Measuring Inhalation and Dermal Exposures to Disinfection By-products

Project Scope

Disinfection by-products (DBPs) have been a public health concern since the 1970s, when chlroform and other trihalomethanes (THMs) were identified in chlorine-treated drinking water. DBPs are produced during chlorination of surface and groundwater, and over 100 DBPs have been identified. People can be exposed to DBPs by ingestion, inhalation, and dermal contact with treated drinking water. To estimate the health risks associated with DBPs in drinking water, it is important to be able to estimate dose associated with each potential exposure route. However, the only DBP for which multi-pathway doses have been well characterized to date is chloroform.

The overall goal of this project was to determine the potential inhalation and dermal exposure during water-centered activities (e.g., showering, bathing) to selected DBPs: haloacetic acids (HAAs), haloketones (HKs), haloacetonitriles (HANs), and chloral hydrate (CH). The specific objectives were to:

- Determine the particle number and size distribution of shower droplets, and DBP concentrations in aerosols;
- Characterize dermal absorption of the selected DBPs;
- Determine the dose received of selected DBPs following inhalation and dermal exposure at known DBP water concentrations using urinary and breath biomarkers; and
- Compare the potential internal dose of each of the DBPs resulting from inhalation, dermal exposures, and ingestion.

Grant Title and Principal Investigators

Inhalation and Dermal Exposure to Disinfection By-products of Chlorinated Drinking Water (EPA Grant #R825953)

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Key Findings and Implications

Analytical Accomplishments:

- Demonstrated that inhalation and dermal exposures of selected disinfection by-products (DBPs) were meaningful as compared to ingestion exposure, extending previous studies on trihalomethanes.

Implications of Research and Impacts of Results:

- Results from these studies can be used to estimate more realistic values for the parameters used in evaluating inhalation and dermal human exposures with pharmacokinetic models.
- These risk models have been used by EPA to establish population-based exposure estimates and to determine what data is required to accurately predict the most exposed populations for risk assessment.
- The data obtained from this research can be used to update EPA's Exposure Factors Handbook, a widely used compilation of parameters used for estimating human exposures for risk assessment.

Publications include 3 peer reviewed journal articles and 7 conference/symposium presentations.

Project Period: October 1997 to September 2000

To carry out these objectives, a series of studies using a combination of *in vivo* and *in vitro* experiments were conducted. The *in vitro* studies included the following: measurement of aerosol particle size and number distributions in showers; DBP air concentrations in particle and vapor phases resulting from showers; and measurement of dermal fluxes determined using excised skin tissue in a Franz cell. The *in vivo* studies included measurements on urinary and alveolar breath levels of DBPs or their metabolites following exposures to known DBP concentrations in water during showering and bathing.

Relevance to ORD's *Drinking Water Research Multi-Year Plan* (2003 Edition)

This project contributes directly to the first of three Long-term Goals for drinking water research: (1) by 2010, develop scientifically sound data and approaches to assess and manage risks to human health posed by exposure to regulated waterborne pathogens and chemicals, including those addressed by Arsenic, M/DBP, and Six-Year Review Basis.

This research improves the accuracy of exposure assessment to a number of DBPs through routes that have not been previously studied with a majority of the known DBPs (other than chloroform). The project results showed that inhalation and dermal exposure can contribute from 10 to 30 percent of the total dose compared to ingestion exposure for compounds that volatilize from shower water or are lipophilic and can penetrate the skin. This research provides support to EPA efforts to assess population-based human health risk for exposure, through multiple routes, to DBPs.

Project Results and Implications

Particle Number, Size Distribution, and DBP Concentration in Aerosols: The investigators determined the aerosol number and size distribution of the shower air using an optical particle counter, the inlet of which was placed in the breathing zone height (1.5 m) of the shower stall to collect the samples, for a laboratory showering system. Results from the measurements showed an exponential increase in particle numbers was observed while the shower stream was on. This was followed by an exponential decline once the shower water was turned off. The majority of the particles generated were less than 0.2 micrometers. The bulk of the mass (339 $\mu g/m^3$) was in particles larger than 2.0 micrometers, based on the mass distribution calculated by assuming unity density for water and spherical particles. DBP concentrations were measured in the shower aerosol derived from water containing 250 µg/L and 25 µg/L of HAA and HK, respectively. The aerosols were collected using an opened face filter, which collects all particle size ranges and can be used to estimate the upper limit of the inhalation exposure from aerosols. The aerosol HAA and HK air concentrations were 6.3 and 0.13 $\mu g/m^3$, respectively. The estimate of the dose from inhalation exposure of aerosolized DBPs was less than one percent of the ingestion dose, assuming 100 percent of the inhaled aerosols are deposited in the lung of a person. Thus, droplet inhalation is not expected to be an important exposure route for non-volatile water contaminants, unless the lung is the target organ. The vapor phase levels of volatile DBPs, HKs, CH, and HANs, on the other hand, were in the tens to hundreds of $\mu g/m^3$ range, significantly higher than the aerosol concentrations. Exposures to vapor phase DBPs can thus contribute greater than 10 percent of the expected ingestion dose during a shower.

Dermal Absorption: The investigators conducted a series of *in vitro* studies were conducted for HAAs, HKs, HANs, CH, and trihalomethanes (THMs) to characterize their percutaneous absorption using cadaver skin mounted in thermostatically controlled cells at typical environmental concentrations. Results from these experiments demonstrated that HAAs were not found to penetrate the skin significantly at neutral pH (pH = 7), presumably because they are completely ionized at neutral pH and the skin is an efficient barrier to ionic species. The other compounds were found to penetrate the skin within minutes of contact, indicating that dermal penetration occurs within the time frame of showering and bathing. The permeability coefficients calculated using steady state methods for THMs, HKs, HANs, CH, and HAAs were estimated to be 0.2, 0.03, 0.1, 0.04, and 0.002 cm/hour, respectively. Thus, it is predicted, as previously has been reported for chloroform, that dermal absorption from showering for 10 minutes would be important for THMs and for the HANs, (over 30 percent of the ingestion dose) and to some extent HKs and CH (10 percent of the ingestion dose). Based on these results, the investigators suggest that dermal absorption needs to be considered in risk assessments for THMs, HKs, HANs, and CH exposures during showering, but not for HAAs.

Urinary and Breath *In Vivo* Studies: The investigator examined concentrations of HANs, CH, and HKs in both urine and exhaled air, and HAAs in urine as potential biomarkers of DBP exposures during and following inhalation, dermal, and ingestion exposures. Chloroform was used as a reference compound. Human subjects were exposed to a known, controlled amount of selected DBPs dermally by bathing in controlled temperature bath while breathing purified air, by inhalation by standing next to a shower stream in a shower stall while wearing waterproof garments, and by ingestion by drinking water. Exposure levels were selected to be at the upper end of water concentrations reported in the United States. The dermal and inhalation exposure durations were between 10 and 30 minutes. The ingestion exposures were measured after consumption of 0.5 L of water. DBP levels were measured by gas chromatography/electron capture detection (GC/ECD).

Of the urinary HAAs measured, only trichloroacetic acid and dichloroacetic acid were found routinely in pre- or post-exposure urine samples. No consistent increase in the urinary levels of any of the HAAs was observed following either dermal exposure during a 30-minute bath or from a combined dermal and inhalation exposure during a 10-minute shower using water concentrations up to 200 µg/L. The lack of an increased urinary excretion of HAAs could be due to either the lack of dermal absorption, low-inhalation doses, or from complete metabolism of the HAAs prior to excretion. This finding is consistent with the *in vitro* study results suggesting that the HAA dose from showering or bathing would be small. Ingestion studies found limited increases in the excretion of dichloroacetic and trichloroacetic acid, with no increase in monochloroacetic acid or the brominated species. The ingestion studies indicated that metabolism of the monochloroacetic acid and the brominated species is rapid. Because of extensive first-pass metabolism more rapid removal is expected for ingested compounds than from other exposure routes. Although the *in vivo* experiments on HAA did not conclusively rule out significant dermal and ingestion absorption, they are highly supportive of the *in vitro* studies that suggest these exposure routes are not important for the HAAs.

Urinary excretion and exhaled breath concentrations of the HKs were evaluated as potential biomarkers of dichlorophenol (DCP) and trichlorophenol (TCP) exposures. The exhaled breath concentrations were more consistent, had fewer chromatographic interferences, and provided greater time resolution than the urinary measurement, so breath analyses were routinely used to evaluate dermal and inhalation exposures from bathing and showering. During exposure to water containing 25 µg/L, the air concentrations of DCP and TCP were between 35 and 50 $\mu g/m^3$. Breath concentrations during the inhalation exposures were less than 10 $\mu g/m^3$. The air to breath concentration ratio during exposure was higher for the HKs than for chloroform, indicating that the HKs are absorbed more efficiently through the lungs than chloroform. The post-exposure breath concentration for DCP and TCP were less than 1 $\mu g/m^3$ following both inhalation and dermal exposures, again values less than measured for chloroform for similar exposure levels. The lower breath concentrations for the HKs than for chloroform are consistent with their greater solubility in water (or blood) than air (lower Henry's Law constant). Their breath concentration decay appears to be more rapid than chloroform, possibly indicating more rapid metabolism. The breath concentrations following inhalation exposures were greater than the concentration following dermal exposure, suggesting that inhalation is a more important exposure route during showering for these compounds, but that both routes contribute significantly to the total dose. Based on shower exposure and pharmokinetic modeling, as well as measurement from the *in vivo* study, the investigators estimated that a 10 to 15 minute shower can produce an HK internal dose from inhalation equivalent to ingesting 0.04 to 0.01 L of drinking water. The amount of chloroform expired after the 30-minute inhalation exposure in the shower stall was between 2 to 9 percent of the internal dose, whereas the amounts of the HKs expired were approximately 0.3 to 0.4 percent of their internal doses during exposure.

Urinary excretion of HANs and their urinary metabolites (i.e., haloacetamides and thiocyanide) and urinary CH and its metabolites (i.e., dichloroacetic acid and trichloroacetic acid) were evaluated, along with exhaled breath concentrations of HANs and CH. No consistent increase in urinary HAN or

haloacetamides was observed in the urine samples after exposure. Background levels of urinary thiocyanide were greater than would be produced from the HAN dose from drinking water. Expired levels of HANs and CH were elevated following inhalation exposures. Urinary dichloroacetic acid and trichloroacetic acid levels consistently were elevated above their background values following inhalation and dermal exposure to CH. The elevated levels of the HANs and CH biomarkers after inhalation, and dermal exposures to these compounds in water, confirmed these routes of exposure as being important in elevating the body burden of these compounds.

Summary of Major Findings: Inhalation and dermal exposure were found to contribute significantly to the total exposure for HKs, HANs, and CH, but not for HAAs. This was based on increased breath concentrations for HKs, HANs, and CH following inhalation and dermal exposures of human and *in vitro* studies of permeation coefficients and air concentrations in shower stalls. Because aerosol inhalation was found to contribute only slightly to total exposures, differences in volatility were found to be the most important factors determining the relative importance of inhalation exposures to DBPs during showering. Differences in the contribution of dermal exposures to total dose are related mainly to differences in skin permeability to the compound at neutral pH. None of the examined biomarkers could be used to assess inhalation or dermal exposures in field studies because (1) the biological residence times are too short, and (2) the observed concentrations are too low to be measured following exposures at environmental levels. Depending on volatility and skin permeability, inhalation and dermal exposure were found to contribute between 10 to 30 percent of the total dose during showering. These data can be used to evaluate total exposure, absorbed dose, and associated health risk of DBPs in drinking water. This research confirms that future risk assessments for these DBPs need to consider inhalation and dermal exposure routes, and illustrates approaches for incorporating these exposure pathways.

Investigators

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For More Information

NCER Project Abstract and Reports:

http://cfpub2.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/193/report/0

Peer Reviewed Publications

Kim, H.K., and Weisel, C.P. 1998. Dermal absorption of dichloro-and trichloroacetic acids from chlorinated water. Journal of Exposure Analysis and Environmental Epidemiology 8(4):555-575.

Xu, X., Mariano, T., Laskin, J.D., and Weisel, C.P. 2002. Percutaneous absorption of trihalomethanes, haloacetic acids and haloketones. Toxicology and Applied Pharmacology 184(1):19-26.

Xu, X., and Weisel, C.P. 2003. Inhalation exposure to haloacetic acids and haloketones during showering. Environmental Science and Technology 37(3):569-576.