

# A review of potential human carcinogenicity of the chlorophenoxy herbicides MCPA, MCPP, and 2,4-DP

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## Abstract

**For the purpose of assessing the human carcinogenic potential of the chlorophenoxy herbicides MCPA, MCPP, and 2,4-DP, the relevant epidemiological and toxicological evidence is reviewed. These compounds have not produced tumours in animal studies conducted under current test guidelines, giving no reason to predict that they would be carcinogenic to humans. Epidemiological studies have been conducted on three continents; greater emphasis is placed on the studies reported from western Europe, however, as this has been the area of more use. Although several of these studies provide suggestive evidence of associations between exposure to chlorophenoxy compounds and increased risks for some uncommon cancers, it is inconsistent and far from conclusive. None of the evidence specifically implicates MCPA, MCPP, or 2,4-DP as human carcinogens.**

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During the past decade, the potential for chlorophenoxy herbicides to cause certain forms of cancer in humans has come under increasing scrutiny. The initial focus was principally directed at one member of this family of herbicides, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), presumably because of its low level contamination by 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), which had been shown to be an animal carcinogen.<sup>1</sup> In 1979, the US Environmental Protection Agency cancelled most registrations for 2,4,5-T citing as partial justification, a series of case-control epidemiological studies from

Sweden that had linked use of 2,4,5-T to increased risks of soft tissue sarcoma and malignant lymphoma.<sup>2-4</sup>

More recently, the focus on chlorophenoxy compounds has shifted to 2,4-dichlorophenoxyacetic acid (2,4-D) owing to findings of an association between its frequent use and non-Hodgkin's lymphoma.<sup>5-6</sup> A panel of experts was recently convened to review the extensive toxicological and epidemiological data on 2,4-D, and concluded that whereas there was suggestive evidence of a link with non-Hodgkin's lymphoma, it was far from conclusive (Harvard School of Public Health, unpublished 1990).

By comparison, little attention has been given to the other members of the chlorophenoxy family including 4-chloro-2-methyl phenoxyacetic acid (MCPA), 2-(4-chloro-2 methylphenoxy) propionic acid (MCPP), and 2-(2,4-dichlorophenoxy) propionic acid (2,4-DP). Yet MCPA, MCPP, and 2,4-DP continue to be commercially important herbicides with widespread use, particularly in western Europe. This paper reviews the available epidemiological evidence relating to MCPA, MCPP and 2,4-DP, in context with the relevant animal toxicological data, to arrive at a weight of the evidence evaluation of the potential for these compounds to cause cancer in humans.

## Patterns of use for MCPA, MCPP, and 2,4-DP

The chlorophenoxy compounds act as selective herbicides and have been used worldwide for the control of unwanted vegetation. Their individual patterns of use differ somewhat between North America and western Europe. For instance, whereas 2,4-D is the major herbicide used to control weeds in small grains in the United States, it has a much smaller market share in western Europe where MCPP is currently the principal product of choice for this purpose.

In North America, 2,4-DP is used primarily on non-cropland (for forestry purposes and to clear rights of way) whereas it is used extensively on small grain crops in Europe; MCPA is used in similar ways on both continents, but has traditionally had a much larger market share in Europe than in the United

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States. These patterns of use suggest that, among studies that have not specified a principal phenoxy product, those conducted in Europe should be given greater attention when assessing the potential for MCPP, MCPA, and 2,4-DP to cause human cancer. Indeed, for this reason many of the studies conducted outside Europe are not relevant to this review and so have been given either little or no attention.

It is also critical to recognise that, compared to the acetic acids, the racemic propionic acid derivatives were introduced into commerce recently and 2,4-DP and MCPP were not actively marketed until the late 1950s. Consequently, there has been less than 30 years of latency possible with these products.

More recently, MCPP-P and 2,4-DP-P were introduced in the market. Both compounds consist of the herbicidal active D-form whereas MCPP and 2,4-DP are a mixture of the L- and D-forms with a ratio of 1:1.

By contrast, MCPA and the other chlorophenoxy compounds have been in use more than 40 years. It is apparent then, that the available epidemiological studies can only evaluate the hypothesis that 2,4-DP and MCPP are human carcinogens which act with short to moderately long latency.

### Summary of toxicology

Evidence from toxicological studies conducted on laboratory animals or cell cultures is often useful for interpreting the biological plausibility of findings obtained from observational epidemiology. Particularly helpful for evaluating a carcinogenic potential are studies in which animals receive the test compound over their life span (chronic toxicity and carcinogenicity studies). The species routinely used are mice and rats. For pesticides oral administration is preferred to simulate the possible uptake of residues in food. For the applicator it is generally accepted that dermal exposure is most relevant, then inhalation exposure, whereas oral exposure is negligible.

Nevertheless, oral carcinogenicity studies can also be used for the applicator, because like 2,4-D, other compounds such as MCPA, MCPP, and 2,4-DP are also hardly metabolised<sup>7-9</sup>; thus after dermal adsorption no difference in systemic toxicity would be expected.

Genotoxicity assays are conducted to test a chemical's capacity to damage cellular genetic material as shown by the formation of genetic mutations. A positive result in a mutagenicity test suggests a greater likelihood that a chemical will be carcinogenic in intact animals, but does not provide definitive evidence. Indeed, there is considerable published debate about the importance of positive results in mutagenicity studies and their potential to cause cancer in humans. Negative results in mutagenicity tests cannot exonerate a potential car-

cinogen, as mechanisms other than a direct attack on genetic material may be responsible for tumour development. For these reasons, it is essential to interpret mutagenicity as only a single component of the weight of the evidence evaluation of potential carcinogenic effects in humans.

### CHRONIC TOXICITY AND CARCINOGENICITY STUDIES

#### MCPA

The herbicide MCPA was administered to groups of male and female Wistar rats at doses of 0, 20, 80, and 320 ppm in the diet for 24 months.<sup>10</sup> At doses of 80 ppm and above evidence of toxicity was found. The target organs identified were the kidneys, liver, and red blood cells. No substance related changes were found in the 20 ppm (~1.33 mg/kg/day) dose group. There was no increase in the incidence of total or specific neoplasms at any dose.

Similarly, MCPA given in the diet to B6C3F1 mice at doses of 20, 100, and 500 ppm for two years produced some toxicity to the kidneys of the animals in the highest dose group, but no carcinogenic response.<sup>11</sup>

#### 2,4-DP

Technical grade 2,4-DP was administered in the diet of Fischer 344 rats at doses of 0, 100, 300, 1000, and 3000 ppm for two years.<sup>12</sup> The major target organs identified were the kidneys and liver. No substance related toxic effects were found in the 100 ppm (~6.7 mg/kg/day) dose group. There was no increase in total or specific neoplasms at any dose, thus showing the lack of carcinogenic potential of 2,4-DP in rats.

A carcinogenicity study in mice with 2,4-DP-P (optically active D-form) will be initiated after the completion of a respective range finding study. A subchronic range finding study in B6C3F1 mice indicates that 2,4-DP is less systemically toxic than MCPA.<sup>13</sup>

#### MCPP

The herbicide MCPP was given in the diet of male and female Wistar rats for two years at doses of 0, 20, 100, and 400 ppm.<sup>14</sup> As for 2,4-DP and MCPA the kidney was a target organ. No substance related effects were noted at 20 ppm (~1.3 mg/kg/days). There was no increase seen in total or specific neoplasms at any dose, thus showing the lack of carcinogenic potential of MCPP in rats.

A carcinogenicity study in mice with MCPP-P (optically active D-form) will be initiated after the completion of a respective range-finding study. A subchronic range finding study in B6C3F1 mice indicates that racemic MCPP is less systemically toxic than MCPA.<sup>15</sup>

### *Mutagenicity*

All three phenoxy herbicides were investigated for mutagenic properties in various studies, either sponsored by the producer or openly published.<sup>7,9</sup> All three endpoints of genetic damage (point mutation, chromosomal aberration, and DNA damage and repair) have been studied.

MCPA has not caused point mutations when tested in the Ames test or the host mediated assay or in mammalian (V79) cells.<sup>9</sup> No increase occurred in chromosomal aberrations in Chinese hamster bone marrow cells after oral exposure of the animals. A weak increase in the rate of sister chromatid exchange was found in the same animal strain at toxic doses, whereas at non-toxic doses there were no adverse effects. A DNA-binding study of radiolabelled MCPA did not show any interaction of the compound with the genetic material of the liver cells. Other test systems showed equivocal results (SLRL test, assays in yeast cells). Considering all mutagenic studies carried out with MCPA, it can be concluded that most tests were negative, but that in some tests a weak mutagenic potential was found at high toxic doses. For completeness it should be mentioned that worker exposure studies have been conducted with pesticide formulations containing also MCPA when the sister chromatid exchange rate in peripheral lymphocytes was measured and a chromosomal analysis was performed.<sup>16,17</sup> No genotoxic effect was noted in either study.

2,4-DP was not mutagenic in several Ames tests.<sup>8</sup> Inconclusive results were obtained in an *in vivo* chromosomal aberration test in Chinese hamsters. An increased incidence of sister chromatid exchange in the same animal strain was found only at toxic doses. Besides tests with racemic 2,4-DP (L- and D-form) new studies with optically active 2,4-DP-P (D-form) showed no evidence of mutagenicity in the Ames test and in a chromosomal aberration test *in vivo* in Chinese hamsters.<sup>18</sup> When evaluating all mutagenicity studies carried out with 2,4-DP no definite mutagenic potential can be ascribed to the active ingredient.

For MCPP the situation is similar; MCPP was negative for point mutation in several Ames tests and in mammalian cells (CHO-HGPRT test).<sup>7</sup> No conclusive results were obtained in an *in vivo* chromosomal aberration study in Chinese hamsters. An increased incidence of sister chromatid exchange was only found at overtly toxic doses. As well as tests with racemic MCPP (L- and D-form) new studies with MCPP-P (D-form) showed no evidence of mutagenicity in the Ames test and in a chromosomal aberration test *in vivo* in Chinese hamsters.<sup>19</sup> When evaluating all mutagenicity studies carried out with MCPP no definite mutagenic potential can be ascribed to the compound.

In conclusion, there is no evidence of carcino-

genicity of MCPA, MCPP, and 2,4-DP in chronic toxicity and carcinogenicity studies in laboratory animals. Genotoxicological findings were negative except in a few tests, where weak positive results occurred at highly toxic doses.

### **Methodological issues in epidemiology**

Epidemiological studies relevant to the chlorophenoxy herbicide and cancer question have been of three basic types: ecological (geographical correlational), case-referent, and retrospective cohort. Of these three designs, the ecological studies are considered to provide the weakest evidence because they fail to consider the exposure and disease relation at the level of individual subjects.<sup>20</sup> They are useful only for generating hypotheses and do not provide an appropriate basis for policy decisions.

Case-referent studies provide somewhat firmer evidence. They are efficient for studying rare diseases, like site or tissue specific cancers, but they are difficult to do well and consequently their interpretation is often controversial. Questions about selection bias and differential misclassification of exposure (recall or interviewer bias) are frequently cited as criticisms.<sup>21</sup> Recall and interviewer bias are of concern because typically all of the information about exposures derives solely from interviews conducted after the diseases of interest have already been diagnosed. Possible exposure misclassification is particularly relevant to a review of the phenoxy herbicide case-referent studies, because it has not yet been shown that subjects or their next of kin can recall detailed information about past use of pesticides with sufficient accuracy.<sup>22</sup> For this reason, several reviewers have concluded that the final answers to the herbicide and cancer question can only come from well conducted, retrospective cohort studies.<sup>23,24</sup>

The cohort studies have typically focused on groups suspected of having the highest exposures, which increases the power of the studies to detect exposure related effects if they truly exist. Cohort studies also have the advantage of using exposure information that was documented before the occurrence of any disease outcomes of interest. This enhances confidence in classification of exposure. A limitation of the cohort design is the requirement for large numbers of study subjects to be able to detect or rule out modest increases in risk of uncommon diseases such as individual types of cancers. Pooling of data from several smaller studies is being promoted as one method for overcoming this limitation.<sup>25</sup>

### **Summary of relevant epidemiology studies**

#### ECOLOGICAL STUDIES

Farmers and other agricultural workers have been the focus of many studies of risks due to pesticides

because presumably they are exposed more often and to higher amounts of these substances than are many other groups.

Blair *et al*<sup>26</sup> reviewed the available evidence from much of this research and concluded that, although farmers seem to be at lower risk of mortality from all causes combined and particularly from alcohol and smoking related cancers, they consistently display higher rates of leukaemia, non-Hodgkin's lymphoma, multiple myeloma, and cancers of the lip, stomach, prostate, skin, brain, and connective tissues. Excessive exposure to ultraviolet radiation is strongly believed to account for the high rates of lip and skin cancer. The reasons for excess cancer at other sites are not known, but there has been speculation for roles by chemical pesticides or solvents, zoonotic viruses, or chronic antigenic stimuli.<sup>27</sup>

Initial studies designed to identify aetiological agents were ecological in their design and attempted to relate risks of certain types of malignancies with prevailing agricultural practices based on county of residence. Although associations were reported between numbers of pounds of herbicides, fertilisers, or insecticides that were applied and various crops grown such as corn and soybeans, the findings have been very inconsistent and no clear pattern of exposure and risk has emerged.<sup>26</sup>

Several of the ecological studies have attempted to correlate cancer risks specifically with the use of chlorophenoxy herbicides. For instance, Yamamoto *et al*<sup>28</sup> calculated environmental pollution indices by dividing the amount of agricultural chemicals annually distributed in Japan to each prefecture by its total land area. They then correlated environmental pollution indices for more than 300 specific chemicals, among them MCPA, with mortality from cancer of the biliary tract and several other sites.

Statistically significant positive correlations were found between the environmental pollution studies for MCPA and cancers of the biliary tract, stomach, and pancreas. A negative correlation was found between MCPA and liver cancer. These correlations were consistently seen among men, but not among women. Noting the limitations of their ecological approach, the authors urged a cautious interpretation of the findings and suggested that further studies were needed.

Lyngé *et al*<sup>29</sup> evaluated time trends of incidence of soft tissue sarcoma and mortality within Denmark in relation to annual consumption of phenoxy herbicides, mainly MCPA. Even after allowing for a possible 20 year latency period, there was no apparent correlation between consumption of phenoxy herbicides and incidence of soft tissue sarcoma or mortality. Wiklund and Holm<sup>30</sup> performed a similar analysis among Swedish agricultural and forestry workers and found no association between time

trends in phenoxy acids used and the incidence of soft tissue sarcoma.

#### CASE-REFERENT STUDIES

The original case-referent studies from Sweden did not distinguish among the various types of phenoxy herbicides.<sup>24</sup> An exception was the second study in this series, which attempted to analyse products likely to have been contaminated by 2,3,7,8-TCDD (2,4,5-T) separately from those that were not.<sup>3</sup> This seemed to have little effect on the odds ratios, which were reported to be in the range of 4 to 6. The Swedish case-referent studies have been controversial because of suspected bias in the selection of cases and controls, potential recall and interviewer bias, and confounding.<sup>31-33</sup> Subsequently, the authors have attempted to answer some of the criticisms by a series of replicate studies,<sup>34-36</sup> but the most important questions remain unanswered. Perhaps this series of work is best looked upon as hypothesis generating. It has spawned additional case-referent research on three continents.

In general, the follow up case-referent studies done in the United States and in New Zealand have not provided support for the strong associations reported from Sweden.<sup>5 37-41</sup> Yet, as noted earlier, MCPA, MCPP, and 2,4-DP have been used less often in those countries than in Europe. Consequently, the United States and New Zealand case-referent studies may not be directly relevant to the discussion at hand. Instead, attention will be focused on the case-referent studies done elsewhere in Europe. Table 1 presents a summary of their findings.

Vineis *et al*<sup>42</sup> conducted a case-referent study of soft tissue sarcoma in an area of northern Italy where rice growing is the principal agricultural activity and phenoxy herbicides have been used since the early 1950s. According to official government statistics, 2,4-D, MCPA, and 2,4,5-T were all used until 1970 when 2,4,5-T was banned. Among men, there was no association seen between exposure to phenoxy herbicides and soft tissue sarcoma. For women, a non-significant odds ratio of 2.4 was reported based on five cases considered to have been either definitely or possibly exposed.

LaVecchia *et al*<sup>43</sup> studied Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma among patients admitted to teaching and general hospitals in the greater Milan area. They reported significant associations between having been employed in agriculture and all three diseases. Significant trends for duration of exposure to herbicides were found for non-Hodgkin's lymphoma and Hodgkin's disease but the associations were stronger for overall occupation in agriculture than with the specific question of herbicide use. No mention was made of the types of herbicides used but, according to the authors, cereal grains were major agricultural crops grown in the

Table 1 Summary of recent European case-referent studies relating to the chlorophenoxy herbicides\*

Author	Cases	Controls	Interview	Exposure classification	Odds ratio (95% CI)	
Vineis <i>et al</i> <sup>42</sup>	68 STS (37 men, 31 women)	158 general population	Personal and postal	Not exposed, uncertain exposure, certainly exposed to phenoxy compounds	Men 0.91 (0.6–10.3) <sup>†</sup> Women 2.42 (0.6–12.4) <sup>†</sup>	
Cartwright <i>et al</i> <sup>46</sup>	437 NHL hospital based	724 hospital-based	Personal	Exposed or unexposed to fertiliser or herbicide	1.3 (1.0–1.8)	
LaVecchia <i>et al</i> <sup>43</sup>	69 HD hospital-based	396 hospital-based	Personal	Duration of exposure to herbicides	1–10 years <sup>‡</sup>	> 10 years
	153 NHL 110 multiple myeloma				0.9 (NS)	3.5 (NS)
	263 bladder cancers	287 hospital-based	Personal	Duration of exposure to herbicides	1.7 (NS)	2.1 (NS)
LaVecchia <i>et al</i> <sup>44</sup>	263 bladder cancers hospital based	287 hospital-based	Personal	Duration of exposure to herbicides	1.2 (NS)	0.7 (NS)
Francheschi <i>et al</i> <sup>45</sup>	208 NHL hospital-based	401 hospital-based	Personal	Exposed or unexposed to herbicides and pesticides	∞ (NS)	4.3 (NS)
					1.01 (0.58–1.77)	

\*Excludes studies from Sweden that are summarised in the text.

<sup>†</sup>90% CIs.

<sup>‡</sup>Authors did not report odds ratios, these are estimates.

STS = Soft tissue sarcoma (or connective tissue cancer); HD = Hodgkin's disease; NHL = Non-Hodgkin's lymphoma; NS = not specified.

area. These authors later conducted a similar study of bladder cancer<sup>44</sup> and reported significant associations with employment in the dyestuffs industry, chemical and pharmaceutical manufacturing, and herbicide use.

A hospital based case-referent study of non-Hodgkin's lymphoma in the north east of Italy reported that farmers did not seem to be at increased risk.<sup>45</sup> An odds ratio of 1.01 was found for exposure to herbicides and pesticides.

Finally, Cartwright *et al*<sup>46</sup> reported a non-significant odds ratio of 1.3 for use of fertiliser or herbicide in a case-referent study of non-Hodgkin's lymphoma in the Yorkshire Health Region. Once again, no mention was made of the types of herbicides used by the subjects.

#### RETROSPECTIVE COHORT STUDIES

The ability to link large occupational cohorts to centralised disease registries in certain countries has created a new type of retrospective cohort design, often referred to as a linkage study. Several of these studies have examined pesticide applicators and table 2 summarises these.

Wigle *et al*<sup>47</sup> linked records of almost 70 000 Saskatchewan men identified as farmers from the 1971 Canadian Census of Agriculture to mortality records complete through 1985. Among all farmers, they found deficits of mortality from most cancers including soft tissue sarcoma and non-Hodgkin's lymphoma. Data on direct exposures of farmers were not available; however, farmers were categorised according to the number of acres they reported

Table 2 Summary of linkage type cohort studies of pesticide applicators

Author	Exposed group	Reference group	Exposure classification	Relative risk estimates (95% CIs)			
				Total cancer	STS	HD	NHL
Wigle <i>et al</i> <sup>47</sup>	69 513 male Saskatchewan farm operators	Male population of Saskatchewan	Acres sprayed for weeds	0.81 (0.78–0.84)	0.89 (0.53–1.40)	—	0.92 (0.75–1.11)
Wiklund and Holm <sup>30</sup>	354 620 Swedish agricultural and forestry workers	Male population of Sweden	Six subcohorts defined by level of phenoxy herbicide use	—	0.9 (0.8–1.0)	—	—
Wiklund <i>et al</i> <sup>48–50</sup>	20 245 Swedish licenced pesticide applicators	Swedish general population	Years since licence issued, year of licence	0.86 (0.79–0.93)	0.94 (0.34–2.04)	1.20 (0.60–7.16)	1.01 (0.49–1.87)
Corrao <i>et al</i> <sup>51</sup>	25 945 Italian licenced pesticide applicators	Local Italian general population	Birth cohort, village clusters defined by similar agricultural activity	0.7 (0.6–0.8)	—	1.4 (1.0–1.9)	

For abbreviations see table 1.

spraying for the control of insects or weeds, and dollars spent for pesticides or fuel and oil used for farm purposes. On farms of less than 1000 acres, the authors reported significant positive trends for risk of non-Hodgkin's lymphoma and negative trends for risk of lung cancer with increasing numbers of acres sprayed for weed control and increasing fuel and oil expenditures. These findings did not hold on farms of 1000 acres or more. The authors estimated that 2,4-D constituted over 90% and 75% by weight of all herbicide active ingredients used agriculturally in Saskatchewan during the 1960s and 1970s. It is uncertain whether exposure to MCPA, MCP, or 2,4-DP had occurred as they were not mentioned among the list of other herbicides used by Saskatchewan farmers.

Wiklund and Holm<sup>30</sup> linked records of more than 350 000 Swedish agriculture or forestry workers to a central cancer registry. According to the authors, MCPA was the phenoxy herbicide used most often in Swedish agriculture, whereas in forestry both 2,4,5-T and 2,4-D were used most heavily. No increased risk for soft tissue sarcoma was found among either the total group of workers or among any of six subsets defined by presumed level of exposure to phenoxy herbicide. Moreover, no time related increase in these cancers was found despite the greatly increased use of phenoxy acid herbicides between 1947 and 1970. These same authors linked records of more than 20 000 licenced pesticide applicators in Sweden to the central cancer registry.<sup>48-50</sup> An estimated 72% of the applicators had exposure to phenoxy herbicides, mainly MCPA, MCP, and 2,4-DP, but also to 2,4-D and 2,4,5-T. Significant deficits were found for total cancer, including cancers of the liver, pancreas, lung, and kidney. No excess incidence of soft tissue sarcoma, non-Hodgkin's lymphoma, or Hodgkin's disease was seen in the total group of applicators, nor in subsets defined by latency or year of licensing.

Corrao *et al*<sup>51</sup> studied more than 25 000 farmers from the southern piedmont of Italy who were licensed between 1970 and 1974 to buy and use

pesticides classified as highly acutely toxic. Once again, data on pesticide exposures of individual workers were not available, nor was there mention made of the types or patterns of phenoxy herbicides used. The cohort was linked to a regional hospital discharge data base to identify cases of cancer of the bone, connective tissue or skin, brain or other parts of the nervous system, or lymphatic or haematopoietic tissue tumours. Bone and connective tissue cancers were ignored in the analysis after a quality control check found large discrepancies in these diagnoses.

Overall, non-significantly increased risk ratios were seen for tumours of the skin and lymphatic tissue. The excess skin cancer appeared mainly among the oldest farmers, whereas the risk of cancer of the lymphatic tissue was independent of birth cohort. A cluster of villages with the highest percentage of arable farming land seemed to have the highest risk of lymphatic tissue cancer. In view of potential biases introduced by the use of hospital discharge diagnoses, the authors urged a cautious interpretation of their findings.

Studies of herbicide manufacturers have provided some of the best documentation yet of exposure to the phenoxy herbicides. There have been two European studies conducted of producer cohorts which focused on MCPA exposures. Table 3 presents a summary of their findings.

Lynge<sup>52</sup> studied 4459 chemical workers from two of four companies that had produced phenoxy herbicides in Denmark. These workers were engaged in the manufacture of diverse chemical products including not only herbicides but dyes and pigments as well. Roughly one third of them had been assigned to phenoxy herbicide production or packaging. MCPA and MCP were the predominant phenoxy herbicides produced, then 2,4-D and 2,4-DP. Apparently, only small amounts of 2,4,5-T had been made. A slight deficit of total cancer was noted among the combined group of chemical workers. There were five cases of soft tissue sarcoma reported among the men *v* 1.8 expected (relative risk = 2.7; (95% confidence interval) 0.88-6.34) and no cases among

Table 3 Summary of cohort studies of MCPA manufacturing workers

Author	Cohort	Reference group	Exposure classification	Observed/expected			
				Total cancer	STS	HD	NHL
Lynge <sup>52</sup>	4563 chemical workers; 940 of whom produced phenoxy compounds	Denmark general population	Ever/never exposed to phenoxy compounds mainly MCPA	41/41.6	1/0.5	0/0.09	
Coggon <i>et al</i> <sup>53</sup>	5784 men engaged in production or spraying of phenoxy compounds	England and Wales general population	Graded exposure (high, low, background) to mainly MCPA and duration of exposure	297/314.0	1/0.9	1/3.5	2-5.5

For abbreviations see table 1.

the women *v* 0.75 expected. Only one of the five cases had been assigned to working with chlorophenoxy compounds, and his total employment in the chemical plant was limited to three months. Seven cases of malignant lymphoma occurred among all male chemical workers *v* 5.4 expected, and one case among the women *v* 1.2 expected. None of the lymphomas occurred among the employees who had been assigned to work with chlorophenoxy compounds. Lung and rectal cancer were significantly increased among the men within this subgroup, and cancer of the cervix was increased among the women. No analyses were attempted by duration or estimated intensity of exposure to phenoxy compounds; nor was there any control for possible confounding due to exposure to tobacco or other chemical substances. Citing these limitations, as well as the problem of multiple comparisons, the authors were reluctant to link the excess cancers to exposures to phenoxy herbicide.

Coggon *et al*<sup>53</sup> examined mortality and incidence of cancer among 5784 men who had been employed in the manufacture or spraying of MCPA by a company in the United Kingdom. Workers were classified according to their potential for exposure into high, low or background based on their job titles. Overall mortality in the cohort was less than that expected from national death rates, as was mortality from all neoplasms, heart disease, and diseases of the respiratory system. Compared with expected levels based on rates for rural areas of the United Kingdom, mortality from cancer in the cohort was slightly increased, but not significantly so. Only one death from soft tissue sarcoma occurred compared with about one expected. Three men died from malignant lymphoma compared with about nine expected. An excess of cancer of the nose and nasal sinuses was found among subjects with more than background exposure to MCPA; however, it was based on only three deaths and there was a suggestion that at least one of the cases had other risk factors. The authors concluded that their findings do not exclude the possibility that MCPA could be a human carcinogen, but that if there is a hazard of soft tissue sarcoma due to MCPA, it must be smaller than suggested by the Swedish case-referent studies.

### Discussion

The findings from controlled animal experiments provide little reason to predict that MCPA, MCPP, or 2,4-DP might be carcinogenic to humans. Using current test guidelines, none of the three compounds has produced an increase in tumours in animals tested even at levels that caused systemic toxicity. This does not, however, completely preclude the possibility that these chemicals could be human carcinogens. There are some examples of chemicals (arsenic and benzene) that tested negative in standard

carcinogenicity bioassays but which were confirmed as human carcinogens in epidemiological studies. Nevertheless, it has been uncommon.

Although there is substantial epidemiological evidence available on the chlorophenoxy compounds as a group, little of it is specific to MCPA, MCPP, and 2,4-DP. Any assessment of published work on chlorophenoxy compounds is complicated by a failure of many of the studies to distinguish between the various products in either data collection or analysis, and the mixed exposures of many applicators to multiple pesticides and other potentially hazardous substances. As a consequence, it is not possible to isolate a particular phenoxy product as being responsible for any of the positive associations reported to date.

The ecological studies suggest that, whereas agricultural workers enjoy greater longevity than other groups, they are at increased risk for certain types of malignancies, particularly those of the haematological system. The reasons for the increased risks are unknown, but there has been speculation that chlorophenoxy compounds may be playing some part. One study<sup>28</sup> suggested correlations between exposure to MCPA and increased risks for cancers of the biliary tract, stomach, and pancreas. This evidence is weak and is not sufficient on its own to raise concerns about the human carcinogenicity of MCPA. It is doubtful that further ecological studies will be helpful in identifying risk factors for cancer among agricultural workers. Instead, more analytical studies that gather information about the joint relation of use of herbicides and cancer among individual study subjects are needed.<sup>26</sup>

A remarkable aspect of the case-referent studies is the substantial variability in risk estimates among them. Some studies have suggested links between exposure to phenoxy herbicides and increased risks of soft tissue sarcoma or Hodgkin's disease,<sup>2-4 34 36 42</sup> whereas other studies found no associations.<sup>5 37 40</sup> Similarly, several studies seem to support an association with non-Hodgkin's lymphoma,<sup>4-6 35 43</sup> but still other studies do not.<sup>38-51 45 46</sup>

Possible explanations for the inconsistent results among the studies have included differences in the levels and types of exposures of the underlying populations; distribution of other risk factors for the cancers being studied; methodology employed to gather and analyse the data that may have resulted in the underestimation of the strength of associations in some reports or overestimates in others; and the precision with which the associations could be estimated. None of these explanations is an obvious candidate.<sup>23 27</sup>

More case-referent studies will undoubtedly be carried out. Yet, until it has been established that interviews can provide valid and reliable estimates of subjects' exposures, further case-referent studies are

unlikely to resolve the herbicide and cancer question. More importantly perhaps, the validity of the results of the case-control studies will be in doubt until they have been replicated via good cohort studies, something that has not happened yet.<sup>24</sup>

Generally speaking, the two cohort studies on workers who manufactured MCPA and other phenoxy herbicides have been reassuring.<sup>52 53</sup> Total mortality from cancer was at or below expected levels for those groups, indicating that exposures at occupational levels do not pose major health problems. Although each of the studies reported increased cancer at one or more organ sites, the findings were not mutually reinforcing. Moreover, potential confounding exposures and chance were considered by the authors to be viable alternative explanations. These two cohort studies deserve special consideration because the exposures received by the underlying populations have been more intense, more frequent, and better documented than those of most subjects considered exposed in the case-referent studies.

A weakness of the cohort studies has been their limited statistical power for detecting or ruling out modest increases in risk for some of the more uncommon types of cancer such as soft tissue sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma. The linkage type studies<sup>30 47-51</sup> are an exception to this; however, their gains in statistical power were offset by their use of unvalidated, surrogate measures of exposure. Consequently, those studies have somewhat limited value for confirming or refuting a possible carcinogenic role for the phenoxy compounds. Yet, the best prospects for solving the herbicide and cancer question may lie in refinements to those studies. Consideration should be given to conducting prospective case-referent studies within these large applicator cohorts. Such studies could combine interview data with biological and environmental monitoring to improve exposure classification.

In summary, although there is some suggestive evidence from epidemiological studies of associations between chlorophenoxy herbicides and increased risks for several uncommon cancers, it is inconsistent and far from conclusive. None of this evidence specifically implicates MCPA, MCPP, or 2,4-DP. Furthermore, the results of experimental studies in laboratory animals provide no reason to believe that exposure to any of these three compounds would cause cancer in humans.

This review was prepared at the request and expense of the phenoxy herbicide (TPH) committee. The views expressed are those of the authors and do not necessarily reflect those of the committee or its individual member companies.

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