



Systematic review and meta-analysis of mortality in crop protection product manufacturing workers

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ABSTRACT

Objectives: The potential health effects of the manufacture and use of crop protection chemicals were investigated through systematic review and meta-analysis of studies of cohorts of workers in the crop protection product manufacturing industry.

Methods: Several computerised literature databases were searched from inception until December 2003, with references listed in identified articles checked for further relevant articles. Random effects meta-analyses of log standardised mortality ratios (SMRs) were carried out. Heterogeneity was explored through subgroup analyses and meta-regression; sensitivity analyses of different approaches for zero events were performed.

Results: 21 references reporting information on 37 separate cohorts for mortality were identified. The meta-SMR for all cause mortality was 0.94 (95% CI 0.88 to 1.00) (37 cohorts). Significantly raised mortality was found for cancers of the buccal cavity and pharynx, oesophagus, rectum, larynx, lung, and lymphatic and haematopoietic system with little heterogeneity being observed. Excluding studies with zero events identified additional excesses.

Conclusions: Evidence of multiple excesses, particularly in subgroups exposed to phenoxy herbicides contaminated with dioxins, substantiates previous findings. The importance of careful treatment of zero cases was highlighted. Future systematic reviews and meta-analyses would benefit from availability of results for a standard list of causes of disease.

The manufacture and use of crop protection chemicals and pesticides in general and their potential effects on humans are an area of public concern. Phenoxy herbicides, chlorophenols and their contaminants, particularly dioxins, have been the subject of several publications, some of which have included the results from a large international register set up by the International Agency for Research on Cancer (IARC) of cohorts of workers involved in manufacture and spraying.^{1,2} These have highlighted excess risks for all neoplasms, cancers of the lung, other respiratory organs and other endocrine organs, and soft tissue sarcoma.

An evaluation of 461 epidemiological studies of mortality and cancer incidence in chemical industry workers published from 1966 to 1997, including those from the crop protection sector, was carried out by Greenberg *et al*³ and included a meta-analysis of 185 cohort studies of chemical workers in the USA or Western Europe whose employers qualified for membership of the American Chemistry Council (ACC). Greenberg *et al* reported mortality below the expected level for all causes, cardiovascular disease, non-cancer respiratory

disease, cirrhosis of the liver, and external causes. Mortality was consistently raised only for deaths from cancers of the bladder, the lymphatic/haematopoietic system and the bronchus, trachea and lung. The meta-analysis of Greenberg *et al* did not carry out separate analyses by industry subsector and issues such as heterogeneity and publication bias were not addressed. Here we seek to address these limitations as well as to update the set of primary studies considered. We present results specific to the crop protection sector, and focus on evaluation of heterogeneity and publication bias and on the handling of zero events. Since the pesticides manufacturing sector encompasses a variety of potential exposures, in addition to the main analyses seeking sector-wide estimates of risk, we include separate analyses for phenoxy herbicide manufacturing; available data were, however, generally too limited to allow specific analyses in other subsets of the sector. A supplementary document providing further details includes figures and tables prefixed with "S".

METHODS

The methodology has been described in more detail elsewhere.⁴ Briefly, we developed literature search strategies using relevant crop protection references from an existing ACC database of papers published between 1966 and 1997 on health effects in cohort studies of chemical workers in the USA or Western Europe used by Greenberg *et al* (see appendix A of the supplementary material). Searches of Medline, Toxfile, Cancerlit, EMBASE, CA Search, BIOSIS previews, SciSearch, Pascal and the National Technical Information Service (NTIS) were conducted between January and May 2004 for papers published worldwide in English between 1966 and December 2003. Potentially relevant references were identified by examining the title and abstracts and also the references lists of identified papers. Any bias due to omission of papers in languages other than English may be expected to be small but positive.⁵

We included cohort studies of workers employed in crop protection manufacture where results were reported in the form of standardised mortality ratios (SMR) and/or standardised incidence ratios (SIR) based on an external comparison group (or data allowing such outcomes to be derived). The most recent data on as many outcomes as available were extracted in order to calculate the SMRs or SIRs, together with associated standard errors for the log_e(SMR) and/or log_e(SIR). The data were usually from the most recently published reference for each cohort, but included some drawn from earlier papers if results for a particular outcome

were not reported in the latest publication. Causes of death and sites of cancer were coded according to the International Classification of Diseases, ninth revision (ICD-9); we recoded if earlier ICD versions had been used.

Data on the following cohort/study characteristics were also extracted where available in each publication: the dates when the study was carried out, inclusion and exclusion criteria, the comparison population, the percentage of the cohort that was male, the average age of the cohort, the average duration of employment, the country and geographical area of the cohort, study sponsorship, author affiliation(s), study design, industry sector, chemicals produced and used, industry processes, and study quality. A modified version of the Newcastle-Ottawa scale for assessing the quality of observational studies (see www.ohri.ca/programs/clinical_epidemiology/oxford.htm) was developed (see appendix B of the supplement).

Methods for quantitative synthesis

Overall pooled estimates of the SMR and SIR, denoted meta-SMR and meta-SIR respectively, together with associated 95% confidence intervals (CI) were obtained using random effect meta-analysis methods.⁶ A test for heterogeneity between study results was performed. Meta-regression techniques⁷ and subgroup analysis were used to explore the influence of cohort and study characteristics (including study quality) listed above on heterogeneity where data were sufficient. No formal correction for multiple comparisons was made, but due regard was given to broader patterns in interpreting individual results. In particular, cause-specific analyses were divided into two groups for interpretation: (i) those seeking confirmation or otherwise of the general Greenberg results in the crop protection sector (summarised above and indicated in more detail in table S3) and (ii) those estimating effects in diseases identified as of interest in this sector in earlier primary studies or reviews.

For studies in which there were zero observed and/or expected events, one was added to both the observed and expected events so that estimates of the $\log_e(\text{SMR})/\log_e(\text{SIR})$ and associated standard errors could be obtained. Sensitivity analyses to this approach were undertaken in which either (i) studies with zero observed events and/or expected events less than 0.001 were excluded from the analysis or (ii) the observed number of events was set equal to the expected number of events, and in the case when the expected number of events was zero the value assumed was 0.001. The influence of individual studies on the overall meta-SMR (or meta-SIR) was assessed by re-estimation of the overall effect omitting each study in turn. Publication bias was also assessed graphically by means of a funnel plot, and by using Egger's test.⁸

A subgroup of cohorts of workers involved in the manufacture of phenoxy herbicides was identified a priori for separate subgroup analyses.

The analyses were carried out in Stata 8.2 using a combination of available⁹ and specifically developed macros.

RESULTS OF THE LITERATURE SEARCH

Forty three references were available from the original ACC database. Five of these were excluded from the meta-analyses because of lack of results or because of study design considerations. A further 17 papers were identified in the search update giving a total of 55 papers. From these papers, 21 were identified as including relevant primary data and giving the most recent results (see references M1–M21 in box 1); data for 37 separate cohorts were identified for the mortality analyses and for five

for the incidence analyses (although for two of the latter results were only given for one cancer). Results are not presented for cancer incidence because of the small number of papers; more detail is presented in the supplementary material.

As mentioned above, a large international study of phenoxy herbicide and chlorophenol production and spraying workers from different countries and plants is being co-ordinated by the IARC. Initial analyses published in 1991¹ included 20 cohorts and a second publication in 1997² of updated results included the same 20 cohorts together with an additional 16 cohorts (four from Germany and 12 from the USA). We were able to obtain an unpublished report (see M10 in box 1) that gave separate results for each of the 20 cohorts from the first IARC analysis and thus enabled us to exclude four cohorts of sprayers from our meta-analysis. From this report we extracted data for 15 production cohorts (table 1, IARC (1)–IARC (15)); we extracted more recent results for one production cohort from the Netherlands from a separate publication (see M9 in box 1). We were unable to obtain updated results for any of the 36 individual cohorts in the second IARC publication.² However, separate results were available for the four German cohorts from two publications (see M3 (Becher (1) – (3)) and M8 in box 1), but not for the 12 US production worker cohorts which were therefore excluded from our meta-analysis although they were included in the IARC pooled results.²

Table 1 indicates which papers relate to each cohort, together with a summary of the characteristics of the populations studied. (Each paper is described in detail in appendix C of the supplement, and earlier and related papers, including nested case-control studies, are also listed.)

Studies have been carried out in the USA, several European countries, New Zealand and China and included fewer than 100 subjects to over 4000. Fourteen of the mortality cohorts included women, although in most women were a small proportion of the total. Twenty of the cohorts were workers involved in phenoxy herbicide manufacture. Other cohorts were exposed to a wide range of substances including organochlorines, organophosphates, pentachlorophenol, arsenicals and triazine herbicides.

RESULTS OF THE QUANTITATIVE SYNTHESIS

Table 2 and fig 1 give the meta-SMR estimates for each outcome. (The outcome data from each specific study that contributes to each meta-SMR are available on request.) Although the number of papers reporting data varied by cause, most were based on over 20 cohorts and many on over 30 (see tables S1 and S2 for detailed reporting patterns). Meta-analysis results for the incidence data are not considered further here because of the very limited numbers of primary studies in which such data were reported, but the principal results are shown in appendix D of the supplementary material.

Mortality from all causes of death was low and there was a significant decrease for cardiovascular disease (meta-SMR 0.91 (95% CI 0.84 to 0.99), based on 35 studies). The meta-SMRs for other non-malignant causes of death varied around 1. The meta-SMRs for many of the cancer groups were raised; significant excesses were found for cancers of the buccal cavity and pharynx (meta-SMR 1.42 (95% CI 1.01 to 2.00), 28 studies), oesophagus (meta-SMR 1.64 (95% CI 1.20 to 2.24), 26 studies), rectum (meta-SMR 1.37 (95% CI 1.07 to 1.76), 28 studies), respiratory system (meta-SMR 1.26 (95% CI 1.09 to 1.45), 36 studies), larynx (meta-SMR 1.58 (95% CI 1.09 to 2.31), 23 studies), lung (meta-SMR 1.22 (95% CI 1.05 to 1.41), 32 studies), lymphoma (meta-SMR 1.98 (95% CI 1.45 to 2.69), 26

Table 1 Characteristics of each cohort

Paper	Mortality (M)/cancer incidence (CI)	Country	Number of subjects	% Males	% White	Employed during	End of follow-up	Occupational setting	Major chemicals used or produced
Acquavella (1996)	M	USA	1036	81	100	1961–93	1993	Acetanilide herbicide manufacture	Alachlor
Amaateng-Adjepong (1995)	CI	USA	1025	81	100	1969–93	1993	Pesticide manufacturing	Organochlorines (aldrin, dieldrin, endrin) Organophosphates (azodrin, vapona) Dibromochloropropane
	M		2384	90	97	1952–82	1991		
Becher (1996)*	M	Germany				1952–89	1989	Phenoxy herbicides; chlorophenol	
(1)			135	100	NS†			Bayer Uerdingen plant	2,4,5-TCP
(2)			520	100	NS			Bayer Dormagen plant	2,4-D; 2,4-DP; 2,4,-DCP; 2,4,5-T; 2,4,5-TP; MCPA; MCPP
(3)			680	100	NS			BASF Ludwigshafen plant	2,4,-D; 2,4-DP; 2,4,5-T; MCPA; MCDP
Brown (1992)	M	USA				1965–87	1987	Organochlorine pesticides	
(1)			405	100	100			Illinois plant	Chlordane
(2)			305	100	100			Tennessee plant	Heptachlor; endrin
(3)			328	100	100			California plant	DDT
Burns (2001)	M	USA	1517	100	NS	1945–94	1994	Manufacture, formulation or packing of 2,4-D	2,4-D; 2,4,5-T; MCPA; Silvex
Cheng (1993)‡	M	China	144	NS§	0	1974–90	1990	Pentachlorophenol production	Pentachlorophenol; PCDD; PCDF
De Jong (1991)¶	CI	Netherlands	434	NS	NS	1979–90	1990	Organochlorine insecticide manufacture	Aldrin; dieldrin; endrin; telodrin
Flesch-Janys (1998)*	M	Germany	1189	100	100	1952–92	1992	Boehringer Ingleheim phenoxy herbicide plant	PCDDs; PCDFs
Hooiveld (1998)**	M	Netherlands	1156	92	NS	1955–85	1991	Phenoxy herbicide manufacture	Chlorophenoxy herbicides; 2,4,5-trichlorophenoxy acetic acid; TCCD; PCDD
IARC (1992)†† (1)	M	Austria	128	98	NS	1971–87	1987	Phenoxy herbicide manufacture	2,4,D; MCPA; 2,4,5-T; 2,4,5-TCP; 2,4,5-TCP; PCDD; TCDD
IARC (1992) (2)	M	Denmark	3833	79	NS	1947–81	1982	Phenoxy herbicide manufacture	2,4,D; MCPA; 2,4,5-T; 2,4-DP; MCPP
IARC (1992) (3)	M	Denmark	614	60	NS	1951–81	1981	Phenoxy herbicide manufacture	MCPA; 2,4-DP
IARC (1992) (4)	M	Finland	58	53	NS	1939–84	1985	Phenoxy herbicide manufacture	2,3,4,6-TCP
IARC (1992) (5)	M	Italy	325	93	NS	1970–76	1986	Phenoxy herbicide manufacture	2,4,5-TCP
IARC (1992) (6)	M	Italy	81	51	NS	1967–84	1986	Phenoxy herbicide manufacture	2,4-D; MCPA
IARC (1992) (7)	M	Netherlands	1142	92	NS	1965–86	1986	Phenoxy herbicide manufacture	2,4-D; 2,4-DP; MCPA; MCPP
IARC (1992) (8)	M	New Zealand	1026	92	NS	1969–84	1987	Phenoxy herbicide manufacture	2,4,5-T; 2,4-D; MCPA; 2,4,5-TCP; 2,4,6-TCP
IARC (1992) (9)	M	Sweden	269	84	NS	1965–78	1986	Phenoxy herbicide manufacture	2,4,5-T; 2,4-D; 2,4-DP; MCPA; MCPP; DCP; 2,4,5-TCP; 2,4,6-TCP
IARC (1992) (10)	M	UK	1474	100	NS	1947–75	1987	Phenoxy herbicide manufacture	2,4-D; 2,4-DB; MCPA; MCPB; MCPP; 2,4-DP
IARC (1992) (11)	M	UK	145	100	NS	1949–81	1985	Phenoxy herbicide manufacture	PCP
IARC (1992) (12)	M	UK	1140	100	NS	1975–85	1987	Phenoxy herbicide manufacture	2,4,5-T; 2,4,5-TP; 2,4-D; 2,4-DB; 2,4-DP; MCPA; MCPB; PCPP
IARC (1992) (13)	M	UK	271	100	NS	1969–85	1987	Phenoxy herbicide manufacture	2,4-D; 2,4-DB; 2,4-DP; MCPA; MCPB; MCPP
IARC (1992) (14)	M	UK	345	100	NS	1963–84‡‡	1987	Phenoxy herbicide manufacture	2,4-D; MCPB
IARC (1992) (15)	M	UK	485	100	NS	1969–85	1987	Phenoxy herbicide manufacture	2,4,5-T; 2,4-D; 2,4,5-DP; MCPA; MCPP
Lynge (1985)	CI	Denmark	4459	76	NS	Plant 1: 1933–81; plant 2: 1951–81	1982	Phenoxy herbicide production	2,4-D; MCPA; 2,4,5-T; 2,4-DP; MCPP

Continued

Table 1 Continued

Paper	Mortality (M)/cancer incidence (CI)	Country	Number of subjects	% Males	% White	Employed during	End of follow-up	Occupational setting	Major chemicals used or produced
Mabuchi (1980)	M	USA	1393	75	NS	1946–77	1977	Pesticide manufacture	Arsenical pesticides; arsenic acid; lead arsenate
MacLennan (2002)	CI	USA	2045	90	68	1985–92	1997	Triazine herbicide manufacture	Altrazine; chlordimeform
MacLennan (2003)	M	USA	2213	91	67	1970–97	1997	Triazine herbicide manufacture	Altrazine
Olsen (1995)	M	USA	509	100	NS	1957–77	1989	Exposure to DBCP	DBCP
Ott (1980) (1)	M	USA	99	100	NS	1942–69	1976	EDP manufacturing unit	Ethylene dibromide (EDP); bromine; ethylene; sulphur dioxide; chlorine
Ott (1980) (2)	M	USA	57	100	NS	1920–76	1976	EDP manufacturing unit	EDB; bromine; ethylene; hydrogen; iodine; ammonia; silica; copper; vinyl bromide; acetate; nickel acetate
Popp (1992)§§	CI	Germany	49	100	NS	1965–86	1990	Synthesis of chlordimeform	4-Chloro-o-toluidine
Ramlow (1996)	M	USA	770	100	95	1940–89	1989	Workers exposed to PCDDs	PCDD; trichlorophenol; 2,4,5 trichlorophenoxyacetic acid; pentachlorophenol; other chlorophenols
Rapiti (1997)	M	Italy	505	100	NS	1952–70	1991	Multiple chemical production including organic chemicals and insecticides	Acid mists; detergents; organochlorines; organophosphates; phthalic anhydride; maleic anhydride
Sobel (1988)	M	USA	611	100	NS	1919–56	1982	Arsenic-containing insecticide manufacture	Lead arsenate; copper arsenate; calcium arsenate; copper acetoarsenate; magnesium arsenate
Swaen (2002)	M	Netherlands	570	100	NS	1954–70	2000	Insecticide production	Aldrin; dieldrin
Thiess (1981)	M	Germany	602	NS	NS	1928–80	1980	Alkylene oxide production	Ethylene oxide; propylene oxide; other alkylene oxides; butylenes oxide; dioxane; epichlorohydrin; dichloropropane; ethylene chlorohydrin; propylene chlorohydrin

*Included in IARC pooled analysis by Kogevinas *et al* 1997 (2); †non-German workers were excluded; ‡data only available for all causes of death; §not stated but probably all male; ¶data only available for all malignant neoplasms; **included in IARC pooled analyses (1) and (2); ††internal report relating to IARC (1991) (1) giving separate results for each cohort; ‡‡1982–84 formulators and packers; 1967–84 handymen; 1963–84 process workers; §§data only available for cancer of the bladder. NS, not stated.

studies) and lymphatic and haematopoietic system (meta-SMR 1.34 (95% CI 1.12 to 1.60), 28 studies). Forest plots showing the effect sizes from the individual studies for all causes, all malignant neoplasms and the outcomes listed above are provided in fig S1. As all but three of the studies included males and the proportion of females in the 14 mixed cohorts was small, the results for males were very similar to those for the total crop protection sector, including the significant excesses. Only all respiratory cancer (meta-SMR 2.49 (95% CI 1.34 to 4.44)) and lung cancer (meta-SMR 2.49 (95% CI 1.37 to 4.53)) were significantly raised for females, based on 13 studies. Full results for males and females are given in table S3.

Between study heterogeneity

Table 2 also gives the between study variance and heterogeneity for each cause. Apart from all malignant neoplasms, all respiratory cancer and lung cancer, there was little evidence of heterogeneity among the cancers. However, heterogeneity was present for all causes of death, cardiovascular disease and several other non-malignant diseases. A few specific studies contributed to this heterogeneity, as illustrated by the outlying points in the Galbraith plot for all cause mortality given in fig S2.

The covariates listed in the Methods section were explored as potential sources of heterogeneity using subgroup analyses and

meta-regression, where sufficient data were available. Meta-regression showed negative associations for all cause mortality for the male proportion of the cohort and for the mid-cohort year, and a positive association with a marker of the proportion of the cohort lost to follow-up. Similar results were found for the male proportion of the cohort for mortality from lung cancer and cardiovascular disease, with maximum length of follow-up also significantly negatively associated for both diseases and the proportion lost to follow-up indicator positively associated for lung cancer. More detailed results are given in table S4 and fig S3.

Influence of individual studies

The studies contributing to heterogeneity also appeared to have an influence on the meta-analysed results. Figure 2 shows, for all causes of death, the investigation of the influence of individual studies (via systematic “leave one out” exclusion). Some of the studies appearing to contribute to heterogeneity also influence the meta-SMR (eg, Mabuchi (1980), Hooiveld (1998), IARC (1992) (12), MacLennan (2003), Becher (1996) (2) and Swaen (2002)). These studies had a tendency to influence other mortality outcomes also, in particular all malignant neoplasms, cancer of the lung, skin and kidney, and cardiovascular disease.

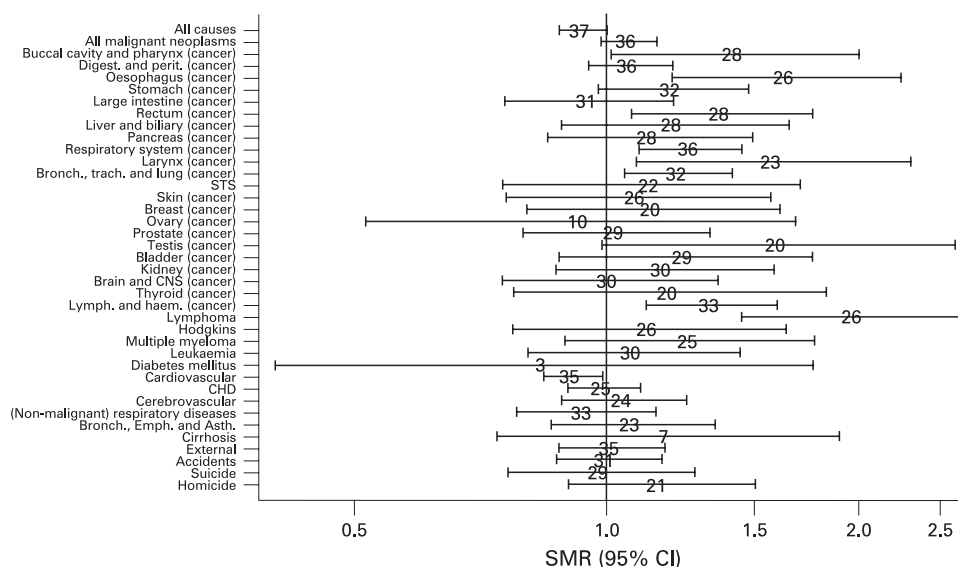


Figure 1 Random effects pooled mortality estimates with 95% confidence intervals for all cohorts. The numbers located at each point estimate show the number of studies reporting that disease. Asth., asthma; Bronch., bronchus/itis; CHD, coronary heart disease; CNS, central nervous system; Digest., digestive organs; Emph., emphysema; haem., haematopoietic cancer; Lymph., lymphatic cancer; perit., peritoneum; SMR, standardised mortality ratio; STS, soft tissue sarcoma; trach., trachea.

Assessment of publication bias

For the total cohort and males, there was evidence of publication bias from plots and statistical tests for many cancers (buccal cavity and pharynx, liver, larynx, skin, prostate, kidney, brain, lymphatic and haematopoietic, lymphoma, multiple myeloma and leukaemia) and some non-malignant diseases (external causes, suicide and homicide), with excess mortality tending to be found in larger studies and smaller studies having reduced effects. Figure S4 illustrates this with a funnel plot for lymphatic and haematopoietic cancer. For females there was evidence of publication bias for all malignant neoplasms, breast cancer, cardiovascular disease, non-malignant respiratory disease, bronchitis, emphysema and asthma, external causes and homicide.

Zero cases

As we were able to obtain detailed results on many causes of death from many separate cohorts in this industry sector, an investigation of the influence of approaches to handling zero cases was carried out. Table 3 gives results for selected causes of death; fuller results are given in appendix E of the supplementary materials. In general, both excluding studies for which observed cases are zero and/or expected cases are approximately zero, and setting observed equal to expected values in those studies (as an example of a simple imputation approach) result in an increase in meta-SMRs and a widening of the confidence intervals compared to our default method of adding 1 to both observed and expected values.

Phenoxy herbicide workers

Separate analyses were carried out for the 20 crop protection cohorts where workers had been potentially exposed to phenoxy herbicides. As can be seen from table 2, qualitatively very similar results to the total cohort analysis were found, with statistically significantly raised meta-SMRs for cancers of the oesophagus, respiratory system, larynx and lung, lymphatic and haematopoietic cancer and lymphoma, although the power of

the test is limited. Cancers of the buccal cavity and pharynx and rectum, and external causes, accidents and homicide were non-significantly raised. Patterns for males and females separately and for heterogeneity were also qualitatively similar to those of all the total cohorts (see table S3).

DISCUSSION

The meta-analyses reported here extend and update the earlier study by Greenberg *et al* of chemical industry workers, and allow more specific assessment of risks in the pesticide manufacturing sector. Although this meta-analysis found an overall deficit from all causes of death, only one non-malignant cause of death was significantly decreased (cardiovascular disease) and many of the results for non-malignant diseases were slightly raised. Hence, here the evidence of a healthy worker effect¹⁰ is more equivocal than in many other analyses of occupational workers, including the rubber sector of chemical manufacturing.⁴ Several of the meta-SMRs for malignant disease were significantly raised, including cancers of the buccal cavity and pharynx, oesophagus, rectum, larynx and lung, and lymphoma and lymphatic leukaemias overall. Similar patterns were found when analyses were restricted to cohorts of workers exposed to phenoxy herbicides, although the magnitude of the effect estimates varied. There was marked lack of a healthy worker effect in the phenoxy herbicide cohorts.

Table 1 highlights the fact that the workers investigated in these studies could potentially have been exposed to a wide range of pesticides, for example phenoxy herbicides, organochlorines, organophosphates, acetanilide herbicides, triazinine herbicides and arsenical pesticides and many different chemicals within these broad groups, all having potentially different toxic effects. The primary studies generally suffer from a lack of exposure assessment to specific substances; broad classes of chemicals or pesticides are most often used in analysis. A recent narrative review¹¹ of studies in pesticide manufacturing noted similar problems. The potential for carrying out meta-analyses for specific chemicals and for exposure-response relationships was thus limited.

Table 2 Results for mortality meta-analyses using random effects models

Mortality outcome*	Total cohorts				Phenoxy herbicide cohorts			
	Pooled estimate (95% CI)	No. of studies	Between study variance	Test for heterogeneity p value	Pooled estimate (95% CI)	No. of studies	Between study variance	Test for heterogeneity p value
All-cause	0.94 (0.881 to 1.002)	37	0.022	<0.001	1.00 (0.902 to 1.105)	20	0.028	<0.001
All malignant neoplasms	1.06 (0.986 to 1.149)	36	0.013	0.055	1.10 (0.986 to 1.228)	20	0.011	0.187
Buccal cavity and pharynx (Ca)	1.42 (1.014 to 1.999)	28	0.101	0.279	1.48 (0.942 to 2.309)	20	0.248	0.149
Digestive organs and peritoneum (Ca)	1.07 (0.952 to 1.199)	36	0.002	0.437	1.05 (0.892 to 1.230)	20	<0.001	0.565
Oesophagus (Ca)	1.64 (1.198 to 2.244)	26	<0.001	0.792	1.57 (1.088 to 2.253)	20	<0.001	0.755
Stomach (Ca)	1.2 (0.979 to 1.476)	32	<0.001	0.597	1.07 (0.821 to 1.392)	20	<0.001	0.932
Lower intestine (Ca)	0.95 (0.758 to 1.202)	31	<0.001	0.990	0.90 (0.646 to 1.265)	20	<0.001	0.977
Rectum (Ca)	1.37 (1.071 to 1.762)	28	<0.001	0.788	1.34 (0.959 to 1.861)	20	<0.001	0.875
Liver and biliary passage (Ca)	1.21 (0.883 to 1.654)	28	<0.001	0.930	0.85 (0.566 to 1.283)	20	<0.001	1.000
Pancreas (Ca)	1.13 (0.85 to 1.497)	28	<0.001	0.931	1.23 (0.864 to 1.748)	20	<0.001	0.735
Respiratory system (Ca)	1.26 (1.093 to 1.45)	36	0.065	0.003	1.34 (1.128 to 1.596)	20	0.029	0.191
Larynx (Ca)	1.58 (1.086 to 2.31)	23	<0.001	0.710	1.51 (1.006 to 2.278)	20	<0.001	0.667
Bronchus, trachea and lung (Ca)	1.22 (1.054 to 1.414)	32	0.051	0.030	1.28 (1.076 to 1.518)	20	0.022	0.252
STS	1.13 (0.752 to 1.703)	22	<0.001	0.995	0.96 (0.621 to 1.492)	20	<0.001	1.000
Skin (Ca)	1.09 (0.759 to 1.572)	26	<0.001	0.996	0.91 (0.596 to 1.402)	20	<0.001	1.000
Breast (Ca)	1.14 (0.805 to 1.61)	20	<0.001	0.887	1.29 (0.893 to 1.849)	17	<0.001	0.987
Ovarian (Ca)	0.93 (0.516 to 1.681)	10	<0.001	1.000	0.93 (0.516 to 1.681)	10	<0.001	1.000
Prostate (Ca)	1.03 (0.796 to 1.327)	29	<0.001	0.979	1.16 (0.851 to 1.57)	20	<0.001	0.998
Testis (Ca)	1.61 (0.989 to 2.614)	20	0.270	0.182	1.72 (0.936 to 3.157)	16	0.553	0.078
Bladder (Ca)	1.24 (0.878 to 1.761)	29	0.177	0.167	1.18 (0.777 to 1.793)	20	0.136	0.264
Kidney (Ca)	1.17 (0.871 to 1.583)	30	<0.001	0.758	1.22 (0.844 to 1.771)	20	<0.001	0.863
Brain and CNS (Ca)	1.01 (0.751 to 1.356)	30	<0.001	0.989	0.93 (0.638 to 1.358)	20	<0.001	1.000
Thyroid (Ca)	1.19 (0.777 to 1.827)	20	<0.001	0.919	1.24 (0.780 to 1.966)	17	<0.001	0.812
Lymphatic and haematopoietic (Ca)	1.34 (1.117 to 1.597)	33	<0.001	0.995	1.42 (1.086 to 1.852)	20	<0.001	0.921
Lymphoma (Ca)	1.98 (1.451 to 2.692)	26	0.079	0.278	2.01 (1.377 to 2.927)	20	0.077	0.322
Hodgkin's disease (Ca)	1.13 (0.772 to 1.642)	26	<0.001	0.962	1.15 (0.742 to 1.783)	20	<0.001	0.886
Multiple myeloma (Ca)	1.26 (0.894 to 1.769)	25	<0.001	0.994	1.24 (0.822 to 1.862)	20	<0.001	0.989
Leukaemia (Ca)	1.08 (0.805 to 1.444)	30	<0.001	1.000	1.02 (0.707 to 1.463)	20	<0.001	1.000
Diabetes mellitus	0.84 (0.402 to 1.77)	3	<0.001	0.558				
Cardiovascular disease	0.91 (0.842 to 0.991)	35	0.023	<0.001	0.99 (0.869 to 1.121)	20	0.033	0.003
Coronary heart disease	0.99 (0.9 to 1.097)	25	0.018	0.038	1.08 (0.931 to 1.244)	17	0.031	0.027
Cerebrovascular disease	1.05 (0.885 to 1.246)	24	0.031	0.198	0.90 (0.743 to 1.080)	17	<0.001	0.762
Respiratory disease (non-ca)	0.95 (0.781 to 1.146)	33	0.110	0.004	0.91 (0.681 to 1.211)	20	0.136	0.031
Bronchitis, emphysema and asthma	1.08 (0.859 to 1.351)	23	<0.001	0.870	1.06 (0.814 to 1.381)	16	<0.001	0.799
Cirrhosis	1.19 (0.742 to 1.899)	7	0.188	0.052				
External causes	1.02 (0.879 to 1.174)	35	0.065	0.002	1.22 (0.999 to 1.484)	20	0.049	0.088
Accidents	1.01 (0.873 to 1.164)	31	<0.001	0.964	1.17 (0.906 to 1.516)	20	<0.001	0.993
Suicide	0.99 (0.765 to 1.275)	29	0.127	0.046	1.21 (0.882 to 1.671)	20	0.120	0.102
Homicide	1.16 (0.898 to 1.505)	21	0.103	0.065	1.30 (0.984 to 1.720)	16	0.069	0.171

Ca, cancer; STS, soft tissue sarcoma.

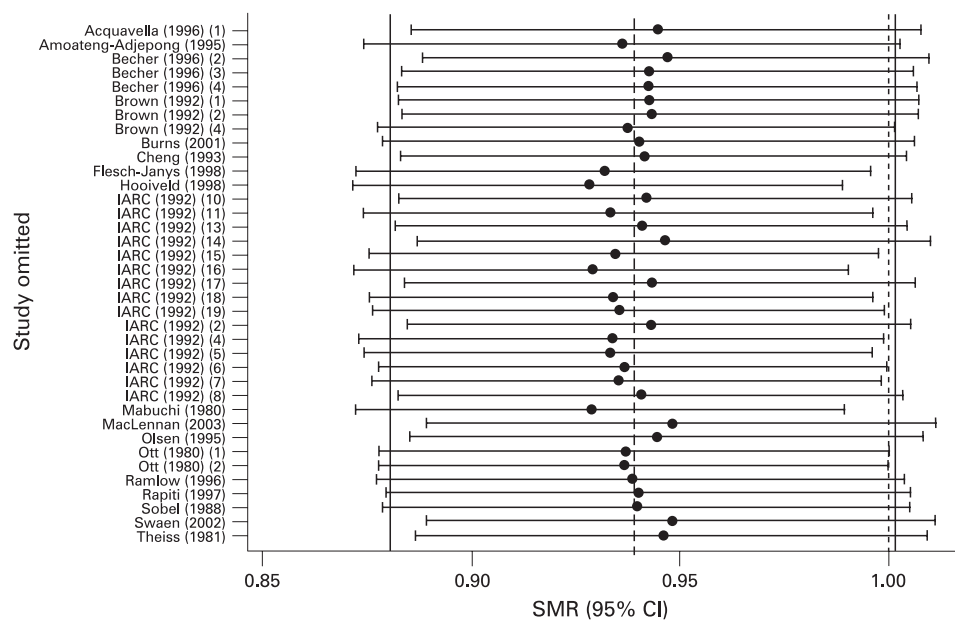
Phenoxy herbicides have been used extensively as weed killers and for defoliation worldwide. One of the major concerns about their toxicity relates to their potential contaminations with dioxins, particularly 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Workers exposed to them have consistently been shown to be at increased risk for all cancers and for specific neoplasms such as lung cancer, soft tissue sarcoma and non-Hodgkin's lymphoma.¹² In the multinational study of 36 cohorts of sprayers and production workers, subjects were classified as exposed to phenoxy herbicides or chlorophenol with or without exposure to dioxins.² Significant excesses were found in the total cohort for all neoplasms and cancers of the lung, other respiratory organs and other endocrine organs. Many of the risk estimates were higher in the subgroup exposed

to dioxins, although some had reduced significance, perhaps due to the smaller numbers of cases.

We were able to exclude four cohorts of sprayers from this multinational study but were unable to obtain separate results for all the cohorts included in the most recent pooled IARC analysis,² in particular 12 US studies of production workers, all exposed to herbicides contaminated with dioxins. An analysis of the influence of the individual cohorts in this multinational study showed that omission of the US studies decreased the pooled SMRs.² It is thus likely that inclusion of these 12 cohorts in our meta-analysis would also increase our risk estimates.

The classification of TCDD as a carcinogen is still a controversial topic. In 1997 the IARC classified it as a group 1 carcinogen based on limited evidence in humans, sufficient

Figure 2 Effect on all-cause mortality for total cohort of omitting each study in turn. SMR, standardised mortality ratio.



evidence in animals and extensive information on mechanisms of action.¹² One of the main reasons for this classification was the evidence from both human and animal studies that TCDD was judged to cause an increase in cancers at many sites and not just a few sites. Many of the studies used in our meta-analysis contributed to this judgement. It has been argued that the epidemiological evidence available to the IARC was compatible only with inadequate evidence of carcinogenicity to humans, with a lack of adjustment for confounders such as smoking and the potential for other relevant exposures such as asbestos to have influenced the results being given as reasons for this uncertainty.¹³ However, a review of more recent studies highlights exposure–response analyses using newly developed job-exposure matrices; these give positive significant exposure–response trends for all cancers which the authors suggest strengthens the evidence for the IARC classification.¹⁴ There were insufficient data in the papers used in our study to carry out any meta-analyses of exposure–response relationships.

The consistency of the results for cancers in our meta-analysis was supported by the lack of heterogeneity for many of the cancers. Studies that influenced the heterogeneity occurring in all neoplasms and respiratory cancer also influenced heterogeneity found in all causes of death and several non-malignant diseases. Meta-regression indicated that a larger proportion of males reduced the meta-SMR for lung cancer, a result which was reflected in the significantly raised meta-SMR for lung

cancer in females. Data on smoking habits were not available for any of the individual cohorts. It has been pointed out that several of the excesses in the phenoxy herbicide workers occur in smoking-related cancers.¹⁵ This is reflected in our results. However, meta-SMRs for non-malignant smoking-related diseases, such as respiratory and cardiovascular diseases, are reduced, indicating that smoking is unlikely to be the only cause of the excesses found for the relevant cancers. Although we investigated the impact of markers of study quality, there was no evidence that the results were influenced by these markers.

There was evidence of publication bias in this meta-analysis for some causes, with a lack of reporting of results with reduced SMRs in smaller studies. In addition, we explored several approaches to addressing the situation where zero observed cases occur. Our default approach was to add 1 to both observed and expected values when zeros occurred, some continuity correction being necessary for use of a log transformation. This produced several individual low SMRs (less than 1). The other methods either excluded these low SMRs by excluding these studies or set them equal to 1 by setting the observed equal to the expected. In addition to increases in the estimates for those causes that were statistically significantly raised using the default, the alternative methods suggested several new significant excesses, for example, cancers of the liver, skin, testis and bladder, Hodgkin's disease and multiple myeloma. These

Table 3 Results of sensitivity to zeros analyses

Disease	Excluding studies with no cases		Adding 1 to observed and expected		Setting observed = expected		Number of studies with no cases
	SMR (n)	95% CI	SMR (n)	95% CI	SMR (n)	95% CI	
Cancer of the buccal cavity and pharynx	2.34 (12)	1.45 to 3.77	1.42 (28)	1.01 to 2.00	2.06 (28)	1.49 to 2.93	16
Cancer of the oesophagus	2.25 (14)	1.55 to 3.29	1.64 (26)	1.20 to 2.24	2.07 (26)	1.45 to 2.96	12
Cancer of the stomach	1.35 (20)	1.06 to 1.72	1.20 (32)	0.98 to 1.48	1.30 (32)	1.04 to 1.79	12
Cancer of the rectum	1.57 (17)	1.19 to 2.07	1.37 (28)	1.07 to 1.76	1.52 (28)	1.16 to 1.97	11
Cancer of the larynx	3.49 (8)	1.98 to 6.14	1.58 (23)	1.09 to 2.31	2.69 (23)	1.63 to 4.46	15
Cancer of the lung	1.23 (30)	1.06 to 1.43	1.22 (32)	1.05 to 1.41	1.23 (32)	1.06 to 1.42	2
All lymphatic and haemopoietic cancer	1.41 (25)	1.17 to 1.69	1.34 (33)	1.12 to 1.60	1.39 (33)	1.16 to 1.66	8
Lymphoma	2.79 (14)	1.97 to 3.97	1.98 (26)	1.45 to 2.69	2.57 (26)	1.88 to 3.52	12

Box 1 Reference list of papers included in the meta-analysis from which data were extracted

- M1. **Acquavella JF**, Riordan SG, Anne M, *et al.* Evaluation of mortality and cancer incidence among alachlor manufacturing workers. *Environ Health Perspect* 1996;**104**:728–33.
- M2. **Amoateng-Adjepong Y**, Sathiakumar N, Delzell E, *et al.* Mortality among workers at a pesticide manufacturing plant. *J Occup Environ Med* 1995;**37**:471–8.
- M3. **Becher H**, Flesch-Janys D, Kauppinen T, *et al.* Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. *Cancer Causes Control* 1996;**7**:312–21.
- M4. **Brown DP**. Mortality of workers employed at organochlorine pesticide manufacturing plants - an update. *Scand J Work Environ Health* 1992;**18**:155–61.
- M5. **Burns CJ**, Beard KK, Cartmill JB. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94: an update. *Occup Environ Med* 2001;**58**:24–30.
- M6. **Cheng WN**, Coenraads PJ, Hao ZH, *et al.* A health survey of workers in the pentachlorophenol section of a chemical manufacturing plant. *Am J Ind Med* 1993;**24**:81–92.
- M7. **De Jong G**. Long-term health effects of aldrin and dieldrin: a study of exposure, health effects and mortality of workers engaged in the manufacture and formulation of the insecticides aldrin and dieldrin. *Toxicol Lett* 1991;Suppl:1–206.
- M8. **Flesch-Janys D**, Steindorf K, Gurn P, *et al.* Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ Health Perspect* 1998;**106**(Suppl 2):655–62.
- M9. **Hooiveld M**, Heederik DJJ, Kogevinas M, *et al.* Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. *Am J Epidemiol* 1998;**147**:891–901.
- M10. **Kogevinas M**, Winkelmann R, Saracci R, *et al*, eds. *Cancer mortality in an international cohort of workers exposed to chlorophenoxy herbicides, chlorophenols and contaminants*. IARC Internal Report 92/002. Lyon, France: International Agency for Research on Cancer, 1992.
- M11. **Lyng E**. Cancer incidence in Danish phenoxy herbicide workers, 1947–1993. *Environ Health Perspect* 1998;**106**(Suppl 2):683–8.
- M12. **Mabuchi K**, Lilienfeld AM, Snell LM. Cancer and occupational exposure to arsenic: a study of pesticide workers. *Prev Med* 1980;**9**:51–77.
- M13. **MacLennan PA**, Delzell E, Sathiakumar N, *et al.* Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A* 2003;**66**:501–17.
- M14. **Olsen GW**, Bodner KM, Stafford BA, *et al.* Update of the mortality experience of employees with occupational exposure to 1,2-dibromo-3-chloropropane (DBCP). *Am J Ind Med* 1995;**28**:399–410.
- M15. **Ott MG**, Scharnweber HC, Langner RR. Mortality experience of 161 employees exposed to ethylene dibromide in two production units. *Br J Ind Med* 1980;**37**:163–8.
- M16. **Popp W**, Schmieding W, Speck M, *et al.* Incidence of bladder cancer in a cohort of workers exposed to 4-chloro-toluidine while synthesising chlordimeform. *Br J Ind Med* 1992;**49**:529–31.
- M17. **Ramlow JM**, Spadacene NW, Hoag SR, *et al.* Mortality in a cohort of pentachlorophenol manufacturing workers, 1940–1989. *Am J Ind Med* 1996;**30**:180–94.

Box 1 Continued

- M18. **Rapiti E**, Fantini F, Dell'Orco V, *et al.* Cancer mortality among chemical workers in an Italian plant. *Eur J Epidemiol* 1997;**13**:281–5.
- M19. **Sobel W**, Bond GG, Baldwin CL, *et al.* An update of respiratory cancer and occupational exposure to arsenicals. *Am J Ind Med* 1988;**13**:263–70.
- M20. **Swaen GMH**, De Jong G, Slangen JJM, *et al.* Cancer mortality in workers exposed to dieldrin and aldrin: an update. *Toxicol Ind Health* 2002;**18**:63–70.
- M21. **Thiess AM**, Frentzel-Beyme R, Link R, *et al.* Mortality study on employees exposed to alkylene oxides (ethylene oxide/propylene oxide) and their derivatives. In: *Prevention of occupational cancer*. Geneva, Switzerland: International Labour Office, 1981:249–59.

sensitivity analyses show the importance of considering carefully the treatment of studies where zero cases are known to have occurred. Different statistical approaches for combining data where zero events occur and for choosing the size of the continuity factor (our default was 1) have been addressed by several authors, particularly in the context of studies such as case-control studies with binary outcomes.^{15–19} It has been pointed out that the magnitude of the continuity factor influences the estimates of the variance and hence the weighting given to each study in a meta-analysis.¹⁹ In practice it is often not known whether zero events have occurred or whether authors have decided not to report these, an example of outcome reporting bias. Where cause-specific results are not reported in individual publications, it is often assumed either that no cases occurred or that a deficit occurred. Collins *et al*²⁰ have considered other approaches to dealing with unreported results. None of the methods investigated is entirely satisfactory, although the sensitivity analyses do directly indicate the potential impact of any particular set of assumptions. In principle, the best procedure would be to contact the authors of the primary studies included in the review, seeking fuller information about the nature of the zeroes, but this is not always possible in practice.

Selective reporting may occur through editorial decisions on space. The increasing publication by journals of web-based supplementary material offers the opportunity for routinely publishing results from observational studies for a standard list of causes of disease. Selective reporting of outcomes may be an important source of bias²¹; to counteract this, Paddle²² suggests use of a standard set of disease categories in epidemiological study reports. It would be timely to open the debate on what constitutes a “standard” list as there is no doubt that future systematic reviews and meta-analyses would benefit from this initiative. In addition to any such standard set of diseases or disease groups, in any given study there may be additional causes highlighted in earlier, related studies. These should be separately identified and justified. Further, it will usually be helpful to identify a small subset of causes as those of prior interest to help avoid problems of multiple testing.

In broad terms, a similar approach could be adopted with benefit as regards the reporting of covariates, to limit, for example, unnecessary variation between primary studies in respect of reporting population characteristics and exposures.

Main messages

- ▶ Greenberg *et al*'s earlier meta-analysis of chemical industry workers has been updated with more specific assessment of risks in the pesticide manufacturing sector.
- ▶ Although the all cause mortality experience of workers involved in the manufacture of crop protection chemicals is better than that of the general population, there is a lack of healthy worker effect for other non-malignant diseases. Significant excesses were found for several malignant diseases in both the total cohort and the subgroup of workers exposed to phenoxy herbicides.

Policy implications

- ▶ These meta-analyses directly illustrate the importance of better quantification of exposure and measurement of confounders in primary studies, since these ultimately limit the conclusions which can be drawn even if detailed and relatively sophisticated meta-analyses are performed.
- ▶ Selective reporting may occur through editorial decisions on space. The increasing publication by journals of web-based supplementary material offers the opportunity for routinely publishing results from observational studies for a standard list of causes of disease.
- ▶ Sensitivity analyses show the importance of considering carefully the treatment of studies where zero cases are known to have occurred.

More generally, guidelines²³ for the conduct and reporting of primary studies have an important role to play in improving the quality of systematic review and meta-analysis results.

Many issues will only be addressed through improved conduct and reporting of the primary studies on which systematic reviews and meta-analyses are based (in other words, "garbage in, garbage out"). There is, however, scope for improvement of meta-analytical procedures and reporting per se in occupational epidemiology contexts, although some concerns about completeness of evidence, publication biases, heterogeneity and study quality which are naturally highlighted in performing systematic reviews apply at least equally in alternative approaches, and the transparency offered by the systematic approach should be welcomed.

In conclusion, this meta-analysis shows that, although the all-cause mortality experience of workers in the manufacture of crop protection chemicals is better than that of the general population, there is a lack of healthy worker effect for other non-malignant diseases. Significant excesses were found for several malignant diseases in both the total cohort and the subgroup of workers exposed to phenoxy herbicides. However, these crop protection sector meta-analyses directly illustrate

the importance of better quantification of exposure and measurement of confounders in the primary studies reviewed, since these ultimately limit the conclusions which can be drawn even if detailed and relatively sophisticated meta-analyses are performed.

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