Aspects of Exposure Estimates of Disinfection By-Products from Water: A Review of Water Intake and Contact and the Uptake of Disinfection By-Products by Different Exposure Routes

Final Report to the Department of the Environment, Transport and the Regions

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ASPECTS OF EXPOSURE ESTIMATES OF DISINFECTION BY-PRODUCTS FROM WATER: A REVIEW OF WATER INTAKE AND CONTACT AND THE UPTAKE OF DISINFECTION BY-PRODUCTS BY DIFFERENT EXPOSURE ROUTES

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EXECUTIVE SUMMARY

There is continued interest in the possible health effects of by-products of drinking water disinfection. After initial concern regarding the potential carcinogenicity of a number of disinfection by-products, possible adverse effects on reproductive endpoints are now receiving increasing attention in epidemiological studies, particularly in the USA. Attempts are being made to refine the methods used in such studies to estimate the exposure of individuals to disinfection by-products. Some researchers have made detailed assessments of the consumption of drinking water by the subjects under study. However, exposure to disinfection by-products can also result from showering, bathing and swimming with dermal absorption and inhalation as potentially important routes of uptake. The importance of these exposure routes will differ between disinfection by-products, depending on their volatility and the extent to which they are absorbed through the skin.

The first part of this review investigates the extent of the data available on the exposure of UK adults, and pregnant women in particular, to water through different activities. It compares this information with data for the population of the USA. UK data on the frequency and duration of showering and bathing are limited and little is known about the amount of time which UK adults spend in swimming pools. There is little information specific to pregnant women in the UK. Nonetheless, the available data on drinking water intake, showering/bathing and swimming habits suggest that these are, overall, not dissimilar between the UK and the USA.

However, it is apparent from the available information that there is enormous inter-individual variability within both countries between the individuals within each country in the frequency and duration of showering, bathing and, in particular, swimming. Such exposures could make major contributions to the internal doses of some individuals if there was significant absorption of disinfection by-products during these activities. It is possible, therefore, that exposure assessments based on average exposures or which take only ingestion of drinking water into account may result in misclassifications of exposure. Part Two of the report, therefore, examines the available information on how different exposures to water relate to internal doses of disinfection by-products.

Some disinfection by-products, such as the trihalomethanes (THMs), volatilise readily in showers and swimming pools, often resulting in significant exposure by inhalation. These compounds are also lipophilic and can be fairly readily absorbed through the skin. In contrast, the haloacetic acids are non-volatile and penetrate the skin poorly. For THMs, and other disinfection by-products with similar properties, exposure assessments which do not take into account swimming, showering and other water-based activities are likely to lead to misclassification. However, for other classes of disinfection by-products which are non-volatile (or less volatile) and poorly absorbed dermally, the

contribution of such exposures is unlikely to be significant, and an accurate assessment of the consumption of drinking water and drinking water-derived drinks may be more important.

The third part of the report discusses the methodologies that would be needed to fill gaps in our present knowledge. For information about habits of bathing, showering, swimming or attendance at swimming pools by members of the UK population, it would be straightforward to conduct surveys with data recorded by diary. If attention were to be focussed on pregnant women, the recruitment of the survey sample would be more difficult, but the diary method would still be used. However, to obtain information about the relative contributions of different types of exposure to the total uptake of disinfection by-products, the required studies would involve serial measurements of intakes and uptake. Such studies would be complicated and expensive to carry out.

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1. INTRODUCTION

The potential for by-products of water disinfection to produce adverse effects on the health of consumers has been a subject of study for several decades. Initial concerns stemmed from studies which demonstrated that some disinfection by-products were carcinogenic in laboratory animals. Interest was further fuelled by some positive associations of cancers with exposure to trihalomethanes in epidemiological studies. More recently, the focus of new research on the potential health effects of disinfection by-products has shifted to the investigation of a possible association with adverse reproductive outcomes such as still-birth, low birth-weight and congenital abnormalities. A number of epidemiological studies have been carried out, primarily in the USA, some of which have found a weak positive association with one or more adverse reproductive outcome.

As epidemiological research investigating health effects possibly mediated by drinking water has developed, the methods used to assess the exposure to disinfection by-products of the individuals studied have been refined. Early studies tended to use the consumption of drinking water derived from surface or groundwaters as surrogate measures for high or low disinfection by-product concentrations, respectively. Later studies used actual measurements of trihalomethanes in the water supplies. The most recent studies investigating adverse reproductive outcomes are prospective studies which enabled the accurate record-keeping of water consumption by the pregnant women involved without recall bias.

In order to aid the interpretation of epidemiological studies some investigators, primarily in the USA, have examined the consumption of tap water by the general population and pregnant women in particular. However, exposure to disinfection by-products can also result from showering, bathing and swimming with dermal absorption and inhalation as potentially important routes of uptake. The importance of these exposure routes will differ between disinfection by-products, depending on their volatility and the extent to which they are absorbed through the skin. Differences in the metabolism of compounds when absorbed by different routes may also be important. Weisel and Jo (1996) found that chloroform ingested in tap water was completely metabolised before entering the blood stream, whereas the doses from other routes were not.

There have been studies by WRc and, more recently, DWI on tap water consumption. However, a report by WRc for the Foundation for Water Research noted that that exposure from swimming pool environments was unquantified. The variety of different swimming pool disinfection procedures employed also needs to be borne in mind. Data are likely to be more readily available for the general population than for specific groups, such as pregnant women. It was, therefore, considered important to determine whether the exposure of pregnant women to water contaminants differs from that of other sectors of the population. Information on the exposure of adults, and pregnant women in particular, in the UK and the USA to water through different activities, was gathered and presented in Part One of the report.

It became apparent from the available information that there is enormous inter-individual variability in the frequency and duration of showering, bathing and, in particular, swimming. If there was significant absorption of disinfection by-products during these activities, such exposures could make major contributions to the internal doses of some individuals. It is possible, therefore, that exposure assessments based on average exposures may be inaccurate for some individuals. Similarly, exposure assessments which take only ingestion of drinking water into account may also result in misclassifications of exposure. Part Two of the report, therefore, examines information on how different exposures to disinfection by-products relate to internal dose.

Part Three of the report discusses the methodologies that would be needed to fill some of the data gaps identified in the previous two sections of the report.

PART ONE

EXPOSURE OF ADULTS, AND PREGNANT WOMEN IN PARTICULAR, TO WATER

ACKNOWLEDGEMENTS TO PART ONE

Thanks are due to Dr Naomi Rees, of the Ministry of Agriculture, Fisheries and Food, and her group, for kindly providing data from the National Diet and Nutrition Survey of British Adults and for suggesting other sources of useful information.

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2. AIMS AND OBJECTIVES OF PART ONE

The information on the exposure of UK adults to water, which is the object of this review, is intended to contribute to the design and interpretation of epidemiological studies investigating the potential health effects of water contaminants. The aim of the review and any subsequent data collection exercise is to obtain accurate data on the exposure of UK adults to water. This is intended to allow epidemiological investigators to use more accurate estimates in their studies. An understanding of how the exposure of pregnant women to water may differ from other adults in the UK would allow an assessment of whether exposure estimates for this section of the population need to be different from those used for other UK adults.

Another aim of the review is to ascertain how similar exposures to water are for individuals in the UK and the USA. Much of the data from epidemiological studies conducted so far have been generated in the USA. A knowledge of the similarities and differences between the exposure of adults in the UK and USA to water will allow a better assessment of the extent to which associations demonstrated in epidemiological studies carried out in the USA may be applicable to the UK. A comparison of the exposures of pregnant women in the UK and the USA would also allow an evaluation of how relevant US studies on reproductive outcome are to the UK situation.

3. INFORMATION ON THE UK

3.1 Consumption of drinking water

3.1.1 DWI Tap Water Consumption Survey - 1995

One of the most recent sources of information regarding the consumption of tap water in the UK is a report of a survey carried out in 1995 by M.E.L. under contract to the DWI (DWI, 1996). For this reason, the findings of this survey are presented here in more detail than those of a previous survey carried out by the Water Research Centre (WRc). This later survey used questionnaire and diary methods to gather information on the consumption of tap water and other liquids of 1,018 individuals within 476 households in England and Wales. The survey covered all members of the household, including babies and infants. The main survey period was between 12th February and 2nd March 1995, although respondents were also asked to provide information on how their consumption varied with season and any trends over the previous 5 years.

Average consumption

M.E.L. found that the average total liquid consumption was 1.561 litres per day and that, of this, 1.138 litres per day was tap water (DWI, 1996). However, it should be noted that this value is the mean for all the individuals included in the survey and is, therefore, not specific to adults

It was also noted that, rather than a normal distribution, the distribution of water intakes is strongly positively skewed, with a relatively small proportion of the population exposed to relatively high levels of consumption. M.E.L. concluded from this that it was not useful to continue with the use of a standard arithmetic “population mean” intake figure because they considered that

- the non-normality of the sample dictates that the arithmetic mean is not a reliable measure of the central tendency of the distribution
- the reliance on the population mean as an indicator or general population exposure to tap water contamination does not give a focus on the exposure of the groups with highest tap water intakes.

It should be borne in mind that the data of all age groups were analysed together in this study. The majority of individuals with the lowest intakes will be children and infants and, therefore, the distribution of adults consumption is likely to be even more positively skewed.

Analysis by age

The consumption of both total liquid and tap water varies with age; individuals in adult age groups consume more than infants and children, as would be expected. Total liquid intake increases with age to a peak in the 46-55 age group and then declines slightly. The pattern of tap water consumption is slightly different and appears to reach a fairly steady plateau, declining less than total liquid intake in the older age groups. This means that drinking water provides the highest percentage of total liquid intake in the oldest (65+) age group. M.E.L. draw attention to a number of factors which may lead to these patterns:

- retired individuals are more likely to spend much of their time at home and, hence, tend to draw more water from tap sources than those with more mobile lifestyles

- there may be a "cohort" effect in operation, with younger generations having different preferences; it may, therefore, be that the high proportion of tap water consumption amongst the elderly may not persist when today's youth are the older generation (DWI, 1996).

Although data are presented on the mean consumption by different age categories, the report contains no information on the number of individuals in each age category in the sample questioned so it is not possible, without access to the original data, to directly calculate the mean consumption for adults only.

Analysis by gender

The M.E.L survey concluded that consumption of total liquid was higher by males (1.617 litres per day) than females (1.515 litres per day). However, females drank more (1.149 litres per day) tap water than males (1.127 litres per day) (DWI, 1996).

It should be noted that no information is provided on the number of individuals in each age range included in these analyses, nor any indication as to whether these numbers were similar for the two genders.

Analysis by socio-economic status and geographical region

An analysis of total liquid and tap water intake by social group indicated that there was very little difference between groups. Differences between regions (North, Midlands/Wales and South) found the highest total and tap water consumption in the North and the lowest in Midlands/Wales (DWI, 1996).

Analysis of those with particularly high intake

The 26 individuals with the highest water consumption (approx. 2.5% of the sample) had an average tap water consumption of over 2.4 litres per day, roughly double that of the population average. Although recognising that the sample size was smaller than

recommended for the purpose and that there may be a high degree of inter-correlation of the variables, M.E.L. carried out further analyses which indicated that these individuals were more likely to be found:

- in the older age groups
- amongst the retired or not economically active
- in the Northern region (DWI, 1996).

Behavioural analysis of tap water drinking

As much as 81.5% of all tap water consumption was reported to be taken as tea, coffee or other hot drinks. Tap water itself provided 9.2% of the consumption and other cold drinks comprised 7.5% (the remaining 1.8% is designated as other sources).

M.E.L. also examined the ownership and use of appliances for the preparation of water prior to its consumption. The most significant ownership (12% of households) was of water filtering jugs, and half of these owners reported using the jugs most days or every day. Only 16% of owners of "soda-stream" type appliances (10% of households) reported using it most days or everyday. As many as 41% of the 9% of households with cold water dispensers in the fridge said their used was confined to certain times of the year, and 26% never used it.

In response to a question as to whether they treated the water in any way prior to consumption, 11% of households reported that they boiled tap water and allowed it to cool before using it, 9% reported filtering it and 2% said they used sterilising tablets (DWI, 1996).

It should be noted that the questionnaire used by M.E.L. requested information on the source of tap water in drinks, so that the surveyors could allocate it to the domestic water supply or as being obtained from a commercial premises. Information as to whether tap water was consumed at home or outside the home is not provided in the report.

Consumption of bottled water

Only 1% of the households reported that there were members of the household which do not use tap water at all for drinking or for making drinks. However, 31% reported using other sources of water of which most (30%) referred to bottled water. Although 95% of households reported that people in the household used water from the kitchen cold tap to make drinks, 3% said that people often used the kitchen hot tap and a further 7% said that this occurred sometimes.

30% of the households surveyed reported using bottled water for drinking. Although M.E.L indicated the need for further analysis, they suggested that the apparent increase in both bottled water and tap water consumption in the years preceding the survey, while the total liquid consumption remained almost totally static, suggested that bottled water has acted as a substitute for other drinks rather than replacing tap water (DWI, 1996).

Seasonal changes in water consumption

Individuals in the survey were asked to comment on how their consumption of various types of drinks varied with season. Most respondents indicated that their consumption of tea and coffee was broadly constant throughout the year although some, particularly in the younger age groups, drank more in the winter than summer (a smaller number of individuals drank more tea in summer). Consumption of squash and bottled water showed more seasonal variation, with the older age groups showing more seasonal variation than younger ones in their consumption of these drinks. M.E.L. commented that these trends indicate that the survey results may suggest an over-representation of tea and coffee and an under-representation of cold drinks when compared to the true annual average consumption, although this was regarded as a speculative point. They also pointed out that this may also have led to an over-estimation of the tap water fraction of total liquid intake, if the consumption of cold drinks has a lower tap water fraction than for tea and coffee (DWI, 1996).

3.1.2 WRc Drinking Water Consumption Survey - 1978

The WRc report on drinking water consumption in Great Britain (Hopkin and Ellis, 1980) used methods of data collection similar to those later employed by M.E.L. (i.e. diaries and interviews) although the differences in study design prevent any direct comparisons being made. A total of 3632 individuals from 1320 households were included in the sample; 2722 of these were adults (i.e. at least 16 years old). The survey included Scotland, England and Wales but not Northern Ireland.

Because they are older than the data collected by M.E.L., the results of this survey are not considered in great detail here. However, the summary data are included for comparison with the later information gathered for DWI. In addition, the detail provided in the report allows the derivation of average consumption for adults only.

Average consumption

Hopkin and Ellis (1980) reported a mean total liquid intake of 1.589 litres per day and a mean total tap water consumption of 0.955 litres per day. These figures are not dissimilar from the figures found in the M.E.L. survey in 1995.

Analysis by age

By combining the data for the three adult age groups, the data from the survey were used to calculate the mean consumption for adults only. The mean total liquid consumption for adults was 1.79 litres per day and the mean tap water consumption was 1.07 litres per day. Hopkin and Ellis found that total liquid intake increased with age up to the range 18-30 and then decreased.

Analysis by gender

By combining the three adult age groups, the data from the survey show that the mean total liquid consumption for adult males was 2.04 litres per day and that the mean tap water consumption was 1.13 litres per day. The corresponding figures for women were 1.55 litres per day and 1.04 litres per day.

Analysis by socio-economic status and geographical region

This survey found that the intake of both total liquid and tap water decreased with higher economic status.

The highest intake of both total liquid and tap water was reported in the North of England, followed by Central England/Wales. Consumption of total liquid was higher in Scotland than in Southern England, but drinking water consumption was lower.

Behavioural analysis of tap water drinking

The Hopkin and Ellis report contains considerable detail on the types of drink consumed by each age/gender group which are beyond the scope of this report. However, data for adults indicate that of the 1.07 litres per day mean total tap water intake, 0.95 litres per day (88.8%) was taken as hot drinks and 0.12 litres per day (11.2%) as cold drinks.

One important factor included in the report is the split between consumption within and away from the home. The consumption of total liquid at home was found to be similar for males and females. Adult males, whose intake is higher than for adult females, therefore tended to consume more outside the home than females. Men also tended to consume more tap water away from the home than women.

3.1.3 The National Diet and Nutrition Survey of British Adults, 1986-7

This survey collected information for the Ministry of Agriculture, Fisheries and Food on the dietary intake of non-pregnant adults aged 16-64. It was designed primarily to provide information on nutrition, but also provides information on water consumption which is believed to be fairly reliable (data provided by MAFF).

Average consumption

The mean consumption of total liquids by all adults in the survey was found to be 1.589 litres per day, while the mean figure for tap water consumption was 0.932 litres per day.

Analysis by age

The average intake of both tap water and total liquids was found to increase with age, tailing off slightly in the oldest age category. The total liquid intake decreases more than the tap water intake, meaning that tap water is a higher percentage of total liquid intake for this age group than for younger individuals.

Analysis by gender

The consumption of tap water by males (0.950 litres per day) and females (0.915 litres per day) was found to be fairly similar, while males, on average, consume more total liquid (1.849 litres per day) than females (1.335 litres per day).

Analysis by geographical region

The data from the National Diet and Nutrition Survey have been examined by four regions: Scotland; Northern England; Central and South West England and Wales; and London and the South East of England. In Scotland, 3.6% of the individuals questioned did not drink tap water, whilst all participants in the survey in the other regions drank tap water. The highest consumption was found in Central and South West England and Wales (0.96 litres per day) closely followed by London and the South East (0.95 litres per day). Average consumption in Northern England was 0.91 litres per day while the average intake for the population in Scotland was 0.82 litres per day.

Seasonal changes in water consumption

The consumption of tap water by adults was found to vary with season. For males, the highest consumption was in the summer (0.98 litres per day), dropping to 0.97 litres per day and 0.95 litres per day in the autumn and spring, respectively, with a low of 0.89 litres per day in the winter. This pattern was different for women, with lower intakes reported in the winter (0.87 litres per day) and summer (0.88 litres per day) than in the autumn (0.93 litres per day) and spring (0.98 litres per day).

3.1.4 Summary

Table 3.1 contains information on the mean consumption of total liquid and tap water as found by the various surveys in the UK.

Table 3.1 UK consumption of total liquid and tap water

	DWI, 1996 (total population)	Hopkin and Ellis, 1980 (total population)	Hopkin and Ellis, 1980 (adults)	MAFF (adults)
Mean consumption of total liquid (litres per day)	1.561	1.589	1.79	1.589
Mean consumption of tap water (litres per day)	1.138	0.955	1.07	0.932

3.2 Frequency and duration of showering and bathing

Much of the research into the use of showers and baths in the UK has been carried out to provide information related to water demand and, therefore, concentrates on the volume of water consumed rather than on an individual's exposure to the water. Market research into showers tends to concentrate on what types of products are sold and to whom, rather than the way they are used once they have been purchased (David Hodges, WRc-NSF ETC, pers comm). For these reasons, there appear to be few accurate data available on the frequency and duration of individuals' showering in the UK.

Nonetheless, estimates for showering and taking baths which are often used are:

- Showers 7 times per week, 6 minutes duration
- Baths Twice per week, 13-27 minutes duration

Other factors taken into account are that women are reported to spend longer in the bath than men and that consumption by showers is rising due to the greater use of "combination boilers" in houses (David Hodges, WRc-NSF ETC, pers comm).

A report for the Department of the Environment (Herrington, 1996) examined the demand for water in the UK, attempting to predict demand up until the year 2021 with a particular emphasis on the "South and East" of England and Wales. Amongst the data and assumptions used in calculating water demand, Herrington cites a preferred length of time spent in a power shower as 7.5 minutes (obtained from a study by Three Valleys Water Services plc in 1989). This survey also found that, on average, individuals took 0.73 baths and/or showers per day and Herrington concluded that the average total washing frequency in the South and East was unlikely to rise above 0.8/head/day by 2021 (i.e. 5½ baths and/or showers per week) (Herrington, 1996).

As part of a project to relating to different micro-components of domestic water demand, WRc has obtained data on water flows in five different residences. From the flow characteristics it is possible to identify some uses of water such as filling baths, taking showers, washing machine cycles and toilet cistern refilling with a good degree of

certainty. However, there is a possibility of some mis-classification and a so-called "Hawthorn effect", which leads people to change their water-use habits (reducing their use) when they know that it is being monitored, also needs to be borne in mind (Mark Kowalski, WRc, pers comm.). The data in Table 3.2 summarise the data on showering and bathing obtained from these five residences. The households contained between 3 and 5 individuals and were monitored for time periods of between 1.5 and 15 days. Sites 1, 3, and 5 were monitored over longer time periods (12, 15 and 14 days respectively) than sites 2 and 4 (3.5 and 1.5 days respectively) and, therefore, data from these sites should be regarded as more reliable. Because the information was obtained from water flow characteristics, data for the length of time for which individuals remained in the bath are not available. No information is available as to the ages of the individuals, nor as to whether any member of the household was pregnant.

Table 3.2 Frequency of showering and taking baths in five residences

Site	Mean number of showers per person per day	Mean number of baths per person per day	Mean number of showers and/or baths per person per day	Mean duration of showers (minutes)
1	0.56	0.28	0.83	3.52
2	1.09	0.29	1.37	5.75
3	0.22	0.44	0.67	2.26
4	0.33	0.17	0.50	0.93
5	1.31	0.64	1.95	8.61
Total of all sites	*0.72*	*0.43*	*1.15*	*6.39*

Source: WRc

Obviously these data are limited and conclusions should be drawn with caution. Nonetheless, a wide variation in the number of showers/baths taken and the duration of showers between residences can be seen. However, it is of interest that the average duration of all the showers taken in all residences (6.4 minutes) is similar to the estimate reported to be widely used (6 minutes) and the reported (Herrington, 1996) preferred length of time spent in a power shower (7.5 minutes). The average mean number of showers/baths per person per day, at 1.15 is higher than the 0.8 predicted by Herrington (1996) as the maximum estimated for 2021.

For comparison, researchers in the Netherlands have also been active in measuring the contribution of showering to domestic household demand. Groot-Marcus *et al.* (1995) examined the use of showers by 233 individuals. An average shower frequency of

0.6 litres per day was found, with an average showering time of 5 minutes. No difference in the time spent showering was found between the sexes, but younger people took longer showers than older ones. Achtienribbe (1996) found individuals took an average 0.63 showers and 0.17 baths per day in 1995.

3.3 Frequency and duration of swimming

The various sports councils in the UK hold data on participation in sports in the UK. These data are collected as part of General Household Surveys carried out within the Regions and, as such, are limited in detail. Nonetheless, summary data (Table 3.3) and, in some cases, more detailed data have been obtained from Sport England, Sport Scotland and Sport Wales. Data included on Great Britain as a whole is obtained from the General Household Survey (Sport England/UK Sport, 1999) and has also been presented by the Institute of Sport and Recreation Management (ISRM) (Taylor and Kwok, 1998).

Table 3.3 Participation of UK adults in swimming

Adults	England 1996 (note *)	Wales 1997-98 (aged 15 years or over)	Scotland 1995-97 (data for the most popular two months for the sport)	GB 1996 (Swimming: indoor)
% participating in swimming in the previous month	12%	13%	21%	12.8%
% participating in swimming in the previous 12 months	35.1%	ND	ND	35.1%

* The data for England were provided by Sport England over the telephone. However, it seems likely that they have been derived from the General Household Survey report for Great Britain.

Additional data available on participation are included in Table 3.4.

Table 3.4 Additional information on participation in swimming

	Wales	Scotland	GB (Swimming: indoor)
Frequency of swimming	Of those who swim, the average frequency in the previous four weeks was 3.8.	56% participate less than once a week 24% participate once a week 20% take part more than once a week	Of those who swim, the average frequency in the previous four weeks was 4. The average frequency of participation per adult per year was 6
Gender differences	10.9% of men participated in last 4 weeks 15% of women participated in last 4 weeks	60% of participants are women 40% of participants are men	11 % of men participated in last 4 weeks 15% of women participated in last 4 weeks 32 % of men participated in last 12 months 37% of women participated in 12 months
Age	Age Group: 15-24, 25-34, 35-44, 45-54, 55-64, 65+ % taking part: 25.3, 19.4, 14.5, 10.4, 6.6, 2.9	Age Group: 16-24, 25-34, 35-55, 55+ % of pop: 15, 20, 33, 32 % of those taking part: 21, 31, 36, 12	Age Group: 16-19, 20-24, 25-29, 30-44, 45-59, 60-69, 70+ % taking part in last 4 weeks: 18.2, 16.2, 17.8, 19.5, 9.6, 7.6, 2.9 % taking part in last 4 weeks: 56.6, 50.2, 52.5, 50.5, 28.7, 17.7, 6.2

In addition, the National Sports Medicine Institute carried out a literature search for papers on participation in swimming using the "SPORT" database. Very few published papers were located, none of them more recent or comprehensive than the statistics cited above.

3.4 Differences in exposure between pregnant women and other adults

There appear to be few data available to indicate how the exposure of pregnant women to water might differ from that of other adults in the UK. However, it was considered that women might receive advice during pregnancy which may influence their behaviour in

ways which alters their exposure to water. Therefore, a number of organisations involved in providing advice to health care practitioners were consulted for details of the guidelines which they provided for their members on this issue. A key source of advice appears to be "The Pregnancy Book", a 130-page publication which the Health Education Authority (HEA) distributes, through health professionals, to all first-time mothers during the first three months of their pregnancy. The book contains a short section with advice for pregnant women on what to eat and drink and on physical activity. Professional organisations such as the Royal College of Midwives (RCM), the Community Practitioners and Health Visitors Association (CPHVA), the Royal College of Nurses (RCN) and the Royal College of Obstetricians and Gynaecologists (RCOG) were also consulted. In addition, information was received from 6 pregnant women or recent mothers at WRc/WRc-NSF on the advice they received during their pregnancy.

A potential source of information regarding the water intake of pregnant women is the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) being conducted by Professor Golding of Bristol University. This study has followed several thousand mothers and children in Avon from pregnancy through to school age. Detailed questionnaires are used to collect data on many aspects of the health and habits of the mother and the environment in which the children grow up. These include questions about the intake of food and drink and, although tap water is not included as a category, respondents are asked about their consumption of tap water based drinks such as tea and coffee and also to provide details of their intake of "other drinks" (Children of the 90s questionnaires, 1991/2).

3.4.1 Consumption of drinking water

The Health Education Authority's (HEA) Pregnancy Book contains advice on foods which are recommended during pregnancy as well as those to avoid. Pregnant women are advised to "Have drinks which contain caffeine - coffee, tea and colas - in moderation, as there may be a slight risk that too much caffeine will affect your baby's birth weight. Try decaffeinated coffee, fruit juice or mineral water."

The Community Practitioners and Health Visitors Association (CPHVA) indicated that their members would ask pregnant women about their normal intakes of caffeinated drinks and, if the intake is particularly high, might suggest that they reduce their intake. It is, therefore, likely that this intake might be replaced by tap water. However, they wouldn't specifically advise women to avoid coffee in the same way that they would advise them to avoid unpasteurised cheese, for example. They would also not specifically advise pregnant women to drink bottled water; indeed, if asked they would advise that bottled waters can contain very different mineral contents and some might not be appropriate. If pregnant women are concerned about lead from piping in old houses then they would be advised to run the water before drinking (pers comm). The Royal College of Midwives also indicated that they do not consider there are any special requirements for pregnant women with respect to drinking water (pers comm).

Some of the pregnant women/recent mothers at WRc/WRc-NSF commented that although they had not specifically been advised to drink more water during pregnancy, the advice that they received to avoid or reduce intake of alcohol and caffeine-containing drinks meant that they drank more tap water. None reported having been advised to drink bottled water in place of tap water (pers comm).

3.4.2 Frequency/duration of showers and bathing

No information was found which would allow an assessment of whether the showering/bathing habits of pregnant women are any different from other adults.

3.4.3 Frequency/duration of swimming

The HEA's Pregnancy Book recommends that women should keep up their normal daily physical activity or exercise for as long as they are comfortable doing so, but also specifically suggests that they may wish to try swimming, because the water will support their increased weight (HEA, 1997). The Community Practitioners and Health Visitors Association (CPHVA) indicated that their members give advice to pregnant women along the lines of that contained in the HEA's Pregnancy Book. Women who regularly exercise (e.g. running, keep fit classes etc.) are advised to reduce the amount and intensity of the exercise during pregnancy, allowing the body to dictate. Swimming is suggested as a good exercise (pers comm). The Royal College of Midwives indicated that they would not actively encourage previously inactive women to swim, but that pregnant women intending to exercise would be advised that swimming is the best form of exercise for pregnant women (pers comm.) The Royal College of Obstetricians and Gynaecologists do not have an official guideline regarding advice on exercise and fluid intake during pregnancy, and a spokesperson indicated that advice given by General Practitioners on these matters was more likely to be based on personal experience than scientific evidence (pers comm).

All six of the women at WRc/WRc-NSF had been advised that swimming was a good exercise to participate in while they were pregnant, and a number had been given the details of aqua-aerobics or aqua-natal classes run at local pools by a health visitor or midwife (pers comm). The Institute of Sport and Recreation Management (pers comm) also commented that specific swimming classes are run for pregnant women. It is, unfortunately, unlikely that any data are available which would indicate the extent to which such advice is followed by pregnant women, and how much it changes their usual patterns of behaviour.

The National Sports Medicine Institute carried out a literature search for papers on participation in swimming using the "SPORT" database. No papers relating specifically to the exposure of pregnant women were located.

4. INFORMATION ON THE USA

A number of national and local studies have been carried out in the USA to consider the exposure of individuals to water. Summaries of the key studies can be found in the United States Environmental Protection Agency (US EPA) Exposure Reference Handbook (US EPA, 1997) which is intended to provide suitable defaults for exposure estimates. The International Life Sciences Institute (ILSI) have also published a useful compilation (Johnson *et al.*, 1999). The following section does not attempt to summarise these data and concentrates, instead, on the key studies used by the USEPA to derive suitable assumptions for exposure.

4.1 Consumption of drinking water

In a document intended to provide suitable defaults for exposure estimates, the US EPA have reviewed a number of surveys of water intake carried out in the USA and elsewhere (US EPA, 1997). A summary of the reports considered by the US EPA to be key or relevant is contained in Table 4.1.

The reviewers considered the studies by Ershow and Cantor (1989) and the Canadian Ministry of Health and Welfare (1981) to be the key studies and based their recommendations on the findings from these findings. The US EPA's recommendations resulting from this review were that a value of 1.41 litres per day be used as tap water intake of adults. The value expressed on a ml/kg bodyweight basis was recommended as 21 ml/kg bodyweight/day. An intake of 2.35 litres per day (or 34.2 ml/kg bodyweight/day) is recommended as the 90th upper percentile value.

The reviewers considered the key studies on which these recommendations were based to be of high quality and representative of the US population. However, they rated their confidence in the tap water intake recommendations only as medium as the data, although regarded as excellent, are not current.

Table 4.1 Tap water consumption rates

Mean (litres/day)	90th percentile (litres/day)	Country	Reference
1.38	2.41	Canada	Canadian Ministry of Health and Welfare, 1981
1.41	2.28	USA	Ershow and Cantor, 1989
1.30 (age higher than the US average)	2.4	USA	Cantor *et al.*, 1987
1.63 (calculated)	-	Calculated from a number of sources (largely references on physiology)	NAS, 1977
1.25	1.90	New Zealand	Gillies and Paulin, 1983
1.04 (25 to 30 yrs)	-	USA	Pennington, 1983
1.26 (60 to 65 yrs)	-	USA	Pennington, 1983
1.04-1.47	-	USA	US EPA, 1984
1.37 (20 to 64 yrs)	2.27	USA	Ershow and Cantor, 1989
1.46 (65+ yrs)	1.46	USA	Ershow and Cantor, 1989
1.15		USA	USDA, 1995
1.07	1.87	Great Britain	Hopkin and Ellis, 1980

Adapted from US EPA (1997).

Studies examined also indicated variations in total fluid and total tap water intake with increased temperatures and increased physical activity. The US EPA (1997) noted that data on intake rates for individuals undertaking strenuous exercise under different environmental conditions were limited, but suggested the use of data from the US Army be used: 6 litres per day for active adults in temperate climates and 11 litres per day in hot climates.

Behavioural aspects

Shikomura *et al.* (1998), in a study of pregnant women and their male partners (see Section 4.4.1) obtained detailed information on the storage of tap water before consumption. Slightly over half (53%) of the 33 women drank tap water at home and, of these, 28% stored the water before consumption, for an average 1.4 ± 0.8 days. Of the women who drank tap water-based beverages (59% of those in the survey) all stored the beverage prior to consumption, for an average 5.1 ± 3.1 days. Most (89%) beverage containers were closed during storage.

A survey of drinking water intake of 71 pregnant and 43 non-pregnant women in Colorado (see Section 4.4.2) also collected information on behavioural differences relating to drinking water. The use of bottled water as the primary source of drinking water at home was 14.1% by pregnant women and 11.6% by nonpregnant women and the use of a water filter at home was 11.3% by pregnant women and 16.3% by non-pregnant women; neither of these differences was significant at the $p<0.05$ level. It should be noted that the study population was drawn from women visiting health clinics and is a group weighted towards those of lower socio-economic status and probably not representative of the US population as a whole (Reif *et al.*, 1999 and John Reif, pers comm).

4.2 Frequency and duration of showering and bathing

A review of studies on activity patterns in the USA is included in the US EPA Exposure Factors Handbook. One of the studies (Tsang and Klepeis, 1996) includes information on bathing and showering habits, based on recall of the day previous to an interview. The data collected include information on the frequency and duration of showering and bathing and also on the length of time spent in the bath/shower-room immediately after the bath/shower. The data used were collected between October 1992 and September 1994 as part of the National Human Activity Pattern Survey (NHAPS) conducted by the US EPA. The dataset is regarded as being representative of the US population and has been adjusted to be balanced geographically, seasonally and for day and time of day (US EPA, 1997). These data have been used as the basis for the US EPA's derivation of recommendations of default exposures to use in risk assessments.

Bathing

Approximately 7% of the participants in the NHAPS study indicated they had either taken or given at least one bath in the day. The majority of these correspondents had taken or given one bath. The recommended bathing duration chosen by the US EPA is 20 minutes, based on the 50th percentile value of the NHAPS distribution; the reported 90th percentile is 45 minutes (US EPA, 1997). However, it is not clear how relevant these data are to the estimation of average exposure of adults to water through bathing. It must be remembered that the majority of respondents (all but 7%) had not indicated giving or taking a bath and that a proportion of these records could have been adults giving baths to children. Nonetheless, the US EPA considers it has high confidence in the recommendation for bathing frequency (US EPA, 1997)

Showering

The data from the NHAPS study indicate that approximately 38% of the respondents had taken at least one shower the previous day. These individuals reported having taken between one and ten showers the previous day, with a majority (76%) having taken one. The US EPA have based their recommended shower frequency of one shower per day on this information and indicated high confidence in this recommendation (US EPA, 1997).

The US EPA recommended a showering time of 10 minutes, and has high confidence in this recommendation (US EPA, 1997). This is described as being based on professional judgement, and also the data collected by Tsang and Klepeis (1996) (US EPA, 1997). The majority of all respondents taking showers reported spending either 0-10 minutes (46%) or 10-20 minutes (38%) in the shower and these figures were similar for adults (aged 18-64) only: 47% and 37%, respectively. A shower duration of 10 minutes was the 25th percentile, not only when all correspondents were considered, but also when data for males, females or adults aged 18-64 were considered separately. The 50th percentile was 15 minutes for all these categories, while the 91st percentiles were 30 minutes (Tsang and Klepeis, 1996; cited in US EPA, 1997).

"Bathing events" - showering and bathing

Other studies are also available regarding showering and bathing habits:

Tarshis (1981; cited in US EPA 1997) compiled data on the habits, tastes, lifestyles and attitudes of the American people which included data on showering and bathing. The US EPA (1997) noted the study has limitations such as its age and the fact that data are compiled from a number of other sources (small surveys, magazines, the newspaper advertising bureau) but, nonetheless considered these frequency data to be useful. Data of relevance to adult exposures to water are:

- 90% of all Americans take some sort of bath in an average 24 hour period
- 5% average more than 1 shower or bath a day
- 75% of men shower, 25% take baths
- 50% of women shower, 50% take baths
- People are more likely to shower than bathe if they are young and have a higher income
- Showering is more popular than bathing in large cities.

Data reported by Robinson and Blair (1995; cited in Johnson *et al.*, 1999) also suggest a higher frequency of showering/bathing than that reported in the NHAPS survey. The data, as summarised by Johnson *et al.*, indicated that 91% of respondents had taken either a shower or an bath on the sample day, with 15% of respondents having taken a bath and 76% a shower.

Prior to the compilation of the recent Exposure Factors Handbook, the US EPA (1992; cited in US EPA, 1997) had recommended a central and upper recommended default for dermal exposure via "bathing" (presented to be representative of baths as well as showers) of:

- Central 10 mins/event, 1 event/day, 350 days/yr, exposure duration 9 years
- Upper 15 mins/event, 1 event/day, 350 days/yr, exposure duration 30 years

Time spent in the bathroom/shower room immediately after bathing or showering

The amount of time spent in the shower room or bathroom after showering or bathing was also examined in the NHAPS study. This is particularly relevant to inhalation exposure to volatile contaminants of water.

The majority of adults aged 18-64 (72%) spent 0-10 minutes in the shower room immediately after showering. This proportion was slightly lower for females (all age groups, 66%) than males (all age groups, 77%). The 50th percentile for all these groups was 5 minutes. However, whilst the 90th percentile for males (all age groups) was 15 minutes, the 90th percentile for females (all age groups) and adults aged 18-64 (both sexes) was 20 minutes.

The majority of adults who had taken or given baths also reported spending 0-10 minutes in the bathroom immediately after bathing (68% for the 18-64 age group). The 50th percentile was 5 minutes for males, females, adults age 18-64 and for all adults. The 90th percentile was 12 minutes for males (both adult age groups) and 20 for females (both adult age groups), 15 minutes for the 18-64 age group (both sexes) and 20 minutes for the overall sample (reflecting 30 minutes for the >64 age group).

4.3 Frequency and duration of swimming

The US EPA used data collected in the NHAPS study by Tsang and Klepeis (1996) as the basis for their recommendations for assumptions of swimming frequency. About 7% of the participants in the survey reported having been swimming in a freshwater pool in the previous month, with some individuals having gone swimming as many as 60 times. However, 23% of those respondents who swam reported swimming once a month. The US EPA, therefore, have suggested one event/month as the recommended swimming frequency for the general population. The recommended swimming duration is 60 minutes per swimming event. This is the 50th percentile value found in the NHAPS survey; the 90th percentile is 180 minutes per swimming event (based on one event per month). The US EPA consider that they have high confidence in the derived recommended activity pattern for swimming.(US EPA, 1997).

However, it should be noted that these recommendations are based on data for the full age range. Table 4.2 shows separate data for older children and adults as well as for all respondents who swam. It should, however, be borne in mind that the majority of respondents had not reported swimming in the previous month at all.

Table 4.2 Number of minutes spent swimming in a month in a freshwater swimming pool (minutes/month)

Category	10th Percentile	50th Percentile	90th Percentile
Overall	15	60	180
Male only	10	45	180
Female only	15	60	180
Age 12-17	20	60	180
Age 18-64	10	45	180
Age >64	10	40	120

Adapted from US EPA (1997) citing Tsang and Klepeis (1996)

Prior to the compilation of the recent Exposure Factors Handbook, the US EPA (1992; cited in US EPA, 1997) had recommended a central and upper recommended default for dermal exposure via swimming of:

- Central 0.5 hr/event, 1 event/day, 5 days/yr, exposure duration 9 years
- Upper 1.0 hr/event, 1 event/day, 150 days/yr, exposure duration 30 years

4.4 Differences in exposure between pregnant women and other adults

4.4.1 Drinking water

Data gathered in the 1977-78 Nationwide Food Consumption Survey (NFCS) by the United States Department of Agriculture (USDA) was analysed by Ershow and Cantor (1991) to estimate the effects of pregnancy and breast-feeding on the intake of total fluid and total tap water by women (Table 4.3). The intake by pregnant, lactating and control women aged between 15 and 49 was compared. The highest intakes were by lactating women, whilst the intake by pregnant women was only slightly higher than for control women.

Table 4.3 Mean intake of tap water and total fluids by pregnant, lactating and control women

	Total fluid intake		Total tap water intake	
Reproductive status	Mean (litres/day)	90th percentile (litres/day)	Mean (litres/day)	90th percentile (litres/day)
Control	1.940	2.831	1.157	1.983
Pregnant	2.076	3.028	1.189	2.191
Lactating	2.242	3.169	1.310	1.945

Adapted from USEPA, 1997; citing Ershow *et al.*, 1991

The US EPA have based their recommendations for assumptions regarding drinking water intake rates for pregnant and lactating women on this study:

- Mean for pregnant women 1.2 litres per day (18.3 ml/kg bodyweight/day)
- Mean for lactating women 1.3 litres per day (21.4 ml/kg bodyweight/day).

It is, therefore, worth noting that, although the drinking water intake of pregnant women has been found to be more than other women of child-bearing age, it is still less than the average for the adult population as a whole.

A more recent study comparing water intake by pregnant and non-pregnant women has recently been carried out by Reif and co-workers in Colorado. They found a much higher daily intake of tap water by both pregnant (3.4 litres) and non-pregnant (3 litres) women than reported by Ershow *et al*. This is likely to be due to both the dry climate in Colorado and, possibly, some double reporting of categories of intake. The differences in intake between pregnant and non-pregnant women were not statistically significant. It should be noted that the study population was drawn from women visiting health clinics and is a group weighted towards those of lower socio-economic status and probably not representative of the US population (Reif *et al.,* 1999 and John Reif, pers comm).

Shimokura *et al.* (1998) compared the water intake of pregnant women and their male partners and found that their water consumption habits were similar. Cold tap water consumption at home differed with employment status (see Table 4.4).

Table 4.4 Water intake by pregnant women and their male partners (litres)

	Mean	10th percentile	50th percentile	90th percentile
Daily intake of total water				
Women	1.86	1.17	1.75	2.33
Men	1.68	0.70	1.59	2.39
Daily intake of tap water				
Women	0.78	0.20	0.62	1.39
Men	0.78	0.25	0.81	1.23
Daily intake of cold tap water at home				
All women	0.37	0	0.26	0.97
Employed full time	0.28	0	0.15	0.60
Employed part-time or less	0.47	0	0.42	1.04
All men (91% employed)	0.29	0	0.15	0.69

Data from Shimokura *et al.*, 1998.

In contrast to the individuals studies by Reif *et al.*, the individuals studied by Shimokura *et al.* were from a high socio-economic group.

4.4.2 Frequency and duration of showering/bathing

The US EPA Exposure Factors Handbook contains no information on the frequency and duration of showering and bathing which is specific to pregnant women.

A recent questionnaire survey by Reif *et al.* of the exposure of 71 pregnant and 43 non-pregnant women to water included information on showering and bathing. Showering habits were nearly identical, with a mean frequency of 7.1 showers per week and a mean duration of 13.9 minutes per shower recorded for both pregnant and non-pregnant women. Bathing was significantly ($p<0.05$) more frequent among pregnant women (3.0 per week) than non-pregnant women (1.4 per week) but the average duration was longer among non-pregnant women, although not significantly so (Reif *et al.*, 1999 and John Reif, pers comm).

Another study (Shimokura *et al.,* 1998) comparing the habits of 33 pregnant women and 32 of their male partners found that 79% of the women and 94% of men took showers at least daily for an average of 11.6 ± 4.0 and 10.4 ± 4.8 minutes, respectively. However, 47% of showers taken by women and only 25% of showers taken by men were longer than 10 minutes in duration. Of the pregnant women, 18% took a bath at least daily and 21% bathed occasionally. The corresponding figures for men were 3% and 3%. The average duration of baths was 22.9 ± 10.1 minutes for women and 21.3 ±12.4 for men. Whilst these data indicate difference in the bathing habits in a small sample of men and pregnant women, it does not establish whether these differences are due to the pregnancy or, more likely, to gender differences.

4.4.3 Frequency and duration of swimming

The US EPA Exposure Factors Handbook contains no information on the frequency and duration of swimming which is specific to pregnant women.

5. COMPARISON BETWEEN UK AND USA BASED ON AVAILABLE DATA

5.1 Consumption of drinking water

The consumption of drinking water reported from studies in the UK (see Table 5.1) is less than the 1.4 litres recommended by the US EPA for default exposure assumptions. However, it is of interest that a number of studies on tap water consumption in the USA have reported mean intakes lower than this, some of them not dissimilar from the consumption for adults in the UK reported by Hopkin and Ellis (see Table 4.1).

Table 5.1 UK consumption of tap water

	DWI, 1996 (total population)	Hopkin and Ellis, 1980 (total population)	Hopkin and Ellis, 1980 (adults)	MAFF (adults)
Mean consumption of tap water (litres per day)	1.138	0.955	1.07	0.932

There may be behavioural differences between drinking water consumption in the UK and the USA. For example, Shimokura *et al.* (1998), in a study in the USA, found that cold tap water-based beverages were stored for an average of 5 days before consumption.

Regional differences have been noted in the UK and are likely to be even more significant in the USA, where there is a wider range of climatic conditions. There is considerable variation in consumption between individuals in the surveys on both sides of the Atlantic.

5.2 Frequency and duration of showering and bathing

The US EPA (1997) recommendations for exposure assessment by showering and bathing are shown in Table 5.2. However, these are based on data in which a wide variation in bathing habits is apparent (see Section 4.2).

Table 5.2 US EPA recommendations for exposure assessment of bathing activities

	Showers		Baths		Showers/Baths	
	Frequency (per day)	Duration (minutes)	Frequency (per day)	Duration (minutes)	Frequency (per day)	Duration (minutes)
US EPA (1997)	1	10	-	20	-	-
US EPA (1992) (Central)	-	-	-	-	1	10 mins

Estimates of bathing and showering habits derived in the UK from various sources (see Section 3.4.2) are shown in Table 5.3. Although the WRc data are based on a very limited sample size (18 individuals) monitored over a limited period, they also showed considerable variation.

Table 5.3 Estimates of showering and bathing habits in the UK

	Showers		Baths		Showers/ Baths
	Frequency (no per day)	Duration (minutes)	Frequency (no per day)	Duration (minutes)	Frequency (no per day)
Common Estimates	1	6	0.3	13 - 27	
Herrington		7.5			0.73 (1989) 0.8 (predicted)
WRc data	0.72	6.4	0.43		1.15

5.3 Frequency and duration of swimming

Table 5.4 compares information on swimming habits in the UK and the USA. The number of participants in this activity is relatively low in both countries, as assessed by a question about participation in the previous month. The wide variations in frequency of swimming should be noted and it should also be borne in mind that swimming is likely to be, at least in part, a seasonal activity.

Table 5.4 Comparison of swimming habits in Great Britain and USA

	GB 1996	USA (NHAPS, 1994-96)
% participating in swimming in the previous month	12.8%	7%
% participating in swimming in the previous 12 months	35.1%	
Average duration		50th percentile: 60 minutes
Frequency	4 per month (average frequency of swimmers)	1 per month (26% of swimmers; USEPA recommended frequency)

5.4 Differences in exposure between pregnant women and other adults

Data from the USA indicate that pregnant women drink slightly more tap water than other women of childbearing age, but that the mean intake is lower than for US adults in general. The following table (Table 5.5) compares the consumption by adult women in the UK with information on non-pregnant, non-lactating women in the USA (Ershow and Cantor, 1991, cited in US EPA, 1997). This suggests that intake of total liquid by women in the USA is higher than in the UK, but that consumption of tap water in the two countries is more similar. Whether this is a sufficient basis to assume that intake by pregnant women is also likely to be broadly similar in the UK and USA is not clear. It is possible that social factors influencing habits during pregnancy could be different on different sides of the Atlantic, leading to different exposures.

Table 5.5 Comparison of water intake by adult women in the UK and USA

Data for **adult females**	Ershow and Cantor, 1991 (control** women) USA	DWI, 1996 (all age groups)	Hopkin and Ellis, 1980 (adults) *	MAFF (non-pregnant adults)
Mean consumption of total liquid (litres per day)	1.940	1.515	1.547	1.335
Mean consumption of tap water (litres per day)	1.157	1.149	1.044	0.915

* Calculated from data presented in the report
** i.e. non-pregnant, non-lactating

6. GAPS IN DATA FOR UK ADULTS IDENTIFIED

6.1 Consumption of drinking water

National surveys of drinking water consumption have been undertaken in recent years. However, water consumption figures in the most recent report (DWI, 1996) are for the population as a whole; data for the adult population only are not presented. These data on drinking water consumption in England and Wales collected by M.E.L. for the DWI have been subjected to preliminary analyses. However, constraints on available resources precluded analyses which may have yielded additional useful information. M.E.L. themselves suggested that "further analysis could be carried out on the existing data to characterise the distribution and patterns of behaviour in more detail". They also concluded that "more information is needed on particular seasonal or temperature-related consumption patterns to identify periods of higher exposure than revealed in the annual average" (DWI, 1996). However, more detailed analyses were presented in the earlier WRc report (Hopkin and Ellis, 1980).

6.2 Frequency and duration of showering and bathing

There appear to be few reliable data on showering and bathing habits of UK adults which relate to their potential exposure to contaminants in water. Much of the research into bathing habits has been geared towards an assessment of water demand. Estimates, such as those by Herrington (1996) have attempted to take trends in bathing habits into account, such as an increased ownership and use of showers, when predicting water demand. Limited data on use of showers obtained by using meters to monitor water flow has shown a wide variation in habits, although the average obtained was fairly similar to some of the estimates used.

Data on the length of time spent in the shower/bathroom after showering/bathing and on the extent to which bathrooms are ventilated do not appear to be available.

6.3 Frequency and duration of swimming

Data on the proportion of the population which participates in swimming is collected as part of the General Household Survey and is held by the UK sports councils. Information on the average frequency at which participants swim is also available. However, a far larger proportion of those surveyed reported having been swimming in the previous 12 months compared with those who had been swimming in the previous 4 weeks. What is not clear is whether this is because swimming is an occasional activity for a large number of people or whether participation is concentrated seasonally. Information on the length of time spent in the pool also appears to be lacking.

6.4 Differences in exposure between pregnant women and other adults

There appear to be few data available specific to the exposure of pregnant women although the ALSPAC study (see Section 3.4.1) may be a potential source of information on the drinking and swimming habits of pregnant women in one county of the UK. National surveys of drinking water consumption do not include separate data for pregnant women, nor do the available statistics on bathing/showering and participation in swimming.

It would appear that the advice given to pregnant women in the UK by health professionals may result in them drinking more cold tap water (in place of caffeinated drinks such as tea and coffee). It is not clear whether total tap water intake would also be increased, in response to a reduction in consumption of caffeinated soft drinks and alcohol. Participation in swimming may also be increased.

6.5 Other exposures and indirect exposures

As well as the exposures considered in this report, there are many other everyday activities during which individuals are exposed to water. These include washing dishes and clothes, for example.

Various uses of domestic drinking water, such as washing machines and dish-washing, as well as showering, can increase the air concentration of contaminants present in the water. These will affect the exposure of other members of the household in addition to the person engaged in the activity. Johnson *et al.* (1999), considering data available in the US, concluded that a variety of sources were available relating to the frequency and times of activities producing direct exposures to water, the duration of these activities and the quantity of water used. However, he considered that more data were needed to adequately characterise the indirect exposures that occur when one member of a household is exposed through the water-related activities of other household members.

Attendance at a swimming pool (while a child is participating, for example) is another potential source of exposure to disinfection by-products by inhalation. Aggazzoti *et al.* (1985) found an increase in alveolar concentrations of trihalomethanes after individuals had rested at the poolside for one hour, indicating that exposure of swimming spectators may be significant.

7. DISCUSSION

7.1 Inter-individual variability

Data on the exposure of pregnant women to contaminants in water are very limited. However, the data which do exist indicate that, although there may be an increase compared with the exposure of non-pregnant women there will be a very substantial overlap.

The comparisons of "average" data for the UK and USA in Section 5 suggest that exposures to water through various activities might not be hugely different in the two countries. However, the data available indicate very large variations in habits between individuals within each country. Only a small proportion of the population swims in treated pools, for example, but some do so frequently and for considerable lengths of time. This variability brings into question the value to epidemiological studies of obtaining more accurate values for "typical" exposures. Having an accurate indication of exposures to water for the "average adult" may be of little benefit in estimating the exposures of individual subjects in an epidemiological study.

Even relatively small inter-individual variations in behaviour may have important effects on exposure to disinfection by-products. Kuo *et al.* (1998) found that the relevant importance of ingestion, inhalation and skin absorption to an individual's dose of chloroform changed from 3:4:3 for those who took a 10 minute shower to 1:7:2 for those taking 20 minute showers under the same conditions. It should be noted that the variation in inter-individual exposure to non-volatile by-products of disinfection is likely to be less than for volatile ones, due to the decreased importance of the inhalation route for these compounds.

7.2 Effects of temperature and exertion

As well as differences in individual behaviour patterns, the concentrations of disinfection by-products in the water to which the individuals are exposed are, obviously, of key importance in determining exposure to these compounds. However, a number of other factors which are less immediately apparent are also important.

For swimming, the intensity of the exercise undertaken as well as the degree of turbulence of the water, are important variables. For example, Levesque *et al.* (1994) used alveolar chloroform concentrations to measure the exposure of swimmers to disinfection by-products in chlorinated swimming pools and found that the intensity of the exercise taken and physiological characteristics of the individuals were significant variables in determining the body burden.

Heating treated water also alters the balance of the disinfection by-products present. Heating is often assumed to reduce the concentration of volatile organic compounds (VOCs) such as chloroform and other trihalomethanes in the water due to volatilisation. However, Weisel and Chen (1994) found that heating water increased the concentrations

of trihalomethanes, with the size of the increase dependent on the chlorine residual present. Haloacetonitriles and halopropanones decreased in concentration. They reported that overall THM exposures calculated using the THM concentration in heated water were 50% higher than those calculated using the THM concentration present in cold water. Assessments of the dermal absorption of chloroform whilst bathing have also indicated that absorption in subjects bathing in water at 40 °C was much higher than those in water at 30 °C, as demonstrated by their exhaling approximately 30 times as much chloroform (Gordon *et al.*, 1998).

7.3 Refinement of exposure estimates

From the discussion above it is clear that the exposure of individuals to water as a result of different consumption and activity patterns is very variable. The details of such exposures (e.g. the temperature of the water when bathing or the level of physical exertion when swimming) which are also variable are important in determining the internal dose of water contaminants received by individuals.

The current emphasis on the need for accurate, individual exposure estimates for subjects in epidemiological studies investigating the effects of trihalomethanes is well summed up by Dr David Ashley of the Centre for Disease Control (CDC) in the USA: “The exposure estimate is a critical aspect of this area of research. Previous attempts at estimating exposure have not been able to give a good individual exposure measurement. I strongly believe that either internal dose levels need to be measured or a model must be carefully evaluated that will relate questionnaire information to internal dose levels. It is clear that questions about consumption of glasses of water or other beverages or disinfection plant measurement do not suffice as an estimate of exposure.” (pers comm). However, it is recognised that there would be very significant difficulties and costs associated with this, and the practicalities are uncertain.

Thus, it is suggested that the collection of data in order to improve the exposure of an “average” adult or an “average” pregnant woman to water is unlikely to be justified in terms of its contribution to the accuracy of epidemiological studies investigating the health effects of disinfection by-products. Indeed, unless the ways in which different exposures to water relate to internal dose of disinfection by-product are characterised, accurate data on the exposure of the subjects in such studies to water may not give sufficient information to significantly improve the exposure estimate. Efforts are being made by the research community in the USA to address these issues.

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PART TWO

SIGNIFICANCE OF DIFFERENT ROUTES OF EXPOSURE TO DISINFECTION BY-PRODUCTS IN WATER

8. AIMS AND OBJECTIVES

In the initial stage of this project, information has been gathered on the exposure of individuals to water by different routes. The aim was to improve the design and interpretation of epidemiological studies investigating possible health effects of contaminants of water, such as disinfection by-products. Part one of the report presented statistics on the exposure of adults, and pregnant women in particular, in the UK and USA to water via ingestion, showering, bathing and swimming. It became apparent from the available information that there is enormous inter-individual variability in the frequency and duration of showering, bathing and, in particular, swimming. If there was significant absorption of disinfection by-products during these activities, such exposures could make major contributions to the internal doses of some individuals. It is possible, therefore, that exposure assessments based on average exposures may be inaccurate for some individuals. Similarly, exposure assessments which take only ingestion of drinking water into account may also result in misclassifications of exposure.

This stage of the project examines the information available on how different exposures to disinfection by-products relate to internal dose. Literature relating to the absorption of disinfection by-products from bathing, swimming and showering are examined and compared with that from ingesting water. The influence of water temperature on the absorption of disinfection by-products is also investigated. The significance of the data available for exposure assessments in different types of epidemiological study is discussed.

9. OCCURRENCE AND PROPERTIES OF DISINFECTION BY-PRODUCTS

9.1 Factors governing the formation of disinfection by-products

9.1.1 Water treatment

There are many factors which influence which by-products are formed during the chlorination of drinking water and the concentrations at which they are produced. The level and type of natural organic matter (NOM) and bromide concentrations in the source water are important determinands. Treatment processes, which may reduce the NOM content, and the dose and type of disinfectant used are also of primary importance. The concentrations of some disinfection by-products can change within distribution, with the chlorine residual and water temperature being important factors in the extent to which this occurs. It is beyond the scope of this report to review all the information on this topic. However, a brief summary is included in order to demonstrate the complexity of the subject and to demonstrate the difficulties inherent in estimating exposure to different disinfection by-products.

Chlorine, like other disinfectants, is a strong oxidising agent and highly reactive. It reacts with the NOM in water to produce a wide spectrum of halogenated or oxygenated carbon compounds. Although many of these compounds have not yet been identified, a large proportion of the smaller disinfection by-products have been characterised and have been found to be generally dominated by trihalomethanes (THMs) and haloacetic acids (HAAs). When the water being disinfected contains high levels of bromide, this is oxidised by the added aqueous chlorine (hypochlorous acid, HOCl) to form hypobromous acid (HOBr), which also reacts with the NOM (Krasner, 1999a). Therefore, organic compounds substituted with chlorine and/or bromide are formed, with chloroform (trichloromethane), bromodichloromethane (BDCM), dibromochloromethane (DBCM) and bromoform (tribromomethane) having received particular attention.

Although HOCl is a more powerful oxidant, HOBr is a more efficient halogen substitution agent. As the ratio of bromide to organic matter increases, either due to an increase in bromide concentration or a decrease in organic matter, the percentage of brominated disinfection by-products increases (Amy *et al.*, 1991; cited in Krasner 1999a). Thus, although chloroform is the dominant THM in many finished waters, this is not always the case; in a survey of waters with low NOM and high bromide, brominated THMs were found to dominate (Krasner, 1999b).

THMs are usually the disinfection by-products which occur at the highest concentrations in chlorinated waters (Krasner *et al.*, 1989; cited in Krasner, 1999a). However, HAAs have been found to exceed the levels of THMs in drinking water derived from sources with high NOM and low bromide content (Krasner, 1999b, Singer *et al.*, 1995; cited in Krasner 1999a). The pH has also been found (Stevens *et al.*, 1989; cited in Krasner, 1999a) to affect the levels of disinfection by-products. THM formation was found to be

higher with increasing pH. The formation of dichloroacetic acid (DCAA) did not vary with pH while levels of trichloroacetic acid (TCAA) produced were lower at pH 9.4 than at pH 5 or 7.

9.1.2 Distribution system

Because a chlorine residual is normally maintained in the water throughout the distribution system, further reactions can take place and levels of THMs at the tap are often higher than in water leaving the treatment works. This increase is more significant for chlorinated compounds than for bromine substitution because HOBr, once formed, reacts very quickly (Krasner, 1999b). Chen and Weisel (1998) studied changes in disinfection by-product concentrations within a distribution system containing water which had been disinfected with chloramine and left the treatment plant with a free chlorine residual of 0.5 mg/l. They found that concentrations of THMs (due mainly to an increase in chloroform in this low-bromide water) increased with increasing residence time in the distribution system, while concentrations of HAAs decreased. Concentrations changed more rapidly in warm months (water temp >10 °C) than in winter. Both temperature and chlorine residual were found to be important parameters controlling the concentrations of disinfection by-products.

9.1.3 Changes according to use in the home

Heating treated water alters the balance of the disinfection by-products present. Heating is often assumed to reduce the concentration of volatile organic compounds (VOCs) such as chloroform and other trihalomethanes in the water due to volatilisation. However, Weisel and Chen (1994) found that heating water at 65 °C under sealed conditions increased the concentrations of trihalomethanes, with the size of the increase dependent on the chlorine residual present and the time for which the water was heated. This type of situation, and the timescales used, could be relevant to domestic hot water tanks. In contrast to the THMs, trichloropropanone was found to be thermally labile and disappeared to below the limit of detection within 30 minutes at the elevated temperature. The concentration of dichloropropanone increased during the first hour of heating but then decreased to low levels during the subsequent 7 hours of heating. Trichloroacetonitrile (TCAN) was below the detection limit in all samples and bromochloroacetonitrile (BCAN) remained low and unchanged in all samples. Dichloroacetonitrile (DCAN) was also found to be thermally labile and decreased over the 8 hours of heating. Dichloroacetic acid (DCAA) concentrations have been shown not to change significantly (after adjusting for the change in water volume due to evaporation) when water is boiled. In contrast, trichloroacetic acid (TCAA) concentrations reduced by an average of 39% (Kim, 1997; cited in Weisel *et al.*, 1999).

9.2 Factors governing exposure to disinfection by-products

Exposure to disinfection by-products in water can occur during many different activities and by a number of routes. Regulators and advisory bodies have tended to take into account only exposure via ingestion when determining safe levels of contaminants in

drinking water. However, there is evidence that, for some compounds, dermal exposure (for example during bathing) and inhalation of compounds released to the air (for example during showering) could also be significant. The importance of these routes depends upon a number of factors including the physico-chemical properties of the contaminants, the temperature of the water and the way in which it is used. Heating the water prior to use can also alter the concentrations of disinfection by-products present.

9.2.1 Showering

Inhalation exposure - Volatilisation

The extent to which a chemical volatilises from water depends on the amount of water used, the temperature of the water, the volatility of the compound and its solubility in water. The tendency of a compound to volatilise from water is usually expressed in terms of its Henry's Law Constant (HLC) (Weisel, 1998). The importance of the Henry's Law Constant in determining the overall mass-transfer was confirmed by Moya *et al.* (1999) who investigated the volatilisation of several volatile organic compounds from an experimental shower.

Chloroform and other THMs are among the most volatile of disinfection by-products and exposure via inhalation during swimming and showering has been shown to be significant in a number of studies (see Sections 10.3 and 10.3.2). Although recent studies have considered aerial release of contaminants from washing machines and other appliances, volatilisation from showers has been studied most intensively as it has been shown to be the most significant contributor (Little and Chiu, 1998). Flow models, which take into account the nature of the water use (a plug-flow model is used for showers while it is assumed that water in a bath is completely mixed) have been developed to predict the transfer of contaminants from water to air during different uses (Little and Chiu, 1998).

Studies in a one-third scale model shower (Andelman *et al.*, 1986; cited in Giardino and Andelman, 1996) have shown that air concentrations of chloroform as a result of volatilisation were strongly influenced by drop height (which determines the residence time in the air), initial water concentrations, air exchange rate and water temperature. At high water temperatures both the rate and the overall extent of volatilisation were increased, making temperature the dominant factor. Between 50 and 90% of the chloroform was volatilised. The rate of volatilisation has also been found to be related to the distribution of the sizes of the water drops, which is influenced by the rate of flow of the water through the showerhead (Giardino *et al.*, 1992; cited in Giardino and Andelman, 1996).

Similar results were found in a full-size shower (Giardino and Andelman, 1996). Water temperature was, again, found to have a dominant effect on the volatilisation of chloroform which varied from 43.8% (26 °C) to 61.8% (at 42 °C). The air concentration of chloroform was found to increase approximately linearly during a 10 minute shower and did not reach a steady state due to air flow within the shower. In contrast, air concentrations of the less volatile (only 5.5 to 31.4% volatilised) 1,2-dibromo-3-

chloropropane (DBCP) were able to reach steady state during the 10 minute shower. Andelman (1990, cited in Giardino and Andelman, 1996) has explained the implications of these differences for exposure assessments. For compounds such as DBCP, whose concentration in the shower air rapidly reaches steady state, inhalation exposure would be approximately directly proportional to the time spent in the shower. For chloroform, the inhalation exposure is proportional to the time spent in the shower squared. It should be noted that the extent of ventilation of the shower unit is an important influence on volatilisation patterns.

Chloroform concentrations in shower air were not increased significantly when water impacted on a body compared to an empty shower, suggesting that such additional losses of volatile compounds are small compared to simple volatilisation from the shower water (Jo *et al.*, 1990).

Inhalation exposure - Aerosols

Inhalation exposure to non-volatile compounds in water can also occur. Droplets (diameter >10 μm) and aerosols (diameter ≤10 μm) are produced during many water uses. Droplets are not in equilibrium with their environment and are expected to evaporate, either to dryness or to produce aerosols, depending on humidity and temperature. Volatile chemicals will be transferred to the gas phase during evaporation while the mass concentration of non-volatile compounds (expressed in a per volume of air basis) remains constant. Droplets are too large to be respirable and are only important in the context of inhalation exposure as precursors of aerosols (Pandis and Davidson, 1998).

Therefore, inhalation exposure to non-volatile compounds in water will depend upon their concentration in the water, the amount of aerosols produced, the size distribution of the aerosol, their growth and shrinkage and how they become distributed around the building (Weisel, 1998). The distribution of droplet and aerosol sizes produced in showers depends upon the water flow rate, the design of the shower head and the way in which showers which adjustable heads are used. Droplets can be shattered by bouncing off the person in the shower, probably increasing the production of respirable aerosols (Pandis and Davidson, 1998).

Keating *et al.* (1997) found variations in the efficiency of transfer of chloroform from water to air in an experimental shower system depending on the characteristics of the shower nozzle used. Other studies (Giardino *et al.*, 1992; Keating and McKone, 1993; both cited in Keating *et al.*, 1997) have found higher transfer efficiencies in systems which produce smaller droplets. Keating *et al.* (1997) report a higher transfer efficiently for a nozzle producing larger droplets; the authors suggest that this unexpected finding was due to a longer residence time in the air as this nozzle dispersed the water more widely (60^{o} compared with 30^{o}) than the nozzle producing smaller droplets. An increase of transfer efficiency of 5-10% for every 0.1 seconds increase in the residence time for shower droplets has previously been reported (Giardino *et al.*, 1992; cited in Keating *et al.*, 1997). However, Moya *et al.* (1999) found temperature to be the factor with the

greatest influence on chemical stripping efficiencies in a shower. Spray type (coarse or fine) and water flow rate had little influence, particularly for the more volatile chemicals tested.

Keating *et al.* (1997) caution that the ability of the water-to-air transfer efficiency to predict measured air concentrations is variable between different shower situations, and that effects such as droplet deposition on walls and surfaces may have an effect.

Dermal and ingestion exposures

It should be borne in mind that the air-stripping of volatile compounds from water when it is sprayed from a tap or used in a shower (Weisel, 1998b) will decrease the concentration remaining in the water to which individuals are exposed dermally or by ingestion.

9.2.2 Swimming pools

Individuals in indoor swimming pools are exposed dermally and by inhalation to contaminants in the water and are also likely to ingest small amounts of the water. Non-participating spectators at swimming pools will also be exposed via inhalation of chemicals which have volatilised or are contained in aerosols. Disinfectants are added to swimming pools to maintain bacteriological quality, and this results in higher concentrations of disinfection by-products than encountered in drinking waters. Lahl *et al.* (1981) found a 20-30% increase in THM levels 5 hours after chlorination of a pool. The concentration and profile of disinfection by-products in swimming pools is dependent upon the organic precursor and bromide content of the source water and the dose of disinfectant, as for drinking water. However, the swimmers themselves also contribute to the generation and distribution of disinfection by-products. The production of THMs was found (Lahl *et al.*, 1981) to vary in a complex manner with the number of pool visitors because: contamination with organics which act as precursor for THMs increased with the number of swimmers; contamination with compounds which reacted with chlorine to produce compounds other than THMs (i.e. “competitive reactions” increased with the number of swimmers; in order to guarantee disinfection, chlorination doses needed to be increased when higher number of swimmers are in the pool.

Aggazzotti *et al.* (1995) also observed that the chlorine residual was increased as the number of swimmers increased. In one study (Aggazzotti *et al.*, 1990) the same researchers found that the levels of chloroform in the water correlated to the number of swimmers, and suggested that this might be a result of the reaction of chlorine with organic matter introduced by the swimmers. However, in a survey of 12 indoor pools (Aggazzotti *et al.*, 1995) the number of swimmers was found to be negatively correlated with the concentration of chloroform in the water. This is probably the result of increased off-gassing (see next section).

Inhalation

Lahl *et al.* (1981) found that the outgassing of THMs from water into the surrounding air increased with the turbulence of the water surface and, therefore, depended on the number of swimmers in the pool. Water and air temperatures, the concentration of the chemical in the water and the intensity of air circulation were also highlighted as important factors in determining the air concentration.

Ventilation in indoor swimming pools will have a substantial impact on the concentrations of chemicals in the air, and WHO (1998) caution that practices in different countries need to be determined in order to allow refinement of predictions of air concentrations. Lahl *et al.* (1981) found that, in spite of ventilation, chloroform concentration decreased considerably with height above the water. They comment that, due to continuous ventilation resulting in different air currents and turbulences, concentrations in different parts of the same swimming pool building could vary by several 100%.

It should also be noted that ventilation could be with 100% fresh air, in which case volatile compounds will be discharged from the swimming pool atmosphere, or with recirculated air (up to 90% recirculation) in which case the content of volatile chemicals is retained. Ventilation practices may not only vary between different countries, but may change over time.

Dermal

Individuals in a swimming pool immerse almost their whole body in the water for varying lengths of time. In past exposure assessments, the US EPA have assumed that 75 - 100% of the skin surface is exposed during bathing and swimming (US EPA, 1997). Therefore, there is significant dermal exposure to the water, with a potential for absorption, particularly of the more lipophilic substances.

Ingestion

The amount of water ingested in swimming pools will depend upon a number of factors including the type of activity engaged in and the number of other participants in the pool disturbing the water surface. Some estimates have been made of typical ingestions. Borneff (1979; cited in Lahl *et al.*, 1981) suggested that normal swimming leads to the ingestion about 50 ml water and Beech (1980) suggested that extreme situations, such as children playing and diving, may lead to the ingestion of 500 ml during a visit to a pool. Cotruvo (1999, pers comm) chose to use an approximate mid-point ingestion value of 250 ml ingestion per 1 hour swimming session for both children and adults for comparative purposes. Kim and Weisel (1998) calculated that ingestion by four adults varied between 12 ml and 45 ml during a 30 minute swim.

9.2.3 General household exposures

Inhalation

Exposure to disinfection by-products by inhalation resulting from the volatilisation of compounds during normal household uses of water, such as showering and the use of washing machines and dishwashers, can be significant for the more volatile compounds such as the THMs. Volatilisation and/or aerosol production during these types of activities will result in other individuals within the house, as well as the person directly engaged in the activity, being exposed via inhalation.

Dermal

As well as the activities considered in this report (drinking, swimming, showering and bathing) there are other household activities through which individuals' skin may be exposed to water. These include dish-washing and clothes-washing by hand, for example. In addition, there is the potential for dermal contact with vapours and aerosols released from water. However, the dermal absorption from this route is predicted to be much lower than that resulting from direct skin contact (Weisel, 1998; Bunge and McDougal, 1998).

9.3 Differences in absorption, distribution and metabolism

9.3.1 Dermal absorption

The extent to which a compound penetrates the skin is represented by its permeability coefficient which is largely governed by its octanol/water partitioning coefficient (Weisel, 1998; Bunge and McDougal, 1998). Although the different layers of the skin exhibit different affinities for hydrophobic chemicals, experiments have shown that penetration through the skin can be reasonably well represented by Fick's first law of diffusion, which deals with diffusion through a pseudo-homogenous membrane. This treats the skin as a reservoir which "fills up" as the chemical permeates across the skin, before it the chemical can enter the blood stream. At this point, when entry of the chemical into the outer layer of the skin occurs at the same rate as loss from the skin into the blood stream a steady state occurs (Bunge and McDougal, 1998). The USEPA (1997) recommend using a non-steady state approach for estimating the absorption of organics which exhibit octanol-water partitioning. This accounts for uptake from the skin into the blood which may occur after the exposure event has finished and is also thought to more accurately reflect typical human exposure conditions, as the short exposure times associated with bathing and swimming are unlikely to allow steady state to occur.

The extent of absorption across the skin is different at different points of the body due to differing thicknesses of the layers of the skin and variations in blood flow to different parts of the body. Absorption is also affected by the condition of the skin. Absorption of hydrophilic substances has been shown to be increased by injury, while that of hydrophobic substances was decreased (Bunge and McDougal, 1998). Hydration of the

skin can also affect the permeability of the skin to chemicals, with absorption increasing with increasing hydration. However, Bunge and McDougal (1998) consider that studies on hydration carried out over hours or days are not relevant to the situation in showers and bathing. Similarly, a reported *in vitro* study in which hydration increased absorption only after two hours (in Bunge and McDougal, 1998) suggests that hydration it may not be relevant to normal swimming activities either. There is also evidence that soaps and surfactants may alter the absorption of chemicals from contaminated water, although the data are insufficient to assess the significance to showering and bathing.

Skin temperature can also impact on the rate of penetration of chemicals. Increasing the temperature of skin has been shown in *in vitro* studies to increase penetration by a direct effect on the skin. However, the long timescales required in these studies make the data of doubtful relevance to showering and bathing exposures (Bunge and McDougal, 1998). It is more likely that a higher temperature increases the blood flow to the skin and, therefore, increases the amount of chemical absorbed (Gordon *et al.*, 1998).

9.3.2 Metabolism

The route by which exposure to a compound occurs can profoundly influence its metabolism and distribution within the body. Chloroform ingested at environmental concentrations is completely metabolised during the first pass through the liver (Weisel *et al.*, 1999) producing the biologically active metabolite phosgene. The other prevalent THMs in drinking water are also rapidly oxidatively metabolised by the same enzyme system as chloroform, producing phosgene analogues (Pegram, 1999). Because phosgene is highly reactive, little of an ingested dose of chloroform will reach other organs unless the dose is sufficiently large to saturate the metabolic capacity in the liver. In contrast, following inhalation and dermal exposures chloroform will enter the blood, meaning that organs other than the liver may receive significant doses. Physiologically-based pharmacokinetic (PBPK) modelling confirms this and has predicted that, for the same amount of internalised chloroform, ingestion exposure results in a higher dose of chloroform to the liver, while more chloroform is circulated throughout the body and to other organs following inhalation and dermal exposures (Blancato and Chiu, 1993 cited in Weisel and Jo, 1996). This does not inevitably mean a higher potential for toxicity to all other organs, however, as phosgene (or other active metabolites) will only be formed in tissues with the relevant metabolic capabilities.

Chlorinated water contains a complex mixture of disinfection by-products. This can have direct implications for the risk assessment of chemicals which act through the same mechanism of action and are, therefore, likely to have dose-additive effects. This is the basis for a single standard for total THMs, for example. Components of a mixture may also influence each others' uptake, metabolism (by inhibiting, competing for or inducing metabolic enzymes) and biological effects (by interacting with receptors, for example). Da Silva *et al.* (1999 a,b), using animal studies, found that blood concentrations of one THM was higher following co-administration in a binary mixture with another THM than following administration alone and that the effect was more marked with DBCM and bromoform than for the more chlorinated THMs. Simulations with a PBTK (physiologically based toxicokinetic) model and *in vitro* studies investigating tissue:blood partition coefficients lead the authors to suggest that the observed changes

in blood kinetics of THMs is likely to be a consequence of a metabolic interaction. Such competitive interactions could potentially increase the amount of THMs which enters the bloodstream following oral administration, or result in a greater significance of the generally minor pathways of THM metabolism (i.e. reduction resulting in free radicals and, for the brominated THMs, glutathione conjugation forming mutagenic intermediates (Pegram, 1999)). However, it should be noted that such interactive effects have usually been demonstrated experimentally at high doses and it is unclear to what extent they apply to exposures at environmentally relevant levels.

In the case of haloacetic acids (HAAs), it is the parent compounds which primarily exert the biological activities. Dihaloacetic acids (DHAAs) such as DCAA are extensively metabolised to a number of intermediates but the metabolites, which include stable endogenous compounds, do not appear to be involved in the toxicity of the compounds. Trihaloacetic acids (THAAs) are less readily metabolised and a significant proportion of the internal dose of TCAA, in particular, is excreted unchanged in the urine. Metabolites of some THAAs may, nonetheless, be toxicologically relevant; bromodichloroacetic acid, for example, is metabolised to DCA and BDCM (Pegram, 1999).

9.4 Measurement and estimation of internal dose

Apart from local effects, such as irritation of the skin or the lung, the severity of toxic effects following exposure to chemicals is dependent upon the amount which enters the body and is distributed to the various organs. This is referred to as the internal dose and will depend not only on the level of exposure but also on the extent to which the chemical is absorbed by the relevant route of exposure : how well it is taken up from the gastro-intestinal tract following ingestion; how readily it permeates the skin following dermal contact; how it partitions between air and blood in the lungs. It is, therefore, the internal dose which is of most relevance in risk assessment. The amount of the compound, or its active metabolite, which reaches organs which are vulnerable to its toxic effects is also important, and this may vary depending upon the route of exposure.

9.4.1 Biomarkers

In order to study the extent to which individuals have been exposed to a chemical, or in order to assess the internal dose from an exposure to a chemical, it is useful to be able to measure a compound in the blood, urine or exhaled air. This could be the chemical itself or a stable metabolite. Such indicators, which provide information on the extent to which individuals have been exposed to compounds, are known as biomarkers of exposure. Biomarkers which provide early indications of toxicity can also be used; these include elevated enzyme levels or adducts.

In the case of THMs, the concentrations of the parent compounds in blood or exhaled air have been found to correlate well with dermal and inhalation exposures and have been used as biomarkers of exposure. However, because of the first-pass metabolism of these compounds in the liver (see Section 9.3.2), this method is not suitable for investigating ingestion exposure. In the case of HAAs, urinary excretion of TCAA appears to be a marker of exposure to the compound (Weisel *et al.*, 1999; Kim *et al.*, 1999). However,

exposures from sources other than water need to be taken into account when using HAAs as biomarkers, since TCAA, for example, is a metabolite of trichloroethylene (trichloroethene) and may be present in the urine as a result of occupational exposure to solvents.

Many of the studies referred to in the following sections of this report have used measurement of biomarkers to investigate exposure to disinfection by-products.

9.4.2 PBPK modelling

Physiologically-based pharmacokinetic (PBPK) modelling, which takes into account the rates and paths of absorption, distribution, metabolism and excretion (ADME) of compounds can be used to aid the understanding of how an exposure relates to an internal dose. PBPK modelling has been used to investigate disinfection by-products, particularly THMs, in order to assess the human relevance of data from animal toxicity studies and also to calculate internal doses resulting from different exposures (Corley *et al*. 1990; Chinery and Gleason, 1993, Blancato and Chiu, 1993, McKone, 1993, Roy *et al*. 1996). In some cases, PBPK models have been linked to models of indoor air quality, to give a broad picture of the potential impact of a household use of water to a number of residents (Wilkes, 1998).

10. USE OF BIOMARKERS TO ASSESS EXPOSURES TO TRIHALOMETHANES

10.1 Ingestion

Chloroform and other THMs are largely metabolised in the first pass through the liver following ingestion. This makes measurements of levels in blood or exhaled breath poor indicators of the internal dose received. Weisel and Jo (1996), for example, were unable to detect any chloroform in the exhaled breath of individuals who had ingested 0.5 litres of water containing 20 µg/l. Similarly, Backer *et al.* (1999) found an increase in the concentration of blood BDCM of only 1.2 µg/l above the baseline in subjects who had drunk 1 litre of tapwater, compared within an increase of 16.1 µg/l in those who had showered for 10 minutes and 14.7 µg/l following a 10 minute bath.

10.2 Bathing

Weisel and Jo (1996) investigated dermal-only exposures to chloroform whilst bathing for 60 minutes in water at 40 °C containing 11-15 µg/l, by requiring their subjects to breathe purified air. They calculated that 0.33-0.56 µg was exhaled for each µg/l in the water.

Gordon *et al.* (1998) investigated the dermal absorption of chloroform in volunteers bathing in water of different temperatures (inhalation exposure to contaminants volatilising from the bath water was prevented by the wearing of face masks) by measuring the concentration of chloroform in exhaled air. Exhalation of chloroform after bathing in water at approximately 40 °C was about 30 times more than the same subjects bathing in water of about 30 °C (see Table 10.1). The authors suggest that this is due to changes in blood flow characteristics due to the body's heat-conserving or heat-dissipating mechanisms. They also use this theory to explain the very different assessments of the importance of dermal absorption in other studies of showering and swimming (Table 10.2).

Roy *et al.* (1996) used a distributed parameter physiologically-based pharmacokinetic (DP-PBPK) model to represent the absorption of chloroform into the skin and the systemic circulation. A systemic dose of 8 µg was predicted to result from 30 minutes dermal-only exposure to 100 µg/l chloroform in water.

Table 10.1 Mean exhaled chloroform dose for subjects exposed dermally to bath water at three temperatures (exposures of 24 – 30 minutes)

	Conc. in water (µg/l)	Time in bath (minutes)	Maximum breath conc. (µg/m^3)	Exhaled* dose (µg)
Low temperature (30 °C)	83.4 ± 14.3	26.6 ± 5.4	3.2 ± 2.7	0.2 ± 0.3
Medium temperature (35 °C)	90.0 ± 5.5	30.3 ± 0.9	19.0 ± 9.7	2.3 ±1.4
High Temperature (40 °C)	85.8 ± 15.6	27.4 ± 2.6	44.9 ± 15.3	7.0 ± 2.0

*Exhaled dose calculated by integrating the area under breath concentration/time curve (adjusted for background concentration) from the beginning of exposure until breath levels had reduced to background
Adapted from Gordon *et al.*, 1998

Table 10.2 Proposed explanations for the different importance of dermal absorption in different exposure conditions

Activity	**Conditions**	**% of exposure due to dermal absorption**	**Explanation given by Gordon *et al.* (1998)**	**Ref**
Showering	With or without waterproof clothes (to determine importance of dermal exposure)	50%	Hot water used in showering	1
Swimming	Exercising for at least part of the time (45 - 65% exertion)	25%	Lower water temperatures	2
Swimming	Rigorous training	75%	Rigorous training increases capillary blood flow.	3

References
1. Jo *et al.* (1990)
2. Levesque *et al.* (1994)
3. Lindstrom *et al.* (1997)

Weisel and Chen (1994) found that THM levels in water increased during heating. If this finding is relevant to household water heaters, THM exposures could be as much as 50% higher than those calculated using the THM concentration present in cold water.

10.3 Showering

Following the finding in the early 1980s that sufficient carbon tetrachloride was volatilised from contaminated water during showering to cause individuals to faint (Maxwell *et al.*, 1991) attention began to be focused on the potential for exposure to water contaminants by routes other than by ingestion. Researchers began to use mathematical models to assess the likely air concentrations resulting from the volatilisation of chemicals from water during showering and other household uses. In addition, some researchers investigated exposure by measuring biomarkers.

Because chemicals volatilised during showering can remain in the indoor air and be further distributed within the house, exposure continues after the shower itself has finished and can also result in the exposure of other individuals within the house (see Section 10.5).

10.3.1 Chloroform

Jo *et al.* (1990 a,b) measured breath chloroform concentrations of individuals taking a 10 minute shower. In order to investigate dermal and inhalation exposures separately, the study was repeated with the individuals wearing waterproof clothes. The authors found dermal and inhalation exposure to contribute approximately equally to an overall dose of 32 µg. A later study by the same group (Weisel and Jo, 1996) confirmed the approximately equal importance of dermal and inhalation exposures to chloroform whilst showering, although the absorbed doses calculated were found to be higher than in the previous study. These data, and estimated exposures calculated using models, are presented in Table 10.3.

Weisel *et al.* (1999) asked 49 women (who had previously participated in an epidemiological study investigating neural tube birth defects, Klotz and Pyrch, 1998) to sample their breath to determine THM concentrations following a shower. Statistical differences were found between women in the same exposure category (low THMs) depending on how soon after the shower ceased the samples had been taken. These data illustrate the difficulty of the investigation of exposure to THMs, as the levels in blood and exhaled breath decrease rapidly after exposure ceases. These data, along with those for the studies detailed above, are presented in Table 10.4.

Table 10.3 Estimates of absorption of chloroform whilst showering

Study	Activity	Estimated total dose	Estimated inhaled dose	Estimated dose by dermal absorption	Estimated dose by ingestion	Comments
Jo *et al.*, 1990b	10 minute shower	0.46 µg/kg bw i.e. 32 µg for 70 kg adult	0.24 µg/kg bw i.e. 16.8 µg for 70 kg adult	0.22 µg/kg bw i.e. 15.5 µg for 70 kg adult	Not considered	Water containing 23.5 µg/l
Weisel and Jo, 1996	10 minute shower		Calculated as 30-80 µg	Similar to inhaled dose (30-80µg)	Not accounted for	Water containing <10-50 µg/l
McKone 1993	10 minute shower Estimated total dose	1.31 µg per µg/l	Total lung volume 1 µg per µg/l Alveolar volume 0.43 per µg/l	0.31 µg per µg/l		PBPK model, based on data from Jo *et al.*, 1990 a,b
	Estimated metabolised dose	0.41 µg per µg/l	0.24 µg per µg/l	0.17 µg per µg/l		Metabolised dose based on liver metabolism .
Chinery and Gleason, 1993	10 minute shower	10.9 µg	6.2 µg	4.7 µg		Modelled based on water concentration of 20 µg/l

Table 10.4 Breath concentrations following exposure to chloroform in showers

Study	$CHCl_3$ conc. in water	$CHCl_3$ conc. in air	Activity	$CHCl_3$ conc. in exhaled air	Exhaled chloroform per µg/l in water	Comments
Jo *et al.*, 1990 (a)	5.3 - 35.9 µg/l		Pre-exposure	< 0.86 µg/m^3 (< l.o.d.)		Statistically significant differences found between breath concentrations following normal showers and inhalation only exposures.
			10 minute shower	6-21 µg/m^3 mean = 13 µg/m^3		Dermal and inhalation exposure contributed approximately equally to the internal chloroform dose
			10 minute shower wearing rubber clothes and boots (inhalation only)	2.4 - 10 µg/m^3 mean = 7.1 µg/m^3		
	22 - 35.6 µg/l	119 - 313.4 µg/m^3	10 minute shower			Air concentrations were not significantly affected by the presence of a person in the shower
	12.9 - 40.0 µg/l	58.1 - 326.9 µg/m^3	10 minute shower without an individual in the shower			

Study	$CHCl_3$ conc. in water	$CHCl_3$ conc. in air	Activity	$CHCl_3$ conc. in exhaled air	Exhaled chloroform per µg/l in water	Comments
Weisel and Jo, 1996	10 - 50 µg/l		10 minute shower wearing waterproof clothing (inhalation only)		0.02 - 0.05 µg	Water at 40 ± 2°C Expired $CHCl_3$ calculated assuming a respiration rate of 0.01 m^3/min
	10 - 41 µg/l		10 minute shower breathing purified air (dermal only)		0.02 - 0.13 µg	
				means		
Weisel *et al.*, 1999	<10 µg/l TTHM		"Normal" showering (n=6)	*4.0 µg/m^3		Breath sample collected < 5 min after end of shower
	>10 µg/l TTHM		(n=7)	54 µg/m^3		
	<10 µg/l TTHM		(n=7)	*1.5 µg/m^3		Breath sample collected 5-20 min after end of shower
	>10 µg/l TTHM		(n=7)	134 µg/m^3		
	<10 µg/l TTHM		(n=4)	1 µg/m^3		Breath sample collected >20 min after end of shower
	>10 µg/l TTHM		(n=2)	20 µg/m^3		
						*Statistically different ($p<0.05$) by Mann-Whitney test

10.3.2 Other haloforms

Recent studies have also begun to look at exposure to haloforms other than chloroform. Backer *et al.* (1999) measured levels of THMs in the blood following showering or bathing for 10 minutes or drinking 1 litre of tap water in 10 minutes. The highest levels of THMs were found in blood samples from individuals who had taken showers. Median levels of BDCM in blood rose from 3.3 µg/l pre-exposure to 19.4 µg/l ten minutes after the shower finished, dropping to 10.2 µg/l 20 minutes later. DBCM was also found in blood samples.

Weisel *et al.* (1999) were able to detect BDCM, DBCM and bromoform in exhaled air following showering (see Table 10.5).

10.4 Swimming

Various studies have been undertaken to try to assess the significance of swimming as a source of exposure to chloroform. These have been carried out in a number of countries and in pools containing different levels of chloroform. Most have used measurements of levels of chloroform in the blood or in exhaled air during or after swimming to indicate the total exposure during swimming. Others (e.g. Levesque *et al*. 1994) have attempted to assess the contributions from inhalation and dermal exposure separately. Many of these studies have also shown that non-swimming visitors to indoor pools are exposed to chloroform through inhalation of the air in the pool building.

The level of chloroform found in the blood and/or exhaled air of individuals has been found to depend largely on the concentration in the air above the pool (Aggazzotti *et al*. 1990, 1993 and 1995). This is partly determined by the concentration of chloroform in the pool water but the number of swimmers in the pool has also been found to exert an important influence. The turbulence caused by the swimmers increases the outgassing of THMs from the water into the air (Aggazzotti *et al*. 1990 and 1995; Lahl *et al*. 1981). As would be expected, the time spent in the pool is also positively correlated with the amounts of chloroform absorbed (Aggazzotti *et al*. 1990).

Some studies have investigated the influence of the intensity of exercise on the uptake of chloroform whilst swimming. Aggazzotti *et al*. (1990, 1993, 1995) found that absorption by competitive swimmers during intensive training sessions was higher than by beginners during lessons. Similarly, Weisel and Shepard (1994) reported higher alveolar air concentrations in active swimmers compared with individuals resting in the pool.

Table 10.5 Exposure to other haloforms during showering

Study	Water conc.	Air conc.	Activity	Bromoform in exhaled air	DBCM in exhaled air	BDCM in exhaled air	BDCM in blood	Comments
Backer *et al*. , 1999	NR	NR	Pre exposure (n=11) 10 minute shower (n=11)				3.3 ppb 19.4 ppb	Samples taken 10 minutes after exposure ceased Similar pattern of results obtained for DBCM and chloroform. Bromoform not detected.
Weisel *et al*. , 1999	<10 µg/l TTHM >10 µg/l TTHM		"Normal" shower (n=6) n=7)	means 0.6 µg/m^3 2.3 µg/m^3	means 1 µg/m^3 4.8 µg/m^3	means 1.4 µg/m^3 10 µg/m^3		Breath sample collected <5 minutes after end of shower
	<10 µg/l TTHM >10 µg/l TTHM		(n=7) (n=7)	0.6 µg/m^3 1.2 µg/m^3	1 µg/m^3 2.8 µg/m^3	0.3 µg/m^3 13 µg/m^3		Breath sample collected 5-20 minutes after end of shower
	<10 µg/l TTHM >10 µg/l TTHM		(n=4) (n=2)	0.6 µg/m^3 0.6 µg/m^3	1 µg/m^3 1 µg/m^3	0.3 µg/m^3 0.3 µg/m^3		Breath sample collected 5-20 minutes after end of shower

The increased breathing rate of individuals exerting themselves whilst swimming is one probable reason for the increased chloroform absorption. An increase in dermal absorption due to increased capillary blood flow in the skin is likely to be another contributory factor. Non-swimming visitors to pools have consistently been found to have a lower exposure to chloroform than participants in the water (Aggazzotti *et al*. 1990, 1993, 1995; Weisel and Shepard 1994; Lindstrom *et al*. 1997). Non-swimming visitors are, obviously, not exposed dermally to the pool water. Inhalation intake is also likely to be lower than for swimmers: the levels of chloroform in the air have been shown to decrease with increasing height above the water and these resting individuals are likely to have a reduced breathing rate compared with active swimmers.

The contribution of dermal exposure to swimmers' body burdens of chloroform was demonstrated by Levesque *et al*. (1994) who studied swimmers with or without scuba tanks. Although exhaled breath concentrations were lower when inhalation of the pool air was prevented, significant increases were, nonetheless, apparent even when scuba tanks were used. Lindstrom *et al*. (1997) reported alveolar chloroform concentrations in two competitive swimmers following a 2-hour training session more than twice the concentration in the air above the pool. This, and the fact that a three-compartment model provided a good fit for chloroform elimination demonstrated the contribution of dermal exposure. They calculated that approximately 80% of the swimmers' internal dose of chloroform was absorbed trans-dermally. The authors explained the importance of dermal absorption in these individuals by their long swimming sessions (2 hours) resulting in hydrated skin and their intense exercise, leading to high capillary perfusion.

A two-phase pattern of exhalation of chloroform following swimming or resting in a pool (i.e. an initial decline in alveolar concentrations followed by a second peak) also suggests the significance of dermal exposure; it is consistent with a rapid (inhalation) and a slower (transdermal) route of absorption. In contrast, the alveolar elimination by individuals who had rested at the poolside (i.e. exposed by inhalation) showed no second peak. Aggazzotti *et al*. (1995), however, failed to find any evidence of a two-phase elimination but suggested that this may have been an artefact resulting from the intervals between sampling.

Table 10.6 summarises the data relating to measurements of chloroform in individuals' blood/breath following exposure in indoor swimming pools. Table 10.7 presents estimates of internal doses of chloroform resulting from swimming and the likely significance of different routes of exposure.

Table 10.6 Exposure to chloroform at swimming pools

Study	$CHCl_3$ conc. in pool	$CHCl_3$ conc. in air	Activity (n = number of subjects)	$CHCl_3$ conc. in exhaled air	$CHCl_3$ conc. in blood	Comments
Copaken 1987	38 µg/l 3.6 µg/l		2 hour swim (n=6) 2 hour swim (n=2)		Increase of 0.6 µg/l Decrease of 0.48 µg/l	Chlorinated pool – $CHCl_3$ conc. lower than average Electronically purified pool
Aggazzotti *et al*. 1990/95 (Italy 1987/88)	17-47 µg/l	66-653 µg/m^3	Competitive swimmers training, daily (n=102) Swimming course, (non-competitive) (twice/week) (n=16) Non-swimming visitors (n=9) Controls (unexposed) (n=40)		Mean values 1.2 µg/l 0.4 µg/l 0.3 µg/l 0.1 µg/l	Blood samples taken 1-40 mins after exposure. $CHCl_3$ conc. in blood varied with: • pool/air concentrations • time spent • number of swimmers • intensity of exercise • age Variance attributed to: • air conc. 62%, intensity of exercise 6% (1990); or • air conc. 48%, intensity of exercise 5%, age of subject 1.5% (1995)
Aggazzotti *et al*. 1993/95 (Italy 1988/89)	19-95 µg/l	49-282 µg/m^3	Competitive swimmers training, 90 mins (n=120) Beginners swimming 90 mins (n=12)	Mean values 104 µg/m^3 75 µg/m^3		$CHCl_3$ conc. in exhaled air varied with: • air concentrations • intensity of activity • age Variance attributed to: • air conc. 54%, age 13%, exertion level 5%

Study	$CHCl_3$ conc. in pool	$CHCl_3$ conc. in air	Activity (n = number of subjects)	$CHCl_3$ conc. in exhaled air	$CHCl_3$ conc. in blood	Comments
			Non-swimming visitors, 90 mins (n=31) Controls (unexposed) (n=77)	59 $\mu g/m^3$ 12 $\mu g/m^3$		
Aggazzotti *et al*. 1998 (Italy, 1996)	25-43 µg/l (mean = 33.7 µg/l)	mean = 20.7 $\mu g/m^3$ 69-103 µg/m3 (mean = 91.7 $\mu g/m^3$) 135-195 $\mu g/m^3$ (mean = 169.7 $\mu g/m^3$)	Pre-exposure Sitting at poolside for 1 hour Competitive swimmers training for 1 hour	9.3 $\mu g/m^3$ 29.4 $\mu g/m^3$ 76.5 $\mu g/m^3$		Air concentration increased where 45-50 swimmers were in the water compared with above a pool with no individuals present
Levesque *et al*. 1994 (Canada, 1993)	159-568 µg/l 568 µg/l	597-1630 ppb 1296 ppb	Swimming (55 mins) (n=11) Swimming (55 mins) with scuba tank (n=11)	Pre-exposure: 52.6 ppb (Average peak: 104-1094 ppb Average peak: 209 ppb		High pre-exposure concentration due to contamination of the locker room. Body burden varied with: • intensity of exercise • physiological characteristics of individuals
Weisel and Shepard 1994 (New Jersey, USA)	32-150 µg/l (mean = 85 µg/l)	23-120 $\mu g/m^3$ (mean = 87 $\mu g/m^3$)	NB Same individual in each case Swimming (30 mins) (3 occasions) At rest in water (30 mins) At rest 3 m from poolside (30 mins)	Pre-exposure usually <0.5 $\mu g/m^3$ Highest peak 26.5 $\mu g/m^3$ 14.0 $\mu g/m^3$ 11.0 $\mu g/m^3$		Two peaks, consistent with rapid (inhalation) and slow (dermal) routes of absorption

Study	$CHCl_3$ conc. in pool	$CHCl_3$ conc. in air	Activity (n = number of subjects)	$CHCl_3$ conc. in exhaled air	$CHCl_3$ conc. in blood	Comments
Lindstrom *et al*. 1997 (Montana, USA)	63-73 μg/l	145-148 $\mu g/m^3$	Competitive swimmers, training for 2 hours (one male, one female)	Pre-exposure 3.0-3.5 $\mu g/m^3$ Peak: male 371 $\mu g/m^3$; female 339 $\mu g/m^3$		Dermal absorption estimated at 80%. Possibly high because of: • water at 84 ºF • long session resulting in skin hydration • total immersion • intense exercise leading to high capillary perfusion

Table 10.7 Estimates of absorption of chloroform whilst swimming

Study	Activity	Estimated Total Dose	Estimated dose by inhalation	Estimated dose by dermal absorption	Estimated dose by ingestion	Comments
Lahl *et al.*, 1981	30 minute swim in a 1 hour visit	Adult: 50 µg or 0.77 mg/kg Children: 15 µg/kg Extreme conditions: 500 µg per visit		Ignored	Ignored	Estimated exposure based on a 30 minute swim in a 1 hour visit. Extreme exposure based on 1 hour swimming crawl in turbulent water
Weisel and Shepard 1994	Swimming 1 hour/day, 3 days/week in an indoor pool with $CHCl_3$ conc. in air above the water of 100 µg /m^3	420 µg /week	Inhalation of 300 µg /week resulting in an internal dose of 210 µg /week	Dermal internal dose assumed to be equivalent to inhalation dose i.e. 210 µg /week	Ignored	The calculation of inhaled dose is based on an inhalation rate of 1 m^3/hour and assumes 70% is absorbed across the lung. The authors compare this with an estimated intake from showering daily for 10 minutes of 180 µg/week (Jo *et al.*, 1990)
Aggazzotti *et al.* 1995	Competitive swimmer training for 45 minutes 3 times per week	1100-2800 µg /swim				I understand that these estimated doses have been incorrectly calculated and Aggazzotti is re-addressing this (Cotruvo, pers comm 1999)
Shatkin and Brown, 1991	20 minute swim			4800 µg		Calculated dermal dose based on Beech *et al.'s* data on THM levels in outdoor pools

Study	Activity	Estimated Total Dose	Estimated dose by inhalation	Estimated dose by dermal absorption	Estimated dose by ingestion	Comments
Beech *et al.*, 1982	3 hours swimming session	2820 µg	866 µg	1650 µg	79 µg	Calculation based on a study of a 6 year old boy immersed in water containing $CHCl_3$ at 500 µg/l
Levesque *et al.*, 1994	Swimming for 1 hour/day	65 µg/kg/day i.e. 4550 µg/swim for 70 kg adult		24% (i.e. approx. 1,110 µg)		
Aggazzotti *et al.* 1998	Swimming for 1 hour	Males (n = 3) 193-209 µg Females (n = 2) 134 -146 µg				Calculations based on breath sampling of five competitive swimmers during training
Kaas and Rudiengaard 1988	Swimming for 2 hours		12,900 µg	700 µg (skin) 200 µg (absorption by oral and nasal tissue)		Calculated for a water concentration of 150 µg/l
Pleil and Lindstrom 1997	2 hours high intensity swimming	100 µg				This is the lower bound estimate of total dose from a water concentration of 70.5 µg/l and an air concentration of 147 µg/l.

Although most work on THMs in swimming pools has centred on the presence and absorption of chloroform, some studies have also looked at brominated THMs. Among these was a study by Aggazzotti *et al.* (1998) which investigated the uptake of THMs in swimmers. As the brominated compounds were present in smaller concentrations than chloroform, their uptake was correspondingly lower. Nonetheless, BDCM and DBCM were found in the exhaled breath of individuals following exposure in the swimming pool, both after sitting at the poolside for an hour and after an hour of swimming (Table 10.8). Pleil and Lindstrom (1997) used measurements of BDCM in exhaled air to estimate exposure of two athletes during a 2 hour intensive swimming session. Although BDCM was undetectable in the pool water, 2.7 $\mu g/m^3$ was found in air above the pool. Maximum blood concentrations of 0.13 and 0.24 $\mu g/l$ were estimated while the lower bound estimates of total dose during the swimming session were 1.42 and 1.5 μg.

Data collected during this study also illustrate the effect of swimmer-induced turbulence on the concentrations of THMs in the air of indoor pools. Table 10.9 shows an approximate doubling of concentrations during an hour when 40-50 competitive swimmers were training compared air concentrations above a pool in which no-one was swimming. As well as increasing the concentration of volatile compounds in the air, it is also likely that such turbulence results in the ingestion of larger volumes of water whilst swimming.

10.5 General household exposures

Showering, like other uses of water in the home, results in the release of volatile chemicals into the air. This will, to a greater or lesser extent (depending on ventilation and the characteristics of the building) affect the air quality in other areas of the house. Thus, individuals within the home can be exposed by inhalation to volatile contaminants such as chloroform as a result of water use by someone else. A number of models have been developed to investigate the significance of such exposures. Early estimates of inhalation doses of VOCs from household uses of water, such as that by Andelman (1985a, 1985b) used simple, single compartment models (i.e. treating the entire volume of the house as one) and assumed complete volatilisation. More refined models were developed, such as that by McKone (1987) which treats indoor air as three-compartments (shower-stall, bathroom and the remainder of the house) and calculates time-dependent air concentrations based on normal water use patterns and taking into account the transfer efficiency of chloroform to air.

Table 10.8 THMs in ambient and alveolar air before, during and after swimming (µg/m^3)

		Pre-exposure (in biomedical sciences building)	After resting at pool side for 1 hour	After swimming for 1 hour	1 hour after swimming (not in pool building)	1½ hours after swimming (not in pool building)
Chloroform	Ambient air	20.7 ± 5.3	91.7 ± 15.4	169.7 ± 26.8	20.0 ± 8.4	19.2 ± 8.8
	Alveolar air	9.3 ± 3.1	29.4 ± 13.3	76.5 ± 18.6	26.4 ± 4.9	19.1 ± 2.5
BDCM	Ambient air	< l.o.d.	10.5 ± 3.1	20.0 ± 4.1	< l.o.d.	< l.o.d.
	Alveolar air	< l.o.d.	2.7 ± 1.2	6.5 ± 1.3	2.7 ± 1.1	1.9 ± 1.1
DBCM	Ambient air	< l.o.d.	5.2 ± 1.5	11.4 ± 2.1	< l.o.d.	< l.o.d.
	Alveolar air	< l.o.d.	0.8 ± 0.8	1.4 ± 0.9	0.3 ± 0.2	0.20 ± 0.1
Bromoform	Ambient air	< l.o.d.	0.2[a]	0.2[a]	< l.o.d.	< l.o.d.
	Alveolar air	< l.o.d.	< l.o.d.	< l.o.d.	< l.o.d.	< l.o.d.

[a] Only one positive sample
Note. < l.o.d. = less than the limit of detection

From Aggazzotti *et al.*, 1998

Table 10.9 Effect of turbulence caused by swimmers on air concentrations of THMs

THMs in water (μg/l)			THMs in environmental air (μg/m^3)			
	Mean	Range	No swimmers in pool		40-50 swimmers in pool	
			Mean	Range	Mean	Range
Chloroform	33.7	(25-43)	91.7	(69-103)	169.7	(135-195)
BDCM	2.3	(1.8-2.8)	10.5	(7.0-14)	20.0	(16-24)
DBCM	0.8	(0.5-10)	5.2	(4.0-7.0)	11.4	(9.0-14)
Bromoform	0.1	(0.1)	-	0.2[a]	-	0.2[a]

[a] Only one positive sample

Adapted from Aggazzotti *et al.*, 1998

Maxwell *et al.* (1991) compared the predictions from these models with experimental data for inhalation exposure to chloroform whilst showering, assuming the same water concentrations as in the experimental studies. They also compared dermal exposure estimates derived by Jo *et al.* (1990 a,b) with a model developed by Brown *et al.* (1984) for dermal exposure in a bath. The results of the doses calculated for individual exposure events are presented in Table 10.10, along with estimates of lifetime doses which take into account different exposures during childhood. Maxwell *et al.* concluded that exposure to chloroform from inhalation was probably in the range of 0.6 - 1.5 times that for ingestion, but this ratio could be as high as 5.7; for dermal exposure a ration of 0.3 compared with ingestion exposure was considered likely, but it could be as high as 1.8 times. The higher significance of inhalation exposures compared with direct dermal exposures reflects the potential importance of indirect inhalation exposures resulting from general household uses of water.

Estimates of exposure to waterborne VOCs by inhalation have been further refined by the development of models such as MAVRIQ (Model for Analysis of Volatiles and Residential Indoor Air Quality). This can incorporate information on building characteristics and individual behaviour patterns to allow for an estimate of inhalation exposure tailored for a specific individual or situation (Wilkes *et al.*, 1992; 1996; 1998).

Table 10.10 Some estimated inhalation and dermal doses assuming a concentration of chloroform in tap water of 23.5 mg/l

	Estimated dose	Units	Reference
Inhalation exposures			
1. One compartment model	4.0	µg /(kg.day), adult	Andelman (1985a, 1985b)
2. Implied lifetime dose	5.1	µg /(kg.day), lifetime	Derived from Andelman (1985a, 1985b)
3. Three-compartment model, reference estimate	1.1	µg /(kg.day), lifetime	McKone (1987)
4. Three-compartment model, upper-bound estimate	4.2	µg /(kg.day), lifetime	McKone (1987)
5. Actual showers	0.24	µg /(kg.shower), adult	Jo *et al*. (1990a, 1990b)
6. Implied life dose	0.45	µg /(kg.day), lifetime	Derived from Jo *et al*. (1990a, 1990b)
Dermal exposures			
7. Actual showers	0.22	µg /(kg.shower), adult	Jo *et al*. (1990a, 1990b
8. Implied lifetime dose	0.24	µg /(kg.day), lifetime	Derived from Jo *et al*. (1990a, 1990b)
9. Model for baths, based on Fick's law	1.2	µg /(kg.bath), adult	Brown. *et al*. (1984)
10. Implied lifetime dose	1.3	µg /(kg.day), lifetime	Derived from Brown. *et al*. (1984)

From Maxwell *et al*., 1991

10.6 Comparisons of different exposures

Some authors of exposure studies have also compared the exposures resulting from the activity under examination with other exposures to chloroform. Some of these comparisons are shown in Table 10.11. The possible significance of swimming compared with other exposures is indicated by the data of Levesque *et al.* (1994) who estimated that, for the competitive swimmers studied, the dose from swimming could be 140 times the exposure from showering and 90 times greater than from tap water ingestion.

Because much of the chloroform ingested is metabolised in the first pass through the liver, the use of exhaled or blood chloroform as a biomarker is not applicable to measure exposure via drinking water. Therefore, most authors have calculated the exposure from drinking water using defaults for average consumption and using relevant concentrations and assuming 100% absorption (e.g. Weisel and Shepard, 1994). These have been compared with calculated or measured internal/systemic doses from inhalation or dermal exposure. It is worth bearing in mind that these are not strictly comparable, since very little of the exposure from ingestion reaches the systemic circulation (see Section 9.3.2). An exception to this is a comparison by McKone (1993) who used PBPK modelling to estimate total (1.31 µg per µg/l in the water) and metabolised (0.41 µg per µg/l in the water) doses resulting from showering and also calculated a metabolised dose of 0.62 µg per µg/l following ingestion of 1 litre of tap water (assuming that all the ingested chloroform is continuously introduced directly to the liver).

It should be noted that exposures calculated by different methods or based on different measurements have resulted in a wide range of estimates of exposure even for similar conditions (e.g. see Table 10.3).

Table 10.11 Comparisons of different calculated exposures to chloroform by authors

	Drinking water	Assumptions	Showering/bathing	Assumptions	Swimming	Assumptions
Weisel and Shepard 1994 (Jo *et al.*, 1990b)	50 µg/day (0.7 µg/kg)	2 litres at 25 µg/l, 70 kg adult	33 µg/day (0.47 µg/kg)	10 minute shower (dermal and inhalation) Water at 23.5 µg/l		
Weisel and Shepard 1994	350 µg/wk	2 litres/day 25 µg/l	180 µg/wk	10 minute shower approx. daily	630 µg/wk	Swims in pool with air concentration of 100 µg/m^3 for 1 hour/day, 3 days/wk
Levesque *et al.* 1994					65 µg/kg/day (i.e. 4550 µg/day)	1 hour/day, intensive training

11. USE OF BIOMARKERS TO ASSESS EXPOSURES TO HALOGENATED ACETIC ACIDS

Trihalomethanes are typically the largest class of disinfection by-products found in chlorinated waters, with halogenated acetic acids (HAAs) forming the second largest group (Krasner, 1999a). As for THMs, chlorinated forms tend to dominate (except in high bromide waters with low levels of natural organic matter) and, therefore, much attention has focussed on dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA).

Dihaloacetic acids (DHAAs) such as DCAA are extensively metabolised to a number of intermediates but trihaloacetic acids (THAAs) are less readily metabolised and a significant proportion of the internal dose of TCAA, in particular, is excreted unchanged in the urine. In studies in rats, Schultz *et al.* (1999) found that DHAAs had short half-lives (<4 hours) following intravenous (iv) administration while the THAAs had half-lives ranging from 8 hours (TCAA) to 0.6 hours tribromoacetic acid (TBAA). Urinary excretion accounted for only 3% of the dose of DHAAs but at least 30% of THAAs. They also investigated the bioavailability of HAAs following oral administration and found that high for TCAA (116%) and other THAAs and also fairly high for DCAA (81%). However, it was found to be low for bromochloroacetic acid (BCAA) (47%) and dibromoacetic acid (DBAA) (30%) which was thought to be due to greater first-pass metabolism. The authors characterised the elimination of TCAA as low metabolism and high renal clearance whereas that for DCAA was described as high metabolism and low renal clearance. Kim and Weisel (1998) found that 2.9% of the dose of TCAA ingested by humans was excreted unchanged in the urine.

Other researchers have observed short plasma half-lives for DCAA in animals of 0.9 to 1.6 hours and a longer half-life for TCAA of 2.2 to 75 hours (cited in Kim and Weisel, 1998). Studies in humans have also confirmed a short half-life for DCAA (20 to 36 minutes following a bolus dose) and a longer half-life for TCAA (30 to 120 hours) (cited in Kim and Weisel, 1998).

Some HAAs are themselves metabolites of other compounds (TCAA, for example, is a metabolite of trichloroethene). This could lead to the misinterpretation of studies using HAAs as biomarkers unless such possible confounders are taken into account. In the studies outline below, for example, subjects were screened for potential industrial exposure to solvents.

Exposure to halogenated acetic acids (HAAs) by inhalation is not likely to be significant because they are non-volatile. Dermal absorption is also likely to be low as they have low skin permeability (Weisel *et al.*, 1999).

11.1 Ingestion

Using biomarkers, Weisel *et al.* (1999) investigated whether water concentration was a good surrogate for exposure to disinfection by-products. They did not find a good correlation between the concentrations of DCAA and TCAA in drinking and the

excretion of these compounds in urine. However, when the drinking habits (volume of water, use of filters, consumption of hot drinks) of the women studied were used to provide an estimate of ingestion exposure, the estimate for TCAA was found to be statistically related to the urinary excretion rate. This correlation was found to be stronger in subjects who did not work outside the home than for the cohort as a whole. The authors concluded that urinary TCAA excretion rate appeared to be a valid biomarker of TCAA ingestion exposure from chlorinated water during routine household use over the time period of the study (48 hours). Urinary DCAA, in contrast, showed no such statistical relationship. Weisel and co-workers suggest that this was because of its short biological residence time.

11.2 Swimming

Kim and Weisel (1998) investigated the extent to which the haloacetic acids DCAA and TCAA were absorbed by dermal contact and ingestion whilst swimming for 30 minutes in pools containing the following concentrations:

	Range	mean (± SD)	median
DCAA	52-647 µg/l	419 µg/l (± 203)	484 µg/l
TCAA	57-871 µg/l	420 µg/l (±333)	278 µg/l

Measurements of urinary DCAA and TCAA were used to determine the absorbed doses. In order to differentiate between dermal absorption and the dose resulting from accidental ingestion of water, subjects also walked around in the pool for 30 minutes. Inhalation was assumed to be unimportant because of the low volatility of these compounds. Urinary levels of DCAA and TCAA rose following both swimming and dermal-only exposure. For DCAA, the amounts attributable to dermal absorption and ingestion were determined. Exposure by ingestion was found to be more significant than dermal exposure. The ingested dose was considerably more variable between subjects than the dermal dose, which the authors attributed to differences in the amount of water swallowed during swimming (Table 11.1).

Table 11.1 Estimated ingested and dermal doses of DCAA whilst swimming

Subject	Ingestion exposure	Dermal dose
A	27 µg	4.7 µg
B	7.0 µg	5.7 µg
C	11 µg	6.0 µg
D	9.1 µg	6.7 µg

NB Calculated assuming that the metabolic rates and fractions of DCAA excreted unchanged in urine are the same following dermal exposure and ingestion exposure (i.e. 3%)
Adapted from Kim and Weisel, 1998

Estimates of weekly exposure for an individual swimming for 30 minutes in water containing the median concentrations of DCAA (484 µg/l) and TCAA (278 µg/l) found in this study three times per week were derived and are presented in Table 11.2.

Table 11.2 Estimates of weekly internal doses of HAAs from swimming

	Dermal	Ingestion	Total weekly dose
DCAA	20 µg/week	30 µg/week	50 µg/week
TCAA	10 µg/week	20 µg/week	30 µg/week

Ref: Kim and Weisel, 1998.

11.3 Comparisons of different exposures

Jo and Weisel (1998) compared estimated weekly doses of DCAA and TCAA from different activities (Table 11.3). These showed drinking water to be the route of over-riding importance.

Table 11.3 Comparisons of different calculated exposures to HAAs

	Drinking water	Assumptions	Showering/bathing	Assumptions	Swimming	Assumptions
DCAA	294 µg/wk	1.4 litres/day at 30 µg/l	2 µg/wk	Assuming constant contact with water at 30 µg/l	50 µg/wk	Swims three times a week for 30 mins and ingests 23 ml of water. Conc. in pool: DCAA 484 µg/l
TCAA	294 µg/wk	1.4 litres/day at 30 µg/l	2 µg/wk	Assuming constant contact with water at 30 µg/l	30 µg/wk	Swims three times a week for 30 mins and ingests 23 ml of water. Conc. in pool: TCAA 278 µg/l

Ref: Jo and Weisel, 1998

12. IMPLICATIONS FOR EXPOSURE ASSESSMENT

The data presented in the previous few sections of this report illustrate the difficulties faced by epidemiological investigators attempting to estimate the exposure of individuals or groups to "disinfection by-products". This term encompasses a large number of compounds, many of which have not yet been identified or characterised. Different classes of disinfection by-product have very different physico-chemical characteristics, such as volatility and lipophilicity, which govern the extent to which they are encountered and absorbed by inhalation and dermal routes. They are also metabolised differently and have different toxicological effects at different target organs. Without knowing which of these compounds is the postulated toxic agent, it is difficult for the epidemiologist to determine the most important types of exposure to water and, hence, a suitable method of exposure assessment. Weisel *et al.* (1999) capture the underlying difficulty: "It is unknown which disinfection by-products, if any, are responsible for adverse health effects. The concentration of individual disinfection by-products can vary relative to each other. Thus, the total THM concentration or amount of chlorine added may not be correlated with the concentration of the biologically active disinfection by-products".

Conventionally, ingestion of drinking water has received the greatest attention. However, data relating to volatile lipophilic compounds indicate that inhalation and dermal exposures may be as important as ingestion, if not more important. Thus swimming, showering and bathing may, depending on an individual's habits, result in higher levels of exposure to chloroform and other THMs than consumption of drinking water.

Conversely, exposure by inhalation is assumed to be irrelevant for the non-volatile HAAs, and dermal exposure through showering/bathing and swimming has been found to be far less significant than consumption of drinking water. Consequently, detailed estimates of drinking water consumption (including adjustments for the extent to which tap water was filtered or heated before use) were found to correlate with biomarkers of exposure to HAAs, particularly for individuals who did not work outside the home (Weisel *et al.*, 1999). HAA concentrations in the supplied water were found not to be good surrogates for exposure (i.e. did not correlate with the biomarker) which the authors suggested that this may be due to large variability between individuals in the amount of chlorinated water consumed. The fact that water and water-based beverages are often consumed outside the home also contributes to household tap-water concentrations being poor surrogates for detailed ingestion-exposure estimates.

In the same study (Weisel *et al.*, 1999) THM concentrations in the water supply were found to correlate with biomarkers for THM exposure (breath concentrations); this correlation was as strong as that for an exposure estimate calculated using information on the duration of showers taken by each individual. This suggests that water concentration provided a better explanation of breath concentration than did shower duration.

Thus, it would appear from the data presented above that exposure estimates for non-volatile, poorly lipophilic compounds such as HAAs are best made using accurate information on the volume of water-based beverages consumed, whilst that of volatile,

lipophilic substances is better approximated by concentrations in the household water. The correlation of THM exposure with water concentration is consistent with the water concentrations varying over two orders of magnitude whilst shower durations differed only by a factor of three. However, the authors themselves (Weisel *et al.*, 1999) caution that this study included only females of a similar age, whose showering/bathing habits were unlikely to vary as much as those of the general population (different age groups and genders tend to have different showering habits).

In addition, inhalation and dermal exposures to THMs whilst swimming may be very significant compared with other exposures, particularly for individuals who swim frequently at high intensity in pools with higher levels of THMs. This suggests that information on showering/bathing and swimming habits or, more probably, biomarker measurements on an individual basis may be required to make meaningful estimates of exposure to volatile, lipophilic disinfection by-products (as it is difficult to take into account in a questionnaire approach factors such as the turbulence of water, the extent of the ventilation of the pool, the temperature of the water and the intensity of the exercise in a questionnaire). The picture is further complicated by the contribution of household exposure from a variety of water uses.

Nonetheless, it might be expected that assessment of exposure to identified disinfection by-products might act as surrogates for compounds with the same general properties. Thus, estimates of exposure to HAAs might be regarded as valid to evaluate whether or not an association of a particular health outcome exists with other (perhaps unspecified) non-volatile compounds which are poorly absorbed dermally, for example. However, in order to accurately estimate the ingestion exposure to DCAA and TCAA, Weisel *et al.* (1999) first had to determine the extent to which these compounds were removed by filtration (found to be 70% in both cases) and any changes in the concentrations brought about by boiling (unchanged in the case of DCAA, whilst 39% of TCAA is lost). Such factors mean that ingestion exposure estimates for one chemical cannot simply be used as a surrogate for another. Similarly air-stripping efficiencies for volatile organic compounds may differ, as may the extent to which they are absorbed in the lung and across the skin.

Even so, the relative importance of different exposure routes is likely to be generally similar for disinfection by-products with similar properties. Modelled estimates of 24-hour exposures from household water use (assuming each contaminant is present at 1000 µg/l) are presented in Table 12.1.

Weisel (1999a) has summarised the data currently available from biomarker studies as indicating that, in the general population, all three exposure routes (ingestion, inhalation and dermal) contribute approximately equally to the total THM dose and suggests that ingestion is the primary route of exposure for HAAs.

Table 12.1 Summary of population exposure distributions of 24 hour dose (µg) assuming each contaminant is present at 1000 µg/l

Chemical class		50th percentile	95th percentile
	Occupants who showered or bathed		
Chloroform	Ingestion	1,300	2,600
	Inhalation	1,300	3,900
	Dermal	600	1,500
	Occupants who did not shower or bathe		
Chloroform	Ingestion	1,300	2,600
	Inhalation	600	2,500
	Dermal	20	50
Non-volatiles	Ingestion	1,300	2,600
	Inhalation	<1	<1
	Dermal	5	11

Adapted from Wilkes (1998) and Weisel (1999b).

However, the difficulties do not stop at estimating the extent to which subjects in a study are exposed to the disinfection by-products of interest. The route of exposure will affect the fate and metabolism of some compounds dramatically, and this needs to be borne in mind. Biomarker studies on chloroform and other THMs, for example, would suggest low absorption of these compounds following ingestion. In fact, it is known that the majority of the chloroform and other THMs ingested undergoes first-pass metabolism in the liver and, hence, is not detected by measurements of concentrations in blood or exhaled breath. The metabolite formed (phosgene) is highly reactive, binds to macromolecules in the liver and, at high doses, causes liver toxicity.

The health end-point of interest now impinges on our exposure assessment: if the epidemiologist is interested in hepatotoxicity, then the ingested dose (which the biomarker methods fail to detect) is the exposure of relevance. If, however, the study is concerned with toxic end points in other tissues, then the ingested dose is of little significance; the majority of it never reaches the blood stream and is not distributed around the body. Weisel and Jo (1996) summarise the implications of such differences in metabolism thus: " for common environmental levels, if the target organ of a waterborne contaminant is the liver or if a long-lived metabolite is the toxic agent, then an ingestion exposure delivers the largest biologically effective dose..... However, if a different organ is the target, and either the parent compound or a short-lived metabolite is the biologically active agent, then inhalation and dermal exposures would deliver a larger biologically active dose than ingestion." Levesque *et al.* (1994) suggested that PBPK modelling to ascertain target organ concentrations may be more suitable for exposure and that risk assessments will vary according to exposure route.

A further complication is the consideration of disinfection by-products in water as a complex mixture. Different disinfection by-products may be additive in their effects, or may act completely independently. The potential for the inhibition of metabolism (such as the influence of co-administration of more than one THM; Da Silva *et al.*, 1999) has been demonstrated. In addition, it is possible that two or more disinfection by-products may act in tandem or sequentially to produce a toxic effect (initiation and promotion of carcinogenesis, for example.) Such considerations are beyond the scope of current exposure estimates.

13. DISCUSSION

It is not clear which disinfection by-products, if any, are the most likely candidates for the causal agent of the adverse effects reported, in epidemiological studies, to be associated with chlorinated water. The lack of consistency between these effects and the toxicology of THMs observed in animal studies suggests that these compounds are unlikely to be causal agents, despite often being present at relatively high concentrations. However, as they have been the emphasis of study for several decades, the majority of occurrence and exposure data on disinfection by-products relate to THMs.

The epidemiologist studying disinfection by-products is, therefore, in a difficult position when trying to decide on the best method of exposure assessment. Assessments based mainly on detailed estimates of ingestion of drinking water and drinking water-derived beverages are more likely to reveal any existing association with non-volatile disinfection by-products. In contrast, estimates of exposure to chloroform and THMs, taking into account inhalation and dermal exposures, may act as surrogates for other volatile, lipophilic disinfection by-products.

By using both types of exposure estimate in the same study, it might be possible to obtain information about the nature of the possible causal agent of any effects observed. If one estimate was found to have a stronger association than the other with the health end-point examined, this might suggest whether the effect (if real) was the result of a volatile, lipophilic compound for which dermal and inhalation exposures are important or a non-volatile compound for which ingestion is the dominant route of exposure.

Although some information on the internal doses resulting from different activities is available, further detailed data regarding the contribution of different activities to internal dose would be useful in order to determine their importance.

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PART THREE

METHODOLOGY FOR OBTAINING MISSING INFORMATION

14. SCOPE AND PURPOSE

The second objective of this contract was to suggest methodology that would enable the gaps in available information to be filled. Initially this task related to the question of quantifying exposures to water *per se*, but was later extended to include the question of how much each of the different routes of exposure to DBPs could contribute to a person's total DBP uptake. Although these two questions are both motivated by concern about the possible health-effects of DBPs, the questions are different enough to give rise to different objectives for future research and hence to two rather different designs of study.

(1) Research to gain better information about people's exposure to water would entail surveys of people's indulgence in activities involving water-contact. Such a survey would aim to reveal the statistical distributions of exposures that apply across a specified population. We refer to this type of study as a *survey of exposures.*

(2) Research to gain information about the relative contributions of different routes of exposure to total uptake of DBPs would entail measurements of the concentrations of DBPs in the different waters to which individuals are exposed and the consequent concentrations of DBPs in one or more of their body fluids (blood, urine, exhaled air) to provide a summary measure of the quantities of DPBs absorbed from all sources. We refer to this type of research as a *study of DBP uptake.*

These two types of study will be discussed in turn. The purpose of this part of the report is to show how the designs of such studies would follow from their objectives, but the discussion leaves open the question of how the objectives should be chosen. The advice provided here concentrates on how the gaps might be filled rather than on which gaps should be chosen for filling.

The design of surveys of exposure is covered in Sections 15-18, while studies of uptake are more briefly mentioned in Section 19. This allocation of space is not a reflection of the need for nor value of the two kinds of work. The consideration of exposure to water came first in this contract and for this there was no readily available source of advice on future studies. The need for suggestions on the design of a study of DBP uptake has, however, already been partly met by the recent proposal to MRC from Imperial College (Nieuwenhuijsen and Elliott 1999) which outlines a suitable methodology for a study of this type.

15. TARGET POPULATIONS AND EXPOSURES TO BE QUANTIFIED

The *target population* in a survey of exposure, (or in an epidemiological study) is the population of people for whom information is needed and about which conclusions will eventually be drawn. It is usually appropriate to include specification of this target population in terms of space, time, age and sex. For example, for the study by Hopkin and Ellis (1980) the target population was the whole of the population of England, Wales and Scotland in Autumn 1978, subdivided into men and women and into six age bands. For the eventual application of results the desired target population for exposure surveys in the United Kingdom would be chosen from the following list of possibilities:

All ages, male and female;

Children, male and female;

Adults, male and female;

Adults, female only;

Adults, female and pregnant;

Adults, female and non-pregnant;.

Information about any two of the last three populations would be needed if the exposures of pregnant and non-pregnant women are to be compared.

The earlier parts of this report have discussed the need for information on four routes of exposure:

Drinking;

Bathing (domestic) and/or showering;

Swimming in swimming pools (i.e. immersion);

Attendance at swimming pools (i.e. not involving immersion).

The adequacy of the available quantitative information on these routes of exposure for the above population groups is summarised in Table 15.1.

The earlier parts of this report have indicated that good enough information exists to describe the mean and spread of exposures only for drinking, and for this there is no UK data on which to compare pregnant women with non-pregnant women of similar age. It can be inferred from other studies that the systematic difference between pregnant and non-pregnant would be small compared with the variation from person to person, but

there are no UK data on pregnant women to substantiate this. For neither bathing, swimming nor attendance at swimming pools are there any satisfactory estimates either of average exposures or extremes.

Table 15.1 Target populations and routes of exposure, for selection of objectives for future surveys

Target population	Exposure route			
	Drinking	**Bathing/ showering**	**Swimming**	**Attendance at pools**
All ages M & F	✓	?	?	?
Children M & F	✓	?	?	?
Adults M & F	✓	?	*	?
Adults F	✓	?	?	?
Pregnant F	#	?	?	?
Non-pregnant F	#	?	?	?
Pregnant v non-pregnant comparison	#	?	?	?

KEY ✓ Information available - further survey not needed
Some information available from US that might be regarded as good enough for UK
* Some information on frequency but not on duration
? Gaps that could be filled for UK only by future surveys.

The first steps in devising studies to fill the gaps in the available information would therefore be to decide on:

a) the target population or populations to be investigated;

b) the types of exposure to be measured.

Under (a), it would be crucial to decide whether information is needed specifically for pregnant women, rather than for a more general group, because this will influence the method of sampling (see Section 16). Under (b), the decision on which types of exposure should be included will not have a profound effect on the methodology of the survey, but it will have a bearing on sample sizes because:

- the average frequencies of participation are very different for the different activities;

- for swimming and attendance at swimming pools there are substantial fractions of the population who never participate at all.

16. METHODS OF SAMPLING

For practical reasons it may not be possible or simply not convenient to draw a sample of members from the whole of a target population in such a way that all members of the population have equal chances of selection. It is therefore often necessary or expedient to introduce the concept of a *study population* that is a subset of the target population but from which the *study sample* can be rigorously drawn.

Statistical methods provide the necessary safeguards for drawing conclusions about the study population from information gathered from the study sample. Such inferences should be rigorous and formal. Inferences from the study population to the target population can, however, be only judgmental or informal. Care is therefore needed in generalising the results if the study population has been defined in a way that could lead to bias. For example, in connection with surveys of showering, it would be quite unsuitable to adopt a study population of people whose water supply was metered, even if it were possible to obtain information from them more easily than from others. The results would need to carry a heavy caveat that only metered customers had been used.

The s*ampling frame* for a survey can be thought of as a list of all of the members of the study population. This list may not exist as such (and may not need to exist) but it must be capable of being generated, at least in theory. The notion of simple random sampling is that every individual in the sampling frame has the same probability of being selected into the study sample, and that the selection of each individual is independent of whether or not any other specific individual has been selected. In large scale surveys this requirement of independence may be modified and some form of cluster sampling employed to give economy of data-gathering, but this has to be allowed for when the data are analysed so that the degree of dependence between the people sampled is properly taken into account.

For surveys in which the target population is the whole of the UK population, or a substantial subset (e.g. women of child-bearing age), there are well established techniques used in market research to enable the selection of suitable samples. This is often done by first selecting households; the sampling frame is thus the totality of members of households, or more particularly the members within the specified age-sex group. These methods were used in the two British studies of drinking water consumption (Hopkin and Ellis 1980; MEL Research 1996) and would be suitable for diary studies of other types of exposure, for general population groups. The methodology for conducting surveys by this approach is fairly standard and the costs fairly predictable, once the details of the design are known. It is also relatively straightforward to carry out this type of work on a contractual basis because market research organisations are accustomed to working in this mode.

For the assembly of a sample from a target population of all *pregnant* women, the standard methods of market research would be possible but very inefficient. This would be particularly so if there were a further stipulation that the mothers had to be recruited at a particular stage of pregnancy, to enable data on exposure to be collected prospectively. For such a target population it would be much more efficient to attempt a method of

sampling based on information held by the medical services. This could possibly be achieved via general practices or, better, via hospital departments responsible for ante-natal care.

While obviously technically feasible, the use of this approach is outside the experience of WRc. From other work in the epidemiological field we should, however, expect to encounter a number of difficulties:

- It is not always possible to establish co-operation from hospital departments, whose staff may or may not be particularly interested in the objectives of the study.

- Therefore it may not be easy to ensure that the centres eventually chosen do cover a good enough geographical and socio-economic cross-section of the UK.

- Medical departments may be reluctant to work as sub-contractors or have not much idea what this involves.

- The involvement of medical agencies would bring the need for ethical approval. This might have to be centre by centre as well as for the study as whole.

These difficulties are administrative rather than technical but suggest that further investigation would be needed before we could be sure of the practicality of using this approach and able to give a reliable estimate of cost. They are also indicative that the arrangements for setting up a survey in this way would be more easily carried out by a research department from within the medical world.

17. SURVEY METHOD

For any of the combinations of exposure and target population considered in Table 15.1, the preferred method of gathering data would be by asking each member of the study sample to keep a diary in which exposure events would be recorded over a specified period of time. This method is more reliable than asking people at interview to recall a series of events, and it provides more detailed information that can be obtained from interview questions of the form, "Have you been swimming in the past fortnight?" The subjects can be asked in advance to measure or estimate how long they are exposed on each occasion, thus yielding data that would be hopelessly unreliable if collected retrospectively.

The diary method has previously been used successfully for obtaining information about how much people drink (Hopkin and Ellis 1980, MEL Research 1996). This gives confidence that a very similar approach could be taken to the other exposures. Diary pro-formas would need to be devised but the details of these need not be developed here.

Section 15 raised the general question of which types of exposure should be investigated. Additional questions now arise whether those different types of exposure should be dealt with in separate studies or in the same study and, if the latter, whether this would entail the keeping of separate diaries operating over different periods of time.

To offer some tentative guidance on this we need to consider the likely frequencies of occurrence of the different types of exposure and hence the quantity of information that would be generated per week of observation. Some typical figures for bathing/showering and for swimming, taken from earlier in the report, are set out in Table 17.1. This table also offers suggestions for durations of monitoring that would provide meaningful data without being unreasonably demanding. If the completion of diaries is made too burdensome the diarists may tire of their task and the quality of the information suffer, for example by under-reporting. We suggest that for bathing and showering it would be satisfactory to record for four weeks. This would, however, fail to provide adequate information about the frequency of swimming (except for very keen swimmers). For swimming it would be desirable to monitor for sixteen weeks but we would suggest eight as a more reasonable compromise, for people's interest to be sustained.

Table 17.1 Assumed Frequencies of exposure and suggested durations for keeping of diaries

	Average Frequency per week	Weeks for diary	Expected number of events recorded
Bathing/showering	3.5	4	14
Swimming (by those who do it)	1	8	8

It follows from these suggestions that the different routes of exposure will in general require separate diaries, if not separate studies. We would recommend that the only desirable combination for diary keeping would be of swimming with pool-side attendance.

If the target population for the study were pregnant women then, because of the difficulty of recruitment, it may be worth asking that the diaries for all exposures be completed by the same study sample, recording

(1) Drinking,

(2) Bathing/showering,

(3) Swimming and attendance at swimming pools.

If, however, the target population is more general. then information about drinking would not be needed and there would not be a strong argument for having diaries of exposure on (2) and (3) kept by the same individuals. The advantage of using the same people would be off-set by the requirement for different sample sizes (as explained in the next section). It might even be advantageous to separate the survey of bathing/showering from that of swimming because the outputs would be of potential interest to different groups of customers. It should be borne in mind that the study of frequency and duration of participation in swimming could be a component within a general survey of people's participation in various sports. While consideration of this possibly is beyond the scope of the present contract, it could help to bring about the desired research.

18. SIZE OF SURVEYS

The required size of sample (i.e. the number of people involved) in an exposure survey would, in theory, be predictable from a quantitative expression of the objectives of the survey. In practice, however, it is not always easy to make a confident prediction, usually because features of the study population are unknown or because the customer has not been able to articulate his objectives in a sufficiently quantitative way. For the surveys of exposure considered in the present report, both of these difficulties apply.

There are at least three ways in which the statistical objective or objectives of the survey might be specified:

(a) to require that the average exposure of the population could be estimated with specified precision, for example to within ± 10%, with 95% confidence;

(b) to enable extreme percentiles (for example the 10 and 90 percentiles, as in Hopkin and Ellis 1980) of exposure to be estimated for the study population as a whole or for specified sub-populations, again with specified precision;

(c) to enable comparisons to be made between different sections of the population, defined in terms of, for example:

- age,
- sex,
- socio-economic group,
- region,
- pregnancy status.

Only with a fairly refined specification of requirements, such as those given above, would it be possible to say how large a survey should be. We do not have a specification and so can offer only an informal indication of the size implications of such requirements.

The easiest type of requirement to work from would be (a), the precision of estimation of the population average frequency of exposure. We do not have much information about the variation in frequencies of exposure either within or between individuals, but could make the very approximate assumption that we are dealing with a system in which the variance of an observed number of events, n, is roughly equal to its expected number, θ. The relative precision with which the population average can be estimated would then be determined by the expected total number of events observed, as shown in Table 18.1.

Dividing the number of events by the expected number per person, from Table 17.1, enables the derivation of the number of subjects that would need to be included in a survey of bathing/showering. For swimming, however, it is necessary to make additional allowance for the fact that only about one third of the population ever go to an indoor pool, and this has been taken into account in arriving at the implied sample sizes in the final column of Table 18.1.

Table 18.1 Expected total number of events that need to be recorded to achieve specified precision of estimation of mean frequency (with 95 percent confidence)

Required precision as % of mean	Required total number of events	Implied sample size for study of bathing/ showering	Implied sample size for study of swimming
± 20%	100	7	38
± 10%	400	30	150
± 5%	1600	115	600

The numbers in Table 18.1 indicate that it would be quite easy to achieve sample sizes that are satisfactory for the estimation of a population mean. However some of these sample sizes would not enable reliable estimates of the percentiles of person-to-person variation. As a very rough rule of thumb it would be advisable to have a sample size of at least 100 subjects to enable the 10 and 90 percentiles to be estimated, and be given confidence limits, for example, by the non-parametric method described by Ellis (1989).

The combination of requirements (a) and (b) can thus still be met with fairly modest sample sizes, for example 100 subjects for bathing/showering and, say, 200 for swimming. This may not, however, be enough to satisfy requirement (c). One very rough and ready approach to (c), without requiring detailed power calculations, would be to assume that the requirements generated by (a) and (b) should be met for each specified subgroup of the population, rather than for the population as a whole. The consequence of this would, for example, be that if levels of exposure are to be contrasted between three socio-economic groups, we would require 100-200 subjects to be sampled from each group. The total sample site would thus be some 300 to 600 overall.

By similar reasoning, if it were desired to carry out a ‘national’ survey of exposures to pregnant women it would be appropriate to recruit subjects in, perhaps, four or five centres aiming to achieve from each centre.

100 diaries for bathing/showering

200 diaries for swimming (of which about 133 would turn out to be void).

19. STUDY OF RELATIVE CONTRIBUTIONS TO INTERNAL DOSE

A study of the uptake of DBPs by people who are potentially exposed to DBPs by different routes involves:

(1) the recruitment of suitable and willing participants, from the specified target population;

(2) the recording of behavioural information describing the frequency and intensity of different types of exposure (in very much the same way as in surveys of exposure);

(3) the measurement of the concentrations of DBPs in a series of samples from each of the types of water to which each participant is exposed;

(4) the measurement of the concentration of DBPs in a series of samples of body fluids (blood, urine, exhaled air) from the same participants;

(5) statistical investigation of the relationships between (4) and (3);

This would be a fairly complicated type of study to carry out, because the measurements must be co-ordinated through space and time, and yet the participants will be continuing to lead their everyday lives.

Because of the particular interest in the possible effects of DBPs on unborn children, the study proposed by Dr M J Nieuwenhuijsen and Professor P Elliott of Imperial College, is concerned with pregnant women. These women would be recruited over an 18 month period from those registering at the obstetrics department of a major London hospital.

It should be noted that the objective of this study is not to estimate the national ranges of exposures and so, as long as there is enough diversity of exposure between subjects, there is no need to achieve a sample that is representative of the national scene. The main difficulties of recruitment from hospital lists (Section 16) would therefore not loom as large as they would in a multi-centre study.

The Imperial College proposal outlines how the samples of drinking water, blood, urine and breath will be taken, but omits to say how swimming pool water will be sampled. It would appear that samples will be needed from the pool or pools used by each subject in the study. However, with the numbers of subjects involved (50 swimmers; 50 non swimmers) the logistics of this should not be insurmountable, because the pools could all be individually surveyed.

20. COSTS AND TIMESCALES

The DWI asked that the methods for obtaining new information should be accompanied by estimates of the costs and timescales of possible future studies. This is difficult to do without having settled on a full technical specification of what the proposed study or studies should be. The estimates given here must be regarded as very rough and ready and not as if they were part of a tender for contract.

For a survey of bathing/showering and swimming based on a study sample drawn from the general public (i.e. not focussing on pregnant women) the sample-size requirements are going to be similar to those for the DWI survey of tap water consumption in 1995, which involved sampling 400-500 households, and obtaining multiple diaries from each. We do not know the cost of the survey carried out by MEL but we do have a detailed break-down of costs for the unsuccessful but similar proposal made by WRc to carry out the same survey. We would estimate that the cost of fieldwork for a survey of other exposures would be similar to this, but the information collected would be less complicated and so perhaps somewhat easier to process. The overall cost of such a survey might be, say, £100 000 to within ± 25%. The survey could be executed within six months of a contract being placed.

For a survey of exposures targeting pregnant women, we have no direct experience on which to base estimates of the costs of recruitment. We speculate that the sampling cost per pregnant woman would be similar to the sampling cost per household in a survey of the general public. If this were so, then a national survey with a sample size of 400-500 pregnant women might cost about the same as a general population survey involving 400-500 households. However, because of the administrative difficulties referred to in Section 16, this estimate is less certain and the exposure survey targeting pregnant women would take longer to initiate and carry out. It would be optimistic to expect that it could be done within a year of a contract being placed.

For a study of uptake, WRc has insufficient information to make an independent estimate of what the costs might be. We do, however, have estimates of cost and timescale associated with the Imperial College proposal to MRC, which was for a total of £400-600 thousand over three years (Nieuwenhuijsen and Elliott 1999).

REFERENCES TO PART THREE

Ellis J C (1989) Handbook on the Design and Interpretation of Monitoring Programmes. WRc Report NS 29 (Section 5.3 and Appendix 5D).

Nieuwenhuijsen M J and Elliott P (1999) Personal communication.

21. OVERALL SUMMARY AND CONCLUSIONS

Data on the exposure of individuals, and pregnant women in particular, to both water and disinfection by-products are limited. This is especially true of data for the United Kingdom. Exposure to water by various activities, particularly swimming, can vary greatly between individuals. Such inter-individual variation is likely to be greater than the variation between groups (i.e. the variation in water exposures between individual pregnant women is likely to be greater than the difference in average exposure of pregnant and non-pregnant women). This presents difficulties in creating accurate exposure estimates in epidemiological studies investigating the possible health effects of contaminants in water.

Studies suggest that exposures whilst swimming, showering and bathing can contribute significantly to the internal dose of volatile, lipophilic disinfection by-products such as chloroform. However, such activities are less relevant for an assessment of exposure to non-volatile (or less volatile) compounds such as haloacetic acids, for which ingestion is the most important route of exposure. The extent to which different activities need to be taken into account in epidemiological studies therefore depends upon the properties of the postulated active agent.

22. RECOMMENDATIONS FOR CONSIDERATION

Despite the uncertainties outlined in Section 21 there are a number of areas for which further detailed information would be of benefit both in designing new epidemiological studies and in interpreting existing epidemiological studies. In particular, there is a need for better data on sources of potential exposure misclassification and on the size of impact of exposure from various activities other than drinking tap water.

1. It would be beneficial to obtain more specific exposure data for the UK on length of time taken in showers or in bathing and on exposure through swimming in chlorinated swimming pools.

2. Several studies investigating possible associations of adverse reproductive outcomes with disinfection by-products have found a greater association in women who remained at home than in those who worked outside the home. Because these women are less likely to consume water-based drinks outside the home than women who work, exposure estimates based on the levels of disinfection by-products in water supplied to the house are more accurate for these individuals. However, there appear to be no studies which specifically investigate differences in exposure to disinfection by-products by inhalation, through the skin and by ingestion of those who remain at home compared with those who work. It would be of benefit to obtain such data, particularly if the critical period of exposure appeared to be in the early or middle part of pregnancy.

3. There is evidence that the concentrations of a number of chlorination by-products change on heating. These changes can result in either the increase or the decrease in the concentration of key compounds. It would be of benefit to obtain more data on the changes in concentration associated with the preparation of hot drinks under a range of circumstances, such as chlorine residuals and water types. It would also be of benefit to determine whether significant changes in concentration occur in hot water systems and what the actual levels of disinfection by-products are in water used for bathing and showering.

4. Although it is suggested that inhalation of volatile disinfection by-products is likely to be a significant source of exposure, there are few data on the actual concentrations of compounds, such as the trihalomethanes, in indoor air under different circumstances. It would be of value to characterise the actual importance of this source of exposure. One possibility would be to apply models of internal air quality to the UK, using disinfection by-product levels and building design information relevant to the UK situation. Such models should be validated by field measurements.

5. There is evidence to suggest that, for some individuals, swimming will be an important source of exposure to some disinfection by-products. However, published data on levels of disinfection by-products in swimming pools, and the atmosphere of buildings housing swimming pools, in the UK are sparse. Changes in ventilation practices in recent years may also make the use of historical data inappropriate. Swimming could be an important source of misclassification but more data are needed to assess this.

6. Much of the data on exposure to individual disinfection by-products is generated from one laboratory. Although this laboratory has an excellent reputation it is important to have some confirmatory data from a second laboratory.

7. One of the key factors in determining whether a compound is likely to be of significance is to what extent it is able to reach the target organ. This can be achieved by the use of suitable biomarkers such as measuring the parent compound or its metabolites in blood, exhaled air or urine. Such measurements are an important part of the study of exposure in humans and would be of benefit in indicating the potential importance of different routes of exposure and the toxicological importance of different disinfection by-products. It would also be of value to carry out a desk study to determine which substances are likely to reach the foetus (i.e. to enter the systemic circulation and to cross the placenta) and which may, therefore, be of greatest interest.

8. Water supplies in the UK are regularly analysed for THMs in order to fulfil regulatory monitoring and reporting requirements. In contrast, there are few data available on the concentrations of other disinfection by-products. It is unclear which, if any, disinfection by-products may be causative agents of adverse reproductive health effects. However, toxicological data suggest that THMs may not be the only candidates. Information on the levels of other disinfection by-products, such as HAAs, in UK drinking water supplies would, therefore, be valuable. Such information would also give an indication as to the extent to which measurements of THMs are suitable surrogates for concentrations of other disinfection by-products.

APPENDIX A ON-GOING (UNPUBLISHED) RESEARCH PROJECTS OF KEY RESEARCHERS IN THE USA

Table A1 Summaries of information provided by key researchers in the field of disinfection by-product epidemiology and exposure assessment

Individual	Current research and/or information provided
David Ashley Centre for Disease Control, USA	Provided opinions on the approaches required and information on ongoing research: Collection and analysis of blood samples before and after exposure to trihalomethanes through showering, bathing and drinking a litre of water, using water well within the EPA regulations. Examining blood pharmacokinetics after dermal and oral exposure to trihalomethanes through typical household water. Blood internal doses of trihalomethanes of new mothers before and after taking a shower in two different locations in the USA. Participation in a national survey to obtain reference ranges for water and blood trihalomethane concentrations in the USA and to evaluate the water:blood concentration relationship.
Phil Singer University of North Carolina, USA	Provided information on on-going research: Data on water use by pregnant women being collected by members of his research team as part of several projects.
Pauline Mendola US EPA	Provided information on on-going research: Involved in studies with men (semen quality) and new mothers (birth defects) in relation to disinfection by-product exposure via drinking water.

Rebecca Calderon Head of Epidemiology, USEPA National Health and Environmental Effects Research Laboratory (NHEERL)	Dr Calderon is closely involved in the USEPA programme on the reproductive effects of DBPs. She provided a number of contacts who are working in the area of exposure assessment of pregnant women.
Fred Hauchman Assistant Director of NHEERL	He is responsible for the EPA research programme on water which includes EPA funded research on DBPs. He was able to extend the list of contacts provided by Dr Calderon.
John Reif College of Veterinary Medicine and Biological Sciences, Colorado State University	Provided information on a recent study on the exposure of pregnant women to water.
Tye Arbuckle, Health Canada	Provided information on current research and up-coming workshops.