The Relationship between Water Concentrations and Individual Uptake of Chloroform: A Simulation Study

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We simulated the relationship between water chloroform concentrations and chloroform uptake in pregnant women to assess the potential extent of exposure measurement error in epidemiologic studies of the health effects of exposure to water disinfection by-products. Data from the literature were used to assign statistical distributions to swimming pool chloroform concentrations, frequency and duration of swimming, showering and bathing, and average tap water consumption. Measured increases in blood chloroform concentrations after these activities were used to estimate average uptake per microgram per liter chloroform in the water, per minute spent in the activity or per liter consumed. Given average tap water chloroform concentrations from a U.K. epidemiologic study, an average daily uptake over 90 days was simulated for 300,000 mothers. The correlation between simulated uptakes and home tap chloroform concentration was 0.6. Mothers who swam regularly received far greater doses than did nonswimmers. Results suggest there will be considerable attenuation in risk estimates and/or power loss in epidemiologic studies if the putative agent is chloroform. *Key words:* **activity patterns, chlorination, chloroform, disinfection by-products, measurement error.** *Environ Health Perspect* **111:688–694 (2003). doi:10.1289/ehp.5963 available via *http://dx.doi.org/* [Online 9 December 2002]**

Chloroform ($CHCl_3$), along with bromodichloromethane ($CHCl_2Br$), dibromochloromethane ($CHClBr_2$), and bromoform ($CHBr_3$), form a group of compounds known as the trihalomethanes (THMs). These compounds have been identified as major by-products of water disinfection processes involving chlorine. Over the last 10 years, there has been considerable interest in whether chlorination disinfection by-products (DBPs) in drinking water such as the THMs are associated with adverse birth outcomes (Nieuwenhuijsen et al. 2000a). A number of epidemiologic studies have been carried out on the association of DBPs with adverse birth outcomes, and we are currently conducting an association study in the United Kingdom (Toledano et al. 2001). Many of these studies assign an ecologic estimate of average THM concentrations as a marker for DBPs. Our U.K. study, for example, uses quarterly mean THM tap concentrations of water supply zones (areas defined for routine monitoring purposes in which fewer than 50,000 people reside) estimated from routinely collected data provided by the water suppliers (Whitaker et al. Unpublished data).

Exposure to volatile compounds such as THMs in drinking water occurs through multiple routes and pathways and varies from person to person depending on the individual's water usage; exposure to other nonvolatile DBPs such as the haloacetic acids is primarily through ingestion (Nieuwenhuijsen et al. 2000b). Routes of exposure to volatile compounds are ingestion, dermal absorption, and inhalation, and pathways can include any activity involving chlorinated water, such as ingestion of tap water, swimming, bathing, and showering. For example, an individual residing in an area with water with a low THM concentration may experience a relatively high level of exposure by attending a swimming pool, taking many long baths, or by drinking water with a high THM concentration outside the home.

Inaccurate and imprecise exposure estimates in epidemiologic studies may lead to loss of power and precision, and attenuation in health risk estimates (Armstrong 1998). The extent to which this happens depends on the relation between the exposure index that is used and the "true exposure," which in this context is the relation between the mean chloroform concentration of the water zone in which a mother resides and her average uptake of chloroform, respectively.

A number of studies have measured an individual's uptake of DBPs from various activities, using biologic markers such as breath samples, blood plasma samples, and urinary excretion rates (Nieuwenhuijsen et al. 2000b). Chloroform concentrations measured in breath or blood after swimming and showering have been found to be correlated with chloroform concentrations in the water and air (Aggazzotti et al. 1990, 1995; Jo et al. 1990; Lévesque et al. 1994; Weisel et al. 1999) and to increase with the time spent on the activity (Aggazzotti et al. 1990, 1995; Gordon et al. 1998; Lévesque et al. 1994).

In this article we present data from a simulation study to assess the relation between chloroform concentrations in the water supplied to the home, using the water chloroform concentrations estimated for each water supply zone in the U.K. epidemiologic study (Whitaker et al. Unpublished data), and chloroform uptake, taking into account chloroform-related activities. The study focuses only on chloroform—the most prevalent THM—and includes the most important water-use activities: showering, bathing, swimming, and ingestion of tap water. Uptake of chloroform was simulated based on information in the published literature about frequency and duration of each activity, amount of water ingested, and measured increases in blood chloroform concentrations. Results of the simulation study were used to evaluate the relation between our exposure index (the water zone mean chloroform concentration) and the assumed "true" exposure (the simulated chloroform uptake) and so inform on the level of measurement error in the exposure assessment for our epidemiologic study.

Methods

The etiologically relevant exposure period for a mother in epidemiologic studies of DBPs has been taken to be the last trimester (3 months) of pregnancy for birth weight and stillbirth, and the first trimester of pregnancy for congenital malformations (Nieuwenhuijsen et al. 2000a). Therefore, 90 days of chloroform uptake via showering, bathing, ingestion of tap water, and swimming were simulated for each mother and then averaged to give an average daily uptake for all pathways. Our epidemiologic study population includes mothers supplied with water from three U.K. water suppliers. Mean chloroform concentrations for each water zone within each supplier's region

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We thank United Utilities, Severn Trent Water, and Northumbrian Water for providing data on chloroform concentrations. The studentship for H.J.W. was funded by the MRC and Water Research Centre.

The Small Area Health Statistics Unit is funded by a grant from the Department of Health, Department of the Environment, Transport and the Regions, Health and Safety Executive, Scottish Executive, National Assembly for Wales, and Northern Ireland Assembly. The views expressed in this publication are those of the authors and not necessarily of the funding departments.

The authors declare they have no conflict of interest.

Received 28 August 2002; accepted 9 January 2003.

were determined previously (Whitaker et al. Unpublished data). For each of the three water suppliers, we assigned 100,000 mothers (i.e., 300,000 in total) to a randomly sampled water zone mean chloroform concentration. Given this chloroform concentration, we simulated a chloroform uptake for each mother. Figure 1 gives a schematic overview of the simulations.

The distribution of values chosen for each of the input parameters was based on information in the published literature, using U.K. data where possible. We used summary statistics cited in the literature to estimate a plausible distribution for each input parameter. The log-normal distribution, which has the advantage of spanning only positive numbers, proved a reasonable approximation in most cases. Reported means and medians were used to estimate parameters for the log-normal distribution; the fit was then checked against any reported percentiles, and the parameters were modified if necessary. If little information was available, a uniform distribution ranging over a reasonable set of values or a point estimate was used. Uptake parameters were based only on studies measuring blood chloroform concentrations because these were thought to be the most biologically relevant and informative.

Swimming. High concentrations of DBPs have been measured in swimming pools; these concentrations are caused by the continual addition of chlorine and the presence of organic matter, such as perspiration, hair, and lotions (Chu and Nieuwenhuijsen 2002; Kim and Weisel 1998). Typical swimming pool chloroform concentrations are between 50 and 300 µg/L, although some pools can show higher concentrations (Lévesque et al. 1994). Only a few swimming pool chloroform concentrations were available for the United Kingdom (Chu and Nieuwenhuijsen 2002). Mean chloroform concentrations for indoor swimming pools reported in different studies worldwide were therefore used to derive a distribution for the pool chloroform concentration, although ventilation rates and disinfection practices may differ across countries. This resulted in a median pool concentration of 52 µg/L (range, 13–365 µg/L) (Aggazzotti et al. 1995, 1998; Aiking et al. 1994; Camman and Hübner 1995; Chu and Nieuwenhuijsen 2002; Lévesque et al. 1994; Lindstrom et al. 1997; Matthiessen and Jentsch 1999; Weisel and Shepard 1994).

We used average increases in blood chloroform concentrations and average pool concentrations in the studies that measured chloroform blood plasma concentrations before and after swimming (Aggazzotti et al. 1995; Aiking et al. 1994; Camman and Hübner 1995) to estimate the uptake of chloroform during swimming. Intense swimmers in training, who have increased breathing rates and cardiac output, have increased chloroform uptake while swimming (Aggazzotti et al. 1990). Because it is unlikely that pregnant women would be swimming competitively, data for competitive swimmers were excluded. The uptake per microgram per liter chloroform in water per minute spent in the pool was calculated as follows:

$$\begin{aligned}\text{Uptake [µg/(µg/L)min]} &= \{[\text{amount of blood (L)}] \\ &\times [\text{blood } CHCl_3 \text{ conc after swim (µg/L)} \\ &- \text{blood } CHCl_3 \text{ conc before swim (µg/L)}]\} \\ &\div \{[\text{pool } CHCl_3 \text{ conc (µg/L)}] \\ &\times [\text{time spent in pool (min)}]\}\end{aligned}$$

where conc is concentration, the amount of blood in the body was assumed to be 5 L, and a 1-hr swim time was assumed when no data were available on the time spent in pool.

Of the pregnant women involved in the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom, 59% reported that they never swim (i.e., 41% swim), 31% swim < 2 hr/week (76% of swimmers), 9.5% swim 2–6 hr/week (23% of swimmers), and 0.1% swim > 6 hr/week (0.2% of swimmers) (Nieuwenhuijsen et al. 2002). Survey results reported by Sport England (1999) indicated that 15% of (all) women swam in the last month and 37% of women swam within the last year, which suggests that, of the women who do swim, roughly 41% (15%/37%) do so at least once per month. A suitable continuous statistical distribution to fit these data could not be found. Instead, women were split into occasional (less than once per month) and regular (at least once per month) swimmers to estimate a swimming rate (per 90 days), assuming that the proportions of occasional and regular swimmers were the same for pregnant women as for all women.

Data on how long an individual swims were available from the U.S. National Human Activity Patterns Survey (NHAPS), which reported the average swim time as 1 hr (Tsang and Klepeis 1996), whereas an average swim time of 50 min was reported in the United Kingdom (Chu 2000). The median swim time was based on the U.K. data, but the NHAPS data were used to inform on the

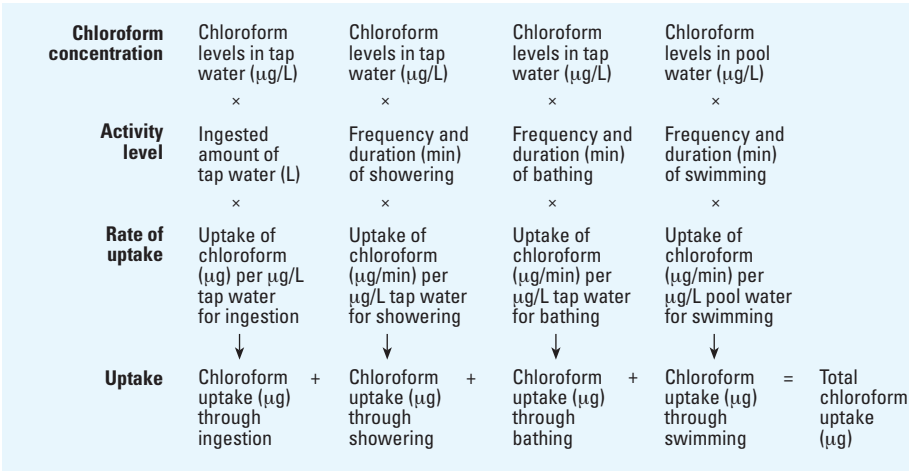

Figure 1. Schematic overview of the simulation of chloroform uptake for a mother.

Table 1. Input parameters for swimming.

Parameter	Distribution/value
Pool chloroform concentration (µg/L)	Log-normal (3.95, 0.77) 5th percentile 15 µg/L, median 52 µg/L, mean 70 µg/L, 95th percentile 184 µg/L
Time spent in pool (min)	Log-normal (3.91, 0.4) 5th percentile 26 min, median 50 min, mean 59 min, 95th percentile 96 min
Proportion of women who swim	41%
Proportion of swimmers who swim occasionally	59%
Swimming rate for occasional swimmers (< once/month) for the 90-day period	Uniform (0, 3)
Swimming rate for regular swimmers for the 90-day period (once/month to 6.5 times/week)	Triangle (3, 84); maximum probability at 3; 0 probability at ≥ 84[a]
Number of swims in 90 days	Poisson (swimming rate)
Uptake (µg/min) per µg/L chloroform in pool	Uniform (0.00102, 0.004537)

[a]For those who swim > 6 times/week, 0.3%; 2–6 times/week, 21%; < 2 times/week, 79%.

shape of the distribution. Table 1 summarizes the input parameters for swimming.

Tap water ingestion. Several studies have reported daily tap water consumption; however, liquid consumption patterns vary across different populations (Hopkin and Ellis 1980). Therefore, ideally the distribution for tap water consumption should be estimated from U.K. studies, which include Hopkin and Ellis (1980) and M.E.L. Research (1996). Mean daily tap water consumption for the entire population based on 3-day diary data was 0.96 L/day in the Hopkin and Ellis study and 1.14 L/day in the M.E.L. Research (1996) study. However, no U.K. studies report tap water consumption for pregnant women. The ratio of water intake to body weight has been found to be similar for pregnant and nonpregnant women in the United States (suggesting that pregnant women drink more) (Ershow et al. 2001). The mean for the distribution of tap water intake was chosen to be similar to the overall U.K. mean (this includes men, who on average drink more than women and so will tend to balance out the fact that pregnant women also drink more than nonpregnant women). However, slightly less variability than that found in the 3-day diary data was assumed because short-term averages are more variable than long-term averages and a 90-day average was required for this simulation study.

The majority (> 80%) of tap water consumed in the U.K. studies was reported to be hot beverages such as tea or coffee. It is necessary to consider how tap water is consumed because volatilization through heating leads to lower concentrations of chloroform. Pouring boiling water has been reported to lead to an average 85% reduction in chloroform concentrations in the water (Batterman et al. 2000). However, the U.K. studies may overestimate consumption of tea and coffee for pregnant women for two reasons. First, the studies were both carried out between February and April, and participants reported that their tea and coffee consumption is higher in the winter (~18% higher), whereas squash (a fruit drink made with cold tap water) consumption is higher in the summer (67% higher). Second, a study in the United States found that pregnant women drank 11% less tea, 19% less coffee, and 19% more plain water than nonpregnant women (Ershow et al. 2001). The drop in consumption of tea and coffee for pregnant women may be greater in the United Kingdom, where consumption is considerably higher among nonpregnant women than that reported in this U.S. study. The distribution chosen therefore reduces the proportion of hot tap water consumption from that reported in U.K. studies of nonpregnant women.

Chloroform uptake from drinking water depends upon water chloroform concentration, amount of water ingested, and the body's chloroform absorption efficiency (Jo et al. 1990). Backer et al. (2000) measured whole-blood chloroform concentrations before and after a subject drank 1 L of tap water over a 10-min period and observed an increase in the blood concentration of approximately 0.015 µg/L. We calculated the total amount of chloroform present in the blood based on the assumption that an individual has 5 L of blood. Uptake (per liter of water ingested per microgram per liter chloroform) was given by the proportion of chloroform in the blood to the total amount of chloroform ingested:

$$\begin{aligned}\text{Uptake [µg/(µg/L)L]} = {} & \{[\text{amount of blood (L)}] \\ & \times [\text{blood } CHCl_3 \text{ conc after ingestion (µg/L)} \\ & - \text{blood } CHCl_3 \text{ conc before ingestion (µg/L)}]\} \\ & \div \{[CHCl_3 \text{ conc in water (µg/L)}] \\ & \times [\text{amount water ingested (L)}]\}\end{aligned}$$

Table 2 summarizes the input parameters for tap water ingestion.

Showering and bathing. It is likely that an individual showers and bathes mostly in the home. Chloroform exposure while showering will depend on the water temperature, water flow rate, shower duration, and ventilation (Jo et al. 1990), but little information is available on this for the U.K. population.

The U.S. Environmental Protection Agency recommends that the showering/bathing frequency should be estimated as one event per day (U.S. EPA 1999). However lower frequencies have been reported, for example, 0.6 baths or showers per day in the Netherlands (Groot-Marcus et al. 1995) and 0.73 baths or showers per day in the United Kingdom (Gowers et al. 1999). These studies may underestimate the frequency for women because they included children. In a 3-day diary in the United States, 18% of women took baths only, 21% took both baths and showers, and 61% women took showers only (Shimokura et al. 1998).

The distribution used for time spent showering was the distribution calculated by Burmaster (Burmaster 1998) based on Australian water-use diary data (James and Knuiman 1987). The distribution for time spent bathing was based on data from NHAPS (Tsang and Klepeis 1996).

Blood chloroform concentrations have been measured before and after showering (Backer et al. 2000; Lynberg et al. 2001) and bathing (Backer et al. 2000). On average, after showering, blood concentrations increased by 0.025 µg/L, ~0.087 µg/L, and 0.19 µg/L where chloroform concentrations in the supplied water were 8.2 µg/L, 31 µg/L, and 84 µg/L, respectively. For bathing, blood chloroform concentrations increased by 0.088 µg/L where the water chloroform concentration was 32 µg/L. The uptake per microgram per liter chloroform in the water per minute was then calculated as per the swimming uptake. A 10-min average shower time was assumed where no average showering time was available. Table 3 summarizes the input parameters for showering and bathing.

Uptakes. Once values for the input parameters had been specified the simulations were run for the 300,000 women using S-PLUS (Mathsoft Inc., Cambridge, MA) We calculated an individual's average daily uptake of

Table 2. Input parameters for tap water ingestion.

Parameter	Distribution/value
Average daily tap water intake (L/day)	Log-normal (–0.15, 0.45) 5th percentile 0.41 L/day, median 0.86 L/day, mean 0.95 L/day, 95th percentile 1.8 L/day
Proportion of drinks made with boiled water	Uniform (0, 1); average, 50%
Chloroform loss from heating and pouring	85%
Uptake (µg) per µg/L chloroform in water per liter consumed	0.003676

Table 3. Input parameters for showering and bathing.

Parameter	Distribution/value
Showering/bathing rate for the 90-day period	Uniform (60, 100); average, 0.9 showers or baths/day
No. of showers or baths for the 90-day period	Poisson (showering/bathing rate)
Percentage of mothers who take baths only	18%
Percentage of mothers who take showers only	61%
Proportion of baths taken for those who bathe and shower	Uniform (0, 1); average, 50%
Time spent showering (min)	Log-normal (1.9705, 0.3869) 5th percentile 4 min, median 7 min, mean 8 min, 95th percentile 14 min
Time spent bathing (min)	Log-normal (2.8, 0.65) 5th percentile 6 min, median 16 min, mean 20 min, 95th percentile 48 min
Uptake (µg/min) per µg/L chloroform in water for showering	Uniform (0.001114, 0.001524)
Uptake (µg/min) per µg/L chloroform in water for bathing	0.001384

chloroform for swimming, showering, and bathing as follows:

Average daily chloroform uptake (μg)
= {(uptake for chloroform per μg/L chloroform in the water per min spent in activity)
× [total time spent in activity (min) over 90 days]
× [chloroform concentration in the water (μg/L)}
÷ 90 (days).

Similarly, an individual's average daily uptake of chloroform for ingestion of tap water was calculated as

Average daily chloroform uptake (μg)
= (uptake per μg/L chloroform in the water per liter ingested)
× [average daily cold tap water (L)]
× 0.15 [average daily hot water intake (L)]
× [chloroform conc in the water (μg/L)].

Uptakes via each pathway were summed to give a total average daily uptake, and uptake via showering, bathing, and ingestion of tap water was summed to give an average daily uptake excluding swimming. These average daily total uptakes were then split into three categories (low, medium, and high), with a third of the simulated population belonging to each category. This gave categories of low (0–0.35 μg), medium (0.35–0.82 μg), and high (> 0.82 μg) for total uptake, and low (0–0.25 μg), medium (0.25–0.57 μg), and high (> 0.57 μg) for total uptake without swimming. For the purposes of the U.K. epidemiologic study previously discussed (Toledano et al. 2001), the chloroform concentrations of the water supplied to the home were categorized into low (< 20 μg/L), medium (≥ 20 to < 40 μg/L), and high (≥ 40 μg/L). The proportions of the simulated population classified as exposed to high, medium, or low chloroform uptake were cross-tabulated against the water chloroform categories to assess the degree of exposure misclassification associated with using tap water concentrations. Correlations between uptake via different pathways and the total uptake were also calculated.

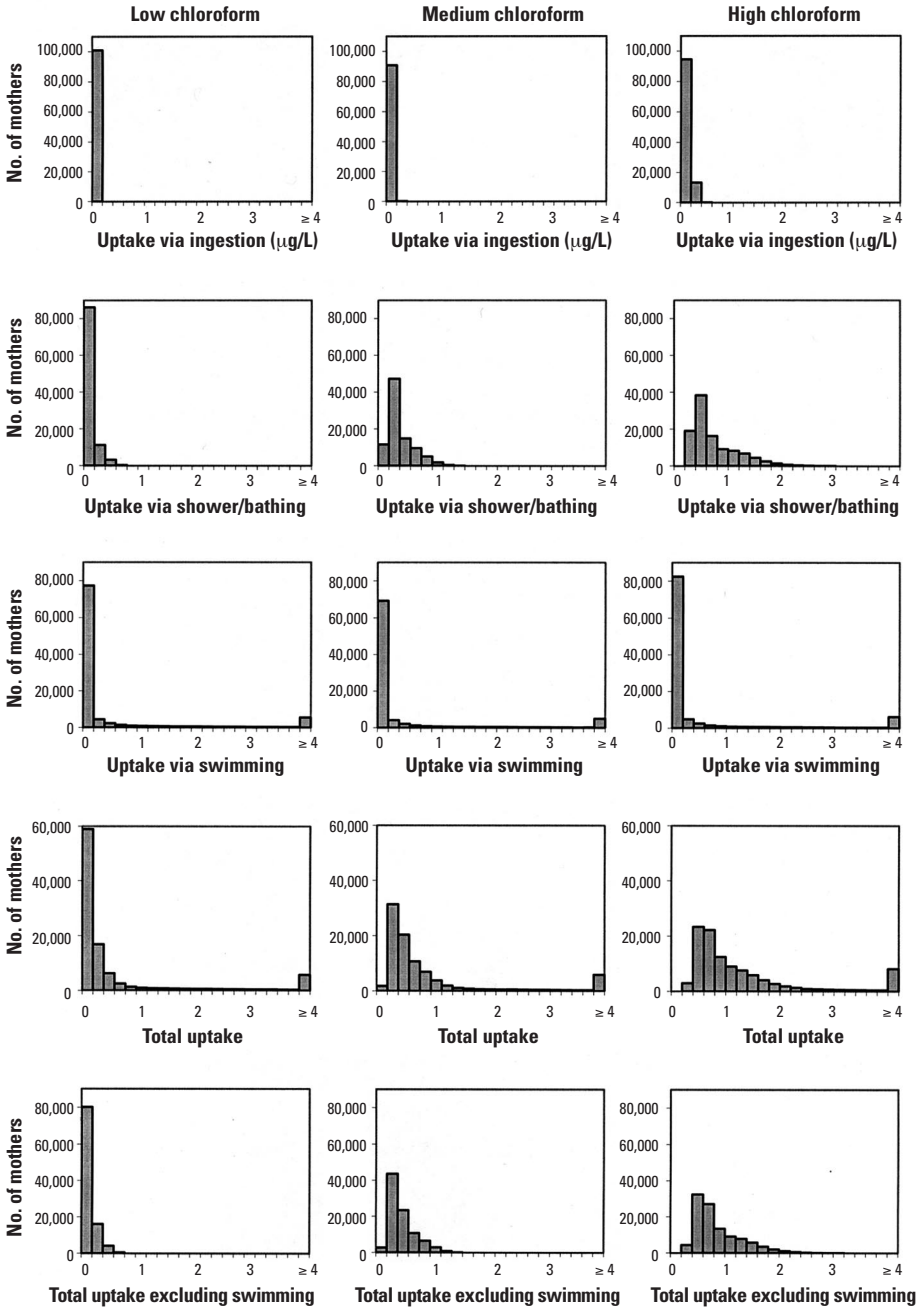

Figure 2. Distributions for simulated average daily uptakes (μg/L) for mothers supplied with water in the low-, medium-, and high-chloroform categories.

Results

Figure 2 shows the uptake via ingestion, showering and bathing, and swimming and the total uptake and total uptake excluding swimming uptake for mothers living in homes supplied with low, medium, and high chloroform concentrations. Estimated uptake concentrations for swimming ranged between 0 μg for the 67% of mothers who did not swim in the 90-day period and 22 μg/day for the most frequent swimmer. Swimming uptake was independent of the chloroform concentration in the water supplied to the home (the three figures differ because the number of mothers in each category differs). Estimated uptake via ingestion, showering, and bathing generally increased with increasing home chloroform concentration. Uptake via ingestion ranged between 0.00006 μg and 0.1 μg (low water chloroform concentration), 0.007 μg and 0.3 μg (medium), and 0.01 μg and 0.6 μg (high), whereas uptake via showering and bathing ranged between 0.0007 μg and 0.8 μg (low), 0.08 μg and 1.6 μg (medium), and 0.2 μg and 3.8 μg (high). Uptake via showering and bathing provided a more significant route of uptake than did ingestion of tap water. It is also clear that swimming had a large impact on an individual's level of uptake.

The Spearman's rank correlation coefficient (r_s) between chloroform concentrations in water and total uptake was 0.60, and 0.87 when swimming was excluded (Table 4). The Spearman's correlation coefficients were used because the uptake distributions were not normally distributed. However, the Pearson correlation coefficients (r_P) calculated after first log-transforming the uptake distributions to

give approximate normality were very similar. For example, the Pearson correlation coefficient (r_P) for the log-transformed total uptake and the (untransformed) chloroform concentration was 0.58, and r_P for the log-transformed total uptake without swimming and the chloroform concentration was 0.81.

The uptake via showering and bathing gave the strongest correlation with the total uptake (r_s = 0.69). The correlation between uptake via swimming and total uptake was similar (r_s = 0.65). Although swimming had a large influence on total uptake, the majority of women did not swim. The correlation between total uptake and uptake via ingestion was lower (r_s = 0.54). There was a very strong positive correlation between uptake via showering and bathing and total uptake excluding swimming (r_s = 0.99). The uptake via bathing had a much stronger correlation with total uptake than did uptake via showering.

Tables 5 and 6 show the number of mothers in each of the total uptake categories (with and without swimming) cross-tabulated with the categories for chloroform concentrations in tap water. As expected, mothers supplied with water that has a high chloroform concentration mostly have high total uptakes, and mothers supplied with water that has a low chloroform concentration mostly have low total uptakes. However, for total uptake, 43% were classified in different exposure categories depending on whether uptake or tap water concentration was used; for total uptake without the swimming uptake, 27% were classified differently.

Discussion

Little information is available on the relationship between chloroform concentrations in home tap water and the actual uptake of chloroform. This information is needed to determine the potential impact of exposure misclassification on the health risk estimates in epidemiologic studies that use ecologic estimates of water chloroform concentrations such as water zone mean concentrations. Because of the difficulty, expense, and time required for collecting the necessary data to address this question empirically, we chose to use a simulation approach in this study. We found a moderate positive correlation between chloroform concentrations in tap water and the simulated uptake of chloroform, as estimated by serum chloroform concentrations for the whole population. The correlation was strong when uptake via swimming was not included. Swimming may be particularly problematic to the exposure assessment of epidemiologic studies because it is a sporadic activity among the general population and the chloroform concentration in a swimming pool is very unlikely to be related to the tap water concentration at its visitors' homes. We found that uptake through both showering and bathing was the strongest predictor of the total chloroform uptake, followed by swimming, and then ingestion. This information suggests that it is important to include showering, bathing, and swimming when individual-level data are collected for epidemiologic studies, if the putative agent is chloroform.

Imprecise exposure estimates may lead to loss of power and precision, and attenuation in health risk estimates, depending on the type of error model (Armstrong 1998). The extent to which this happens depends on the relationship between the exposure index that is used and the "true" exposure. Our epidemiologic study will be carried out using both continuous and categorized (low, medium, and high) THM concentrations as the exposure index. When the exposure index is categorized, exposure misclassification may bias relative risk estimates either upward or downward (assuming an association truly exists). Referring to the results given in Table 5, the 9% of individuals classified in the low tap water chloroform-concentration group who had medium or high uptake would inflate the adverse birth outcome rate for the low (baseline) group, and the 16% of individuals classified in the high tap water chloroform-concentration group who had medium uptake would have the effect of attenuating the relative risk estimate for the high category. When the exposure index is on a continuous scale, the extent of measurement error depends on the correlation between personal uptake of chloroform and mean chloroform concentrations of the water zones (Armstrong 1998). In this study we found that, for the whole population, the (Pearson) correlation between chloroform concentrations in water and predicted chloroform uptake was approximately 0.6, and 0.8 when swimming was excluded. Under the classical measurement error model this may lead to attenuation in relative risk estimates, which can be estimated as follows:

$$RR_{observed} \approx RR^{r_P^2_{true}},$$

where RR denotes the relative risk and r_P^2 denotes the coefficient of reliability, which is equivalent to the square of the (Pearson) correlation coefficient between the true and approximate measurements of exposure (Armstrong 1998). For example, if the true relative risk (RR_{true}) = 2 and the correlation between true and approximate measurements of exposure (r_P) = 0.6, the observed relative risk ($RR_{observed}$) = $2^{0.36}$ = 1.3; if r_P = 0.8, $RR_{observed}$ = $2^{0.64}$ = 1.6. Under the Berkson measurement error model (Berkson 1950), in

Table 4. Spearman's rank correlation coefficients (r_s) between chloroform water concentration and uptake via various pathways and total uptake, including and excluding swimming.

Pathway	Chloroform concentration in home tap water (μg/L)	Total	Total uptake without swimming
Home chloroform concentration (μg/L)		0.60	0.87
Uptake via ingestion (μg)	0.83	0.54	0.79
Uptake via ingestion of cold tap water (μg)	0.72	0.49	0.71
Uptake via ingestion of boiled tap water (μg)	0.72	0.42	0.62
Uptake via showering and bathing (μg)	0.85	0.69	0.99
No. of baths and showers taken		0.11	0.15
Uptake via showering (μg)	0.57	0.16	0.25
No. of showers taken		0.35	0.44
Uptake via bathing (μg)	0.23	0.43	0.55
No. of baths taken		0.35	0.44
Uptake via swimming (μg)		0.65	
No. of times went swimming		0.64	
Total uptake without swimming (μg)	0.87	0.69	

Table 5. Number in each category (percentage of total) by total exposure and chloroform concentration.

	Total exposure			
Chloroform concentration	Low	Medium	High	Total
Low	73,468 (25%)	11,411 (4%)	16,086 (5%)	100,965
Medium	25,574 (9%)	39,576 (13%)	25,809 (9%)	90,959
High	958 (0.3%)	49,013 (16%)	58,105 (19%)	108,076
Total	100,000	100,000	100,000	300,000

Table 6. Number in each category (percentage of total) by total exposure without swimming and chloroform concentration.

	Total exposure without swimming			
Chloroform concentration	Low	Medium	High	Total
Low	88,159 (29%)	11,999 (4%)	807 (0.3%)	100,965
Medium	11,822 (4%)	56,078 (19%)	23,059 (8%)	90,959
High	19 (0.006%)	31,923 (11%)	76,134 (25%)	108,076
Total	100,000	100,000	100,000	300,000

which an individual's true exposure is assumed to vary around the surrogate measure for exposure used, it may lead to less precise health risk estimates, which may reduce study power. Power loss as a result of all nondifferential measurement errors can be measured by the effective loss in sample size, which is equal to r_P^2 (Armstrong 1998). Most exposure errors combine elements of both classical and Berkson-type measurement errors.

This simulation study makes a number of assumptions, and depending on their validity, the potential for exposure misclassification may be more than or less than that indicated here. For example, we assumed that the chloroform concentration supplied to the home was constant. However, this is likely to vary from day to day, leading to further variability in exposure. Chloroform concentrations in water stored in a hot water tank may increase over time, leading to further uptake via bathing and showering (Weisel and Chen 1994). It may be unreasonable to assume that most people primarily drink their home tap water, although this may not have a large impact on the results because ingestion of tap water provides only a minor route of uptake, and ingestion outside the home may still be in the same water zone. An individual who swims regularly receives a far greater dose than an individual who never swims. These regular swimmers may also take an extra shower after swimming, thus further increasing their average daily uptake.

Only the main water use activities were included in this simulation study. We did not incorporate, for example, dish washing, cooking, and use of a washing machine, but these are likely to make only a minor contribution to the total uptake. Where possible, the input parameters were obtained from U.K. data, but because of lack of data, this was not always possible. The distributions used for the tap water ingestion and duration of showering, bathing, and swimming came from only a few studies and may not reflect exactly the population in our study areas, although they were considered the best available. The estimation of the rate of chloroform uptake was derived from a limited number of studies and used the difference between average blood chloroform concentrations at the beginning and end of experiments. It therefore does not take into account metabolism of chloroform during the activities. Furthermore, averages for each study were used, despite the results indicating that there were differences between individuals (Backer et al. 2000; Lynberg et al. 2001). Also, chloroform appears to have a relatively short biologic half-life, around 20–30 min, but the decay appears to be a more complex process, being at least a three-order process, possibly four (Ashley and Prah 1997). The complex decay allows a very short half-life after acute exposure but also bioaccumulation with repeated exposure. This was not explored in our simulations.

Previous studies that aimed to assess an individual's risk to volatile compounds have taken into account the sequence of water-use events in the home, including dish washing and the use of a washing machine (Georgopoulos et al. 1997; Wilkes 1999). Deterministic models were used in their studies to estimate the concentration of the compound in the water and environmental air to which an individual was exposed. However, this requires information on water-use sequences, building characteristics, water flow rates, and air exchange rates, on which little, if any, data are available, particularly in the United Kingdom.

The uptake per microgram per liter chloroform in water per minute was greater for swimming than for showering and bathing. A small proportion of the difference can be accounted for by the fact that the two showering/bathing studies measured whole blood chloroform concentrations, whereas the swimming studies measured blood plasma concentrations (Aggazzotti et al. 1995; Aiking et al. 1994; Backer et al. 2000; Lévesque et al. 1994; Lynberg et al. 2001). Backer et al. (2000) took their blood samples 10 min after the exposures had ended; given chloroform's short biologic half-life, blood chloroform concentrations may have dropped significantly during this period, although the uptake per minute spent showering for this study was very similar to that in the study by Lynberg et al. (2001). Showering/bathing uptake is expected to be greater because of higher water temperatures, which has been shown to increase dermal absorption (Gordon et al. 1998). However, swimming requires more physical activity, and swimming intensity has been found to have a significant impact on chloroform uptake because of increased blood flow and breathing rate (Aggazzotti et al. 1990; Camman and Hübner 1995). It is possible that these differences are due to inconsistencies in the measurement techniques, because the procedures used are fairly complicated and contamination may take place.

In this study, we used chloroform because it is generally the most prevalent by-product and there is more information on the uptake than for other DBPs. However, this does not imply that chloroform is the putative agent for adverse birth outcomes; so far, the toxicologic and epidemiologic evidence has been inconsistent and inconclusive (Nieuwenhuijsen et al. 2000a). Chloroform has various exposure routes and pathways, which results in more variation and hence lower correlation coefficients between chloroform water concentrations and uptake than may be expected when fewer routes or pathways are available. For other nonvolatile DBPs, for which ingestion is the main route of uptake, the correlation between water concentration and overall uptake may be much better than for chloroform, which has multiple routes and pathways. However, two studies found no relation between nonvolatile trichloroacetic acid (TCAA) concentrations measured in urine and TCAA concentrations in home tap water, although personal consumption information combined with the TCAA concentration in tap water was found to be correlated with the TCAA urine concentrations (Weisel et al. 1999; Froese et al. 2002).

This simulation study could be improved by including other water use activities, although data on blood concentration increases are not currently available for any activity other than those used here. It would also be useful to look at uptakes of other DBPs, such as the other THMs or the nonvolatile haloacetic acids.

Despite all the assumptions made, this study is useful because it gives an approximate indication of how chloroform concentrations in the water delivered to the home (similar to the ecologic measure of "exposure" used in most epidemiologic studies) relate with actual uptakes, taking into account the variations in individuals' activity patterns. The results suggest that there is a substantial possibility that exposure misclassification or measurement error will cause bias in relative risk estimates and/or loss of power in epidemiologic studies, if the putative agent is chloroform.

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