Mortality from Parkinson’s disease and other causes among a workforce manufacturing paraquat: a retrospective cohort study

John Andrew Tomenson,1 Clive Campbell2

ABSTRACT

Objective: To assess the risk of Parkinson’s disease (PD) and update information on mortality from major causes of death among a UK workforce who manufactured paraquat (PQ) between 1961 and 1995. There have been no previous studies of the incidence of PD among PQ production workers, although much epidemiological literature exists concerning the relationship between pesticides and PD, and interest has focused on PQ and its users.

Methods: The cohort included all employees who had ever worked on any of the four plants at Widnes where PQ was manufactured between 1961 and 1995, and 926 male and 42 female workers were followed through 30 June 2009. Mortalities for males were compared with national and local rates, including rates for PD as a mentioned cause of death.

Results: Overall, 307 workers had died by 30 June 2009. One male death was due to PD, and no other death certificate mentioned PD. At least 3.3 death certificates of male employees would have been expected to have mentioned PD (standardised mortality ratio = 31; 95% CI 1 to 171). Personal monitoring results were indicative that the exposure of a PQ production worker on a daily basis was at least comparable with that of a PQ sprayer or mixer/loader. Reduced mortalities compared with local rates were found for major causes of death.

Conclusions: The study provided no evidence of an increased risk of PD, or increased mortalities from other causes.

INTRODUCTION

A large body of epidemiological literature exists concerning the relationship between pesticides and Parkinson’s disease (PD), mainly studies which have used a case-control design.1 2 Interest has focused on paraquat (PQ) in part because of its structural similarity to 1-methyl-4-phenylpyridine (MPTP), a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) caused acute parkinsonism in a small group of drug addicts, and several have focused on paraquat (PQ) in part because of its structural similarity to a toxic metabolite of MPTP.

MPTP has been shown to cause permanent parkinsonism in humans, non-human primates and rodents as a result of its ability...
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to cross the blood–brain barrier and cause toxicity after being metabolised to MPP+.
In rodents, evidence of PQ-induced parkinsonism is controversial, but some investigators have reported a significant, but partial, reduction in dopaminergic neurons in the substantia nigra of the mouse brain.

The investigation concluded that exposure to tarry bipyridyl or its subsequent conversion by quaternisation to PQ, or the packaging of PQ solutions, was the most likely cause of the skin lesions. There have been no studies on the incidence of PD among PQ production workers.

PQ was manufactured at Widnes in the northwest of England between 1961 and 1995. During the late 1970s, several shift process workers who had worked in one or more of the plants were found to be suffering from skin lesions, including solar keratosis, squamous-cell carcinoma and Bowen’s disease. As part of a thorough investigation, which included examination of current and past employees and toxicological assessment of the chemicals handled, a cohort of PQ production workers was ascertained. The cohort included all workers who had ever been associated with the production of 4,4′-bipyridyl or its subsequent conversion by quaternisation to PQ, or the packaging of PQ solutions. The investigation concluded that exposure to tarry by-products was the most likely cause of the skin lesions

A retrospective mortality study was later conducted of an extended cohort that included all employees engaged in PQ production at the Widnes site between 1961, when production commenced, and 1983, with follow-up through 31 December 1985. The only suggestion of an adverse health effect was a modest excess of lung cancer deaths (13 observed, 10.5 expected deaths) which was concentrated in the period of follow-up 15 years or more after first exposure (8 observed, 3.8 expected deaths). No information was reported about mortality owing to PD, as this was not a hypothesis of interest when the study was conducted.

This report describes an extension and an update of the cohort mortality study conducted by Paddle et al.

The primary objective of the study is to assess whether there is any evidence of increased PD mortality as the underlying cause of death or as a mentioned cause of death. A secondary objective is to provide updated information on mortality from major causes of death to confirm the absence of an exposure-related effect reported by Paddle et al.

METHODS

Study population and follow-up

The investigation is a retrospective cohort mortality study of workers who worked in PQ production at Widnes, UK. Four plants using different processes were used to manufacture PQ at the site: a high-temperature sodium (HTS) plant (from 1961 to 1969, but used only for quaternisation from early 1964); a magnesium (MAG) plant (1962—1967); a low-temperature sodium (LTS) plant (1966 until 1995 when manufacture of PQ at Widnes ceased); and a plant utilising an ammonia cyanide (AC) process (1985—1993). Small-scale preproduction versions of the MAG and LTS plants were also operated on the site for short periods.

The cohort included all employees who had ever worked on any of these plants, and a further 217 male employees and 10 female employees were added to the cohort established by Paddle et al. in 1983 (729 male employees and 32 female employees). However, 20 male subjects included in the original cohort were excluded because they were found to be not exposed (8) or they had minimal identifying information including no date of birth (12). The final cohort consisted of 926 male employees and 42 female employees.

The vital status of the cohort on 30 June 2009 was ascertained from the Medical Research Information Service of the National Health Service. The underlying cause of death and other causes of death mentioned on the death certificate were coded by the Office of Population Censuses and Surveys to the contemporaneous revision of the International Classification of Diseases (ICD).

The initial investigation was approved by the British Medical Association Ethical Committee, and Section 60 support for the update was granted by the UK Patient Information Advisory Group.

Exposure assessment

Limited information is available to assess the exposures to PQ of the workers in the cohort. However, 1330 static monitoring results were collected between 1979 and 1993, and 100 personal monitoring results were collected between 1983 and 1993. Only summary information was available for static monitoring results collected before 1987. There was insufficient sampling information available to use these measurements to perform a quantitative exposure assessment.

Paddle et al. performed a limited qualitative exposure assessment of male workers based on their highest level of exposure to 11 substances including PQ. The other substances included 2,2′-bipyridyl, 2,4′-bipyridyl, 4,4′-bipyridyl, diglyme, pyridine, piperidine, methyl chloride, dimethyl sulfate, benzene and tarry by-products. Details were not provided in the published paper, and no analyses were reported that utilised the information. Approximately 300 of the 729 male workers were assessed to have had high or medium exposure to PQ. These included engineering maintenance workers on the MAG and LTS plants, and process operators and plant supervisors on all plants. At the time that the qualitative exposure assessment was performed in the mid-1980s, exposures to PQ on the LTS plant were stated to be much lower than during the 1960s, and any workers recruited after that time were unlikely to have experienced exposures to PQ that would have been categorised as high or medium. Exposure levels were not assessed for research staff, plant laboratory workers (day and shift) and technical administrative staff (day and shift), but their exposure was likely to have been low.
Statistical methods

The observed number of deaths from selected causes and groups of causes was compared with the expected number calculated on the basis of national and local age and period-specific mortalities. The standardised mortality ratio (SMR) was calculated as the ratio of the observed to the expected deaths, expressed as a percentage. OCMAP-PLUS was used to sum person-years within categories of age (5 year intervals) and calendar period (generally 5-year intervals to conform with changes in the ICD), and to compute SMRs and their 95% CIs. Female workers were not included in the SMR analyses because their numbers were small; however, their cause of death information was reviewed. Mortalities for England and Wales were used for comparison, and a comparison with local mortalities was made by combining information available between 1981 and 2008 for Halton Unitary Authority (where the plants were located) and the seven surrounding local districts. In local comparisons, mortalities for England and Wales were used for the time period 1960–1980.

Mortalities were also calculated for PD using all certified causes of death listed on the death certificate (conventionally termed ‘mentions’), as well as rates for PD as the underlying cause of death. Information on ‘mentions’ was available for the period 1993–2008, but it was not possible for the UK Office for National Statistics to supply such information before 1993. A conservative estimate of the number of deceased workers whose death certificate would be expected to mention PD was calculated using mortalities for PD as an underlying cause of death to 1992 and a mentioned cause of death after 1992.

Analyses were performed for the entire cohort and the subcohort of workers who had worked for a minimum of 3 months. Mortality owing to PD was also examined in the subcohort of workers who were assessed to have had a high or medium exposure in the original mortality investigation. Duration of employment and latency were treated as time-related variables with the values calculated for each person-year under observation. A subject was allowed to contribute to more than one stratum in each analysis.

RESULTS

Table 1 shows the plants where male subjects had worked. Over 40% had worked on the two earliest plants (HTS and MAG), and almost half had only worked on the LTS plant. A total of 118 workers were assessed to have held jobs that entailed high exposure to PQ, and a further 202 held jobs that entailed medium exposure to PQ. Table 2 shows the vital status of the cohort on 30 June 2009. A total of 10 workers (1.0%) had emigrated or joined the armed forces, and a further nine workers (1.0%) were lost to follow-up. The average age of male employees at first exposure was 32.8 years, and they contributed 28,963 person-years of follow-up.

Table 1 Plants where male subjects were employed

<table>
<thead>
<tr>
<th>Plants</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTS only</td>
<td>79 (8.5)</td>
</tr>
<tr>
<td>HTS and MAG</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>HTS, MAG and LTS</td>
<td>34 (3.8)</td>
</tr>
<tr>
<td>HTS and LTS</td>
<td>27 (2.9)</td>
</tr>
<tr>
<td>HTS, LTS and AC</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>MAG only</td>
<td>79 (8.5)</td>
</tr>
<tr>
<td>MAG and LTS</td>
<td>151 (15.9)</td>
</tr>
<tr>
<td>MAG, LTS and AC</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>LTS only</td>
<td>462 (49.9)</td>
</tr>
<tr>
<td>LTS and AC</td>
<td>75 (8.1)</td>
</tr>
<tr>
<td>AC only</td>
<td>11 (1.2)</td>
</tr>
<tr>
<td>Total</td>
<td>926 (100.0)</td>
</tr>
</tbody>
</table>

AC, ammonia cyanide; HTS, high-temperature sodium; LTS, low-temperature sodium; MAG, magnesium.

Table 2 Vital status on 30 June 2009

<table>
<thead>
<tr>
<th>Vital status</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>616</td>
<td>26</td>
</tr>
<tr>
<td>Dead</td>
<td>292</td>
<td>15</td>
</tr>
<tr>
<td>Emigrated or joined armed forces</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Person years of follow-up</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>926</td>
<td>42</td>
</tr>
</tbody>
</table>

statistic monitoring results had a mean of 0.0120 mg of PQ ion/m$^3$ (range $<$0.002–1.05 mg PQ ion/m$^3$), and the mean of the six personal monitoring results available for this period, all collected for workers in a single location during 1 month, was 0.022 mg PQ ion/m$^3$ (max 0.4 mg PQ ion/m$^3$). The geometric mean of 257 static monitoring results collected between 1987 and 1993 was 0.00328 mg PQ ion/m$^3$ (range $<$0.00012–0.044 mg PQ ion/m$^3$), and the geometric mean of the 94 personal monitoring results collected during the same time period was 0.00258 mg PQ ion/m$^3$ (range $<$0.0006–0.04 mg PQ ion/m$^3$).

Table 3 shows the SMRs for the major causes of death and those of initial interest. Local mortalities for PD were very similar to England and Wales mortalities, and only comparisons with mortalities for England and Wales are described in the text. There was only one death from PD as the underlying cause among male workers (1.8 expected), and the death certificate of this worker was the only one that mentioned PD. At least 3.3 death certificates of male workers would have been expected to have mentioned PD (SMR=31; 95% CI 1 to 171). None of the deceased workers in the high-PQ-exposure group had a death certificate that mentioned PD (0.5 expected mentions), but the one worker whose death certificate mentioned PD had held a job entailing medium exposure to PQ (1.1 expected mentions). None of the death certificates of the 15 deceased female workers...
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Table 3  Observed numbers of deaths and standardised mortality ratios (SMR) for selected causes of death among males

<table>
<thead>
<tr>
<th>International Classification of Diseases-9</th>
<th>Cause of death category</th>
<th>Observed</th>
<th>England &amp; Wales mortalities</th>
<th>Local mortalities†</th>
</tr>
</thead>
<tbody>
<tr>
<td>001–999</td>
<td>All causes of death</td>
<td>292</td>
<td>88* (78 to 98)</td>
<td>76** (68 to 86)</td>
</tr>
<tr>
<td>140–208</td>
<td>All malignant neoplasms</td>
<td>99</td>
<td>99 (81 to 121)</td>
<td>85 (69 to 104)</td>
</tr>
<tr>
<td>160–165</td>
<td>Respiratory system</td>
<td>30</td>
<td>91 (62 to 131)</td>
<td>72 (49 to 103)</td>
</tr>
<tr>
<td>162</td>
<td>Bronchus, trachea and lung</td>
<td>29</td>
<td>93 (62 to 133)</td>
<td>73 (49 to 105)</td>
</tr>
<tr>
<td>320–359</td>
<td>Neurological diseases</td>
<td>1</td>
<td>16* (0 to 88)</td>
<td>16* (0 to 88)</td>
</tr>
<tr>
<td>332.0</td>
<td>Parkinson’s disease</td>
<td>1</td>
<td>55 (1 to 309)</td>
<td>61 (2 to 340)</td>
</tr>
<tr>
<td>332.0</td>
<td>Parkinson’s disease (mentioned)†</td>
<td>1</td>
<td>31 (1 to 171)</td>
<td>32 (1 to 176)</td>
</tr>
<tr>
<td>390–398, 402, 404, 410–429</td>
<td>All heart disease</td>
<td>92</td>
<td>85 (68 to 104)</td>
<td>74** (60 to 91)</td>
</tr>
<tr>
<td>430–438</td>
<td>Cerebrovascular disease</td>
<td>22</td>
<td>89 (56 to 135)</td>
<td>80 (50 to 121)</td>
</tr>
<tr>
<td>460–519</td>
<td>Non-malignant respiratory disease</td>
<td>28</td>
<td>76 (50 to 109)</td>
<td>59** (39 to 85)</td>
</tr>
<tr>
<td>800–999</td>
<td>External causes of death</td>
<td>14</td>
<td>100 (55 to 168)</td>
<td>100 (55 to 168)</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01; SMR significantly different from 100.
†Halton Unitary Authority and the seven surrounding County and Unitary districts.

mentioned PD. Mortality from all neurological diseases (SMR=16, 1 death) was significantly lower than expected (p<0.05), and there were no mentions of secondary PD disease and other movement disorders, or other neurological diseases on the death certificates of male and female employees.

Compared with mortalities for England and Wales, deaths from all causes of death were significantly lower than expected (p<0.05), and deaths due to all cancers, heart disease, cerebrovascular disease and non-malignant respiratory disease were all lower than expected. A similar pattern was seen when comparisons were made with local mortalities, with deaths from all causes of death, heart disease and non-malignant respiratory disease all significantly lower than expected (p<0.01).

Lung-cancer mortality was also lower than expected, especially when compared with local mortalities (SMR=73; 95% CI 49 to 105).

In addition, to the 10 causes of death shown in table 3, comparisons with England and Wales mortalities were also made for a further 52 causes of death. Deaths from none of these causes of death were significantly higher than expected at a p=0.1 level, but deaths from cancer of the rectum and cancer of the colon were significantly lower than expected at this significance level. In total, there were two deaths from colorectal cancer (SMR=19; 95% CI 3 to 58). Mortality from nephritis and nephrosis was of interest because of the acute renal toxicity of PQ, but no deaths were observed (1.8 expected). Some workers were potentially exposed to benzene, but there was no increase in leukaemia mortality (SMR=91; 95% CI 9 to 272, 2 observed deaths) or mortality from lymphohaematopoietic cancers (SMR=81; 95% CI 30 to 177, 6 observed deaths).

Mortality patterns were also examined among the group of 320 workers who had ever held a job entailing high or medium exposure to PQ. Most of these workers started work on PQ production plants in the 1960s, and 159 of them had died by the end of the follow-up. Compared with local mortalities, the all-cause mortality was lower than expected (SMR=89; 95% CI 76 to 105), deaths due to malignant neoplasms were close to expected (SMR=103; 95% CI 78 to 135) among these workers, and there was no evidence of any trends with duration of exposure (<1 year, 1–5 years, >5 years).

**DISCUSSION**

This study has shown no evidence of increased mortality (underlying and mentioned cause) from PD among PQ production workers. Prior to this investigation, information about a possible association between PD and PQ was available from a small number of epidemiological studies, mainly studies which have used a case–control design. This is the first study of workers who manufactured PQ. A comprehensive review has recently been conducted of the studies specific to PQ and the risk of PD, and other studies which provide data on the issue of pesticide exposure and the risk of PD. The PQ-specific studies include one cohort study, eight case–control studies and a cross-sectional study. Another case–control study tested the gene–environment hypothesis that dopamine-transporter genetic variants alone and in combination with residential exposure to PQ and maneb increase susceptibility to PD. In general, information from the case–control and cross-sectional studies is limited, as most had small numbers of subjects exposed to PQ and poor exposure information, but three case–control studies provide some evidence of association and are discussed in more detail.
A small Canadian case-control study reported that out of 57 cases of PD and 122 controls, four cases versus none in the control group reported ever handling PQ. However, there was no evidence of an association in a later study conducted by the same group in the same region of Canada, and in which the investigators noted that they attempted to improve on their previous case-control study by including features designed to improve and control patient recall.

Another case-control study conducted in Taiwan with 120 cases and 240 controls reported a statistically significant OR of 3.22 for PQ use. In analyses adjusted for other potential risk factors, the ORs for 1 to 19 years of PQ use and 20 or more years of PQ use, as compared with no use of PQ, were 0.96 (95% CI 0.24 to 3.88) and 6.44 (95% CI 2.41 to 17.2), respectively. However, these findings did not differ greatly from those reported by the authors for herbicide/pesticide use. In addition, the authors did not define what they meant by PQ use and made no apparent attempt to differentiate between residential and occupational use, or incorporate information on time spent spraying each year. Hence, duration of use cannot be equated to dose.

A further study of 368 incident PD cases and 341 population controls from California reported that residential ambient exposure to both PQ and maneb increased PD risk by 75% (95% CI 1.13 to 2.73). The authors based their exposure estimates on Californian land-use maps and pesticide-use reports made for 1-square-mile tracts of land defined by the US Public Land Survey System. However, they could only infer that residential exposure to PQ had occurred, and it is clear that the specificity of their method is low, as indicated by the fact that over 60% of controls were presumed to have had residential exposure to PQ, even though they resided in counties with largely urban populations. The authors presumed that PQ had been used within 500 m of a subject’s home (residential exposure) if Californian land-use maps showed that a type of crop grown in a field within that distance of the house had been reported to have been treated by PQ in the Public Land Survey System section where the field was located. However, the reported application of PQ could have been carried out as far away as 2256 m (the length of the diagonal of a square-mile section) from the field of interest, which in itself might have been 500 m from the subject’s home. Although the bias is not differential, it will have resulted in much inflated statistical significance. Furthermore, the measure of residential exposure (a weighted sum of application rates) is not related to the amount of the pesticide applied in a zone around a residence. However, another group has used the same Californian data resources to derive an estimate of the amount of pesticide used, and this modification offers considerable potential for future epidemiology studies, especially if occupational exposure can be incorporated.

A prospective cohort study forming part of the US Agricultural Health Study includes 84 738 private pesticide applicators and their spouses recruited between 1993 and 1997, and followed up to 1999–2003. A total of 78 incident cases of PD were diagnosed during follow-up, and 11 of these had reported PQ use as part of the detailed information collected from participants during the recruitment phase on their personal lifetime pesticide use. The RR for incident PD was 1.0 (95% CI 0.5 to 1.9). A further 83 cases of PD were identified at recruitment (prevalent cases), and 14 reported PQ use. The RR for prevalent PD was 1.8 (95% CI 1.0 to 3.5). The authors were not able to explain the reason for differences in results for prevalent and incident cases, but the analysis based on prevalent PD is clearly more vulnerable to differential recall bias than that based on incident cases. Overall, greater weight can be given to the incident PD finding than risk estimates from the other PQ-specific studies because of the better quality of exposure information and the fact that it was collected before diagnosis.

The present study of workers engaged in the manufacture of PQ has the advantage of being a cohort study, with no potential for recall bias. In addition, comprehensive job histories enable workers with the highest potential for exposure to be identified, whereas most of the PQ-specific studies have no satisfactory information about the definition, duration and extent of exposure. A further strength of the study is the likely higher exposure of workers engaged in PQ production than many of the subjects in case-control studies classified as exposed to PQ. The geometric mean of the 94 personal monitoring results collected at Widnes between 1987 and 1993, although well below the UK occupational exposure limit of 0.08 mg/m3 (8 h TWA, respirable fraction), equates to a mean daily intake of 25.8 µg PQ ion (assuming 10 m3 of air breathed during a shift), and exposure levels were almost certainly higher during earlier years of production. In contrast, a recent study of PQ excreted over 24 h in the urine of Costa Rican farm workers who mixed, loaded or sprayed PQ reported a geometric mean urinary PQ level of 3.0 (GSD 3.07) µg/24 h on application days. Although these values cannot be directly equated, the predominant route of excretion is via urine, and the data are indicative that the exposure of a PQ production worker on a daily basis is at least comparable with that of a PQ sprayer. In addition, workers engaged in PQ production had the potential to be exposed daily, whereas workers employed as sprayers are unlikely to have sprayed PQ on a daily basis, and many subjects described as PQ users in case-control studies may have used PQ on an occasional basis only. Only one other study has assessed exposure using measurements of PQ excreted in the urine over 24 h, a more accurate representation of the amount absorbed on a daily basis than a urine spot sample. The investigators failed to detect urinary PQ in a group of Sri Lankan tea plantation workers, and Lee et al. noted...
there was also a low frequency of urinary PQ detection in studies utilising spot urine sampling, but this was likely to be related to a high limit of detection.

A perceived limitation of this study is that cases of PD are identified only if PD is a certified cause of death listed on their death certificate. However, although it is widely regarded that most patients with PD die of its complications and not the disease, the limited information available suggests that PD is coded as the underlying cause of death of many patients and is mentioned on the death certificates of the majority of patients. A UK study reported that PD was coded as the underlying cause of death of 63 (37%) of 171 people with idiopathic PD (108 men and 63 women) but was recorded in either part I or part II of the death certificates of 130 (76%),\textsuperscript{23} suggesting that few of the deceased workers in the present study are likely to have had PD which was not mentioned on their death certificates. There was no evidence that the likelihood of PD being a mentioned cause of death had changed during the study period (1966–1997), differed between the sexes or varied with age at death. Studies from Scandinavia and the USA have generally reported slightly lower instances of PD being a mentioned cause of death for individuals with PD, ranging from 55% to 70%.\textsuperscript{24–29}

The feasibility of conducting a morbidity study of the whole group was also considered. Living workers were on average almost 7 years younger than deceased workers (the average age at death of deceased workers was 69 years). It was also expected that the participation rate would not be high, as many had been enrolled in a surveillance scheme because of the skin lesion problem identified in the late 1970s, but only about a half still attended regularly. At best, a morbidity study was only expected to identify about twice as many cases of PD as a mortality study. However, a large comparison group would be required to estimate the background incidence rate and achieve any improvement in power. It was estimated that the mortality study would have 80% power to detect a 2.84 increase in risk (based on an estimate that four deceased workers would have a death certificate that mentioned PD). This is adequate power to detect the OR of 3.22 for PQ use reported by the Taiwanese investigation,\textsuperscript{15} and it was decided that performing a morbidity study would be not worthwhile unless the results of the mortality investigation indicated an increased risk of PD.

Another limitation of the study is that rates for mentions of PD on death certificates could be calculated only from 1993 onwards, and the analysis of mentions of PD had to use underlying cause of death rates before 1993. However, this resulted in an underestimate of the number of expected mentions of PD. Two UK studies provide some information about trends in mentions of PD on death certificates before 1993\textsuperscript{30} to\textsuperscript{31} and suggest that the age-standardised male mortality for mentions of PD was about 10% higher between 1985 and 1992 than between 1993 and 2000.\textsuperscript{31} Making this assumption, the expected number of mentions of PD on the death certificates of workers in the cohort is increased from 3.3 to 3.5. This latter figure includes 0.13 expected deaths due to PD before 1985 and suggests that the true expected number of PD mentions over the study period is between 3.6 and 3.7, as the expected number of death certificates of workers with PD as a mentioned cause for the period of follow-up 1985–2009 is approximately twice the number of expected deaths with PD as the underlying cause.

A full quantitative exposure assessment was not conducted. No quantitative information about PQ exposure was available before 1979, but the report of the qualitative exposure assessment performed in the mid-1980s noted that exposures to PQ on the LTS plant were much lower then than during the 1960s. Static monitoring results collected between 1987 and 1993 varied little between sampling locations but were about three times lower on average than those collected between 1979 and 1986. Hence, it seems likely that PQ exposure levels continued to fall between 1979 and 1993, even though location information was not available for samples collected between 1979 and 1993. In the case of PD, the absence of additional quantitative exposure information was not a limitation, as there was only one mention of PD on the death certificates of deceased workers. The worker who died of PD was assessed as having medium exposure to PQ.

Lung cancer was also of interest because the initial investigation reported a modest excess (13 observed, 10.5 expected deaths).\textsuperscript{7} However, there was no evidence of an excess of lung cancer in the update, especially when compared with local mortalities (SMR=73; 95% CI 49 to 105). Paddle \textit{et al}\textsuperscript{7} noted that the excess in their study was concentrated in the period of follow-up 15 years or more after first exposure. The excess appears to have been confined to a small group of HTS/MAG process workers with <1 year of exposure, and restricted to the period 15–30 years after first exposure. There was a small, but non-significant excess among these short-term workers (4 observed, 1.3 expected based on local rates), but no new lung cancer deaths had occurred during the additional period of follow-up. There was no excess of lung-cancer deaths among HTS/MAG process workers with longer periods of exposure. Other investigations have reported increased mortality from lung cancer among short-term workers,\textsuperscript{32} and the excess is unlikely to be related to occupation.

In conclusion, there was no evidence of an increased incidence of PD among PQ production workers based on mentions of PD on the death certificates of workers who had died. In addition, there was no evidence of adverse mortality due to other causes including lung cancer mortality.

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Correction notice The “To cite: …” information and running footer in this article have been updated with the correct volume number (volume 1).

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Competing interests Both authors have completed the ICMJE uniform disclosure form at www.icmje.org/coiDisclosure.pdf (available on request from the corresponding author) and declare: JAT had financial support from Syngenta for the submitted work; CC is employed by Syngenta; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval Ethics approval was provided by the British Medical Association Ethical Committee.

Contributors JAT and CC conceived and designed the study. JAT wrote the protocol, supervised the acquisition of data, performed the data analyses and interpreted the results. Both authors contributed to drafting of the manuscript, critically reviewed the manuscript for important intellectual content and approved the final version of the paper.

Provenance and peer review Not commissioned; externally peer reviewed.

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