (1930 - 1970) 0.3 - 35.5 see table
ii) Prebake (1930 - 1970) 0.02 - 0.1 see table.

**Study: Hansen 1989**
Subject : Asphalt plants (1970 - 1980)

Source:In Lindstedt G and Sollenberg J. Polycyclic aromatic hydrocarbons in the occupational environment. With special reference to benzo(a)pyrene measurements in Swedish industry. Scand J Work Environ Health (1982), 8, 1-19.
i) < 0.05 (Adamiak- Ziemba et al , Polish 1972).

Source: Hicks JB. Asphalt industry cross-sectional exposure assessment study. Applied occupational and environmental hygiene. Oc t 1995, vol 10, no 10,840 - 848
Results:
i) Asphalt refinery/terminals 0.16.
ii) roofing felt manufacture 0.16.

Source: Puzinauskas VP and Corbett LW. Report on emissions from asphalt hot mixes. Asphalt institute, College Park, Maryland, Report no RR751A (1975).
Results:
Asphalt hot mix plants
i) 0.003 - 0.02.
ii) 0.014 - 0.022.

**Study: Robertson et al 1980**
Subject:: Carbon black exposure (1935 - 1974).

Source: Rivin D. Effect of carbon black on worker health in the rubber industry. Dangerous properties of industrial materials report. Jan/Feb. 1985 vol 5, no 1, 2 - 11.
Results:
Data is given for BAP content of Carbon blacks of 5, 6.5 and 8 ppm. Mean = 6.5 ppm.
Exposures in **US Tyre Factories** of 0.2 - 5.8 mg/m3. Therefore extrapolated BAP exposure = 0.001 - 0.04.

**Study: Donato et al - 2000**
Subject: Carbon Electrode manufacture (1945 -1971).
Source: Companion paper Monarc et al 1982.
Results:
i)BaP exposure from petroleum pitch/coke at site A - extrapolated from mean total suspended particulate exposure of 0.66 mg/$m^3$ in pilot plant. Concentration of BaP in airborne particulate determined to be 908 $\mu\gamma/\gamma$. Therefore BaP concentration = 0.6.

Source: Greife A. In National Inst for Occupational Safety and Health, Cincinnati, OH Div of Surveillance, Hazard Evaluations and Field Studies. Walk-Through Survey at Airco Carbon, St Mary's, Pennsylvania. Govt-Reports- Announcements-Index, Issue 22, 1988 - data collected 1983.
Results:
ii) BaP exposure from electrode manufacture - 12 results from various activities 1.59, 2.5 and 2.26 remaining samples not detected (limit of detection 0.52 / sample).
PAH profile data given.

Source: Moulin J J et al. Risk of lung, larynx, pharynx and buccal cavity cancers among carbon electrode manufacturing workers. Scan J Work Health 1989;15:30 - 37.
Results:
i) Plant A : mean 2.7 (range 0.59 - 6.2).
ii) Plant B: mean 0.17 (range 0.015 - 0.57).

Source: Petry T et al. Airborne exposure to polycyclic aromatic hydrocarbons and urinary excretion of 1-hydroxypyrene of carbon plant anode workers. Ann Occup Hyg, Vol 40, no 3, 345 - 357. (1996)
Results: All anode plant workers.

Exposure range: 0.16 - 4.88.

Source: H M Van Delft et al. (1998) Monitoring of occupational exposure to polycyclic aromatic hydrocarbond in a carbon-electrode manufacturing plant. Ann occup Hyg, Vol 42, no 2,105 - 114.
Results:
i) intermediate exposure (n = 12, 0.09 - 5.0) 0.37.
ii) high exposure (n = 18, 0.43 - 3.2) 1.2.

Source: Salisbury SA. Health hazard evaluation determination report No HHE7591489. Alcoa Aluminium Company Warwick operations, Newberg. Hazard evaluations and technical assistance branch, NIOSH, Cincinnati, Ohio (1978)
Results:
Exposure range for several jobs 0.3 - 5.9.

**Study: Evanoff 1993**
Subject:: Exposure in chimney sweeps (1906 - 1980).
Source: In Lindstedt G and Sollenberg J. Polycyclic aromatic hydrocarbons in the occupational environment. With special reference to benzo(a)pyrene measurements in Swedish industry. (ref Bagchi NJ and Zimmerman RE. An industrial hygiene evaluation of chimney sweeping. Am Ind Hyg Assoc J. 41, 1980, 297 - 299.)
Results:
During cleaning from the top of the chimney they found a CTPV value of 14.53 mg/m3 and a BAP content of 40 in the breathing zone of the worker (0.275% BAP in CTPV). Cleaning from the hearth was less exposed CTPV= 2.16 mg/m3 by analogy with the given above result you could expect a BAP level of 5.9.

Source: Knech U et al. Atmospheric concentrations of polycyclic aromatic hydrocarbons during chimney sweeping. Br J Ind Med 1989;46:479 - 482.
Results:
TWA shift mean concentrations of 0.02 - 0.21 obtained on 11 days.

**Study Chau et al 1993**
Subject: Coke oven Plant workers (1939 - 1982)
Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification , Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
i) constantly employed on coke ovens (coke oven operators) 0.16 - 33 (ref Blome1981, FRG).
ii) near coke oven and intermittently exposed to ovens. coke-oven conveyor-belt side 0.49 - 0.55. (ref Tanimura, 1968, Japan).
iib) sorting 0.25 - 1.4. (Source: Hemminki K et al. Aromatic DNA adducts in white blood cells of coke workers. Int Arch Occup Envron Health (1990)).
iii) repair/maintenance workshops ?
iv) byproducts in oven gas treatment sector 1.06 - 9.2 (ref Masek 1971, Czechoslovakia).
v) Underground work in coal mines. ?
(PAH profile in IARC)

**Study: Franco et al 1993.**
Subject: Coke oven 1947- 1985.
Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
i)Coke oven plant - constantly employed on coke ovens (coke oven operators) 0.16 - 33 (ref Blome1981, FRG).

Source; Davies G M. Measurement and analysis of airborne emissions from coke ovens with particular reference to worker exposure. Commission of the European Communities, Office for Official Publications, 5 rue du Commerce, l-2985 Luxembourg, 1981, 75 - 95.
Results:
i) coke oven plants: means of several UK plants 1.4 - 11.0.

Source: Masek V. The use of silver membrane filters in sampling for coal tar pitch volatiles in coke oven plants. (1970) Am Ind Hyg J. Vol 31, 641 - 644.
Results: Pitch coke oven battery 9.9 (not personal sampling).

**Study: Sakabe et al 1975**
Subject: Coke ovens (1939 - 1973)

Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
i) Iron and steel works - 1.3 - 159 (ref Masek 1971, Czechoslovakia).
ii) Byproduct workers - 1.06 - 9.2 (ref Masek 1971, Czechoslovakia).
iii) Coke manufacturing - 0.5 - 135 (ref Bjorseth 1978, Norway).

**Study: Swaen et al 1991**
Subject: Coke plant (1918 - 1984)

Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
i) coke oven workers - 0.16 - 33 (ref Blome 1981, FRG).
ii) byproduct workers - 0.19 - 296 (ref Masek 1971, Cze choslovakia).
iii) Tar distillery: 1.06 - 9.2 (ref Masek 1971, Czechoslovakia).
iv) Top oven workers - 8 - 135 (ref Bjorseth 1978, Norway), 20 - 383 (av. 112, ref Braszczynska et al 1978), 5 - 15 (ref Eisenhut et al 1982, FRG), 9.4 - 13.5 (ref Lindstedt et al, 1982, Sweden, 1.27 - 27.4 (ref Yanysheva et al, 1962, USSR).
v) Side oven workers: 0.04 - 3.3 (ref Eisenhut et al 1982, FRG).

Source: Hemminki K et al. Aromatic DNA adducts in white blood cells of coke workers. Int Arch Occup Envron Health (1990).
Results;
i) coke oven workers top side 9.4 - 90, coke-side, 0.54 - 13.6.
ii) byproduct workers (distillation) 3 plants each 0.6.
iii) tar distillery as above 0.6.
iv) top side 9.4 - 90,
v) coke-side, 0.54 - 13.6.

**Study: Mclaren et al 1987**
Subject: Tar distillation workers (1955 - 1976)

Source: From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
i) 1.06 - 9.2 (ref Masek 1971, Czechoslovakia).

Source: Masek V. The use of silver membrane filters in sampling for coal tar pitch volatiles in coke oven plants. (1970) Am Ind Hyg J. Vol 31, 641 - 644.
Results:
ii) Tar distillation plant 4.6 (not personal sampling).

Source: Hemminki K et al. Aromatic DNA adducts in white blood cells of coke workers. Int Arch Occup Envron Health (1990).
Results:
ii) Results: Tar distillation at 3 coke plants 0.6.

**Study: Swaen 1997**
Subject: Tar Distillery and Roofers (1947 - 1988)

Source:Malaiyandi M et al. Measurement of potentially hazardous polynuclear aromatic hydrocarbons from occupational exposure during roofing and paving operations. Polynuclear aromatic hydrocarbons : Physical and biological chemistry, Cooke,M., A J Dennis, and G L Fisher, Editors;Springer-Verlag, New York, p 471 - 489. (1982)
Results:
Coal tar pitch roofing
i) site 1, 0.01, 0.4, 4.22, site 2, 0.08, 1.22, 0.62, site 3, 0.02, 0.93, 11.3.

Source:Herbert R et al. A pilot study of detection of DNA adducts in white blood cells of roofers by 32P-postlabelling.
Results:
Coal tar pitch
i) day 1, 0.53 - 1.78.
ii) day 2, 0.6 - 1.39.

Source:Herbert R et al. Detection of adducts of DNA in white blood cells of roofer by 32P-postlabelling. Scand J Work Environ Health 1990: 16:135-43.
Results:
Coal tar pitch exposure.
i) 0.53 - 2.03.

[From HSE survey (1997). Tar distillation (high temperature) mean exposure 0.3. Tar distillation (low temperature) not found.]

See McLaren study above for exposure in tar distillery workers.

**Study: Doll et al 1972**
Subject: Exposure in gas workers 1948 - 1965.
Source**:** From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results:
Three estimates of exposure;-
i) Heavy exposure in coal carbonisation plant: 200. (ref Lawther et al 1965)
ii) In other gas producing plants: 2 and 7.3 (ref Kreyberg 1959), mean concentration of 4.8 (horizontal retort) and 1.4 and 2.7 in two different verticle retort houses. (ref Lawther et al 1965)
iii) no such expsure/byproducts ?
(PAH profile available in IARC)

Source: In Lindstedt G and Sollenberg J. Polycyclic aromatic hydrocarbons in the occupational environment. With special reference to benzo(a)pyrene measurements in Swedish industry. Scand J Work Environ Health, 8 , 1-19.
Results:
i) Heavy exposure - top of oven men of 134 1-h samples 4.3 (max 33, data from 1964), 13.5 and 9.4 (1980), 25 (range 8 - 78, Thielen 1979)
ii) 25 m from ovens 0.15 (344 samples)
iii) Pitch battery (byproducts ?) up to 40 (Masek 1971).

**Study: Kawai et al 1967**
Subject Exposure in gas generator workers 1933 - 1953.
Source**:** From IARC Monographs on theEvaluation of the Carcinogenic Risk of Chemicals to Humans. Polynuclear Aromatic Compounds, Part 3, Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production and Iron and Steel Founding, Vol 34, IARC,Lyon, France.
Results: Using data from Lawther (1965) and Kreyberg (1959) range 1.4 - 7.3 (4.4).

**Appendix B3: Supplementary estimates of PAH(BaP), for studies in which these were not provided by the authors.**

| Author | Year | Industry | Grouping | Group | Area and Country | BaP exposure | Comment |
|---|---|---|---|---|---|---|---|
| Chau, N., et al. | 1993 | Coke oven | Job type | (1) constantly employed on coke ovens | Lorraine, France | 20 | |
| | | | | (2) in those near the ovens and intermittently exposed to ovens | | 10 | |
| | | | | (3) employed in repair and maintenance workshop | | 1 | Uncertain |
| | | | | (4) exposed to byproducts in the oven gas treatment centre | | 0.5 | Uncertain |
| | | | | (5) underground work in coalmines | | 0.05 | |
| Franco, F., et al. | 1993 | Coke oven | Coke workers | Coke oven plant workers (excluding administrative staff) | Carrara, Italy | 10 | |
| Reid and Buck | 1956 | Coke ovens | 3 groups | (1) Oven workers (top?) | | 20 | |
| | | | | (2) Maintenance | | 1 | uncertain |
| | | | | (3) By-product workers | | 0.5 | |
| Sakabe H et al | 1975 | Coke oven | Coke workers by type of plant | (1) iron and steel works | Japan | 10 | |
| | | | | (2) city gas companies | | 5 | |
| | | | | (3) coke manufacturing companies | | 10 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Swaen, G. M., et al. | 1991 | Coke plant. | Job type | (1) all coke oven workers | 3 coke plants in The Netherlands | 10 | |
| | | | | (2) byproduct workers, | | 0.5 | Uncertain |
| | | | | (3) tar distillery workers | | 0.5 | Uncertain |
| | | | | (4) top oven coke workers | | 20 | |
| | | | | (5) side oven coke workers | | 10 | |
| Kawai M et al | 1967 | Gas workers (in a steel plant) | All gas workers | Gas generator workers in this steel plant | Itakyushu, Japan | ?? | Discarded |
| Doll et al | 1972 | Gas workers. | Heavy, medium, low | (1) heavy exposure in coal carbonisation plants | 8 area gas boards in England | 3 | |
| | | | | (2) with intermittent exposure in coal carbonisation plants or to conditions in other gas producing plants | | 1.5 | Uncertain |
| | | | | (3) no such exposure or exposure only to byproducts | | 0.5 | Uncertain |
| Milham | 1979 | Aluminium production | all | Prebake plant - all workers | WA USA | 0.5 | |
| Moulin, J. J., et al. | 2000 | Aluminium production. | Job type (BaP exposure likely) | All workshops where PAH exposure is likely (potroom, electrode manufacture department, exhaust ventilation operations, pot lining and maintenance) | France | 5 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mur, J. M., et al. | 1987 | Aluminium production. | Job type | Potrooms for prebake processes | | 0.05 | |
| | | | | Potrooms for Soderberg processes | | 15 | |
| | | | | Potrooms for prebake and Soderberg processes together* | France | 11.7 | |
| Rockette and Arena | 1983 | Aluminium production | 3 groups | (1) Soderberg potrooms | USA | 15 | |
| | | | | (2) Prebake potrooms | | 0.05 | |
| | | | | (3) Carbon plant | | 2 | |
| | | | | (4) Soberberg plants -average* | | 4 | |
| | | | | (5) prebake plants-average* | | 0.5 | |
| Donato, F., et al. | 2000 | Carbon electrodes. | All workers | Carbon electrode manufacute workers | Umbria, Central Italy | 1 | |
| Hansen ES | 1989 | Asphalt industry (asphalt plants, roofing felt plants, tar plant) | All workers | Asphalt workers | Denmark | 0.5 | Uncertain |
| Maclaren, W. M. and J. F. Hurley. | 1987 | Tar distillery workers. | All workers | Tar distillation plant workers | 4 plants in England and Wales | 0.5 | Uncertain |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Swaen, G. M. and J. M. Slangen. | 1997 | Tar distillery and roofers | Job type | (1) tar distillery workers<br>(2) roofers | The Netherlands | 0.5 | Uncertain |
| Evanoff, B. A., et al. | 1993 | Chimney sweeps. | All workers | Chimney sweeps | Sweden | 1 | |
| Hansen | 1983 | Chimney sweeps | | | Denmark | 1 | |
| Martin, J. C., et al. | 2000 | Elecricity and gas. | | Semi- BaPitative index - found impossible tp convert to BaP within desired accuracy | France | ?? | Discarded |
| Cammarano, G., et al. | 1986 | thermoelectric power plant . | All workers | Thermoelectric power plants | Milan, Italy | 0.05 | Very uncertain |
| Forastiere, F., et al. | 1989 | thermoelectric power plants. | All workers | Thermoelectric power plants | Latium, Italy | 0.05 | Very uncertain |
| Roberstson J | 1996 | Carbon black | All workers | Carbon black workers | USA. 4 plants | 0.05 | |

* Derived as weighted mean of other estimates.

See text for methods and scale of assessment.

**Appendix B4: Total dust exposure in included industries: a review**

| INDUSTRY | SUB-GROUP | DUST EXPOSURE ($mg/m^3$) | | REFERENCES |
|---|---|---|---|---|
| | | TOTAL PARTICULATE | RESPERABLE | |
| Aluminium | Potroom Soderberg | 15.1 (6.5-20), 4.7 (2-7.4), 12.1 (1-38.2), 2.9 (1.8-4.5). | | Environmental surveys of aluminium reduction plants. P J Schuler and PJ Bierbaum.PB232 776/5WJ, National technical information service, Virginia USA, p33, 1974. (data means of means). |
| | Potroom Prebake | 6.2 (3.9–11.6), 4.6 (3.9 –7.2). | | |
| | Carbon electrode plant | 3.8 (1.5-5.4), 2.9 (1.1-5.7). | | |
| | | - | | |
| | Other | | | |
| | Potroom Soderberg | 8.6 (1-26) | | Data fro 1979. Occupational health control technology for the primary aluminium industry. J W Sheehy. US Dept of health and human services, CDC, NIOSH,1983. |
| | Potroom Prebake | 2.8 (1.7-3.5) | | |
| | Potroom Soderberg | 1.5 (0.346-6.52) | | Mean of 3 potrooms. Polycyclic aromatic hydrocarbons in the work atmosphere. A Bjorseth et al. Scan. J. Work Environ. Health 7 (1881) 223-232. 1981. |
| | Carbon electrode plant | 10.28 and 4.11 | | |
| ASPHALT (coal | Roofers | 0.34. | 0.14. | Hazard Review - Health effects of occupational exposure to Asphalt. US Dept of Health and Human services, NIOSH,December |

| | | | | |
|---|---|---|---|---|
| Tar) | Manufacture | 0.6. | 0.08. | 2000. Table 4.8 p35 adapted from Exxon 1997. (GMs) |
| | Roofers | 1.3 (0.2-1.9) | | Health hazard evaluation determination reportNo HHE75-194-324, Western roofing company….Hervin RL and Emmett EA. Hazard evaluation services branch, NIOSH**.** (1976) |
| | Roofers | 0.77 | 0.18 | Asphalt industry cross-sectional exposure assessment study. Appl. Occup. Environ. Hyg 10(10) 840-848, 1995. (means) |
| | Manufacture | 2.6 | 0.29 | |
| | Roofers | 5.9 (2.1, 2.5, 4, 3.2, 10.3, 13.1) | | Mean of 6 values. V Behrens and G Liss, Hazard evaluations and technical assistance branch, NIOSH, U S Dept of Health and human services, Report no HETA-84-062-1552, 1983 |
| | Roofers | 3.6 (2.6, 6.2, 3.6, 1.8, 3.9) | 0.67 and 1.7 | Tharr D. Health hazards evauation reports No HETA-81-432-1105, Roofing sites, Rochester and Buffalo, New York, NIOSH 1982 |
| | Roofers | 1.9 (1.67, 2.84, 2.2, 1.5, 2.2, 0.76) | | Mean of 6 values. Reed L, Health hazard evaluation report No HETA-83-380-1671, Roofing sites Dayton, Ohio |
| Coal gasworks | Retorts | 0.93-1.1 | | IARC Vol 34 (Year 1984) - cited Lawther (1965) |
| | Other (by-products) | | | |
| Carbon electrode plant | All | 1.6 (0.21 – 8.78) | | US Dept of health, education and welfare, CDC, HIOSH. Health hazard evaluation determination Report No 75-91-489. ALCOA aluminium company. (data 1975 and 1976) |
| Coke oven | Top | Plant A 0.83-7.76 | 0.21-1.1 | Range of averages. Evaluation of coke oven emissions. WM Smith. J.Occ. Med. 1971. |
| | | Plant B 0.84-5.43 | 0.28-2.07 | |
| | | Plant C 0.8-3.0 | 0.24-1.13 | |
| Coke oven | Top | 4.0 – 6.3. | | Measurement and analysis of airborne emissions from coke ovens… Davies G M. Commission of the European Communities, Office for |

| | | | | |
|---|---|---|---|---|
| | Side | 1.9 - 4.0. | | Official Publications, 1981, p75-95. (data 1971) |
| | Other (by-product) | 3.8. | | |
| Coke oven | Top | 12.8 | | Experience in controlling airborne pollutant exposure of operatives at a coke oven. A T Gillies ,Ann. Occup., Hyg Vol 27. No 2, pp 221-222, 1983. |
| | Side | 4.0 | | |
| | Other(coke side assistant) | 9.7 | | |
| Carbon black manu | | 1950-1959 = 8 | | Sorahan et al 2001. Means of factories 1 and 4 over time periods shown |
| | | 1960-1964 = 7.1 | | |
| | | 1665-1969 = 6.0 | | |
| | | 1970-1974 = 5.4 | | |
| Carbon black manu | | 0.44-1.45 | 0.13-0.35 | Geometric means. Occupational exposure to carbon black: aparticulate study. R G Smith and D C Musch. Am. Ind. Hyg Assoc. J 43(12) 925-930 (1982) |
| Carbon black manu | | 0.66-1.72 | | Geometric means. A cross-sectional study of pulmonary function in carbon black workers in the US. J M Robertson et al. . Am. Ind. Hyg Assoc. J. 49(4): 161-166 (1988) |
| Chimney sweeps | | | | |
| Thermoelectric power plants | | | | |

## Appendix C. Estimating unit relative risk increments

### *Model choice*

We fitted two different models for the dependence of relative risk on cumulative exposure:

- Loglinear relative risk model: RR =exp($b_{loglin}$x)
- Linear relative risk model: RR=1+$b_{lin}$x

where x is cumulative exposure in $\mu g/m^3$ years; and the slope b is the unit relative risk increment (URR). (For both models, RR=1 if x=0)

Advantages and disadvantages of each.

In favour of the linear model:

- Arguments from mechanism give more support to the linear than log-linear form (Greenland 1987).
- Plotting results from some of the large studies (Armstrong 1994, Constantino 1996) suggested linear rather than log-linear forms
- Exploratory analysis confirmed that in included studies with several exposure groups, the linear form fitted significantly better, for both lung and bladder cancer. for lung cancer, overall deviance was 85.1 (54 dfs) when linear models were fit to each study, compared to 101.7 (54 dfs) with loglinear models. (Bladder: 38.9 Vs 51.2 on 18 df) The addition of a quadratic term was significant in a single-slope loglinear model (p=0.006), but not in a single-slope linear model (p>0.20).

In favour of the loglinear model.

- Estimates of $b_{loglin}$ have symmetric sampling distributions, but those of $b_{lin}$ do not. This makes blin much harder to treat statistically. We calculated confidence intervals using the likelihood profile method (Mason and Prentice). However standard meta-analysis methods (see below) assume symmetrical (normal) sampling distributions - evaluating significance of patterns, for example differences between industries, may be compromised. We proceeded by estimating standard errors as a quarter of the width of the likelihood profile confidence interval (an approximation to 1/(2X1.96)).

*Model estimation*

Typical data from a study is in the form of the first two rows of Table C1. Where expected cases are not given, these were calculated as $R_k/O_k$. [In a few cases where $O_k$=0 and expected numbers were not given, they were estimated from numbers of all deaths in that group by assuming the proportion of expected deaths that were due to lung or bladder cancer was the same in that group as overall.] Mean cumulative exposures $C_k$ for each group were estimated as described in the "estimating exposures" section.

Assembling the data in this way allowed us to use standard Poisson regression software to estimate the slope b of the loglinear (STATA) or linear (EPICURE) relative risk model. Because the sampling distribution of $b_{lin}$ is known to be skewed in small samples (Prentice & Mason, 1986) we estimated confidence intervals using the profile likelihood.

This method is standard where the relative risks are SMRs, and would seem to be well suited to RRs estimated by Poisson regression. However, for ORs estimated from the three nested case control studies, with few controls per case, they would be expected to underestimate uncertainty. However, comparing our estimates in one study with a method not requiring approximation by a Poisson distribution (Greenland and Longnecker 1992), we found little difference.

Table C1 Data layout for estimation of URRs

| | Group | | | |
|---|---|---|---|---|
| | 1 | 2 | … | K |
| Observed cases | $O_1$ | $O_2$ | | $O_K$ |
| Relative Risk* | $R_1$ | $R_2$ | | $R_K$ |
| Expected cases | $E_1$ | $E_2$ | | $E_K$ |
| Cumulative exposure | $C_1$ | $C_2$ | | $C_K$ |

* SMR, RR estimated from Poisson regression, or OR.

For studies presenting only a single SMR in a group with mean cumulative exposure C we estimated

$$URR_{lin} = 1 + (SMR-1)/(C/100);\ SE(URR_{lin}) = SE(SMR)/(C/100) = \sqrt{O}/(E.C/100).$$

$$URR_{loglin} = SMR^{(100/C)}l;\ GSE(URR_{loglin}) = \exp(1/O)$$

Where O=0, we estimated $SE = \sqrt{E}/(E.C/100) = 1/(\sqrt{E}.C/100)$ and $GSE(URR_{loglin}) = \exp(1/E)$; 95% confidence limits for the SMR and hence $b_{lin}$ and $b_{loglin}$ were estimated using Poisson exact limits for the mean underlying O.

*Method to estimate bin means*

Introduction

To make estimates of exposure-response relationships from published data, it was necessary to have a mean (for linear models) exposure for each exposure group (bin).

Assume the data is in the form:

| Group | Lower bound | Upper bound | Py or freq in controls* | mean |
|---|---|---|---|---|
| 1 | $y1_1$ | $y2_1$ | $f_1$ | ? |
| 2 | $y1_2$ | $y2_2$ | $f_2$ | ? |
| … | | | | |
| k | $y1_k$ | $y2_k$ | $f_k$ | ? |
| | | | | |

* or expected cases

Mean exposures for groups with both lower and upper limits (all except the highest) were estimated by the mid point [(y2-y1)/2] of the interval. The upper bin is problematic.

Strategy

Fit a log-normal distribution to the distribution observed, then calculate bin means. For this we require a proportion of subjects falling in each bin. This is provided by the number of expected cases in each bin (E=O/RR). Exploratory analyses on data for which we knew the true bin means suggested that this was improved by excluding the first bin (often zero exposure); leaving a truncated lognormal distribution.

In stata, this strategy is effected by carrying out interval regression to estimate parameters of a log-normal distribution best fitting the observed proportions, then predicting the mean for the bins from the fitted distribution.

Example Armstrong (1994):

| Obs cases | | Range | RR |
|---|---|---|---|
| 138 | | <10 | 1.00 |
| 94 | | 10-99 | 1.48 |
| 41 | | 100-199 | 2.06 |
| 46 | | 200-299 | 2.06 |
| 19 | | >=300 | 1.85 |

Exp. Cases – obs cases/RR.

This gives:. (Excluding first group):

```
           y1        y2      probs    relfreq      means  truemeans
  1.       10       100   .3953748    .547451   58.18076      40.92
  2.      100       200   .3427276    .171552   140.0813     147.18
  3.      200       300   .1398394    .192473   241.0813     250.48
  4.      300         .   .1215088    .088524    438.102     413.14
* probs = probabilities predicted by lognormal fit
** relfreq = observed relative frequencies of expected numbers
```

## Appendix D: Description of individual studies (by industry)

Coke and coal gas workers

Twelve papers were identified reporting on lung and or bladder cancer risks in coke workers, representing 14 studies, when sub-studies were considered.

Of the two papers reporting on coke workers in Asia, Sakabe et al (1975) reported on lung cancer mortality in coke workers in Japan who had retired between 1949 and 1973 from 11 plants including manufacturing, gasworks and iron and steel plants. 2,178 retirerees were identified, with a maximum 34 years reported duration of employment. This suggests that earliest exposure among the cohort was in 1915. SMRs were generated using national lung cancer rates for comparison. Results were reported by type of plant, a significant increase in risk was only obtained for gas company workers. Xu et al (1996) reported on lung cancer morbidity in a case cohort study among workers and retired employees who had worked for at least 10 years in the coke works of an iron and steel plant in China. 610 incident cases, aged between 30 and 70 were identified between 1987 and 1993 and compared to 959 randomly selected controls. Use of exposure information provided by correspondence with the author and reported smoking adjusted ORs by duration of exposure produced a URR greater than 1, which was statistically significant.

Only one study was conducted in North America. Costantino et al (1995) followed up lung and bladder cancer mortality over a 30 year period in a cohort of 15,818 workers in steel plants in the USA and Canada, selected either from workers employed from 1951 to 1955 in 10 of the plants, or from 1953 7 of the plants. Cancer risks were reported in relation to frequency matched non-oven steel workers. Significant increased risk for lung cancer by cumulative exposure to BSM was reported, but risks reported for bladder cancer in relation to exposure to BSM were not significant.

The remaining 9 papers reported on 11 cohort studies, 9 investigating mortality and 2 morbidity from lung and/or bladder cancer conducted in Europe. All the studies used national mortality or morbidity rates as reference populations, with the exception of one of the 3 UK studies, Reid and Buck (1956), which used rates among other industrial workers and a Swedish study (Gustavsson & Reuterwall 1990) which used local mortality rates in occupationally active men.

Bye et al (1998) reported on a cohort of 888 workers with at least one year of employment during the operational period of a plant in Norway which was from 1964 to 1988. Follow up was from 1962 (some men were employed during the construction period from 1962) to 1993. Risks for lung and bladder cancer morbidity by cumulative exposure to PAH resulted in non-significant greater than 1 (lung) and non significant less than 1 (bladder) URR estimates, based on 7 and 5 cases respectively.

Chau et al (1993) re-examined mortality a cohort of 536 retired workers who had retired from one of two plants in France between 1963 and 1982, extending follow up a further 5 years from 1963 to 1987. The plants started production in 1911 and 1955, with the 1911 plant receiving regeneration in 1963, and thus occupational exposure conditions improving beyond that of the 1955 plant. The year of birth among the cohort ranged from 1902 and 1935, with mean age of death of 64.8. 13.1% of retirees had worked in the old generation of plant A. Workers were classified by job group, with total duration of exposure ranging from 18-24 years. Although a significant increased risk for lung cancer was reported for the whole cohort (2.38, $p<0.001$), risks for lung cancer by job group gave rise to a null estimate for the URR of 1.00 (0.68, 1.46) adjusted for smoking. Due to the small number of observed cases for bladder cancer (1), the risk reported for the whole group was utilised, resulting in non-significant estimate of the URR which was below 1.

Franco et al (1993) investigated mortality in a cohort of 538 workers who had been employed for at least one year between 1960 and 1985 ion a plant in Italy, with follow up from 1960 to 1990, resulting in 10,665 person years with an average of 20 years. The plant was operational from 1947 to 1989, and also from 1943-44. The mean age of entry into the cohort was 37 years, and average length of employment was 18.6 years. A significant increase in risk for lung cancer was observed, applying estimated generic exposures to these data, a URR of 1.41 (1.07, 1.79) was estimated.

Swaen et al (1991) reported on a cohort of 5,639 workers who had worked for at least 6 months between 1945 and 1969 at one of three plants in The Netherlands, had Dutch citizenship and were resident in the Netherlands. Coke production started in 1918 - 1929 and ended in 1968. The cohort were followed up for mortality from 1945 to 1984, during which time 273 deaths from lung cancer and 38 from bladder cancer were identified. Using risks reported by job group and relevant estimated generic exposures, URRs greater than 1 were estimated for both lung and bladder cancer, but neither achieved statistical significance.

Berger and Manz (1992) investigated cancer mortality in a cohort of 4,908 men who had worked in a gasworks in Hamburg, Germany for at least 10 years between 1900 and 1989. 789 of these men had worked in the ovens, their mean duration of exposure was 26.7, mean age at entry was 32, and average age at death was 68. 70% were smokers. As national mortality data was unavailable prior to 1952, a subset of workers was followed up from 1952 to 1989. A highly significant increased risk of lung cancer (SMR 2.88, 2.28, 3.59) was reported for this group. Using data on BaP exposure reported in the paper, a significant URR of 1.15 (1.12, 1.19) was estimated.

Gustavsson and Reuterwall (1990) investigated mortality and incidence of cancer in a cohort of 295 men who had worked for at least one year between 1965 and 1972 in a Swedish gas plant. The plant started operation in 1893 and coal gas was produced in coke ovens from 1918 to 1972. Prior to 1918, gas was produced in retorts, and since 1972 from cracking of petroleum products. Follow up was from 1966 until 1986 for mortality and 1983 for morbidity, using rates for local occupationally active men for mortality, and national rates for morbidity. Lung cancer mortality was reported by job group; 66 men worked in the coke oven department, the only job for which exposure information to BaP was reported, mean length of exposure was 11.9 years. No cases of lung cancer were observed, giving rise to a non-significant URR less than 1.

The earliest of the 3 UK studies was reported by Reid and Buck (1956). All men who had died during the period 1949-1954 and were registered on the books of NCB (National Coal Board) coking plants were investigated. About 8000 men were employed in NCB coking plants during this time. Mortality risks for lung cancer mortality, in comparison to rates from other industrial workers, were reported according to job group. Combining these with estimated generic exposures, a non-significant URR below 1 was estimated.

Doll et al (1972) reported on mortality in two cohorts of workers at gas boards; termed "original" and "additional". Follow up for the original cohort (1953-1961) was extended a further 4 years to 1965. The cohort included men who were employed by or were in receipt of a pension from one of 4 area gas boards in 1953, were aged 40 - 65 and had been employed for more than 5 years. 2,449 men working as coal carbonising processors and 579 by-product workers were identified. The additional cohort was identified from 4 additional gas boards, and included men employed or retired in 1957 (3 boards) or 1959 (1 board) with follow up to 1965. 1,176 carbonising plant workers, 1,430 men with intermittent exposure (maintenance in gas plants and processors in gas producing plants other than retort houses) and 2,081 men with minimal or no exposure were identified. Using exposure information based on measurements made by Lawther et al (1965), reported lung and bladder cancer mortality risks by job group gave rise to statistically significant increased risks (URRs >1) for lung cancer in both cohorts, but increased risks (URRs >1) for bladder cancer did not reach statistical significance.

A more recent study of mortality among BSC (British Steel Corporation) and NSF (National Smokeless Fuels Ltd - a subsidiary of the National Coal Board) cohorts was reported by Hurley (et al 1983). The BSC cohort comprised all male manual workers employed between 1966 to mid 1967, and the NSF cohort comprised all workers employed at the beginning of 1967. A total of 6,767 workers were identified from 14 BSC works and 13 NSF works. A more in depth (unpublished) research report on the study with additional follow up to 1987 was made available to us by the author (Hurley, approx date 1988?). Using data from this report, which included exposure information to BSM, reported lung cancer risks by cumulative exposure gave rise to significant increased risks for the NSF cohort but not for the BSC cohort. Bladder cancer risks were reported for the whole group for each

cohort: a URR below 1 was estimated for the BSC cohort, and above 1 for the NSF, neither result was significant.

Aluminium

Eight studies were identified; 6 of which were cohort studies and 2 case-cohort. Of 5 studies conducted in North America, 3 reported risks according to cumulative exposure to BaP or proxies to BaP. Armstrong et al (1994) studied lung cancer mortality during the period 1950 to 1988 in men who had worked for at least one year between 1950 and 1979 at a plant in Quebec, Canada. 338 lung cancer deaths were observed and compared to a random sample (sub-cohort) of 1, 138 drawn from the 16,297 aluminium workers eligible for inclusion. Based on reported risks by cumulative exposure to BaP, a statistically significant URR of 1.22 (1.09, 1.37) was estimated. Tremblay et al (1995), using the same cohort, investigated bladder cancer morbidity - 138 cases of bladder cancer were identified and compared to three matched controls drawn mainly from the same sub-cohort. Using risks (rate ratios) reported by cumulative exposure to BaP, a significant URR was estimated (1.48 (1.24, 1.76)) for bladder cancer morbidity. Spinelli et al (1991 reported morbidity risks for both lung and bladder cancer by cumulative exposure to coal tar pitch volatiles (CTPV, measured as BSM) in a cohort of 4,213 men who had worked for at least 5 years at a Soderberg plant in British Columbia, Canada between 1954 and 1985. A total of 60,590 person years were observed, with 2.9% accounted for by 204 men with over 20 BSM years exposure. Risks were compared to regional rates, with a 3 year lag period and follow up from 1959 to 1985. A URR greater than 1 was derived for both cancers, but did not reach statistical significance for either cancer.

Mortality was investigated in a cohort of 2,103 men who had worked at least 3 years, with at least one year between 1946 and 1962, at a pre-bake aluminium plant in Washington State in the United States by Milham (1979). The cohort was followed up for 30 years from 1946 to 1976. Number of cases of lung cancer were reported by duration of exposure, in 5 year bands from 3-4 years exposure to over 25 years, and compared to that expected from national rates. Using these results, and applying estimated generic exposures, a URR of less than 1 was estimated, but did not reach statistical significance. An SMR of less than one was reported for bladder cancer mortality, but this result was not significant, and was based on only 1 case in a non-exposed worker.

Rockette and Arena (1983) reported on a cohort of 21,829 workers with five or more years employment in 14 plants in the US between 1946 and 1977, which were also followed up from 1946 to 1977. The earliest start up date was 1903. Seven of the plants were prebake only, 6 Soderberg and the remaining two mixed. Results were reported by duration of exposure and according to the type of plant for lung cancer mortality, these were utilised to generate sub-group specific URRs: 1.85 (0.53, 6.53) for Soderberg plants and 0.06 (0.00, 9.58) for prebake plants. The number of bladder cancer deaths were reported according to job group and compared to national rates, a non-significant URR (>1) was derived.

The three remaining cohort studies were conducted in Europe and only one reported exposure information (Romundstad et al 2000). Moulin et al (2000) reported on mortality among 2,133 male workers who had been employed in a plant in France for at least 1 year between 1950 and 1994. The cohort was followed up for an average of 16.5 years for mortality from 1968 to 1994, giving a total of 35,145 person years. Lung and bladder cancer risks were reported by duration of exposure, and were based on comparison with regional rates. Non-significant URRs were derived for both cancers. Both prebake and Soderberg anodes were used in this plant, although only prebake has been used since 1982. Mur et al (1987) also reported on mortality in workers in plants in France. A cohort of 6,455 workers who had worked for at least one year in one of 11 plants between 1950 and 1976 was followed up for mortality also from1950 to 1976, giving a total of 113,671 person years. The earliest date of exposure was 1907, and the majority of plants used both prebake and Soderberg processes. The majority of workers, about two thirds, had been employed for over 10 years, and a third for over 20 years. Numbers of deaths from lung cancer for all plants collectively were reported by duration of exposure and compared to national rates, resulting in a non-significant URR below 1. Romunstad et al (2000) updated results from 6 previous cohort studies in Norway. Cancer incidence was investigated

among 11,103 men employed for more than 3 years between 1953 and 1996, with follow up also from 1950 to 1996, giving 272,554 person years. The earliest start up date of the 6 plants was 1914. Lung and bladder cancer incidence in relation to national rates were reported by cumulative exposure to PAH. No increase in lung cancer risk (rate ratio) was observed. Although a weakly significant increased risk was reported for bladder cancer incidence with increasing PAH exposure, URR estimates in relation to BaP concentration based on these data did not reach significance (1.19 (0.88, 1.61).

Carbon workers

Three papers reported on 4 studies (3 cohort and one case control) in carbon workers, one paper from China and two from Europe, only one of which produced a significant URR estimate. Liu et al (1997) investigated cancer mortality among a cohort of 6,635 male carbon workers who had been employed for more than 15 years in seven factories including one aluminium plant. The cohort was followed up from the cohort entry date, 1st Jan 1971 to 1985, resulting in 95,847 person years. 89 were lost to follow up, of the remaining 6,546, 56.2% were smokers. Measurements of BaP were taken at the Shanghai carbon plant in 1986-7, using glass fibre filters with analysis by high performance liquid chromatography (HPLC). Mortality risks were reported in relation to those of 11,470 other steel workers employed in rough rolling mills. 222 of the total 390 deaths (all cause) were among non-smokers. Using results reported by 4 exposure levels (including non-exposed), a statistically significant URR greater than 1 was estimated for lung cancer mortality. A significantly positive relationship was also found for lung cancer mortality for the overall group (SMR= 2.16, $p<0.01$). Results (SMRs) were also reported for lung cancer risks among non-smokers for exposed and highly exposed workers of 3.00 ($p<0.01$) and 5.34 ($p<0.01$) respectively.

Donato et al (2000) reported on cancer mortality among a cohort of 1,006 workers who had been employed for at least one year between 1945 and 1996 in a carbon (graphite) electrode plant in Umbria, Italy, which has been in production since 1901. From 1945-1971, petroleum derived coke, coal tar pitch and petroleum pitch were all used as raw materials; petroleum coke was used as a basis, and pitches as binding materials. Follow up was carried out from 1955 to 1996, (mean 39.5 years), giving 34,248 person years. Lung and bladder cancer mortality risks were reported according to duration of employment in relation to national mortality rates. Applying relevant generic exposure estimates to these results non-significant URRs below 1 were estimated for both lung and bladder cancer

Moulin et al (1989) reported results from two studies: morbidity and mortality from selected cancers among carbon electrode workers were investigated in two plants (A and B respectively) in south eastern France. Personal and area exposure measurements were taken in both plants in 1983-84 using glass fibre filters and analysed for PAHs including BaP by HPLC. Within each cohort, a case-referent study was conducted, as results by duration of exposure were reported for lung cancer in the case-referent studies, these results were utilised in the lung cancer meta-analysis.

Cancer morbidity was reported among a cohort of 1,302 men who were employed at one plant (Plant A) on 1st January 1975, with 11 years of follow up to 1985. 153 men (11.8%) were lost to follow up. This plant began operation in 1895, but graphite electrode manufacture was only initiated in 1950. The earliest exposure among cancer cases was 1934. Lung cancer incidence risks were reported by duration of exposure in comparison to randomly chosen referents from within the cohort matched for smoking (3 per case). Applying reported personal exposure measurements (2.7 $\mu g/m^3$ BaP) to these results a non-significant URR greater than 1 was estimated. Lung cancer risk (SIR) reported from the cohort study was also non-significant, but less than 1. Smoking adjusted risks for bladder cancer incidence were reported, in relation to local rates from a nearby district, for the overall cohort group. Applying reported exposure data to these results, a non-significant URR of less than 1 was derived.

Cancer mortality was investigated among a cohort of 1,115 men in Plant B who were employed on 1st January 1957, with 28 years of follow up to 1984. The vital status was unknown for 150 workers (13.5%) who were born abroad. Plant B was set up in 1897, and the earliest exposure among cancer

cases was 1911.. Smoking data was not available for this plant. Again, lung cancer risks were reported according to duration of exposure from the case-referent study (3 referents per case), however, risks were not adjusted for smoking in this plant. Applying reported exposure measurements for this plant (0.17 µg/$m^3$ BaP) to these results, a URR of less than 1 was also estimated for lung cancer mortality. Lung cancer risk (SMR) from the cohort study was greater than 1, but did not achieve statistical significance. Risks for bladder cancer mortality were reported, using national mortality rates as the reference population, for the overall cohort group. Applying reported exposure data to these results, a non-significant, very imprecise URR (> 1) was estimated.

Asphalt

This category included those workers who use asphalt (such as roofers, waterproofers, pavers) rather than those who are involved in the production (distillation) process. Asphalt is composed of stone and/or sand and a binder. Results are complicated by the change in composition of asphalt over time and in its definition between countries. In Europe asphalt refers to the stone and binder, while in North America, asphalt refers to the binder only. Binders were historically composed of coal tars or tar, while bitumen is now more commonly used in paving applications, although coal tars are still used in some roofing applications. Modern asphalts (bitumens) are manufactured by non-destructive vacuum distillation of crude petroleum oils, whereas coal tars are products of the destructive distillation of coal and coal tar pitches are residues from the distillation of coal tars. IARC (1984) considered that there was sufficient evidence of carcinogenicity only for extracts of steam refined or air refined bitumens, based on animal data.

Four studies were identified, all of which were cohort studies and three of which reported exposure data.

An increased risk 1.55 (95% CI 0.5-3.61) for bladder cancer incidence was reported by Hansen (1989) in a cohort of 679 Danish mastic asphalt workers identified from 1959 to 1980, with follow up to 1985. A risk (SIR) was also reported for lung cancer morbidity, (SIR) of 3.44 (95% CI 2.27-5.01), however as the same cohort was later evaluated for lung cancer mortality, with follow up extended to 1986 (Hansen 1991), applying our inclusion criteria, we used results from this paper to feed in to the meta-analysis. 25 cases were observed in the later study with an SMR of 2.9 (95% CI 1.88-4.29).

Hammond et al (1976) reported on a cohort of 5,939 men currently or previously employed as roofers and waterproofers in the USA who had been in the union for at least 9 years. 121 cases of lung cancer and 15 of bladder cancer were observed and compared to national population rates, giving rise to URRs of 5.63 (0.89, 35.53) and 3.94 (0.52, 22.65) respectively. The study which did not report exposure data, was the only study to report non-significant increased risk for lung cancer: Swaen and Slangen al (1997) reported on a cohort of 866 roofers who were employed for at least 6 months between 1947 and 1988 in The Netherlands and were followed up until 1988, no exposure data were reported. Increased risks for lung and bladder cancer were observed, although the SMRs were not statistically significant for either.

Tar distillery

Three cohort studies were identified, none of which contained data on exposure. Hansen (1989) followed up 1320 workers employed in the asphalt industry for 10 years and compared their lung and bladder cancer mortality rates to unexposed workers in Denmark. Non-significant increases were observed for both cancers. Swaen and Slangen (1997) also reported on a cohort 907 tar distillery workers, in which elevated risks of lung cancer (48 cases), and a reduced risk of bladder cancer (2 cases) were observed, although the SMRs were again not statistically significant. MacClaren and Hurley (1987) followed up 255 British tar distillery workers employed on 1 January 1967 from 1967 to 1983, non-significant increases in both lung and bladder cancer deaths were observed.

Chimney sweeps

Two cohort studies without exposure information were identified. Evanoff et al (1993) investigated mortality and morbidity in a cohort of 5,542 Swedish chimney sweeps employed through their national trade union at any time between 1918 and 1980, with follow up to 1987 for incidence and 1990 for mortality. Mean duration of exposure was estimated at 12 years. URRs derived from risks reported for duration of exposure suggested a non-significant increase in risk for lung cancer and a non-significant decrease in risk for bladder cancer. Hansen (1983) followed up mortality in a cohort of 713 Danish chimney sweeps from 1970 to 1975 and compared this to mortality in the national working male population. The mean length of exposure of those who died was 30 years, employing an estimated generic exposure for chimney sweeps of 1 $\mu g/m^3$ BaP per year, estimates based on this study also resulted in a significant URR greater then 1 for lung cancer mortality.

Thermoelectric power (Code 10)

Three cohort studies, all investigating lung or bladder cancer mortality, based in Italy and reporting no exposure information were identified. Cammarano et al (1986) followed up mortality for 25 years, until 1985, in all workers employed between 1960 and 1969 who had at least 10 years employment at a plant in Milan established in 1928. Based on mortality rates compared to those in the male regional population, non-significant URRs greater than 1 were estimated for both lung and bladder cancer. Petrelli et al (1989) reported on lung cancer mortality only in a cohort of 1,307 workers employed at two power plants (which used coal since 1968) near Venice between 1968 and 1980. The cohort were followed up until 1984, giving 12,581 person years at risk, of which 28% were attributable to workers who had had more than 10 years exposure. Using the male Italian population mortality rates as a reference, a non-significant increase in risk - SMR of 1.3 was reported. Forastiere et al (1989) reported on a cohort 406 workers employed between 1968 and 1970 at two plants near Latium, one of which started operation in 1953 as a coal-fired plant, but changed to oil in 1962. The second plant started operation in 1964, using oil. The cohort was followed up from 1968 to 1986, comparison to national male mortality rates produced a non-significant increase in risk (SMR = 1.74, (0.3, 5.5)) for bladder cancer. Results were reported by duration of employment for lung cancer, giving rise to a non-significant URR of (-0.00, >1000).

Carbon black

Two studies of carbon black workers were identified, one from the USA and one from the UK. Robertson and Inman (1996) reported on an update of an earlier mortality cohort study among male workers aged 15 or more who were employed for at least one year between 1935 and 1994 at one of 4 USA carbon black producing companies. Follow up was from 1935 and extended an additional 20 years to 1994 to give 54,784 person years. Retired workers contributed 20% of the additional person years of follow up. For one of the companies, data from 1975 to 1994 only was included. Using reported results for lung cancer risk (compared to state specific rates) for the whole group and applying appropriate generic estimates for exposure to BaP, a non-significant URR lass than 1 was estimated.

Sorahan et al (2001) investigated mortality among a cohort of 1,147 male workers from five UK factories manufacturing carbon black who had worked for at least one year variously between 1950 to 1971 and 1974, according to the factory from which they were drawn. Entry cohorts were also used - all workers employed on 1 January 1968, 1956 and 1967. By definition, no subject was employed at any time before 1947. Inhalable and respiratory dust measurements were taken at 19 European factories, including two included in this study during the period 1987 to 1995. These were combined with data on job histories to construct exposure estimates for these factories for the late 1980s, job-exposure matrices were then constructed for inhalable dust exposure and combined with changes in the site histories to construct mean exposure levels for each of the 12 job categories for all the earlier periods. These were then used to produce individual estimates of cumulative carbon black exposure. The cohort was followed up for mortality from 1951 to 1996. Results for lung cancer risk, using

national rates as a comparison, were reported by cumulative exposure to carbon black (mg/m3yr). 64 cases were reported among workers aged 30 - 84 years. Using conversion factors to derive cumulative exposure to BaP, a non-significant and very imprecisely estimated URR of greater than 1 was derived. This was in contrast to lung cancer risks reported for the whole group, which were highly significant with an SMR of 1.73 (1.32, 2.22). Bladder cancer risks were reported for the whole group, leading to a non-significant, extremely imprecise estimate for URR

## Appendix E: meta-data on exposure-response (lung cancer preferred contrasts)

| cname | grp num | cum_exp | cases | exp. cases | Rel. risk |
|---|---|---|---|---|---|
| Berger92 | 1 | 747.6 | 78 | 27.10 | 2.88 |
| Bye et85 | 1 | 0.0 | 4 | 5.56 | 0.72 |
| Bye et85 | 2 | 1.1 | 0 | 1.40 | 0.00 |
| Bye et85 | 3 | 4.4 | 0 | 0.70 | 0.00 |
| Bye et85 | 4 | 10.0 | 3 | 0.83 | 3.60 |
| Chau, 93 | 1 | 0.0 | 6 | 2.63 | 2.28 |
| Chau, 93 | 2 | 0.3 | 1 | 1.35 | 0.74 |
| Chau, 93 | 3 | 21.9 | 6 | 1.39 | 4.33 |
| Chau, 93 | 4 | 24.0 | 2 | 0.84 | 2.37 |
| Chau, 93 | 5 | 230.0 | 8 | 3.17 | 2.52 |
| Chau, 93 | 6 | 454.0 | 2 | 1.14 | 1.75 |
| Costan95 | 1 | 0.0 | 203 | 203.00 | 1.00 |
| Costan95 | 2 | 14.8 | 34 | 27.42 | 1.24 |
| Costan95 | 3 | 73.7 | 43 | 27.56 | 1.56 |
| Costan95 | 4 | 162.4 | 56 | 28.72 | 1.95 |
| Costan95 | 5 | 251.2 | 39 | 19.31 | 2.02 |
| Costan95 | 6 | 339.9 | 27 | 10.04 | 2.69 |
| Costan95 | 7 | 805.4 | 56 | 17.89 | 3.13 |
| Doll e72a | 2 | 10.0 | 11 | 14.67 | 0.75 |
| Doll e72a | 1 | 60.0 | 99 | 54.70 | 1.81 |
| Doll e72b | 1 | 0.0 | 16 | 30.19 | 0.53 |
| Doll e72b | 2 | 30.0 | 40 | 23.26 | 1.72 |
| Doll e72b | 3 | 60.0 | 23 | 17.16 | 1.34 |
| Franco93 | 1 | 186.0 | 19 | 10.00 | 1.90 |
| Gustav90 | 1 | 28.7 | 0 | 0.90 | 0.00 |
| Hurley83a | 1 | 0.0 | 28 | 28.00 | 1.00 |
| Hurley83a | 2 | 23.8 | 11 | 18.64 | 0.59 |
| Hurley83a | 3 | 71.4 | 11 | 22.45 | 0.49 |
| Hurley83a | 4 | 262.9 | 9 | 5.92 | 1.52 |
| Hurley83b | 1 | 0.0 | 100 | 100.00 | 1.00 |
| Hurley83b | 2 | 23.8 | 33 | 37.93 | 0.87 |
| Hurley83b | 3 | 71.4 | 32 | 24.24 | 1.32 |
| Hurley83b | 4 | 252.9 | 17 | 8.17 | 2.08 |
| Reid a56 | 1 | 10.0 | 3 | 3.00 | 1.00 |
| Reid a56 | 2 | 20.0 | 14 | 14.00 | 1.00 |
| Reid a56 | 3 | 400.0 | 4 | 5.00 | 0.80 |
| Sakabe75 | 1 | 200.0 | 15 | 11.72 | 1.28 |
| Swaen,91 | 1 | 0.0 | 107 | 122.99 | 0.87 |
| Swaen,91 | 2 | 10.0 | 104 | 104.00 | 1.00 |
| Swaen,91 | 3 | 200.0 | 62 | 48.06 | 1.29 |
| Xu et 96 | 1 | 0.0 | 172 | 172.00 | 1.00 |
| Xu et 96 | 2 | 123.8 | 8 | 2.05 | 3.90 |
| Xu et 96 | 3 | 453.8 | 14 | 4.12 | 3.40 |
| Armstr94 | 1 | 2.3 | 138 | 138.00 | 1.00 |
| Armstr94 | 2 | 40.9 | 94 | 63.51 | 1.48 |
| Armstr94 | 3 | 147.2 | 41 | 18.39 | 2.23 |
| Armstr94 | 4 | 250.5 | 46 | 21.90 | 2.10 |
| Armstr94 | 5 | 413.1 | 19 | 10.16 | 1.87 |
| Milham79 | 1 | 10.5 | 4 | 3.85 | 1.04 |
| Milham79 | 2 | 22.5 | 4 | 5.71 | 0.70 |
| Milham79 | 3 | 37.5 | 9 | 5.73 | 1.57 |
| Milham79 | 4 | 52.5 | 14 | 7.57 | 1.85 |
| Milham79 | 5 | 67.5 | 4 | 5.19 | 0.77 |
| Milham79 | 6 | 99.2 | 0 | 1.63 | 0.00 |
| Moulin00 | 1 | 0.0 | 4 | 8.51 | 0.47 |
| Moulin00 | 2 | 25.0 | 5 | 7.25 | 0.69 |
| Moulin00 | 3 | 70.0 | 4 | 4.76 | 0.84 |
| Moulin00 | 4 | 120.0 | 3 | 5.36 | 0.56 |
| Moulin00 | 5 | 200.0 | 3 | 4.29 | 0.70 |
| Mur, J87 | 1 | 58.5 | 8 | 4.12 | 1.94 |
| Mur, J87 | 2 | 175.6 | 3 | 4.29 | 0.70 |
| Mur, J87 | 3 | 248.2 | 6 | 5.56 | 1.08 |
| Rocket83a | 1 | 20.0 | 6 | 12.68 | 0.47 |
| Rocket83a | 2 | 50.0 | 15 | 15.03 | 1.00 |
| Rocket83a | 3 | 70.0 | 24 | 23.60 | 1.02 |
| Rocket83a | 4 | 90.0 | 11 | 17.11 | 0.64 |
| Rocket83a | 5 | 116.1 | 8 | 5.41 | 1.48 |
| Rocket83b | 1 | 2.5 | 28 | 21.96 | 1.27 |
| Rocket83b | 2 | 6.3 | 23 | 22.07 | 1.04 |
| Rocket83b | 3 | 8.8 | 19 | 29.83 | 0.64 |
| Rocket83b | 4 | 11.3 | 26 | 23.51 | 1.11 |
| Rocket83b | 5 | 15.4 | 37 | 45.40 | 0.81 |
| Romund00 | 1 | 0.0 | 66 | 66.00 | 1.00 |
| Romund00 | 2 | 10.6 | 36 | 32.73 | 1.10 |
| Romund00 | 3 | 58.7 | 42 | 38.18 | 1.10 |
| Romund00 | 4 | 222.4 | 45 | 45.00 | 1.00 |
| Spinel91 | 1 | 4.0 | 11 | 15.28 | 0.72 |
| Spinel91 | 2 | 24.0 | 9 | 8.82 | 1.02 |
| Spinel91 | 3 | 60.0 | 7 | 6.14 | 1.14 |
| Spinel91 | 4 | 120.0 | 7 | 5.65 | 1.24 |
| Spinel91 | 5 | 251.1 | 3 | 2.10 | 1.43 |
| Donato00 | 1 | 4.5 | 10 | 10.00 | 1.00 |
| Donato00 | 2 | 14.0 | 12 | 13.33 | 0.90 |
| Donato00 | 3 | 36.4 | 12 | 20.34 | 0.59 |
| Liu97 | 4 | 0.0 | 13 | 8.72 | 1.49 |
| Liu97 | 3 | 1.2 | 6 | 5.04 | 1.19 |
| Liu97 | 2 | 4.5 | 5 | 3.29 | 1.52 |
| Liu97 | 1 | 17.3 | 26 | 6.05 | 4.30 |
| Moulin89 | 1 | 0.0 | 1 | 1.00 | 1.00 |
| Moulin89 | 2 | 14.9 | 2 | 0.69 | 2.90 |
| Moulin89 | 3 | 41.8 | 2 | 0.69 | 2.91 |
| Moulin89 | 4 | 94.9 | 2 | 0.49 | 4.07 |
| Moulin89 | 1 | 0.0 | 7 | 7.00 | 1.00 |
| Moulin89 | 2 | 0.9 | 3 | 7.89 | 0.38 |
| Moulin89 | 3 | 2.6 | 2 | 2.27 | 0.88 |
| Moulin89 | 4 | 5.8 | 1 | 3.13 | 0.32 |
| Hammon76 | 1 | 23.4 | 22 | 23.91 | 0.92 |
| Hammon76 | 2 | 40.9 | 66 | 43.42 | 1.52 |
| Hammon76 | 3 | 57.6 | 21 | 14.00 | 1.50 |
| Hammon76 | 4 | 66.8 | 12 | 4.86 | 2.47 |
| Hansen91 | 1 | 20.3 | 25 | 8.62 | 2.90 |
| Swaen,97 | 1 | 10.0 | 39 | 29.70 | 1.31 |
| Hansen89 | 1 | 10.0 | 16 | 11.19 | 1.43 |
| Maclar87 | 1 | 6.0 | 12 | 7.50 | 1.60 |
| Swaen,97 | 1 | 10.0 | 48 | 40.61 | 1.18 |
| Evanof93 | 1 | 4.5 | 4 | 5.19 | 0.77 |
| Evanof93 | 2 | 14.0 | 17 | 8.06 | 2.11 |
| Evanof93 | 3 | 24.0 | 13 | 5.78 | 2.25 |
| Evanof93 | 4 | 40.0 | 19 | 6.74 | 2.82 |
| Hansen93 | 1 | 30.0 | 5 | 1.60 | 3.13 |
| Cammar86 | 1 | 1.0 | 5 | 2.83 | 1.77 |
| Forast89 | 1 | 0.3 | 1 | 0.69 | 1.45 |
| Forast89 | 2 | 0.8 | 5 | 2.56 | 1.95 |
| Forast89 | 3 | 1.5 | 2 | 1.25 | 1.60 |
| Petrel89 | 1 | 1.0 | 6 | 4.41 | 1.36 |
| Robers96 | 1 | 1.0 | 34 | 40.48 | 0.84 |
| Soraha01 | 1 | 0.0 | 16 | 16.00 | 1.00 |
| Soraha01 | 2 | 0.2 | 11 | 14.10 | 0.78 |
| Soraha01 | 3 | 0.4 | 17 | 9.19 | 1.85 |
| Soraha01 | 4 | 0.8 | 20 | 15.15 | 1.3 |

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Rel risk: Risk relative to baseline, or SMR (See Table 2)

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