HEALTH ASPECTS OF ORGANIC COMPOUNDS IN DRINKING WATER:
FEASIBILITY OF A RETROSPECTIVE STUDY OF INDIVIDUALS
TO ASSESS CERTAIN CANCER RISKS ASSOCIATED WITH
DRINKING WATER QUALITY (H4298C)

Final Contract Report to the Department of the
Environment (October 1981 - March 1982)

Author: Shirley A A Beresford *

June 1982

341-M

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distribution:

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* The Royal Free Hospital School of Medicine
Department of Clinical Epidemiology and
General Practice

DOE CONTRACT REFERENCE: PECD 7/7/015
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SUMMARY

Recent epidemiological studies in the London area have suggested that some adverse health effects may be weakly associated with re-used rivers as a source of drinking water. This evidence is consistent with the results of several studies in the United States. There is also a hypothesis arising from a study in this country that the risk of cancer mortality in women is increased in areas supplied with water derived from upland catchments. These health effects are small, but further work perhaps needs to be done to clarify their nature and scale. To this end the present report assesses the feasibility of further research based on retrospective case-control methodology.

The report discusses a number of considerations in the design of case control studies: the choice of cases and of controls, the advantages and disadvantages of matching, and the information that would need to be included about diet and life-style. References are made to recent case control studies that have been carried out in other countries. The report puts forward three possible designs of study and estimates their likely effectiveness and costs.

The report concludes that the decision whether or not to support epidemiological research of this kind should rest on whether the Water Industry would be prepared to act on the strength of evidence that it provides.
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PREFACE

On 1st April 1981 the Department of the Environment placed a contract (Ref. PECD 7/7/015) at the Water Research Centre to evaluate the possible health effects associated with the presence of organic compounds in drinking water; the work to be carried out falling into three broad categories - epidemiology, toxicology and water quality studies.

The work reported here relates to the epidemiological aspects of the contract, the objective of which was to investigate the relationship, if any, between types of water sources, treatments and degree of contamination and diseases such as cancer of the digestive and urinary tracts. The work was undertaken at The Royal Free Hospital, School of Medicine, under sub-contract to the Water Research Centre. This sub-contract ended on 30th September 1981 but was renewed from 1st October to 31st March 1982 so that The Royal Free Hospital could advise the Water Research Centre on the likely value of further epidemiological research into the possible health effects of organic compounds in drinking water, and the relative merits of the different kinds of study which might be attempted. This final report presents the findings of this appraisal and fulfils all the reporting requirements of this part of the overall contract.

A draft of this report (MAWQ/161/82) was presented to the Department of the Environment/Department of Health and Social Security Joint Committee on Medical Aspects of Water Quality at a meeting held on 10 June 1982.
Feasibility of a retrospective study of individuals to assess certain cancer risks associated with drinking water quality

Shirley A.A. Beresford
March, 1982

Introduction

From recent studies in the London area, 1, 2, 3, there is some evidence of adverse health effects which are weakly associated with reused river water as a source of drinking water. The small effects persist independently of social factors, of within-borough variations of estimated rates or ratios, and of adjustment for any geographical clustering. These adverse health effects relate to stomach cancer incidence in females, urinary tract cancer incidence in females, and stillbirth rate. The effects could be so small as to be negligible. However, when considered with the results of several studies in the United States the studies provide consistent epidemiological evidence of a small health risk associated with reused river water.

There is also a hypothesis, emerging from a statistical association found in Great Britain, that the risk of stomach cancer mortality in females is increased in areas served by upland catchments.

Possibilities for further studies

Although the health effects detected are not large, it would be unwise to take no action. In terms of estimated relative risk, that is the ratio of the risk of the disease among the exposed to the risk of the disease among the non-exposed, the health effects associated with reused water are about 1.11 for stomach cancer and about 1.24 for urinary tract cancer.
The corresponding 95% confidence intervals are (0.99, 1.24) and (0.97, 1.44). One possible action would be to quantify the risks with greater precision. Studies on individuals, rather than on aggregated populations, would certainly provide more evidence. There are two possible methods: retrospective studies and prospective studies. Prospective studies are more powerful, and more scientifically persuasive than retrospective studies, but they take several more years to complete and are more expensive, in general. The nature of the diseases involved, namely cancer of the stomach and cancer of the urinary tract, severely limits the range of possible studies. The diseases are not very common (compared for example to lung cancer or cardiovascular disease), and the lag periods for exposure are unknown. These considerations rule out prospective studies.

Retrospective studies: choice of controls

There are different types of retrospective study, but all of them compare a group of cases with a group of controls, with respect to a putative risk factor. It is important that the controls are comparable with the cases, and this implies that there is no bias in the study methodology either in the selection of cases and controls or in the assessment of the putative risk factor. If hospital cases are used, the choice of hospital controls, (with a wide range of diagnoses to avoid overmatching) avoids selection bias in so far as both groups will be users of medical services. Hospital controls also have the advantage of having heightened awareness of previous history, as do the cases, to assess what was responsible for their current spell of illness, so that recall bias is reduced. However, the hospital controls may also be more like cases in terms of exposure to the putative risk factor since they may be in hospital for a condition which has aetiological features in common with the disease under study. The alternative is to use a control group from the general population. This is especially useful if the cases represent a
complete enumeration of the new cancers in a population during a specified
time period since we would have, from a defined population, a random sample of
cases (a 100% sample in fact) and a random sample of controls. In this instance
the two groups are highly comparable and the results are highly generalizable.
This often makes for the most persuasive type of case-control study. The dis-
advantage is that it can be expensive and time-consuming to select a group and
obtain its information in the general population. Also, the individuals so
selected may not be as cooperative as those attending hospital for medical
care.

Matching

One traditional way of increasing the comparability of cases and controls is
to match. Its main purpose is to permit the use of efficient analytical
methods to control confounding by the factors matched for. For a factor to
be confounding, it must be associated both with the cancer under study and with
the exposure of interest. One obvious example of this is socioeconomic status.
This particular factor is difficult to match explicitly. A solution is to use
close neighbour controls, but these would be likely to have the same water quality
as cases. There would be such a great degree of overmatching that the study
would be a waste of time. Socioeconomic status can better be controlled in the
analysis of the study, using controls from the general population, provided the
relevant information is obtained.\textsuperscript{4} Matching is often done on age and sex of
the case, but although these factors are associated with the incidence of cancer,
they are not associated with water quality. It is quite sufficient to obtain
a similar distribution of age and sex among the control group, and this is best
achieved by taking a stratified sample from the potential control population,
and then adjusting for age and sex in the analysis.
Numbers of controls

When the number of available cases is limited, as it is for stomach cancer and urinary tract cancer, it is possible to increase the power of the study by increasing the number of controls. Such advantage can be obtained by using between twice as many and four times as many controls as cases.\(^5\) The decision as to how many controls to use is likely to be influenced by the number of interviewers available, and whether the interviews are to take place in hospital or at home. Two interviewers can probable manage 1000 interviews per year, which is 4 interviews each day on a two days on, two days off basis. Non-interviewing days could be spent coding, checking the completeness of case-inclusion and arranging the following days' interviews.

Reuse study: Number of cases required to detect relative risks between 1.2 and 1.3

Assuming one control per case, and about 50% exposure to reused water compared to ground water, about 2300 cases and the same number of controls would be needed to detect an increased risk of stomach cancer of 24%. If the case recruitment were limited to the age group 25 to 74 years, this would require a catchment population (of all ages and both sexes) of 9.4 million, or 4.3 million over 2 years. This assumes that about 58% of the population are aged 25 to 74 years, and the same order of risk for men as for women, although this was not found in the London aggregate population study. The British study of reuse did lend some support to the latter assumption however, since there was some indication of an excess of male stomach cancer mortality. Such a catchment population might be expected to yield about 1500 cases of bladder cancer over 2 years, which would be sufficient to detect an increased risk of 30% if it existed. All of these calculations have assumed 90% power and 5% significance level.\(^6\)
This means there is 10% chance of missing a difference if it exists (type II error) and 5% chance of saying there is a difference when in fact there is none (type I error). A population of 5½ million is provided by the total of the following boroughs in the London area:

<table>
<thead>
<tr>
<th>Bexley</th>
<th>Hammersmith</th>
<th>Lewisham</th>
<th>Camden</th>
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<tr>
<td>Bromley</td>
<td>Hounslow</td>
<td>Merton</td>
<td>Hackney</td>
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<tr>
<td>Croydon</td>
<td>Kensington</td>
<td>Richmond</td>
<td>Islington</td>
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<tr>
<td>Ealing</td>
<td>Kingston</td>
<td>Southwark</td>
<td>Newham</td>
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<tr>
<td>Greenwich</td>
<td>Lambeth</td>
<td>Sutton</td>
<td>Tower Hamlets</td>
</tr>
<tr>
<td>Dartford</td>
<td>Westminster</td>
<td>Wandsworth</td>
<td>Banstead</td>
</tr>
<tr>
<td>Epsom &amp; Ewell</td>
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</table>

These boroughs give an overall exposure to reused water of 68%. This exposure rate requires a few more cases and controls to detect the risks stated, since these were calculated for 47% exposure, but these would be provided by the slightly larger population in the above boroughs, 5½ million, compared to the 4½ million calculated.

Upland water study: Number of cases required to detect relative risks between 1.2 and 1.3

Similar populations would be required to detect similar risks of stomach cancer attributable to upland water, if they exist. Such population size is easily reached if all the following urban areas were used for study:
N.E. England

Group A  South Shields
(979,000)  Newcastle
Hebburn & Jarrow
Gateshead
Tynemouth
Stanley/Consett
Longbenton/Gosforth
Sunderland
Brandon & Byshottle/Crook/Spennymoor

69% upland, 28% lowland, 4% ground/spring

Group B  Teesside
(651,000)  Hartlepool
Darlington
Bishop Auckland/
Durham/Shildon

36% upland, 42% lowland,
23% ground/spring

N.W. England

Group A  Blackpool
(278,000)  Southport
Lytham-St.-Anne's

51% upland, 47% ground

Group B  Liverpool
(927,000)  St. Helen's
Bootle
Wigan
Widnes

64% upland, 22% lowland, 13% ground

Central Midlands

Group A  Birmingham
(1,179,000)  Warley

83% upland, 7% lowland, 9% ground

Group B  Coventry
(442,000)  Solihull

21% upland, 60% lowland, 20% ground

Wales & the South-West

Group A  Cardiff
(444,000)  Newport
Caerphilly

64% upland, 36% lowland

Group B  Bristol
(511,000)  Bath

57% upland, 25% lowland, 18% ground
These give an overall exposure to upland water of about 60%. The remainder is about $\frac{1}{3}$ ground water and $\frac{2}{3}$ lowland river water.

Some recent retrospective studies of stomach cancer

Such an expensive study could be justified for other purposes as well as an investigation of water quality. Over the last ten years there have been only 3 relevant case-control studies of stomach cancer, one in France, one in Tel Aviv and one in Chile, all of them very small having 40, 166 and 360 cases respectively. Their findings with respect to alcohol consumption, smoking habits, starchy food consumption and 'high risk area' were not conclusive. The French study\(^7\) suggested that alcohol, and particularly red wine, may be an important risk factor for adenocarcinoma of the stomach (RR 6.9; in the presence of smoking this is increased: RR 9.3). They also found a non-significant protective effect of regular lettuce intake (RR 0.5). The dietary information were obtained using a nutritional interview similar to that used in previous studies\(^8\).

The study in Israel\(^9\) revealed a higher consumption frequency of starches among gastric cancer patients than in three matched control groups (P < 0.001 for neighbourhood control group). This finding was not due to a higher consumption frequency of a few items, nor was it related to a socioeconomic differential. The interviewer was not 'blind' as far as the interviews of the neighbourhood controls were concerned. The questionnaire contained as complete a list as possible of food items and prepared foods, numbering 243, eaten by the various population groups in Israel. The Chilean study\(^10\) showed a longer-term residence in high risk areas (i.e. areas with high stomach cancer mortality) in early life by cases than controls (not a very surprising finding), and also an association between stomach cancer and a prior occupation in agriculture
(P =0.1). This latter association was interpreted in terms of exposure to the kind of rural life prevailing in agricultural areas of Chile. This study did obtain a residence history. Strangely, and this finding was not commented on by the authors, the cases had been exposed to significantly fewer years smoking in their first 25 years of life than had the controls (P< 0.01).

Some recent retrospective studies of bladder cancer

There have been a few more case-control studies of bladder cancer, mostly in the U.S. and Canada, concentrating on the risks of smoking and the use of artificial sweeteners. These studies were larger, mostly about 500 cases, although one had 3000 cases 11. These studies frequently used control groups sampled from the general population. One study 12 showed male cigarette smokers aged 20 years or more to have a relative risk of bladder cancer of 1.89 compared to male non-smokers of similar age. The corresponding finding for women was a relative risk of 2.00. The risk was increased among those who smoked heavily and those who inhaled. None of the excess risk associated with smoking was explained by occupational experience. The interviews of 30% of the cases and 16% of the controls were obtained from the spouse or next-of-kin. Another study 13 showed an excess risk of bladder cancer among cigarette smokers, but the relative risks were a little larger (2.2 for males and 2.2 for females). They found an excess of bladder cancer patients with some previous occupational exposure, such as rubber, chemicals and textiles. A weak association with coffee drinking, which was independent of smoking, was found for males (RR 1.9 for those drinking 4 to 6 cups a day). Users of artificial sweeteners were not over-represented among the cases. The study collected data over a six year period, and some amendments of the questionnaire took place. The controls included some cancers which were not thought to be smoking-related.
In the Canadian Study 14, 15, a positive association between the use of artificial sweeteners, particularly saccharin, and risk of bladder cancer in males was found (RR 1.6). They found an even higher risk for cigarette smokers (males RR 3.9, females RR 2.4). Bladder cancer risk was found for workers in the chemical, rubber, photographic, petroleum, medical and food processing industries among males, and for workers of both sexes occupationally exposed to dust or fumes. There was an elevated risk of bladder cancer in males associated with coffee drinking (RR 1.5 for both real ground coffee and instant coffee), and with consumption of drinking water from non-public supplies (RR about 2.0). Other factors investigated were hair dye use, phenacetin use and aspirin use. The controls were mainly neighbourhood controls, and a complete residence history was obtained. The data collection period was just over two years. The largest study 11 (3000 cases) found no elevation of bladder cancer risk in subjects who reported ever having used artificial sweeteners (RR 1.04) or artificially sweetened foods (RR 1.05) or beverages (RR 0.97), although some positive associations were found within several sub-groups, chosen a priori. One sub-group was heavy smokers and another white females not exposed to occupational hazards. The controls numbered nearly 6000 and were an age-sex random sample from the community. The questionnaire included residence history and source of water supply.

**Necessary items for the questionnaire**

From these studies it is clear that, when assessing stomach cancer, information should be gathered on dietary history, especially vegetables, starches and salt, alcohol consumption, smoking history, medical history, socioeconomic status, and country of origin. For bladder cancer, information is needed on fats and oils consumption, alcohol consumption, coffee drinking, use of artificial sweeteners and diet drinks, smoking history, occupational history, education, history of
diabetes, history of urinary infections, obesity, use of hair dyes and race. The lists are similar enough for the study to be run concurrently in assessing the risks of reused water. A complete residence history will have to be obtained in addition, to calculate life-time exposure to different water qualities. A simple aid to obtaining information about events of several decades ago has recently been developed. Dietary recall is notoriously difficult, and may not be reliable, however it is to be hoped that gross differences in diet may be detected.

**Possibility No. 1**

Five year study, with 4 years data-gathering: 2 years for reuse risks, 2 years for upland risks.

Reuse risks are to be assessed in the 25 boroughs in the London area. Over two years the number of new stomach cancer cases from gastroscopy clinic records should be about 2500. The number of new bladder cancer cases from cystoscopy clinic records would be at least 1650. 2500 controls should be obtained from an age-sex stratified sample of the general population residing in the 25 boroughs. The relative risks that should be detectable are at least 1.24 for stomach cancer, and 1.30 for bladder cancer.

Upland risks are to be assessed in the 31 urban areas or aggregates in England and Wales. Over two years the number of new stomach cancer cases found from gastroscopy clinic records and resident in those 31 areas is likely to be 2600. 2600 controls should be obtained from an age-sex stratified random sample of the general population resident in the 31 areas. The relative risks that should be detectable are at least 1.24 for stomach cancer.
**Personnel and costs**

3 months for planning and training, 4 years for data gathering and analysis, 9 months for final analysis and writing up.

<table>
<thead>
<tr>
<th>Role</th>
<th>Duration</th>
<th>Rate</th>
<th>Total Cost</th>
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<tr>
<td>Epidemiologist</td>
<td>5 years</td>
<td>£20,000</td>
<td>£100,000</td>
</tr>
<tr>
<td>Secretary</td>
<td>5 years</td>
<td>£8,000</td>
<td>£40,000</td>
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<tr>
<td>Fieldworkers</td>
<td>7 for 2 yrs</td>
<td>£10,000</td>
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<tr>
<td>Fieldworkers</td>
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<td></td>
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<tr>
<td>Research assistant</td>
<td>4½ years</td>
<td>£12,000</td>
<td>£54,000</td>
</tr>
<tr>
<td>(with programming and</td>
<td></td>
<td></td>
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<td>statistical skills)</td>
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**TOTAL**  
£434,000

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**Possibility No.2**

Three year study, with 2 years data gathering - assessing the risks of reused water only.

Reuse risks are to be assessed in the 25 boroughs in the London area. Over two years the number of new stomach cancer cases from gastroscopy clinic records should be about 2500. The number of new bladder cancer cases from cystoscopy clinic records would be at least 1650. 2500 controls should be obtained from an age-sex stratified sample of the general population residing in the 25 boroughs. The relative risks that should be detectable are at least 1.24 for stomach cancer, and 1.30 for bladder cancer.

**Personnel & costs**

3 months for planning and training, 2 years for data gathering and analysis, 9 months for final analysis and writing up.
Epidemiologist  3 years  @ £20,000  = £ 60,000  
Secretary  3 years  @ £ 8,000  = £ 24,000  
Fieldworkers  7 for 2 years  @ £ 9,500  = £133,000  
Research assistant (with programming and statistical skills)  2½ years  @ £12,000  = £ 30,000  

Costs include overheads, travel and computing  TOTAL  = £247,000

Possibility No. 3

Two and one quarter years study, with 1 year data gathering, assessing the risks of reused water only.

Reuse risks are to be assessed in a subgroup of the 25 boroughs listed, e.g. excluding Hounslow, Ealing, Hackney and Islington. Over one year the number of new stomach cancer cases from gastroscopy clinic records should be about 820. The number of new bladder cancer cases from cystoscopy clinic records would be at least 530. 820 controls should be obtained from an age-sex stratified random sample of the general population residing in the subgroup of the 25 boroughs. The relative risks that should be detectable are at least 1.50 for stomach cancer, and 1.60 for bladder cancer.

Personnel and costs

3 months for planning and training, one year for data gathering and analysis, one year for final analysis and writing-up.
Advantages of assessment of a study for the non-water factors

Provided the dietary recall is not differentially biased between cases and controls, the large number of individuals studied in possibilities 1 and 2 would be a great advantage to detecting dietary differences, such as the supposed protective effect of fresh green vegetables on stomach cancer. The large numbers would almost certainly enable a clear statement to be made about the risks of bladder cancer associated with coffee drinking, independent of smoking habits, alcohol consumption, and occupational hazards.

As possibilities 1 and 2 would be very expensive, it is important to consider all the conclusions that would be possible at the end of the study. As far as the non-water factors are concerned, it is likely that we would be able to make statements such as the following:-

'The relative risk of bladder cancer associated with cigarette smoking can be defined within narrow limits .......

'The relative risk of stomach cancer associated with infrequent consumption of fresh green vegetables is unlikely to exceed .......

'The relative risk of bladder cancer associated with coffee drinking is estimated to be ......., and is likely to exceed .......'
'The relative risk of stomach cancer associated with consumption of starchy foods in early childhood is likely to lie between the following limits .......

This latter is a typical statement which may be all that emerges from possibility No.3.

Effectiveness in resolving outstanding water quality questions

For the water quality, three possible outcomes exist with respect to reuse: If there is a statistically significant relative risk of stomach or bladder cancer associated with reused water, and the risk increases in proportion to the degree of reuse, we may conclude that there is something about reused water which is contributing to the incidence of stomach or bladder cancer. This conclusion would be drawing on consistency of evidence, strength of the association, dose-response relationship, and correct order of putative cause and effect. The definition of the reuse variable will be better for any particular residence of an individual than it was for the aggregate studies, (e.g. the score for a residence in the Borough of Croydon will either be 0 or 13.9 depending on the part of the borough - the aggregate study scored the whole of Croydon 1.39). However, we will be no wiser as to what aspect of the reused water is responsible. It could be any kind of domestic sewage, or particular aspects of that sewage such as degraded steroids, or it could be industrial effluent of a particular kind, or it could be the combination of reused water and chlorine treatment. The only action that could be recommended at that point would be discontinuing the use of the rivers Thames and Lee to transport effluent to the sea.

The second possible outcome is that there is no statistically significant relative risk of stomach or bladder cancer, nor is there any evidence of a dose-response relationship. We may than conclude that any relative
risk associated with reused water is not likely to exceed 1.24 in possibilities 1 and 2, and 1.5 in possibility No.3. This would be a very important conclusion for the water industry.

The third possible outcome is an equivocal one: Either that there is a significant relative risk, but no dose-response relationship - or that there is no significant relative risk but there is some dose-response relationship. Again the conclusions here would be phrased in terms of the likely risk not exceeding a certain figure. Much more confidence can be placed in these bounds of risk than can be placed in those from the aggregate population studies, which had a small number of units of analysis, and in which were there any missing factors, there might be a large error in the estimated risk.

With respect to upland (which is involved only in possibility No.1), although technically the three possible outcomes exist, conclusions from the first cannot be as strong as for reuse. This is because there is no consistency of results. There is also no other evidence from toxicological studies to support a positive finding. Its interpretation would be couched in terms of possible risk associated with soft water, or aggressive water, or water containing natural organics, or water possibly containing bracken derivatives, or any of these aspects of upland water in combination with some aspect of the treatment process.

. Conclusions

In the light of this discussion, the likely rewards from a study of upland waters are not enough to justify the cost of the study. Possibility No.1 should therefore be rejected. The recommendations cannot be made so clearly with respect to water reuse. From studies in the United States, relative risks have been estimated between 1.1 and 2.0. If the water industry is prepared to act on this evidence (from case-control studies in the United States), no case-control
study in the London area is needed. If the water industry is not prepared to act if the true relative risk is 2.0, then no case-control study is needed. Otherwise, we have demonstrated that a case-control study is technically feasible, and could be expected to detect a relative risk of 1.24 for stomach cancer if possibility No.2 is adopted. If we were content to detect only risks above 1.5, the study could be smaller, and so less expensive and possibility No.3 should be adopted.

In conclusion, if the water industry is not prepared to act on the evidence from the U.S., but would be prepared to act on risks above 1.5, a case-control study in the London area would be worthwhile.
References


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